


PERSONAL HABITS AND INDOOR COMBUSTIONS

**VOLUME 100 E
A REVIEW OF HUMAN CARCINOGENS**

**IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS**

PERSONAL HABITS AND INDOOR COMBUSTIONS

VOLUME 100 E
A REVIEW OF HUMAN CARCINOGENS



This publication represents the views and expert
opinions of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon, 29 September-6 October 2009

LYON, FRANCE - 2012

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at <http://monographs.iarc.fr/>.

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Lorenzo Tomatis (1929-2007)
Founder of the *IARC Monographs* Programme

Lorenzo Tomatis, MD, with other colleagues knowledgeable in primary prevention and environmental carcinogenesis, perceived in the 1960s the growing need to objectively evaluate carcinogenic risks by international groups of experts in chemical carcinogenesis. His vision and determination to provide a reliable source of knowledge and information on environmental and occupational causes of cancer led to his creating the *IARC Monographs* Programme for evaluating cancer risks to humans from exposures to chemicals. The first meeting, held in Geneva in December 1971, resulted in Volume 1 of the *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man* [1972], a series known affectionately since as the “orange books”. As a champion of chemical carcinogenesis bioassays, Tomatis defined and promoted the applicability and utility of experimental animal findings for identifying carcinogens and for preventing cancers in humans, especially in workers and children, and to eliminate inequalities in judging cancer risks between industrialized and developing countries. Tomatis’ foresight, guidance, leadership, and staunch belief in primary prevention continued to influence the *IARC Monographs* as they expanded to encompass personal habits, as well as physical and biological agents. Lorenzo Tomatis had a distinguished career at the Agency, arriving in 1967 and heading the Unit of Chemical Carcinogenesis, before being Director from 1982 to 1993.

Volume 100 of the *IARC Monographs* Series is respectfully dedicated to him.

(photo: Roland Dray)

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NOTE TO THE READER

The term ‘carcinogenic risk’ in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word ‘risks’ in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended ‘...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.’ The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic

risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase ‘of chemicals’ was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 ([Stewart & Kleihues, 2003](#)). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups ([IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991](#); [Vainio et al., 1992](#); [IARC, 2005, 2006](#)).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term ‘agent’ refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as

causation of, and susceptibility to, malignant disease become more fully understood.

A cancer ‘hazard’ is an agent that is capable of causing cancer under some circumstances, while a cancer ‘risk’ is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word ‘risks’ in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed ‘carcinogenic’ if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms ‘neoplasm’ and ‘tumour’ are used interchangeably.

The Preamble continues the previous usage of the phrase ‘strength of evidence’ as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation ([IARC, 1991](#); [Vainio et al., 1992](#); [IARC, 2005, 2006](#); see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human

exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (<http://monographs.iarc.fr>). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate

or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) *The Working Group*

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) *Invited Specialists*

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) *Representatives of national and international health agencies*

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) *Observers with relevant scientific credentials*

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at <http://monographs.iarc.fr>).

(e) *The IARC Secretariat*

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine

whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume ([Cogliano et al., 2004](#)).

The names and principal affiliations of participants are available on the *Monographs* programme web site (<http://monographs.iarc.fr>) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC ([Cogliano et al., 2005](#)).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (<http://monographs.iarc.fr>) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

For most chemicals and some complex mixtures, the major collection of data and the preparation of working papers for the sections on chemical and physical properties, on analysis, on production and use, and on occurrence are carried out under a separate contract funded by the US National Cancer Institute. Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result,

the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data
 Studies of cancer in humans
 Studies of cancer in experimental animals
 Mechanistic and other relevant data
 Summary
 Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in

which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production,

which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and

place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case-control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case-control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in

particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph on arsenic in drinking-water*; [IARC, 2004](#)).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case-control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) *Quality of studies considered*

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies.

Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case-control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of

frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies ([Breslow & Day, 1980](#)) and for cohort studies ([Breslow & Day, 1987](#)).

(c) *Meta-analyses and pooled analyses*

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) ([Greenland, 1998](#)).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) *Temporal effects*

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal

relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) *Use of biomarkers in epidemiological studies*

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes ([IARC, 1991](#); [Vainio *et al.*, 1992](#); [Toniolo *et al.*, 1997](#); [Vineis *et al.*, 1999](#); [Buffler *et al.*, 2004](#)). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism

of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) *Criteria for causality*

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality ([Hill, 1965](#)). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and

coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species ([Wilbourn *et al.*, 1986](#); [Tomatis *et al.*, 1989](#)). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans ([Vainio *et al.*, 1995](#)). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. [OECD, 2002](#)).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) *Qualitative aspects*

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence ([Huff et al., 1989](#)). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo

transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) *Quantitative aspects*

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) *Statistical analyses*

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980;

Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls,

particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals ([Haseman *et al.*, 1984](#); [Fung *et al.*, 1996](#); [Greim *et al.*, 2003](#)).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than

one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) *Toxicokinetic data*

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) *Data on mechanisms of carcinogenesis*

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap-junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily

described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis ([Vainio et al., 1992](#); [McGregor et al., 1999](#)). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap-junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published ([Montesano et al., 1986](#); [McGregor et al., 1999](#)).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) ([Vainio *et al.*, 1992](#)). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere ([Montesano *et al.*, 1986](#); [McGregor *et al.*, 1999](#)).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. [Capen *et al.*, 1999](#)).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as

surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) *Other data relevant to mechanisms*

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be

found on the *Monographs* programme web site (<http://monographs.iarc.fr>).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and

the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal

relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In

addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) *Carcinogenicity in experimental animals*

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multi-stage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) *Mechanistic and other relevant data*

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics,

physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as ‘weak’, ‘moderate’ or ‘strong’. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources

have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental

animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity*

in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

Part E of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* contains updated assessments of personal habits and indoor combustions that were first classified as *carcinogenic to humans (Group 1)* in Volumes 1–99.

Volume 100 – General Information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned by updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected A Review of Human Carcinogens to be the topic for Volume 100. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals

Biological agents

Arsenic, metals, fibres, and dusts

Radiation

Personal habits and indoor combustions

Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the toxicokinetic properties of the agent, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results appear in the printed version of Volume 100, and more extensive tables that include all studies appear on the website of the *IARC Monographs* programme (<http://monographs.iarc.fr>). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise; then all sections of each *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, Tumour Site Concordance between Humans and Experimental Animals, will analyse the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, Mechanisms Involved in Human Carcinogenesis, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could render future research more informative. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Specific remarks about the agents reviewed in this volume

Billions of people around the world are exposed to one or several of these agents as part of their everyday life. A common theme is that they cause adverse health effects at levels of exposure that are commonly experienced, and collectively are responsible for a disproportionately high portion of the global burden of cancer. At the same time, some of these agents, notably tobacco in all forms and alcoholic beverages, are also mostly discretionary, although marketing and societal influences have played an important role in promoting their use. Therefore, exposure to these agents is largely preventable, through a combination of individual action and governmental intervention, the latter being especially important, for example, in promoting smoking cessation or smoke-free indoor environments.

Tobacco consumption is the single largest cause of cancer in the world. Tobacco smoking was evaluated as providing *sufficient evidence of carcinogenicity* in humans in Volumes 38 ([IARC, 1986](#)) and 83 ([IARC, 2004a](#)). Some types of smokeless tobacco were evaluated in Volume 37 ([IARC, 1985](#)) as having *sufficient evidence of carcinogenicity* in humans; two decades later, Volume 89 ([IARC, 2007](#)) classified all types of smokeless tobacco in Group 1. In this volume, the tobacco-specific nitrosamines NNK and NNN were also classified in Group 1 based on strong mechanistic evidence in exposed humans ([IARC, 2007](#)). Betel quid, a preparation that includes areca nut with betel leaf and other ingredients, and often tobacco, is chewed by over 600 million people in southern Asia and in Asian-migrant communities across the world. Betel quid with tobacco was evaluated in Volume 37 as having *sufficient evidence of carcinogenicity* in humans, and this classification was reaffirmed and extended to betel quid without tobacco in Volume 85 ([IARC, 2004b](#)). In the latter volume, areca nut, the common ingredient in all betel quid preparations, was also classified in Group 1. Alcohol consumption, another major contributor to the global burden of cancer, was classified in Group 1 in Volumes 44 ([IARC, 1988](#)) and 96 ([IARC, 2010a](#)). Ethanol and acetaldehyde associated with alcoholic beverage

consumption were specifically mentioned as carcinogenic agents in the latter volume. Indoor smoke from solid fuels is yet another major contributor to the global burden of disease. The highest individual risks are seen in households that use unvented coal stoves for cooking and heating, an exposure that was classified in Group 1 in Volume 95 ([IARC, 2010b](#)). Finally, salted fish was evaluated in Volume 56 ([IARC, 1993](#)), with Chinese-style salted fish classified in Group 1.

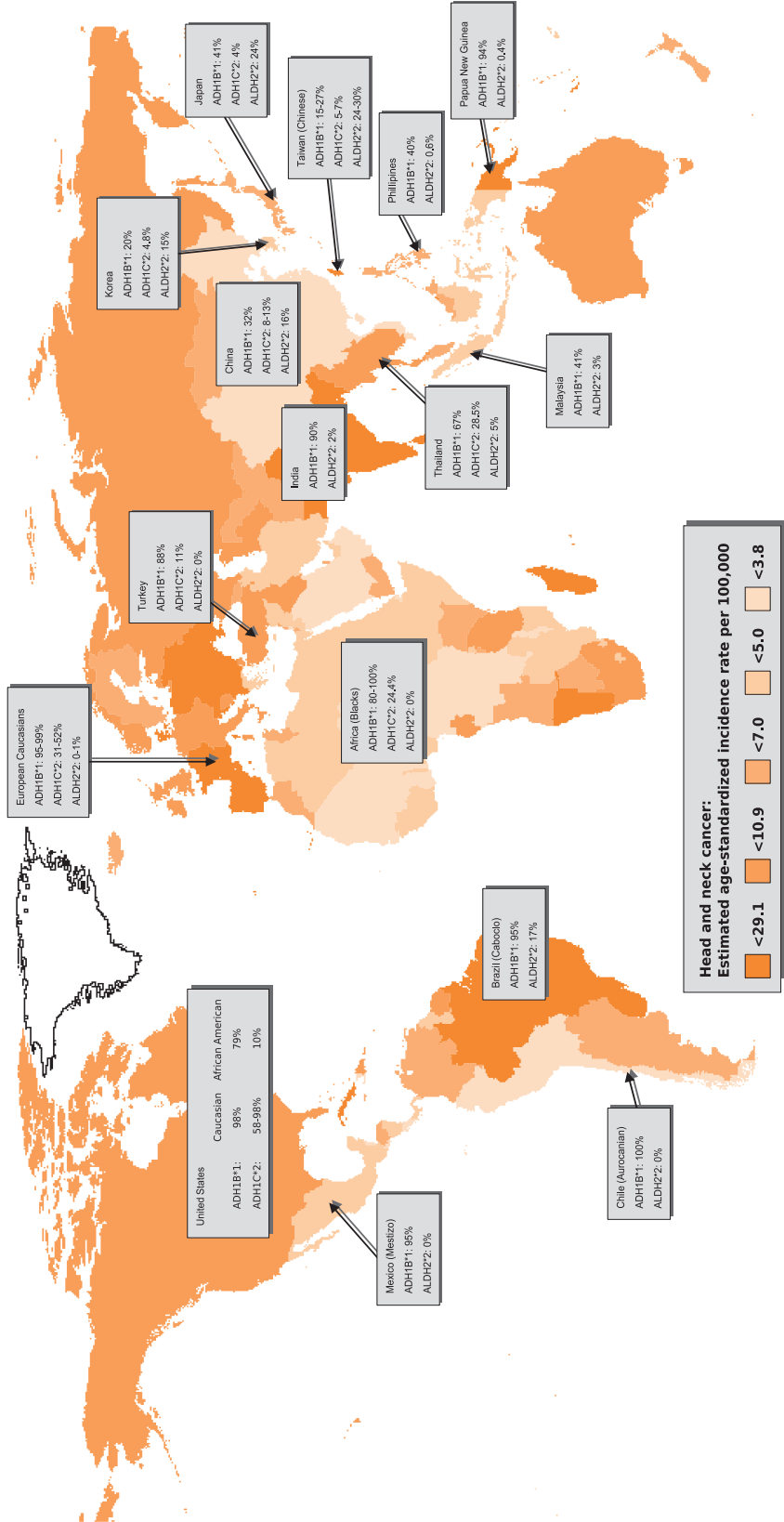
1. Alcoholic beverages, ethanol and acetaldehyde associated with their consumption

Consumption of alcoholic beverages is one of the top-10 exposures responsible for the burden of disease worldwide. Nearly two billion adults consume alcoholic beverages regularly, with an average daily consumption of 13 g ethanol (about one drink). The Working Group that evaluated alcohol consumption recently ([IARC, 2010a](#)) concluded that it causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver and female breast. With respect to the latter cancer type, the risk increases with increasing alcohol intake by about 10% per 10 g per day. Epidemiological evidence shows little indication that the carcinogenic effects depend on the type of alcoholic beverage.

The metabolism of ethanol, the key component in alcoholic beverages, can be essentially described as a two-step dehydrogenation process. In humans, the major enzymes involved are the alcohol dehydrogenases (ADH), which oxidize ethanol to its toxic intermediate, acetaldehyde, and the aldehyde dehydrogenases (ALDH), which detoxify acetaldehyde to acetate. The two groups of dehydrogenases exhibit genetic variations that confer wide differences in enzyme kinetics and substrate specificities and that vary widely across ethnicities (figure). Studies on the carcinogenicity of alcoholic beverages consumption give a striking example of a genetic polymorphism that strongly influences the response to a carcinogen. The variant *ALDH2*2* allele, which encodes an inactive subunit of the enzyme ALDH2, is highly prevalent in certain eastern-Asian populations (28–45%), but rare in other ethnic groups. Most homozygous carriers of this allele (*ALDH2*2/*2*) are abstainers or infrequent drinkers, because the complete deficiency of enzymatic activity would cause a strong facial flushing response, physical discomfort, and severe toxic reactions when consuming alcoholic beverages. In heterozygous carriers (*ALDH2*1/*2*), who have about 10% residual ALDH2 activity, these acute adverse effects are less severe, but these persons have higher levels of acetaldehyde in their blood and saliva after alcohol drinking, and higher levels of acetaldehyde-related DNA adducts in their lymphocytes compared with those with fully active enzyme (*ALDH2*1/*1* genotype). In addition, these individuals are at high risk for several alcohol-related aerodigestive cancers. Examining the role of acetaldehyde as a cause of aerodigestive cancers is further complicated by competing risk factors such as tobacco smoking, areca nut chewing, infection by HPV; in addition, this association may be modified by microflora present in the aerodigestive tract, which have high ADH but low ALDH enzyme activity ([Chang et al., 2011](#)).

The previous Working Group acknowledged the important role of acetaldehyde in the development of alcohol-related cancer, especially of the esophagus, but refrained from making a formal evaluation of this metabolite. The Working Group for this Volume considered that the available epidemiological data clearly indicates that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for development of alcohol-related cancers, and decided to make a separate evaluation for “acetaldehyde associated with alcoholic beverage consumption”.

ADH1B*1& ADH1C*2 (slow ethanol-oxidizing) & ALDH2*2 (null) allele frequencies by population and incidence of head and neck cancer



From [Chang et al. \(2011\)](#) (Supplementary figure)

2. Betel quid with and without tobacco, areca nut and smokeless tobacco

Smokeless tobacco and areca nut are consumed by millions of people across the globe and may be social practices deeply rooted in their respective cultures. In this *Monograph*, any product containing areca nut is referred to as ‘betel quid’, the most common name given for such products.

Smokeless tobacco and betel quid share many features. Both products are addictive ([Warnakulasuriya, 2004](#); [Chu, 2001](#)), and most evidence suggests that users find it difficult to quit these behaviours. Both are typically used orally, being chewed and then spit out. Although generally considered as a social practice, both have other uses: for example, various forms of smokeless tobacco are used as a dentifrice in India. Both products are rarely used alone and are generally consumed with other constituents, added during manufacture or by the user. Notably, both may contain an additive that increases the pH of the product, which has the effect of unprotonating the psychoactive substance, thus making it readily bioavailable: nicotine in the case of smokeless tobacco and arecoline in the case of areca nut (for reviews, see [Chu, 2001](#); [Djordjevic et al., 1995](#)). Other additives to both smokeless tobacco and industrially manufactured betel quid may include flavourings and sweeteners.

2.1 *Disentangling the effects of the various ingredients*

Some populations use only areca nut and slaked lime in their betel quid. Since cancer bioassays have shown that slaked lime is not carcinogenic, studies from these populations provide evidence that areca nut is a cause of cancer in human populations. Studies of betel quids with a variety of other ingredients except tobacco provide evidence for the carcinogenicity to humans of betel quid without tobacco overall. Finally, studies that either assess specifically betel quid with tobacco, or that did not specify whether tobacco was added, or that combined individuals who may or may not include tobacco in their quid, together provide evidence for the carcinogenicity of betel quid with tobacco.

Areca nut and/or smokeless tobacco are highly prevalent in some cultures, e.g. in Sweden, up to 30% of men use smokeless tobacco. In 2002, it was estimated that 600 million people worldwide, primarily in the Indian sub-continent, used areca nut. In the successive IARC Monographs that have addressed either smokeless tobacco or areca nut, new formulations of these products and new populations with such habits have been reported.

New forms of these products are constantly being developed and introduced on the market in formulations that encourage initiation or maintenance of use of these products. For example, portion sizes and packaging render them more convenient for people to use, while flavourings may appeal to young persons.

Finally, no betel quid or tobacco product in any culture has been shown to be safe or free of risk of cancer. Despite the wide variation in added ingredients, method of preparation or manufacture of the product, mode of use and populations concerned, these products have been associated with an increased risk of cancer. Nevertheless, these products are promoted as “safe” alternatives to tobacco smoking and many people consider products such as *pan masala* to be safe. However, one study from North America found that smokers who had switched to smokeless tobacco had a higher death rate than men who quit tobacco entirely ([Henley et al., 2007](#)).

2.2 *Betel inflorescence*

Betel inflorescence grows on *Piper betel* L. and is the male fruit, consumed with unripe areca nut in Taiwan, China. Betel inflorescence contains high levels of phenolic compounds including hydroxy-chavicol and safrole.

Of the different types of betel quid consumed in Taiwan, China, those that include betel inflorescence (*lao-hwa* quid) induced the highest risk for both oral leukoplakia and submucous fibrosis ([Lee et al. 2003](#)), and for oral and combined cancers of the oro- and hypopharynx ([Ko et al. 1995](#); [Chen et al. 2002](#)).

Carcinogenic risk of betel inflorescence and mechanistic pathways should be examined in detail in the future.

2.3 *Cancer burden*

The magnitude of the risks associated with smokeless tobacco and betel quid vary, and can be very high. This, combined with the high prevalence of some behaviours in some parts of the world, leads to a very high cancer burden. In India for instance, the cancer burden from these habits meets or exceeds that of smoking.

3. Tobacco smoke: multiple exposures, multiple chemicals, multiple target sites

3.1 *Tobacco smoke carcinogens*

Tobacco smoke is the most pleiotropic carcinogen ever evaluated by the *IARC Monographs Programme*, with over 20 target sites to which it has been shown to be causally associated. The chemical compositions of mainstream smoke and sidestream smoke are qualitatively similar, although quantitatively different. Tobacco smoke contains over 60 chemicals or other agents that have been shown to be carcinogenic in rodents; for a dozen of those, there is also *sufficient evidence* of their carcinogenicity in humans.

For the agents present in tobacco smoke and that are classified as IARC Group 1 or Group 2A, the table below presents the target sites for which there is *sufficient* or *limited* evidence in humans.

3.2 *Parental tobacco smoking*

The prevalence of exposure to tobacco smoke from parental smoking varies by socioeconomic status and country, ranging up to 60% in some surveys. Exposure of the offspring may occur pre-conception, *in utero* or postnatally. Active smoking by either genitor preconception and maternal smoking during pregnancy both imply direct exposure to mainstream tobacco smoke of the germ cells (spermatozoa and ova) and of the foetus, respectively. In contrast, paternal smoking during pregnancy and parental smoking post-natally represent exposures to second-hand tobacco smoke.

How to evaluate separately the effect of the different exposures and time periods? Early studies generally only assessed the contribution of maternal exposures during pregnancy, whereas recent studies included assessments of exposure preconception, in particular from paternal smoking. Exposure may have occurred in all three periods even when a study reports on only one, or exposure may also be

Target sites associated with some carcinogenic chemical compounds and metals present in tobacco smoke

Agent	Tumour sites or types for which there is <i>sufficient</i> evidence in humans	Tumour sites or types for which there is <i>limited</i> evidence in humans
Chemicals		
1,3-Butadiene	Hematolymphatic organs	
2-Naphthylamine	Urinary bladder	
4-Aminobiphenyl	Urinary bladder	
Benzene	Acute non-lymphocytic leukaemia	Acute lymphocytic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, non-Hodgkin lymphoma
Ethylene oxide		Breast, lymphoid tumours
Formaldehyde	Nasopharynx, leukaemia (particularly myeloid leukaemia)	Sinonasal cancer
o-Toluidine	Urinary bladder	
Vinyl chloride	Hepatocellular carcinoma, hepatic angiosarcoma	
Metals		
Arsenic and inorganic arsenic compounds	Lung, skin, urinary bladder	Kidney, liver, prostate
Beryllium and beryllium compounds	Lung	
Cadmium and cadmium compounds	Lung	Kidney, prostate
Chromium (VI) compounds	Lung	Nasal cavity and paranasal sinuses
Lead		Stomach
Nickel compounds	Lung, nasal cavity and paranasal sinuses	

Adapted from [Cogliano et al. \(2011\)](#)

reported as 'ever' exposed. In addition, parental smoking during each of these time periods tends to be correlated, in particular from the father, because father's smoking habits are less likely to change during pregnancy. Furthermore, paternal and maternal smoking habits are often correlated, and the risks may be increased when both parents smoke. Thus establishing a link between parental smoking and childhood cancer risk relates to several different exposures that are tightly correlated and difficult to disentangle.

The younger the child at diagnosis, the more direct prenatal exposures appear to be relevant compared to post-natal exposures. Stronger associations for cancer in offspring were observed from parental smoking preconception than from maternal smoking during pregnancy. Interestingly, the strongest and most consistent association was observed for hepatoblastoma, an embryonal tumour of presumably foetal origin, which has a median age of diagnosis of about 12 months. Cigarette smoke is a known germ-cell mutagen in mice and a likely germ-cell mutagen in humans. The effect of such mutagenicity on cancer risk in the offspring of smoking parents has now been demonstrated in human populations.

4. Coal Emissions

The use of coal in homes for cooking and heating is a major source of indoor air pollution in Asia, particularly in China. Emissions from the combustion of coal have been associated with a variety of health outcomes, especially lung cancer. The population at risk for illness from indoor air pollution numbers in the hundreds of millions in China alone, and possibly more than a billion worldwide. Women and children bear the largest share of the burden of disease from this exposure since they spend longer periods of time inside the home. Greater awareness of this exposure should be emphasized for these vulnerable groups. The development and implementation of appropriate improvement in ventilation and other strategies to reduce indoor air pollution in developing countries should be supported and encouraged from both the government and interested private parties in the commercial sector. The replacement of coal with cleaner fuels should also be a high priority. However, since many millions of people cannot afford to change the household fuels that they use, alternative efforts are necessary in the interim.

5. Salted fish

The Working Group has evaluated Chinese-style salted fish defined as salted fish consumed in Chinese populations, the majority of studies being from the Southern part of China. The evaluation of epidemiological studies has found *sufficient evidence* for an association with nasopharyngeal carcinoma, and *limited evidence* for an association with stomach cancer. The most consistent association between Chinese-style salted fish and nasopharyngeal carcinoma has been observed for ingestion during weaning or early childhood in the early studies; interestingly, the diet-related lifestyle changes that started in the second half of the 20th century in the Chinese populations, characterized by a large decrease in preserved food consumption and especially the decline in the habit of feeding young children with salted fish, coincides with the lower rate of nasopharyngeal cancer incidence observed in the most recent studies.

Defining a clear mechanism linking salted fish consumption with nasopharyngeal carcinoma has been hampered by the lack of data and by the fact that the composition of salted fish may greatly vary depending on the mode of preparation in different areas of Southern China. Possible mechanisms include the formation of *N*-nitrosamines and other *N*-nitroso compounds during the processing of the fish and/or endogenously after ingestion in the human body.

Another likely mechanism is the interaction between Chinese-style salted fish and Epstein-Barr virus (EBV). EBV involvement in the carcinogenesis of nasopharyngeal cancer in South-eastern China has been clearly demonstrated; its role is also suggested in gastric adenocarcinoma (see Volume 100B). Experimental data have shown that salted fish extracts can reactivate EBV in latently infected cells in vitro. This is an important finding, since EBV is known to be present in a latent form in almost every person unless reactivated.

Aqueous extracts of some other preserved food samples from Tunisia (e.g. *harissa*, a spiced mixture) and Greenland (salted fish), two high risk areas for nasopharyngeal cancer, were also shown to activate EBV in cells in vitro. In addition, other preserved food whose consumption can potentially lead to *N*-nitroso compounds intake is consumed in many part of the world.

The Working Group recommends that IARC undertake a full review of the carcinogenic hazards of preserved food.

A summary of the findings of this volume appears in The Lancet Oncology ([Secretan et al., 2009](#)).

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TOBACCO SMOKING

Tobacco smoking was considered by previous IARC Working Groups in 1986, 1987 and 2002 ([IARC, 1986, 1987, 2004a](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Smoked tobacco products

Smoked forms of tobacco include various kinds of cigarettes (manufactured, hand-rolled, filtered, un-filtered and flavoured), cigars and pipes. While cigarette smoking, particularly manufactured cigarettes, is by far the main form of tobacco smoked globally, in some countries other forms of smoked tobacco are dominant ([IARC, 2004a](#)). In India, for example, bidis (made of coarse and uncured tobacco) account for about 60% of smoked tobacco products whereas cigarettes account for 20% ([Ray & Gupta, 2009](#); [IIPS, 2010](#)). Water pipes, another form of smoked tobacco known by other various names such as gaza, hookah, narghile, shisha, hubble-bubble, are commonly smoked in the Eastern Mediterranean region, in some parts of Asia including India, and in North Africa ([Asma et al., 2009](#)).

1.2 Chemical composition of tobacco smoke

1.2.1 Smoke from cigarettes

One cubic cm of fresh, un-aged cigarette mainstream smoke [the smoke emerging from the mouth end of a cigarette during smoking] has about 4×10^9 particles with a mean diameter of about $0.2 \mu\text{m}$ ([Borgerding & Klus, 2005](#)). The size of the particles increases as the smoke ages. Temperatures in the burning cone of the cigarette are about 800°C during the smoulder period between puffs and increase to $910\text{--}920^\circ\text{C}$ at the periphery of the cone during puffing ([Borgerding & Klus, 2005](#)). Hydrogen is generated in the glowing cone, resulting in an oxygen deficient reducing atmosphere ([Borgerding & Klus, 2005](#)). The approximate composition of mainstream smoke of a plain cigarette is summarized in [Table 1.1](#) ([Borgerding & Klus, 2005](#)). The total particulate matter, after subtraction of the amounts of nicotine and water, is referred to as 'tar'.

Over 5300 compounds have been identified in tobacco smoke ([Rodgman & Perfetti, 2009](#)). Classes of compounds include but are not limited to neutral gases, carbon and nitrogen oxides, amides, imides, lactams, carboxylic acids, lactones, esters, aldehydes, ketones,

Table 1.1 Approximate chemical composition of mainstream smoke generated by a plain cigarette

Compound or class of components	Relative amount w/w (%)
Nitrogen	58
Oxygen	12
Carbon dioxide	13
Carbon monoxide	3.5
Hydrogen, argon	0.5
Water	1
Volatile organic substances	5
Particulate phase	8

From [Borgerding & Klus \(2005\)](#)

alcohols, phenols, amines, *N*-nitrosamines, *N*-heterocyclics, aliphatic hydrocarbons, monocyclic and polycyclic aromatic hydrocarbons (PAHs), nitriles, anhydrides, carbohydrates, ethers, nitro compounds and metals ([Rodgman & Perfetti, 2009](#)).

The addictive properties of tobacco smoke are attributed to nicotine, the principal tobacco alkaloid in smoke ([Hukkanen et al., 2005](#)). Minor tobacco alkaloids include nornicotine, anatabine and anabasine ([Hukkanen et al., 2005](#)). The tobacco alkaloids are not generally considered carcinogenic, but are accompanied by carcinogens in each puff of smoke.

There are over 70 carcinogens in tobacco smoke that have been evaluated by the *IARC Monographs* programme as having sufficient evidence for carcinogenicity in either laboratory animals or humans ([IARC, 2004a](#)). The different chemical classes of carcinogens and representatives of each are presented in [Table 1.2](#) ([IARC, 2004a](#)). Sixteen of these – benzo[*a*]pyrene (BaP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N'*-nitrosonornicotine (NNN), 2-naphthylamine, 4-aminobiphenyl, formaldehyde, 1,3-butadiene, benzene, vinyl chloride, ethylene oxide, arsenic, beryllium, nickel compounds, chromium VI, cadmium, and polonium-210 – are classified as carcinogenic to

humans (Group 1). Structures of some representative carcinogens in cigarette smoke are shown in Fig. 1.1. There are other likely carcinogens in cigarette smoke that have not been evaluated by the *IARC Monographs* programme. These include, for example, PAHs with incompletely characterized occurrence levels and carcinogenic activities; over 500 PAHs have been identified ([Rodgman & Perfetti, 2006](#)).

PAHs, tobacco-specific *N*-nitrosamines, aromatic amines, aldehydes and certain volatile organics likely contribute significantly to the carcinogenic activity of tobacco smoke ([Hecht, 2003](#)).

In the early part of the 20th century, PAHs were identified as carcinogenic constituents of coal tar ([Phillips, 1983](#)). They are products of incomplete combustion of all organic matter and occur, always as complex mixtures, in tars, soots, broiled foods, vehicle engine exhaust and tobacco smoke. PAHs are generally locally acting carcinogens, and some, such as the prototypic compound BaP, have strong carcinogenic activity on mouse skin and in rodent lung. Heterocyclic analogues of PAHs also occur in cigarette smoke. Concentrations of individual PAHs in mainstream cigarette smoke are generally in the range of 1–50 ng per cigarette ([IARC, 2004a](#)).

Among the carcinogenic *N*-nitrosamines in tobacco smoke are tobacco-specific *N*-nitrosamines, which are derived from, and structurally related to, the tobacco alkaloids. Two of the most important of these are NNK and NNN ([Hecht & Hoffmann, 1988](#)). Levels of NNK and NNN in cigarette smoke vary depending on tobacco type and other factors, but are frequently in the range of 50–200 ng per cigarette ([IARC, 2004a](#)).

Aromatic amines were first identified as human carcinogens from industrial exposures in the dye industry in the early part of the 20th century. They include the well known human bladder carcinogens 2-naphthylamine and 4-aminobiphenyl which, along with other

Table 1.2 Tobacco smoke carcinogens evaluated in the IARC Monographs

Chemical Class	Number of Carcinogens	Representative Carcinogens
Polycyclic aromatic hydrocarbons (PAHs) and their heterocyclic analogues	15	Benzo[a]pyrene (BaP) Dibenz[a,h]anthracene
N-Nitrosamines	8	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) N'-Nitrosoornicotine (NNN)
Aromatic amines	12	4-Aminobiphenyl 2-Naphthylamine
Aldehydes	2	Formaldehyde Acetaldehyde
Phenols	2	Catechol Caffeic acid
Volatile hydrocarbons	3	Benzene 1,3-Butadiene Isoprene
Other organics	12	Ethylene oxide Acrylonitrile
Inorganic compounds	8	Cadmium Polonium-210

There are many other carcinogens in cigarette smoke that have not been evaluated in an *IARC Monograph*.
From [IARC \(2004a\)](#)

isomers, are found in cigarette smoke, but their levels are generally quite low (1–20 ng per cigarette) ([IARC, 2004a](#)).

Aldehydes such as formaldehyde and acetaldehyde occur widely in the human environment and are also found in human blood. Concentrations of acetaldehyde and formaldehyde in cigarette smoke are far higher than those of PAHs, N-nitrosamines or aromatic amines but their carcinogenic activities are weak ([Hecht, 2003](#)). Cigarette mainstream smoke typically contains 10–30 µg formaldehyde/cigarette and 800–900 µg acetaldehyde/cigarette ([IARC, 2004a](#)).

Volatile hydrocarbons in cigarette smoke include 1,3-butadiene, a powerful multi-organ carcinogen in the mouse, and benzene, a known human leukaemogen. 1,3-Butadiene (20–40 µg/cigarette) and benzene (12–50 µg/cigarette) are two of the most prevalent strong carcinogens in cigarette smoke ([IARC, 2004a](#)).

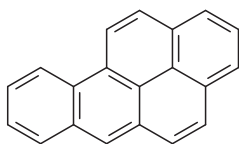
In summary, cigarette smoke is an exceedingly complex mixture which contains over 5300

compounds including multiple toxicants and carcinogens.

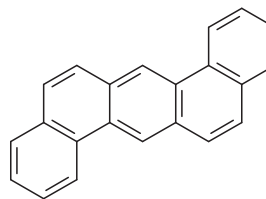
1.2.2 Smoke from other tobacco products

Some constituents have been measured in roll-your-own cigarettes, and their levels are comparable to or higher than those in commercial brands. Carcinogen and toxicant levels expressed per unit are higher in cigars than in cigarettes because of their larger size, and in some instances are also higher per litre of smoke. Levels of nicotine and tobacco-specific nitrosamines were comparable in bidis and commercial Indian cigarettes; bidis also contain high levels of eugenol, as do kreteks. Levels of NNK and NNN in chuttas were considerably higher than in standard cigarettes ([IARC, 2004a](#)).

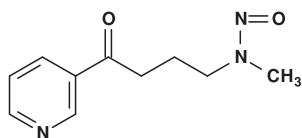
Fig. 1.1 Structures of some representative tobacco smoke carcinogens



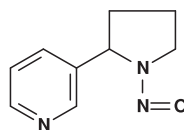
benzo[a]pyrene (BaP)



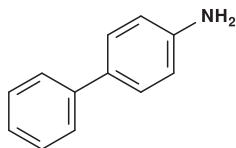
dibenz[a,h]anthracene



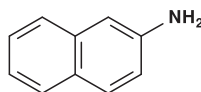
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)



N'-nitrososornicotine (NNN)



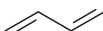
4-aminobiphenyl



2-naphtylamine



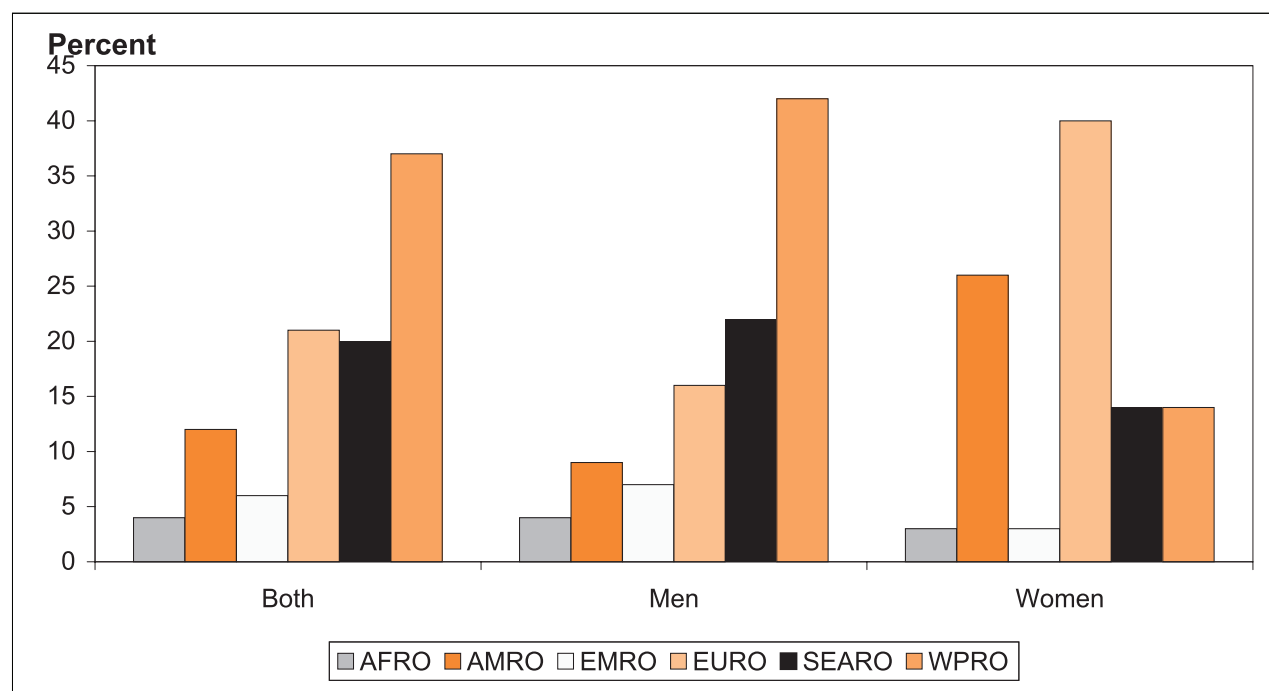
benzene



1,3-butadiene



ethylene oxide

Fig. 1.2 Proportion of adult smokers by WHO region in 2009

From [WHO \(2011\)](#)

1.3 Prevalence of tobacco smoking

1.3.1 Data collection and methods

Data on smoking tobacco are available from WHO's Global Infobase (www.who.int/infobase) and the WHO Global Health Observatory (www.who.int/gho/en) – repositories of information on tobacco use and other risk factors in young people (13–15 years old) and adults (aged 15 years and over). The data span several years and are acquired from government reports, journals and unpublished sources. WHO has in the recent past used and modelled these data to produce estimates of tobacco smoking prevalence, published in the WHO Reports on the Global Tobacco Epidemic. For a complete explanation of methods used, the reader is referred to the Technical Note on Prevalence in the 3rd WHO Report on the Global Tobacco Epidemic ([WHO, 2011](http://www.who.int/2011)). The six WHO regions are: EMRO, Eastern Mediterranean Region; EURO, European

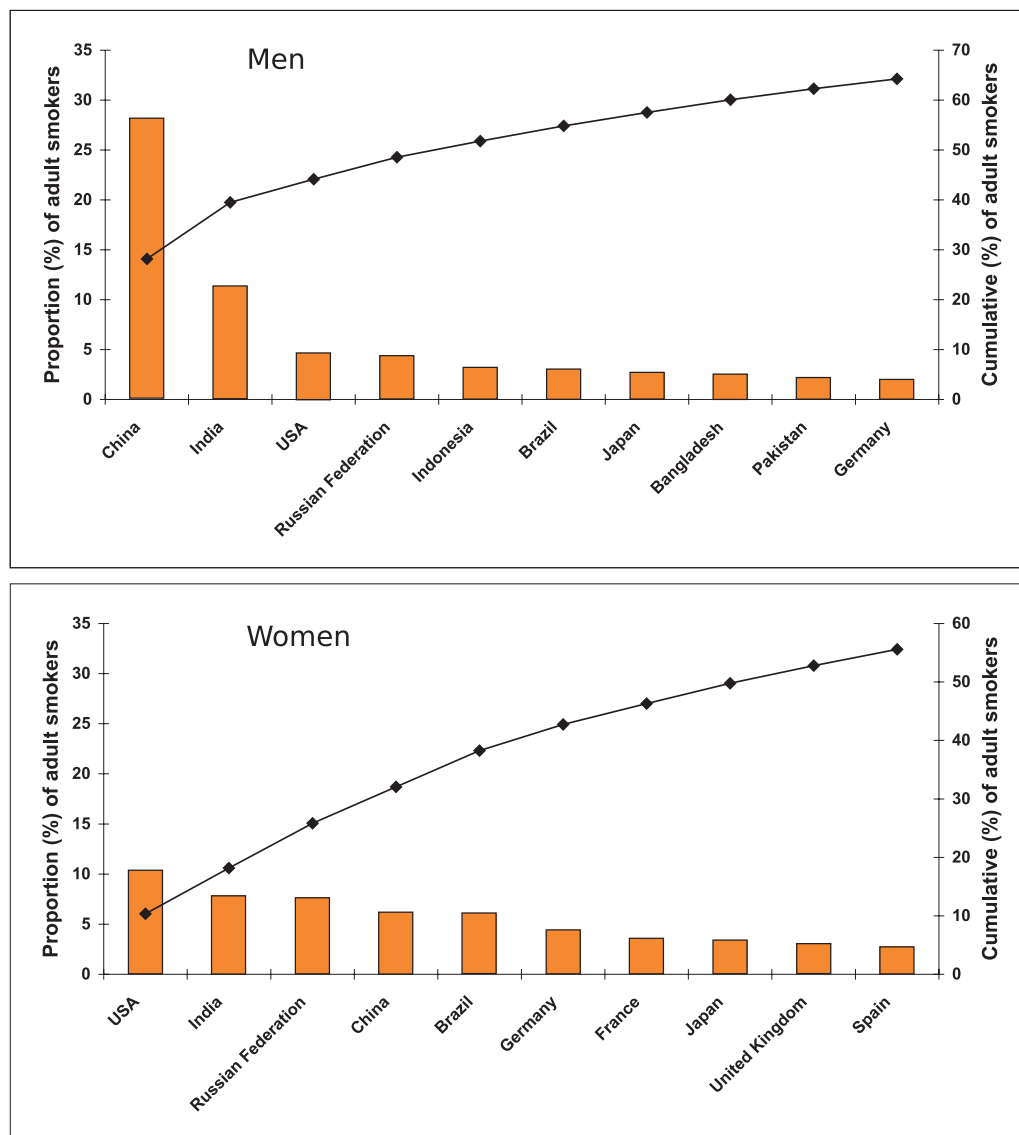
Region; AFRO, African Region; WPRO, Western Pacific Region; SEARO, South East Asian Region; AMRO, Region of the Americas. A listing of the countries in each region can be viewed at <http://www.who.int/about/structure/en/index.html>.

1.3.2 Distribution of smokers by WHO region and country

WHO estimates that in 2009, there was about 1.1 billion adult smokers worldwide, representing nearly a quarter (22%) of the global adult population ([WHO, 2011](#)). A disaggregation by the six WHO regions (Fig. 1.2) shows that over a third of smokers worldwide live in WPRO (highly influenced by the People's Republic of China), followed by SEARO, which has around a fifth of the world's smokers (influenced by India and Indonesia).

The number of smokers in any country is a function of both the prevalence of smoking and the size of the population. A further

Fig. 1.3 Proportion and cumulative percentage of smokers in high-burden countries, in men (A) and women (B) in 2009



From [WHO \(2011\)](#)

disaggregation of the regions by country shows that a few countries account for a large proportion of tobacco smokers. Ranked in descending order of the number of smokers, the five countries of China, India, United States of America (USA), Russian Federation and Indonesia account for about 52% of adult smokers in the world, with China and India alone accounting for 40% (Fig. 1.3). Furthermore, nearly two-thirds of the

world's smokers live in only ten countries of the world.

1.3.3 Distribution of smokers by sex

With a global average smoking prevalence of 36%, men account for just over 80% of all smokers. The male adult prevalence is 4–5 times that for women, at 8%. This difference varies across WHO

regions. Smoking among men, concentrated in the five countries of China, India, Indonesia, Russian Federation and USA (Fig. 1.3), accounts for about 56% of global smoking among men. Women smokers are mostly concentrated in EURO and AMRO. These two regions account for 40% and 26% of all women smokers globally, respectively. The prevalences for women in these two regions are about half of those in men, whereas the difference is substantially greater in the other regions. Just as men smoke more than women everywhere, so too among young people, boys generally smoke more than girls. There is an increasing concern, however, that the gap may diminish, not because of a reduction in boys prevalence but because of an increase in the proportion of girls who are taking up smoking ([Warren et al., 2006](#)).

1.3.4 The four stage smoking model

(a) The four stages of tobacco use

[Lopez et al. \(1994\)](#) used trend data on smoking prevalence and tobacco attributable mortality to show the evolution of tobacco use in a country. Four stages of smoking and attributable mortality have been identified to represent the growth and eventual decline of smoking among men and women (Fig. 1.4).

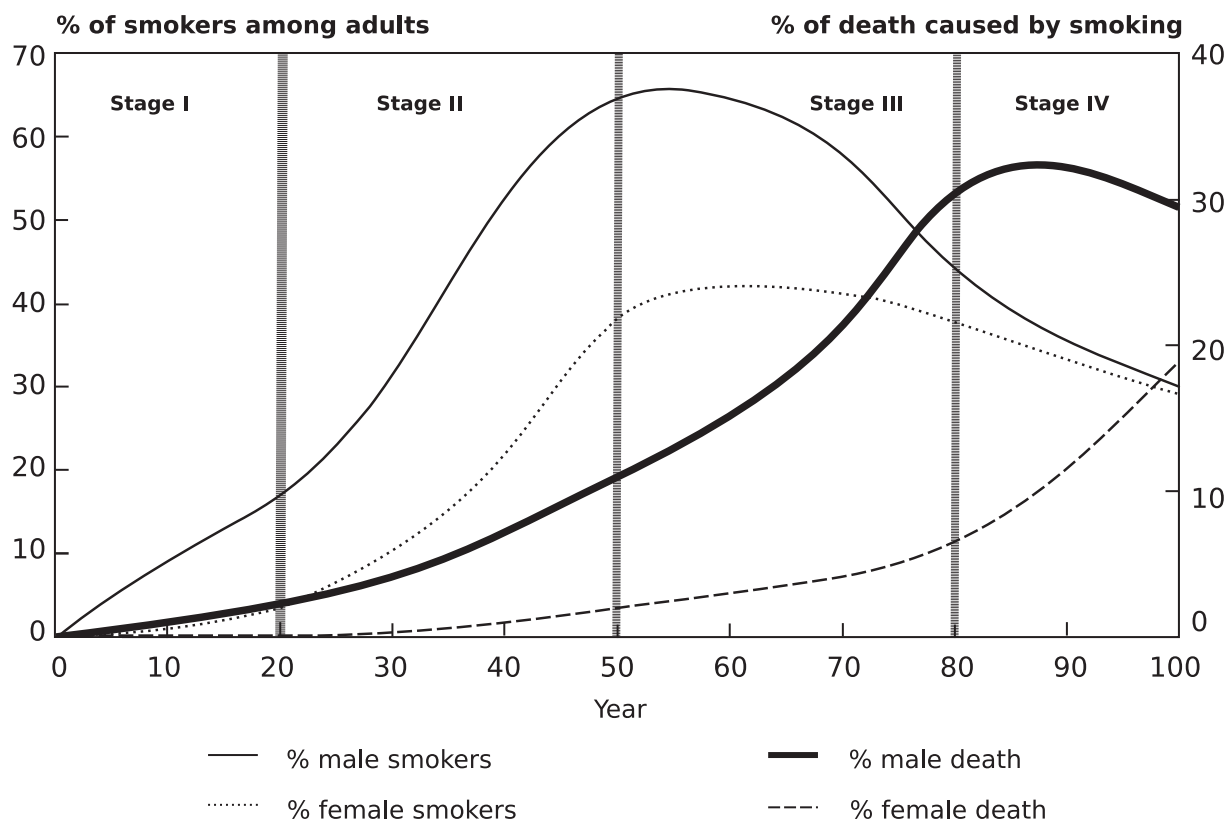
Stage 1 is characterized by low smoking prevalence in men (less than 15%) and very low in women (less than 10%). Death and disease from smoking are not apparent in this phase, as nearly all health effects from smoking are related to past smoking habits and their cumulative effects rather than current smoking. In Stage 2, smoking prevalence in men rapidly increases while it increases more slowly in women. Towards the end of this stage, smoking prevalence in men typically peaks to lie at 50–60%, with 10% of deaths in men attributable to smoking; deaths in women are comparatively fewer. After a protracted period of high smoking prevalence, Stage 3 shows a decline in smoking prevalence in men to around 40%.

Smoking prevalence in women peaks and then begins to decline; towards the end of this stage the gap between men's and women's prevalence starts to narrow. However, smoking attributable deaths in men increase from around 10% to 25–30% within a span of three decades; in women the deaths are increasing but are still quite low. In the final Stage 4, smoking prevalences in both men and women continue to decline albeit relatively slowly in comparison with Stage 3, with the gap substantially narrowing to lie at around five percentage points, and as little as one percentage point in some countries. In Stage 4, smoking mortality in men peaks to between 30–35% and then declines to below 30% at the end of this period. In women, the health effects from past smoking persist, with increasing mortality, but remain lower than in men, and recently have begun to decline in some countries.

(b) Smoking prevalence worldwide

Using prevalence data for men and women collected in 2006 for 140 countries, WHO determined at which stage of the tobacco epidemic countries are in the model of [Lopez et al. \(1994\)](#). In Fig. 1.5, countries have been ranked by smoking prevalence in men in ascending order for Stages 1 and 2, and then in descending order for Stages 3 and 4. (Smoking prevalence in men is almost always higher than in women, with a few exceptions observed in the fourth stage.) While most countries fit the classification, there are a few exceptions, most of which in the last stage. Prevalence between Stage 3 and Stage 4 is discontinuous in both sexes. This is due to the classification followed, which puts countries with a relatively narrow difference in prevalence between men and women in Stage 4 even though their prevalence is largely comparable with those in Stage 3.

Most African countries fall in the first stage of the smoking model, characterized by low smoking prevalence in men and very low prevalence in women. Three of the five high burden

Fig. 1.4 The four stages of the tobacco epidemic

From [Lopez et al. \(1994\)](#)

countries fall in stage 2 (India, Indonesia and China), with the rest comprising a combination of countries from Africa, South East Asia, eastern Europe and the Middle East. At this stage smoking prevalences in women continue to remain very low, most countries having a prevalence in adult women of less than 10%.

Stage 3 includes the fourth high burden country (Russian Federation), along with countries in eastern Europe, South America and western Europe, which fall at the end of Stage 3. Stage 4 is populated entirely by the developed countries of western Europe, North America and Oceania. The USA, the fifth high burden country, fall in the last stage as a result of the relatively small difference in the smoking prevalence between men and women compared to the

other intermediate stages. As mentioned before, Stage 4 includes countries where the smoking prevalence is higher in women than in men, with a small (< 8%) difference.

(c) Age-specific prevalence

Age-specific prevalence for men and women aged 15 years or older is presented for six representative countries for current smoking (Fig. 1.6). There are wide variations in age-specific prevalence between these countries. In men, prevalence varies from less than 10% to 75% in the 15–19 years age range to lie between 10% and 55% in the oldest age range. Prevalence among women varies from less than 1% to as high as 45% in young adults (15–19 years). Unlike men, prevalence in women tends to converge after age

Fig. 1.5 Prevalence of smoking in 140 countries in 2009, staged according to the model by Lopez

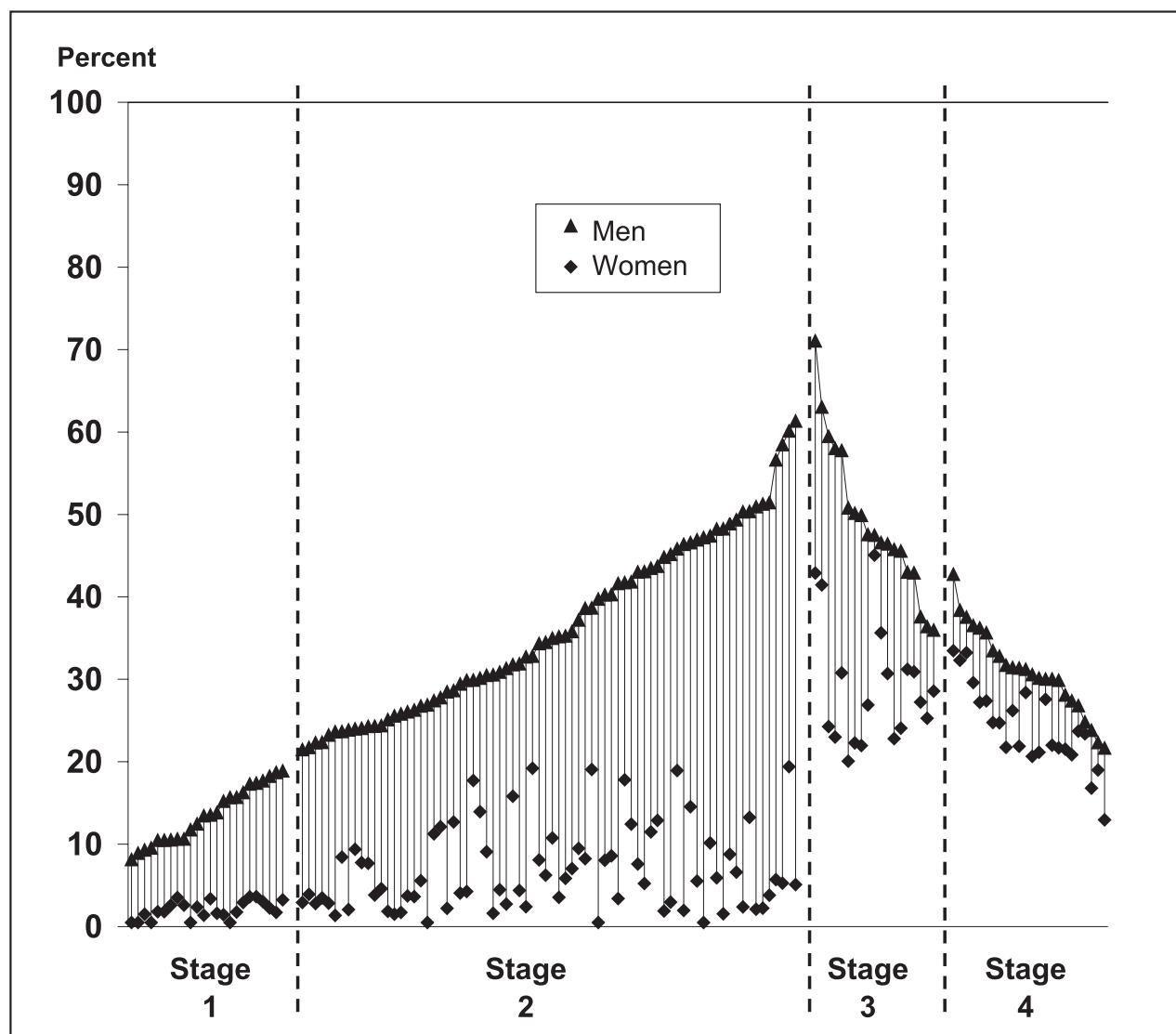
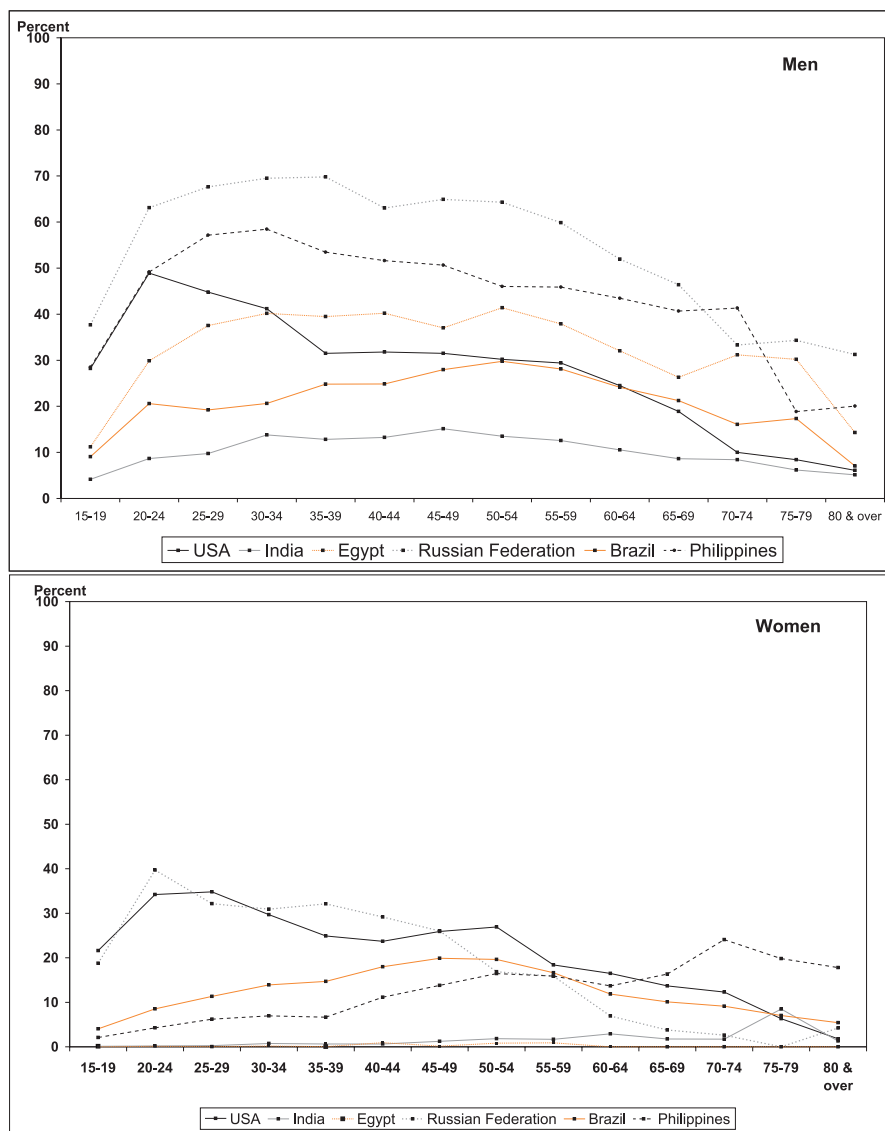


Fig. 1.6 Age-specific rates of smoking prevalence, in men and women in 2009

50, lying within 15 percentage points. Prevalence in women is almost always lower than in men in all age groups.

Initiation of smoking is shifting, and is taking place at earlier ages in both developed and developing countries. In developed countries, quitting smoking is also shifting to occur at a younger age, whereas in developing countries there is no such evidence.

(d) *Smoking in youth*

Information on smoking habits in youth are collected from a variety of youth surveys that include the Global Youth Tobacco Survey (GYTS), Global school-based Student Health Survey (GSHS) and Health Behaviour in School Aged Children (HBSC). Some countries have their own youth surveys, or have them as part of a general health or household survey, such as the Student Survey in Argentina, the Youth Smoking Survey in Canada, and New Zealand's Tobacco Survey.

The GYTS is a school-based survey designed to monitor tobacco use among youths aged 13 to 15 years. The GYTS uses a standard set of questions and sampling methods in over 160 countries. The survey has core questions that span seven thematic areas pertinent to tobacco. In addition to these, countries can include country-specific questions that allow assessment of tobacco use unique to the country. To assess prevalence of smoking, students are asked to report their smoking habits for both cigarettes and other tobacco products that they may have consumed over the past 30 days. Since its inception in 1999, the GYTS has covered over 2 million students. Although most GYTS are national surveys, in some countries they are limited to subnational locations. Further, countries conduct the GYTS in different years, rendering comparison for the same year difficult.

Prevalence of current tobacco use [including smokeless tobacco] in youth in 2004–09 for fourteen high burden low and middle income

countries is shown in Fig. 1.7. The Russian Federation has the highest prevalence of current tobacco use among the high burden countries for which national data are available. Further, in the Americas and Europe the difference in prevalence between boys and girls is smaller than in other regions. In contrast, in Egypt, India and Thailand, prevalences in boys are significantly higher than in girls.

Fig. 1.8 shows the range of current tobacco use by WHO region for boys and for girls and for both sexes combined. There are wide variations in current tobacco use within each region. The largest variations are observed in EMRO and SEARO irrespective of sex, reflecting potentially disparate initiation rates in countries within the region. In AFRO, the range of current tobacco use between boys and girls is virtually the same. In some countries (e.g. Argentina, Peru, Sierra Leone, Bulgaria, Croatia, Cook Islands, New Zealand), tobacco use in girls exceeds that in boys; but overall boys and girls show remarkably similar propensity to take up tobacco use.

[Warren *et al.* \(2006\)](#) present global estimates and regional averages for current tobacco smoking in youth using GYTS data spanning 1999–2005. Their estimates show that one in five boys and one in seven girls currently smoke tobacco. Prevalence of current smoking for both boys and girls combined was highest in AMRO (22.2%) and lowest in WPRO (11.4%). AMRO have the highest average for current tobacco smoking for boys (24%) and for girls (20.4%) whereas the lowest prevalence was in WPRO among boys (15%) and in SEARO among girls (7.1%).

1.4 Regulations and policies: the WHO Framework Convention on Tobacco Control

The WHO Framework Convention on Tobacco Control (WHO FCTC) – the first multi-lateral evidence-based treaty on tobacco control

Fig. 1.7 Prevalence of current tobacco use in youth for selected countries, 2005–2009

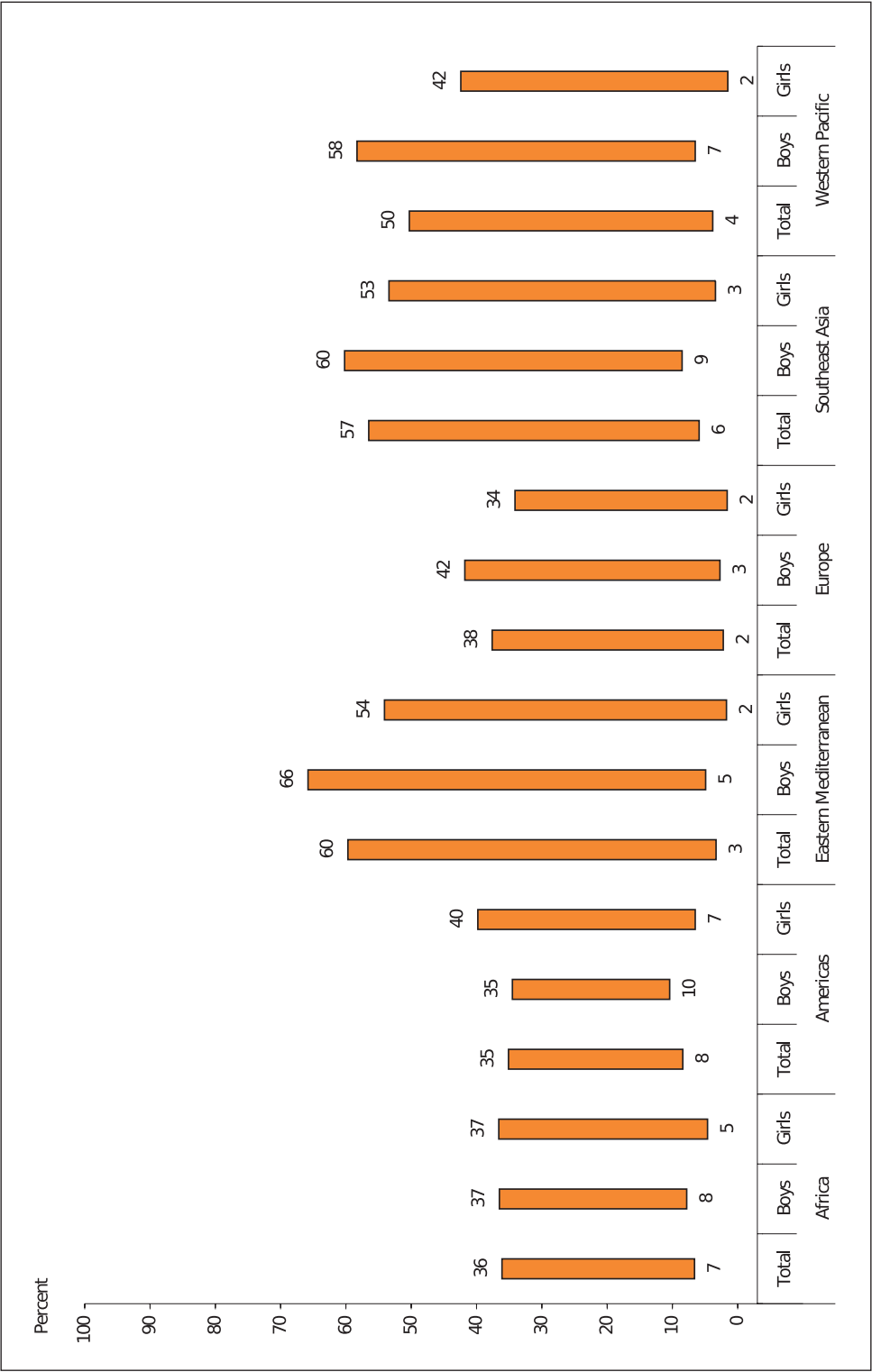
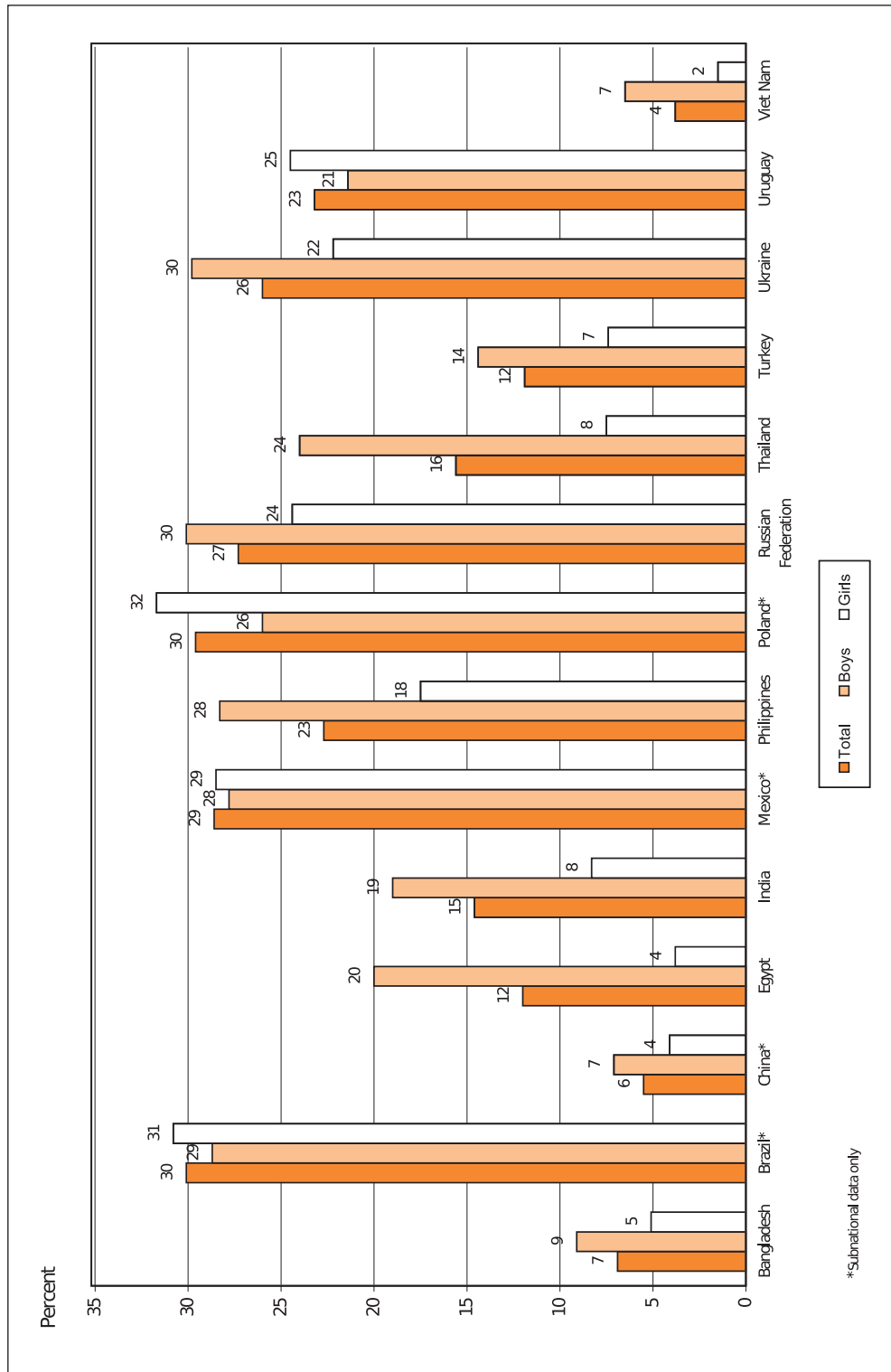


Fig. 1.8 Range of prevalence of current tobacco use in youth, 2005–2009, by WHO region



Figures have been rounded off and show prevalences in countries with national and subnational jurisdiction.

– articulates tobacco control measures available to countries to counter the growing tobacco epidemic. This treaty, which entered into force in 2005, represents one of the most universal treaties in the United Nations history. In 2008, the WHO launched MPOWER, a technical assistance package comprised of six strategies that reflects one or more of the WHO FCTC measures and helps countries meet their commitments to the WHO FCTC.

2. Cancer in Humans

2.1 Introduction

The available knowledge on the relationship between tobacco smoking and a variety of human cancers is based primarily on epidemiological evidence. An immense amount of such evidence has been obtained, and only a small proportion can be referred to here. The cancers considered to be causally related to tobacco smoking in the previous *IARC Monograph* on tobacco smoking ([IARC, 2004a](#)) included lung, oral cavity, nasal cavity and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, oesophagus (adenocarcinoma and squamous cell carcinoma), upper aerodigestive tract combined, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, cervix and myeloid leukaemia. In addition, it was concluded that there was evidence suggesting lack of carcinogenicity for cancers of the breast and of the endometrium.

Since 2002, there have been additional cohort and case-control studies on the relationship of tobacco smoking in different forms to these and other cancers in many countries. A large body of evidence has been obtained from cohort studies with respect to different cancer sites and types of tobacco product. These cohort studies are described briefly in Table 2.1 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.1.pdf>), listed by country.

Case-control studies are described in the sections pertaining to cancer sites. More studies are now available from countries and populations that are still at an early stage of the tobacco epidemic. These studies are prone to underestimate the true strengths of the association between tobacco smoking and any specific cancer as the full effect of duration of smoking cannot be evaluated.

2.2 Cancer of the lung

2.2.1 Overview of studies

The main cause of lung cancer in humans is tobacco smoking and most information establishing this fact comes from epidemiological studies in which the assessment of exposure was based on self-reported information on personal smoking habits via self-administered questionnaire or in-person interviews. Since the previous *IARC Monograph* ([IARC, 2004a](#)), numerous studies have been published on the issues of tobacco smoking and sex and racial/ethnic susceptibility, ‘tar’ yields as measured by machine smoking, the relationship between histological changes and the design of cigarettes, dose-response association, genetic susceptibilities and interactions.

2.2.2 Factors affecting risk

Recent epidemiological studies incorporating measures of smoking metabolites in serum or urine are helping to refine our understanding of exposure-response relationships with tobacco smoke. Dose-response evidence has been obtained from three cohort studies ([Flanders et al., 2003](#); [Boffetta et al., 2006](#); [Yuan et al., 2009](#); Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.2.pdf>) and four pooled analyses ([Lubin & Caporaso, 2006](#); [Lubin et al., 2007a, b, 2008](#); Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.3.pdf>)

since the previous *IARC Monograph* ([IARC, 2004a](#)).

The US American Cancer Society Cancer Prevention Study-II (CPS-II) is the largest cohort study on smoking and lung cancer risk using questionnaire assessment of exposure ([Flanders et al., 2003](#)). In this study cigarette smoking duration is a much stronger predictor of lung cancer mortality than is cigarette smoking intensity, regardless of age in both men and women. These results are qualitatively similar to those reported by [Doll & Peto \(1978\)](#) and are consistent with [IARC \(2004a\)](#).

In a questionnaire-based assessment of the association of tobacco smoking with lung cancer risk, smokers at higher smoking intensities seem to experience a “reduced potency” per pack such that for equal total exposure, the excess odds ratio per pack-year decreases with intensity ([Lubin et al. 2008](#)). Below 15–20 cigarettes/day, the excess odds ratio/pack-year increases with intensity ([Lubin & Caporaso, 2006](#); [Lubin et al., 2007a](#)) while above 20 cigarettes/day, there is an ‘inverse-exposure-rate’ effect ([Lubin et al., 2007a](#)) suggesting a greater risk for total exposure delivered at lower intensity (or a longer duration) than the equivalent exposure delivered at a higher intensity. The intensity effects were also statistically homogeneous across diverse cancer types, indicating that after accounting for risk from total pack-years, intensity patterns were comparable for cancer of the lung, bladder, oral cavity, pancreas and oesophagus. These analyses suggest that the risk of lung cancer increases with increasing tobacco exposure at all dose levels, but there is some levelling-off effect at the highest intensity of tobacco smoking.

However, when serum cotinine was used as a measure of exposure to tobacco smoking, rather than questionnaire-based data, the odds ratio of lung cancer increased linearly over the full range of exposure from ≤ 5 ng/mL through ≥ 378 ng/mL, with an odds ratio of 55.1 (95% confidence interval (CI): 35.7–85.0) in the

highest exposure group. These results suggest that the decreased rate of lung cancer risk at high intensity of tobacco smoke previously described is a statistical artefact. Such an effect may be due to an inaccurate assessment of total tobacco smoke exposure from questionnaire-based studies at high exposure levels ([Boffetta et al., 2006](#)). Somewhat similar results were obtained when both 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and total cotinine in urine were measured in subjects of two large cohort studies from Shanghai men and Singapore men and women ([Yuan et al., 2009](#)). Among smokers with comparable smoking histories (as noted in questionnaire data) there is a 9-fold variation in subsequent risk of lung cancer between those with high and those with low levels of total urinary NNAL and cotinine. Thus measurements of urinary cotinine and total NNAL at a single point in time in a smoker could substantially improve the predictive power of a lung cancer assessment model based solely on self-reported smoking history (number of cigarettes/day, number of years of regular smoking). A positive NNAL-lung cancer association of comparable magnitude was observed in both Shanghai and Singapore subjects despite differences in the NNK content of tobacco smoked. The independent association between total urinary cotinine and lung cancer risk, after adjustment for total urinary NNAL and smoking history, suggests that tobacco smoke compounds other than NNK play a role in lung cancer development in smokers. Further, a single measurement of urinary NNAL may closely predict the average level of NNAL measured over a much longer period of time.

2.2.3 Types of tobacco or of cigarette

(a) Tar levels

In a previous *IARC Monograph* ([IARC, 1986](#)), it was concluded on the basis of the case-control, cohort studies and ecological evaluations

available at the time that prolonged use of ‘high-tar’ and unfiltered cigarettes is associated with greater risks than prolonged use of filter-tipped and ‘low-tar’ cigarettes. More recently ([IARC, 2004a](#)), it has been recognized that the actual quantitative impact of reduced ‘tar’ and filter-tipped cigarettes is difficult to assess because of, respectively, the concomitant increase in tobacco-specific nitrosamines that accompanies the greater use of blend tobacco and the compensatory changes in smoking behaviour by smokers attempting to maintain their accustomed level of nicotine intake. Nevertheless, it was concluded that changes in cigarette types since the 1950s have probably tended to reduce the risk for lung cancer associated with tobacco smoking.

Additional refinement in assessing the health effects associated with smoking cigarettes of various tar content has been possible since the publication of the earlier reports. Compared with smokers of medium tar (15–21 mg) filtered cigarettes risk was higher among men and women who smoked high tar (≥ 22 mg) non-filtered brands but there was no difference in risk among men and women who smoked ‘very low tar’ or ‘low tar’ brands compared with those who smoked ‘medium tar’ brands ([Harris et al., 2004](#)). Regardless of tar content of their cigarettes, all current smokers had a far greater risk for lung cancer than people who had stopped smoking or had never smoked ([Harris et al., 2004](#)).

(b) *Mentholated cigarettes*

In the previous *IARC Monograph* ([IARC, 2004a](#)) the conclusion was drawn that there is no additional risk associated with smoking mentholated cigarettes when total consumption (pack-years) was controlled versus non-mentholated ones. Recent evidence supports that conclusion.

Mentholated cigarettes first appeared in the 1920s, but were not widely used until the mid-1950s ([Bogen, 1929](#); [Federal Trade Commission, 2001](#)). Since the early 1970s, menthol varieties have accounted for 25–60% of all cigarettes

sold in the USA ([Federal Trade Commission, 2001](#)). There are strong ethnic differences in the use of menthol cigarettes; more than 60% of Black smokers of both sexes use menthol brands compared to fewer than 25% of White smokers ([Royce et al., 1993](#); [Hymowitz et al., 1995](#)). Studies have generally not demonstrated an increased risk of lung cancer for mentholated cigarettes versus non-mentholated cigarettes ([Kabat & Hebert, 1994](#); [Carpenter et al., 1999](#); [Brooks et al., 2003](#); [Stellman et al., 2003](#)). Recent evidence also suggests that users of mentholated cigarettes smoke fewer pack-years than those of non-mentholated cigarettes.

The higher incidence of lung cancer among Blacks is an important public health concern but the causes remain unclear. Mentholated cigarette use does not appear to explain the racial disparity observed in lung cancer risk among those having the same total tobacco consumption.

2.2.4 *Histology*

Compiled databases from IARC and other sources indicated that squamous cell carcinoma rates [per 100000 person-years] among men declined by 30% or more in North America and some European countries between 1980–82 and 1995–97, while changing less dramatically in other areas; small cell carcinoma rates decreased less rapidly. In contrast, the proportion of adenocarcinoma cases rose among men and women in virtually all areas, with the increases among men exceeding 50% in many areas of Europe ([Devesa et al., 2005](#)).

Based on a comparison of two large cohort studies initiated by the American Cancer Society (ACS) (CPS-I and CPS-II) in 1960 and 1980, respectively, a stronger association between smoking and adenocarcinoma was observed in recent compared to earlier follow-up periods ([Thun & Heath, 1997](#)). Additionally, an association between cigarette smoking and bronchioloalveolar carcinoma was also found in several

studies ([Falk et al., 1992](#); [Morabia & Wynder, 1992](#)).

A meta-analysis of 8 cohort and 14 case-control studies conducted in Japan among active smokers indicated significant excess lung cancer risks among men for both squamous cell carcinoma (relative risk (RR), 11.7) and adenocarcinoma (RR, 2.30). Among women the risks were 11.3 for squamous cell carcinoma and 1.37 for adenocarcinoma ([Wakai et al., 2006](#)).

2.2.5 Population characteristics

(a) Sex

Meta-analyses on sex-specific susceptibility to lung cancer associated with tobacco smoking are presented in Table 2.4 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.4.pdf>) and cohort studies in Table 2.5 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.5.pdf>).

In the 1990s, two case-control studies indicated that relative risks for lung cancer associated with specific amounts and duration of cigarette smoking may be higher among women than among men ([Risch et al., 1993](#); [Zang & Wynder, 1996](#)).

In the large NIH-AARP [National Institutes of Health-American Association of Retired People] cohort ([Freedman et al., 2008](#)), smoking was associated with lung cancer risk in both men and women. Age-standardized incidence rates for lung cancer tended to be higher in men than in women with comparable smoking histories (for current smokers and for quitters of less than 10 years), and in cases with squamous cell tumours. However, lung cancer risk was generally similar between men and women.

In a joint analysis, results from the Nurses' Health Study of women and the Health Professionals Follow-up Study in men ([Bain et al., 2004](#)) suggest little difference in lung cancer susceptibility between men and women given equal smoking exposure. The hazard ratio

in women ever smokers compared with men was 1.11 (95%CI: 0.95–1.31).

Serum cotinine levels were analysed in lung cancer cases and controls ([Boffetta et al., 2006](#)). The lung cancer odds ratios (ORs) estimated for men and women were very similar for those with comparable serum cotinine levels. Other studies that have carefully quantified tobacco exposure via self-administered questionnaire or interview provide additional evidence of a comparable increase in lung cancer risk in the two sexes ([Kreuzer et al., 2000](#); [Flanders et al., 2003](#); [Bain et al., 2004](#)).

In a meta-analysis of observational studies on cigarette smoking and cancer from 1961–2003 (conducted on 177 case-control studies, 75 cohort studies and two nested case-control studies), dose-response estimates were available in 44 studies: 19 with estimates for men only, 11 with estimates for women only and 14 with separate estimates for men and women ([Gandini et al., 2008](#)). Overall, the risk of lung cancer for men and women increased by 7% for each additional cigarette smoked per day (RR, 1.07; 95%CI: 1.06–1.08). The increased risk appears to be slightly higher in women (RR, 1.08; 95%CI: 1.07–1.10) than in men (RR, 1.07; 95%CI: 1.05–1.08) ($P < 0.001$; adjusting for study type).

(b) Ethnicity

It has been postulated that susceptibility to lung cancer from tobacco smoking may differ by race and ethnicity ([Schwartz & Swanson, 1997](#); [Peto et al., 1999](#); [Stellman et al., 2001](#); [Kiyohara et al., 2004, 2005, 2006](#); [Pinsky, 2006](#); [Wakai et al., 2006](#); [Vineis et al., 2007](#); [Takahashi et al., 2008](#); Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.6.pdf>). Lung cancer incidence rates vary considerable across racial/ethnic groups in the USA and elsewhere. Black men have higher rates than white men, while Hispanics, Asians and American Indians of both sexes have lower rates than whites ([Stellman et al., 2003](#); [SEER, 2004](#)).

Nutritional habits, smoking patterns, type of tobacco smoked and genetic factors may play a role in such differences between racial and ethnic groups.

The association of tobacco smoking and lung cancer does not appear to be as strong among Japanese as among populations of North America or Europe ([Wakai et al., 2006](#)). In a meta-analysis of 8 cohort studies and 14 case-control studies conducted in Japan, the excess lung cancer risks observed for both men (RR, 4.39; 95%CI: 3.92–4.92) and women (RR, 2.79; 95%CI: 2.44–3.20) in both case-control and cohort studies were lower than would have been expected from studies in North America and Europe. The lower lifetime consumption of cigarettes in Japanese, due in part to a later initiation of smoking and a lower consumption per day has been suggested to explain this. Other differences that may have etiological significance include tobacco ingredients, different filters on cigarettes, lifestyle factors including diet, and possibly differences in genetic susceptibility. [The Working Group noted that North American or European populations were not directly included in any of these studies.]

Data from the Asian Pacific Cohort Studies Collaboration, 31 studies involving 480125 persons, evaluated the risk of death from lung cancer associated with smoking habits in Australia, New Zealand and Asia ([Huxley et al., 2007b](#)). Among Asian men the hazard ratio was 2.48 versus 9.87 in men in Australia and New Zealand. Among women, the corresponding estimates were 2.35 and 19.33, respectively. [In these studies, Asian populations smoked fewer cigarettes for a shorter period of time compared to those in Australia and New Zealand.]

Based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER), Chinese women residing in the USA have a fourfold increased risk of lung cancer, and Filipino women a twofold increased risk, compared to that expected based on rates in

non-Hispanic whites in the USA with a similar amount of cigarettes smoked ([Epplein et al., 2005](#)). Among Chinese women, the increased risk was largely restricted to adenocarcinoma and large cell undifferentiated carcinoma. Chinese females residents of the western US mainland have a much higher risk of lung cancer than would be expected from their tobacco use patterns, just as they do in Asia ([Peto et al., 1999](#); [Epplein et al., 2005](#)), the reason for these difference have not been identified. [Controlling for potential confounding factors was limited using aggregate data from SEER.]

Age, sex and race-specific risks of lung cancer mortality among lifetime non-smokers were compared in the two large ACS Cancer Prevention Study cohorts (CPS-I; CPS-II). The mortality rate was higher among African American women than among white women in CPS-II (hazard ratio (HR), 1.43; 95%CI: 1.11–1.36) ([Thun et al., 2006](#)). This suggests an inherent susceptibility difference between white and black women but it could also be explained by access to care, diet, or exposure to environmental carcinogens.

The risk for lung cancer associated with cigarette smoking in 183813 African-American, Japanese-American, Latino, native Hawaiian and white men and women was examined in the Multiethnic Cohort Study in the USA ([Haiman et al., 2006](#)). Information on demographic factors, smoking status, cigarettes/day smoked, years of smoking, years since quitting, diet, occupations, educational level and racial and ethnic group were collected for all subjects through a self-administered questionnaire at enrolment. Information about age of smoking initiation and cessation rates were collected on a subgroup of 5090 study subjects. Incident lung cancer cases were identified by linkage to the SEER cancer registries covering California and Hawaii. Among those who smoked no more than 10 cigarettes/day and those who smoked 11–20 cigarettes/day, relative risks ranged from 0.21 to 0.39 ($P < 0.001$) among Japanese Americans and Latinos and from 0.45

to 0.57 ($P < 0.001$) among whites as compared with African Americans. However, at levels exceeding 30 cigarettes/day, differences between racial/ethnic groups were no longer significant. The differences in lung cancer risk by racial group associated with smoking were observed for both men and women and for all histological types of lung cancer. These findings could not be explained by differences between populations in other known or suspected risk factors, including diet, occupation, and education level or by age at starting smoking or cessation of smoking.

Polymorphisms in glutathione-S-transferase (GST), GSTM1, GSTT1 and GSTP1 genes in humans are associated with reduction of enzymatic activity towards several substrates, including those found in tobacco smoke. In a population based case-control study involving early-onset lung cancer, African Americans carrying at least one G allele at the GSTP1 locus were more likely to have lung cancer compared with African Americans without a G allele after adjustment for age, sex, pack-years of smoking and a history of lung cancer in a first degree relative (OR, 2.9; 95%CI: 1.29–6.20). African Americans with either one or two risk genotypes at the GSTM1 (i.e. null genotype) and GSTP1 loci were at increased risk of having lung cancer compared with those having fully functional GSTM1 and GSTP1 genes (one risk genotype: OR, 2.8; 95%CI: 1.1–7.2 and two risk genotypes: OR, 4.0; 95%CI: 1.3–12.2). No significant single gene associations between GSTM1, GSTT1 and GSTP1 and early-onset lung cancer were observed in Caucasians, after adjusting for age, sex, pack-years and a family history of lung cancer ([Cote et al., 2005](#)).

The cytochrome P450 (CYP) superfamily of enzymes catalyses one of the first steps in the metabolism of carcinogens such as polycyclic aromatic hydrocarbons, nitroaromatics and arylamines. A population-based case-control study of lung cancer in the metropolitan Detroit area found that neither CYP1A1 MspI nor CYP1A1

Ile⁴⁶²Val was associated with lung cancer susceptibility among Caucasians or African Americans. Among Caucasians, however, CYP1B1 Leu⁴³² Val was significantly associated with lung cancer susceptibility (OR for at least one Val allele, 2.87; 95%CI: 1.63–5.07). Individuals with both this polymorphism and exposure to second-hand tobacco smoke were at particularly high risk for lung cancer. Combinations of particular CYP1B1 polymorphisms appeared to increase risk, although no combination differed significantly from the risk associated with CYP1B1 Leu⁴³² Val alone ([Cote et al., 2005](#); [Wenzlaff et al., 2005](#)).

The hypothesis that polymorphisms in TP53 may modulate the risk for lung cancer associated with tobacco smoke was evaluated in a case-control study of lung cancer in Baltimore, Maryland. African-Americans with Pro-T-A-G-G haplotype (combining the polymorphisms TP53_01 (rs1042522), TP53_65 (rs9895829), TP53_66 (rs2909430), TP53_16 (rs1625895), and TP_11 (rs12951053)) had both an increased risk for lung cancer (HR, 2.32; 95%CI: 1.38–4.10) and a worsened lung cancer prognosis (HR, 2.38; 95%CI: 0.38–4.10) compared with those having the Arg-T-A-G-T haplotype. No association of TP53 polymorphisms with lung cancer was observed in Caucasians ([Mechanic et al., 2007](#)). Common genetic variation in TP53 could modulate lung cancer pathways in African Americans. Differences in lung cancer susceptibility may exist based on race, tobacco exposure and selected genetic polymorphisms ([Mechanic et al., 2007](#)).

2.2.6 Interactions

(a) Diet and exercise

Antioxidant vitamins, carotenoids, isothiocyanates, total dietary vegetables and fruit, and physical exercise have been associated with a decreased risk for cancer in some studies but the overall protective effect of diet and exercise account for only a small fraction of the total risk associated with tobacco smoking.

The association of fruit and vegetable with lung cancer incidence among both smokers and non-smokers was evaluated in the European Prospective Investigation into Cancer and Nutrition (EPIC). In current smokers lung cancer risk was significantly decreased with higher vegetable consumption, the hazard ratio being 0.78 (95%CI: 0.62–0.98) per 100 g increase in daily vegetable consumption, and 0.90 (95%CI: 0.81–0.99) per 100 g fruit ([Linseisen et al., 2007](#)). While overall consumption of fruits and vegetables was not found to be protective of lung cancer in the NIH-AARP Diet and Health Study, higher consumption of several botanical subgroups (i.e. rosaceae, convolvulaceae, and umbelliferae) was significantly inversely associated with risk, but only in men ([Wright et al., 2008](#)).

Cruciferous vegetables (i.e. broccoli, cabbage, cauliflower, Brussels sprouts, kale) are rich in isothiocyanates and have been hypothesized to have anticancer properties that may contribute to reduced risk for lung cancer. Isothiocyanates may inhibit the bioactivation of procarcinogens found in tobacco smoke such as polycyclic aromatic hydrocarbons and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone ([Hecht, 2000](#)). Isothiocyanates may also enhance excretion of carcinogenic metabolites before they can damage DNA ([Gasper et al., 2005](#)). Furthermore, sulforaphane, a major isothiocyanate found in broccoli, can induce cell cycle arrest and apoptosis ([Seow et al., 2005](#)). GSTM1 and GSTT1 encode isoenzymes that play an important role in xenobiotic metabolism ([Hecht, 2000](#)). Individuals with homozygous deletion of GSTM1 and GSTT1, or both may metabolize isothiocyanates less efficiently and may be more intensely exposed to isothiocyanates after consumption of cruciferous vegetables. Epidemiological evidence from 30 studies on the association between lung cancer and either total cruciferous vegetable consumption (6 cohort and 12 case–control studies) or specific cruciferous vegetables (1 cohort and 11 case–control studies) was recently evaluated

([Lam et al., 2009](#)). The risk for lung cancer among those in the highest category of total cruciferous vegetable intake was 22% lower in case–control studies (pooled OR, 0.78; 95%CI: 0.70–0.88) and 17% lower in cohort studies (pooled RR, 0.83; 95%CI: 0.62–1.08). The strongest inverse association of total cruciferous vegetable intake with lung cancer was seen among individuals with GSTM1 and GSTT1 double null genotypes (OR, 0.41; 95%CI: 0.26–0.65; *p* for interaction = 0.01). The inverse association was observed in both smokers and non-smokers.

The potential role of vitamin A in the development of lung cancer attracted early research interest ([Bjelke, 1975](#)). Carotenoids were thought to have anti-cancer properties and early evidence from case–control studies tended to support an inverse association of lung cancer incidence with β -carotene intake and with serum concentrations of β -carotene. However, the case–control design is not ideal for assessing the effect of serum carotenoids as a risk factor for lung cancer risk since the disease is likely to effect serum levels. In a meta-analysis of six randomized clinical trials and 25 prospective observational studies, [Gallicchio et al. \(2008\)](#) computed a pooled relative risk for studies comparing β -carotene supplements with placebo of 1.10 (95%CI: 0.89–1.36). Among observational studies, the pooled relative risk for total carotenoid dietary intake from six studies was 0.86 (95%CI: 0.75–0.99) among current smokers. For dietary intake of β -cryptoxanthin, data from six studies gave a pooled relative risk among smokers of 0.75 (95%CI: 0.58–0.96). No other carotenoids significantly reduced the risk in current, former or never smokers.

Based on a review of the literature, antioxidant vitamins show no clear protective effect on lung cancer risk in smokers or non-smokers, although there was some, albeit inconsistent, evidence pointing to a protective role for vitamin C and E. No clear protective role was observed for vitamin A ([Ruano-Ravina et al., 2006](#)).

Increased physical activity has been associated with a reduction in the incidence and mortality from all-site cancer and some site-specific cancers in studies of non-smokers, but less is known about whether physical activity is associated with similar risk reduction in smokers. Several early studies suggested that physical activity is associated with decreased risk of lung cancer in men and women after adjusting for smoking, with risk reductions estimated from 18% (Peterson *et al.*, 2001) to 62% (Kubík *et al.*, 2001). The effect of physical activity on lung cancer risk was assessed in a sample drawn from participants in the Beta-Carotene and Retinol Efficacy Trial. The results suggested that physical activity may play a small role in reducing cancer risk and mortality among those with significant tobacco exposure. The incidence of lung cancer and of all cancer sites combined seemed to be more attenuated by exercise in men than in women, while the attenuation in lung cancer mortality was greater in women than in men. These effects may be more pronounced for younger people and may differ inconsistently by pack-years of smoking (Alfano *et al.*, 2004).

(b) Radon

In a pooled analysis of data from 13 case-control studies of residential radon and lung cancer from nine European countries (7148 cases of lung cancer and 14208 controls), the dose-response relation seemed to be linear with no threshold and remained significant in analyses limited to individuals from homes with measured radon < 200 Bq/m³. The absolute risks of lung cancer by age 75 years at radon concentrations of 0, 100, and 400 Bq/m³ would be about 0.4%, 0.5% and 0.7%, respectively, for lifelong non-smokers, and about 25 times greater (10%, 12% and 16%) for cigarette smokers. These studies show appreciable hazards from residential radon, particularly for smokers and recent ex-smokers (Darby *et al.*, 2005). Similar risks were identified in a

pooling project of North American case-control studies (Krewski *et al.*, 2005).

(c) Asbestos

Exposure to asbestos and tobacco smoking are both known causes of lung cancer in humans (Doll & Peto, 1978; de Klerk *et al.*, 1996). Some studies suggest a multiplicative effect [where the effect of asbestos exposure is a multiple of the effect of smoking] (Hammond *et al.*, 1979; Doll & Peto, 1985), and meta-analyses have suggested that the additive model [where asbestos exposure and smoking are independent of each other] is unsound (Lee, 2001; Liddell, 2001). In a recent study of 2935 asbestos miners, persons exposed to asbestos and tobacco who subsequently quit smoking remained at a 90% increased risk of lung cancer up to 20 years after smoking cessation, compared to never-smoker asbestos workers (Reid *et al.*, 2006a).

(d) Genetic polymorphisms

Lung cancer is plausibly caused by the interplay between environmental factors and several low-risk alleles. Attempts in identifying specific single nucleotide polymorphisms (SNPs) responsible for modulating lung cancer risk have yielded few conclusive results. Recent studies have focused on mechanistically plausible polymorphisms in genes coding for enzymes involved in the activation, detoxification and repair of chemical damage caused by tobacco smoke. Genetic association studies indicate that several inherited genetic polymorphisms may be associated with lung cancer risk, but the data from individual studies with low statistical power are conflicting. Evidence from pooled or meta-analyses, along with some individual studies, is briefly summarized below.

(i) Metabolic genes

Most of the 70 carcinogens in tobacco smoke are procarcinogens that must be activated by phase I enzymes and may then be deactivated by

phase II enzymes. Polymorphisms that alter the function of the genes involved in the activation or detoxification of tobacco smoke carcinogens can potentially influence an individual's risk of developing a tobacco-related cancer.

Meta and pooled analyses of 34 case-control, genotype-based studies were conducted to assess the effect of GSTT1 genotypes and smoking on lung cancer risk. No significant interaction was observed ([Raimondi et al., 2006](#)). A pooled analysis of 21 case-control studies from the International Collaborative study of Genetic Susceptibility to Environmental Carcinogens showed no evidence of increased risk for lung cancer among carriers of the GSTM1 null genotype and there was no evidence of interaction between GSTM1 genotype and either smoking status or cumulative tobacco consumption ([Benhamou et al., 2002](#)). Similarly, in another pooled analysis the summary OR indicated the slow acetylator genotype of N-acetyltransferase 2 (NAT2) detoxification enzyme was not associated with lung cancer risk among Caucasians ([Borlak & Reamon-Buettner, 2006](#)). In a pooled analysis to test the hypothesis of interaction among genetic variants in increasing the individual risk for cancer, the cumulative effect of variants in three metabolic genes, CYP1A1, GSTM1 and GSTT1 was assessed. The risk for lung cancer was increased with the combination of CYP1A1*2B or CYP1A1*4 alleles and the double deletion of both GSTM1 and GSTT1 up to an OR of 8.25 (95%CI: 2.29–29.77). The combination including CYP1A1*4 among never smokers was associated with an OR of 16.19 (95%CI: 1.90–137). These estimates did not change after adjustment by the number of cigarettes smoked and duration of smoking. The results were consistent across ethnicities and were approximately the same for adenocarcinoma and squamous cell carcinoma ([Vineis et al., 2007](#)).

Microsomal epoxide hydrolase 1 (EPHX1) plays an important role in both the activation and detoxification of tobacco-derived carcinogens.

Polymorphisms at exons 3 and 4 of the EPHX1 gene have been reported to be associated with variations in EPHX1 activity. In a meta-analysis of 13 case-control studies the low-activity (variant) genotype of EPHX1 polymorphism at exon 3 was associated with decreased risk for lung cancer (OR, 0.65; 95%CI: 0.44–0.96) among whites. In white-populations, the high activity (variant) genotype of EPHX1 polymorphism at exon 4 was associated with a modest increased risk of lung cancer (OR, 1.22; 95%CI: 0.79–1.90) and the predicted low activity was associated with a modest decrease in risk (OR, 0.72; 95%CI: 0.43–1.22) ([Kiyohara et al., 2006](#)).

(ii) DNA repair and cell cycle pathways

Data from 14 studies of lung cancer were used in a pooled analysis focusing on 18 sequence variants in 12 DNA repair genes, including APEX1, OGG1, XRCC1, XRCC2, XRCC3, ERCC1, XPD, XPF, XPG, XPA, MGMT and TP53 ([Hung et al., 2008a](#)). None of the variants appeared to have a large effect on lung cancer risk. In a recent meta-analysis the X-ray repair cross-complementing protein group 3 (XRCC3) and the xeroderma pigmentosum group D (XPD)/excision repair cross-complementing group 2 (ERCC2) genes were evaluated ([Manuguerra et al., 2006](#)). The authors found no association between these genes and the cancer sites investigated (skin, breast and lung). A significant association was identified for XPD/ERCC2 single nucleotide polymorphisms (codons 312 and 751) and lung cancer.

(iii) Nicotine acetylcholine receptor genes

A series of large genome-wide association studies for lung cancer have identified susceptibility loci for lung cancer in chromosome arms 5p, 6p and 15q ([Landi et al., 2009](#)). In particular, the susceptibility locus at chromosome region 15q25 includes several genes, including three that encode nicotinic acetylcholine receptor subunits (CHRNA5, CHRNA3 and CHRNB4). Nicotinic acetylcholine receptor subunit genes

code for proteins that form receptors present in neuronal and other tissue, in particular alveolar epithelial cells, pulmonary neuroendocrine cells, and lung cancer cell lines ([Wang et al., 2001](#); [Minna, 2003](#)) and bind to nicotine and nicotine derivatives including NNN. An association of CHRNA3 and CHRNA5 variants with nicotine dependence has been reported ([Saccone et al., 2007](#); [Berrettini et al., 2008](#)). These genes may act, at least partially, upon cigarette smoking. Current smokers with one or two copies of the susceptibility variant are likely to smoke between one and two cigarettes more a day ([Spitz et al., 2008](#)). Evidence for an effect of the 15q25 locus among never smokers is conflicting, with an association found in one study in Europe ([Hung et al., 2008b](#)) and one in Asia ([Wu et al., 2009a](#)), but not in others. Whether genes in the 15q25 locus have an effect on lung cancer beyond their propensity to increase numbers of cigarettes smoked is unclear.

Three genome-wide association studies identified genetic factors that modified disease risk. The first was a genome-wide association analysis to identify genetic polymorphisms associated with lung cancer risk in 1154 lung cancer patients of European ancestry who were current or former smokers and 1137 control subjects who were frequency matched to the lung cancer patients by age, sex, race and smoking status. Two SNPs, rs105173 and rs803419, which mapped to a region of strong linkage disequilibrium within 15q25.1, were strongly associated with risk of lung cancer, with an odds ratio for rs105173 of 1.31 ($P = 9.84 \times 10^{-6}$). This finding was replicated with an additional 711 case subjects and 632 control subjects from Texas ($P = 0.00042$) and in 2013 case subjects and 3062 control subjects in the United Kingdom ($P = 2.33 \times 10^{-10}$). The region of interest encompasses the nicotinic acetylcholine receptor subunit genes CHRNA3 and CHRNA5 (as well as CHRNB4) ([Spitz et al., 2008](#)). A second genome-wide association study conducted among 1989 lung cancer cases and

2625 controls from six central European countries confirm these results ([Hung et al., 2008a](#)). In a third genome-wide association study of 665 Icelandic, 269 Spanish and 90 Dutch lung cancer cases and 32244 controls a common variant in the nicotinic acetylcholine receptor gene cluster [chromosome region 15q24] was significantly associated with lung cancer risk (OR, 1.31; 95%CI: 0.1.19–1.44). The variant was observed to have a significant effect on the number of cigarettes smoked per day ([Thorgeirsson et al., 2008](#)). These studies have all shown a link between this variant and lung cancer risk either through a mechanism involving nicotine dependence or a direct role in downstream signalling pathways that promote carcinogens. Together these results provide compelling evidence of a locus at 15q25 and 15q24 predisposing to lung cancer.

(iv) *Alpha(1)-antitrypsin*

Alpha(1)-antitrypsin deficiency ($\alpha(1)$ ATD) is one of the most common genetic disorders, especially among European descendants. Recent results suggest that $\alpha(1)$ ATD carriers are at a 70–100% increased risk of lung cancer, accounting for 11% to 12% of patients with lung cancer ([Yang et al., 2008](#)). [The specific effect by smoking status was not evaluated.]

(v) *Other genes*

Mutations in the checkpoint CHEK2 gene have been associated with increased risk of breast, prostate and colon cancer and a decreased risk of lung cancer among those with the I157T missense variant of the CHEK2 gene. In a large Polish case-control study CHEK2 mutations were protective against lung cancer (OR, 0.3; 95%CI: 0.2–0.5) ([Cybulski et al., 2008](#)).

The Swedish Family-Cancer Database was used to compare the rate of lung cancers among persons without family history of lung cancer to those with a family history ([Li & Hemminki, 2004](#)). A high risk by family history in adenocarcinoma (standardized incidence ratio (SIR),

2.03) and large cell carcinoma (SIR, 2.14) was found, a slightly lower risk among patients with squamous cell carcinoma (SIR, 1.63) and small cell carcinoma (SIR, 1.55). Among siblings, an increased risk was shown for concordant adenocarcinoma and small cell carcinoma at all ages and for all histological types when cancer was diagnosed before age 50. At young age, risks between siblings were higher than those between offspring and parents. These data suggest that a large proportion of lung cancers before age 50 are heritable and due to a high-penetrant recessive gene or genes that predispose to tobacco carcinogen susceptibility.

(e) *Viral infection*

Data are limited regarding lung cancer risk in human immunodeficiency virus (HIV)-infected persons with modest immune suppression, before the onset of acquired immunodeficiency syndrome (AIDS). Among 57350 HIV-infected persons registered in the USA during 1991–2002 (median CD4 counts 491 cells/mm³), 871 cancers occurred. Risk was elevated for several non-AIDS defining malignancies, including cancer of the lung (SIR, 2.6 [$n = 109$]) (Engels *et al.*, 2008). [Specific evaluation with smoking status was not performed.]

2.3 Cancers of the upper aerodigestive tract

Evidence relating to cancers of the upper aerodigestive tract obtained from relevant cohort and case-control studies on specific sites is described in Sections 2.3.1 to 2.3.6; studies that looked at several subsites combined are described in Section 2.3.7. The major potential confounders for the relationship between smoking and cancers of the upper aerodigestive tract are alcohol consumption and use of any form of smokeless tobacco, and for some sites infection with human papillomavirus (HPV) (especially HPV16). In

general, the studies examined by the Working Group had adjusted for these two confounders when appropriate. Some studies also adjusted for dietary intake, especially of fruits and vegetables, although few reported stratified relative risks.

2.3.1 *Cancer of the oral cavity*

Tobacco smoking was found to be causally related to oral cancer (IARC, 1986, 2004a). New studies on the relationship between oral cancer and cigarette smoking published since the most recent IARC Monograph (IARC, 2004a) include four cohort studies (Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.7.pdf>), and eight case-control studies (Tables 2.8–2.11 online; see below).

(a) *Intensity and duration of smoking*

Intensity of smoking was measured in almost all cohort (Table 2.7 online) and case-control studies (IARC 2004a; Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.8.pdf> and Table 2.9 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.9.pdf>). In addition to the number of cigarettes or amount of tobacco smoked daily, cumulative exposure to cigarette smoke was also measured in terms of pack-years, tobacco-years or lifetime tobacco consumption. The link between duration of cigarette consumption and oral cancer was examined in 15 case-control studies. Seven case-control studies also considered age at starting smoking.

One cohort study (McLaughlin *et al.*, 1995) and 14 case-control studies reported a dose-dependent increase in risk with increasing number of cigarettes smoked daily or increasing daily tobacco consumption (Franceschi *et al.*, 1990, 1992, 1999; Nandakumar *et al.*, 1990; Zheng *et al.*, 1990; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Bundgaard *et al.*, 1995; Zheng *et al.*, 1997; De Stefani *et al.*, 1998; Hayes *et al.*, 1999; De Stefani

et al., 2007; Subapriya *et al.*, 2007; Muwonge *et al.*, 2008). Whenever analysed, the trend was always statistically significant (Franceschi *et al.*, 1990, 1992; Oreggia *et al.*, 1991; Bundgaard *et al.*, 1995; McLaughlin *et al.*, 1995; Hayes *et al.*, 1999; Subapriya *et al.*, 2007), except in the study of Muwonge *et al.* (2008) which also included bidi smokers.

Bundgaard *et al.* (1995) used lifetime tobacco consumption divided into four categories and reported a positive, significant trend after adjustment for life-time consumption of alcohol and other risk factors. A positive trend was also found in all studies that have analysed consumption in pack-years or tobacco-years (Zheng *et al.*, 1990; Maier *et al.*, 1992a; Macfarlane *et al.*, 1995; Hung *et al.*, 1997; Zheng *et al.*, 1997; De Stefani *et al.*, 1998, 2007; Applebaum *et al.*, 2007; Muwonge *et al.*, 2008), except Muwonge *et al.* (2008).

Ten studies (Franceschi *et al.*, 1990, 1992; Nandakumar *et al.*, 1990; Zheng *et al.*, 1990; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Zheng *et al.*, 1997; De Stefani *et al.*, 1998, 2007; Znaor *et al.*, 2003; Subapriya *et al.*, 2007; Muwonge *et al.*, 2008) classified the duration of smoking in up to four categories, and all but one (Nandakumar *et al.*, 1990) reported increased relative risks and a positive trend.

Of six studies that considered age at start of smoking (Franceschi *et al.*, 1990, 1992; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Zheng *et al.*, 1997; Balaram *et al.*, 2002) two reported a statistically significant trend of increasing risk with decreasing age at starting (Franceschi *et al.*, 1990, 1992).

(b) Cessation of smoking

Three cohort studies (McLaughlin *et al.*, 1995; Freedman *et al.*, 2007a; Friborg *et al.*, 2007) and nine case-control studies (Zheng *et al.*, 1990; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Franceschi *et al.*, 1992; Ko *et al.*, 1995; Zheng *et al.*, 1997; De Stefani *et al.*, 1998, 2007; Schildt *et al.*, 1998; Balaram *et al.*, 2002; Pacella-Norman

et al., 2002; Muwonge *et al.*, 2008) estimated risks for former smokers which were always lower than those for current smokers and in five studies almost reached unity (Zheng *et al.*, 1990; Choi & Kahyo, 1991; Zheng *et al.*, 1997; Schildt *et al.*, 1998; Muwonge *et al.*, 2008). Twelve case-control studies examined the risk by years since quitting and all reported a negative trend, with relative risks compared with those in non-smokers decreasing to near unity after 10 or more years (Franceschi *et al.*, 1990, 1992; De Stefani *et al.*, 1998, 2007; Schlecht *et al.*, 1999a; Table 2.7 online; Table 2.10 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.10.pdf>).

(c) Type of cigarette

The effect of the type of cigarette smoked was examined in several case-control studies (Table 2.11 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.11.pdf>). The characteristics of the cigarettes included the presence of a filter, the type of tobacco, the tar content and whether the product was manufactured or hand-rolled. Two studies reported a statistically significantly higher risk for black than for blond tobacco (Oreggia *et al.*, 1991; De Stefani *et al.*, 1998, 2007). Similarly, a much higher risk was found for hand-rolled cigarettes than for manufactured cigarettes, and plain cigarettes had a much higher risk than filter-tipped cigarettes (De Stefani *et al.*, 1998, 2007). In one study the differences between black and blond tobacco and between hand-rolled and manufactured cigarettes persisted after stratification by duration of smoking (De Stefani *et al.*, 1998). Smoking cigarettes with a high-tar content led to higher risks than smoking cigarettes with a low-tar content (Franceschi *et al.*, 1992) and the same trend was observed for cigarettes without filter compared to cigarettes with filter (De Stefani *et al.*, 2007).

(d) Sex

Sex-specific effects were examined in two case-control studies ([Zheng et al., 1990](#); [Hayes et al., 1999](#)). In both studies, the relative risks for all categories of intensity, duration of smoking and pack-years were higher for women than for men. [The Working Group noted that the background risk of oral cancer is considerably lower in women than men. Thus, the higher relative risk estimates in women than men indicate a higher proportionate contribution from smoking in women than men, rather than higher absolute risk.]

2.3.2 Cancer of the pharynx

Tobacco smoking was considered to be an important cause of oropharyngeal and hypopharyngeal cancers in the previous *IARC Monographs* on tobacco smoking ([IARC, 1986, 2004a](#)). Since then, results available from three cohort (Table 2.12 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.12.pdf>) and seven case-control studies (Table 2.13 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.13.pdf> and Table 2.14 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.14.pdf>) provide further support for the association. Many studies, however, combine cancers of the oral cavity and pharynx (see Section 2.3.7). This section summarizes the evidence from all eight cohort and 21 case-control studies that reported results specifically on oropharyngeal and hypopharyngeal cancer, or on pharyngeal cancer in general; the latter may include data on nasopharyngeal cancer.

The risk for pharyngeal cancer was significantly increased in smokers in four cohort studies ([Doll et al., 2005](#); [McLaughlin et al., 1995](#); [Freedman et al., 2007a](#); [Friborg et al., 2007](#)) and all but one of the case-control studies ([Rao et al., 1999](#)). The trend of increasing risk associated with increasing daily or cumulative consumption

of cigarettes was evident from all these studies, particularly those from Europe ([Brugere et al., 1986](#); [Tuyns et al., 1988](#); [Franceschi et al., 1990, 1999](#); [Maier et al., 1994](#); [Escribano Uzcudun et al., 2002](#); [Vlajinac et al., 2006](#)), India ([Znaor et al., 2003](#); [Sapkota et al., 2007](#)), Uruguay ([De Stefani et al., 1998, 2007](#)) and the USA ([McLaughlin et al., 1995](#); [Applebaum et al., 2007](#)), and less strongly so in studies from Canada ([Elwood et al., 1984](#)) and the Republic of Korea ([Choi & Kahyo, 1991](#)). The multicentre study in Europe, North and South America of [Hashibe et al. \(2007c\)](#) showed increased risks according to frequency (cigarettes/day) and duration (years) in never drinkers. [Applebaum et al. \(2007\)](#) found a relationship between increasing risk of pharyngeal cancer and increased pack-years of smoking in subjects with negative HPV16 serology but not in those with positive HPV16 serology (p value for interaction = 0.007).

In two case-control studies the risk increased with decreasing age at starting smoking ([Franceschi et al., 1990](#); [Choi & Kahyo, 1991](#)), but adjustment was not made for duration and intensity of smoking. In a case-control study from Spain ([Escribano Uzcudun et al., 2002](#)) the risk increased with the age of starting smoking.

Former smokers had consistently lower relative risks than did current smokers in both cohort ([McLaughlin et al., 1995](#); [Freedman et al., 2007a](#)) and case-control studies ([Choi & Kahyo, 1991](#); [De Stefani et al., 1998](#); [Vlajinac et al., 2006](#)). In comparison with non-smokers, the relative risks for former smokers who had quit smoking for more than 10 years were between 2 and 4 ([Franceschi et al., 1990](#); [De Stefani et al., 1998](#); [La Vecchia et al., 1999](#)), whereas the relative risks for current smokers in these studies were 10–14. In one study in Brazil ([Schlecht et al., 1999a](#)), relative risks for former smokers who had stopped smoking for more than 10 years approached 1, whereas that for current smokers was just below 6. Consumption of black tobacco, hand-rolled cigarettes or plain cigarettes resulted in a higher

risk for pharyngeal cancer than consumption of blond tobacco, manufactured cigarettes or filter-tipped cigarettes (De Stefani *et al.*, 1998; 2007).

2.3.3 Cancer of the nasal cavity and accessory sinuses

In the Life Span Study in Japan (Akiba, 1994) the association of tobacco use with sinonasal cancer was examined. A total of 26 cases of sino-nasal cancer were identified among 61505 adults during follow-up. Relative risk estimates, adjusted for sex, location, population group, atomic bomb exposure, year of birth and attained age, were 2.9 (95%CI: 0.5–) and 4.0 (95%CI: 1.2–) for former and current smokers, respectively, when compared with non-smokers [upper confidence limits were not reported]. The cohort of 34439 British doctors followed up to 50 years (Doll *et al.*, 2005) showed increased risk for current smokers and smokers of more than 25 cigarettes per day, but only six deaths from nasal cavity and sinuses cancers were observed (Table 2.15 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.15.pdf>).

A total of nine case-control studies of nasal cavity and sinus cancers have been conducted. When histological types were combined, all studies found an increased risk associated with cigarette smoking, but only one was statistically significant (Caplan *et al.*, 2000). In seven studies, dose-response in terms of intensity of smoking (cigarettes/day), duration of smoking or pack-years was considered. A positive significant trend was found in five studies (Brinton *et al.*, 1984; Hayes *et al.*, 1987; Fukuda & Shibata, 1990; Zheng *et al.*, 1993; Caplan *et al.*, 2000) and suggested in the other two (Strader *et al.*, 1988; Zheng *et al.*, 1992c).

One study (Zheng *et al.*, 1993a) found a significant decrease in risk for sinonasal cancer associated with increasing number of years since cessation of smoking. In a previous study, the

same authors had found a negative, non-significant association (Zheng *et al.*, 1992c).

Five studies analysed squamous-cell carcinomas and adenocarcinomas separately (Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Zheng *et al.*, 1992c; 't Mannetje *et al.*, 1999). In all studies, there was a significantly increased risk for squamous-cell carcinomas, whereas the risk was generally not increased for adenocarcinomas.

2.3.4 Cancer of the nasopharynx

(a) Cohort studies

The risk for nasopharyngeal carcinoma has been examined in relation to tobacco use in six cohort studies, three of them reported since the last evaluation (IARC 2004a; Table 2.16 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.16.pdf>). In one study, conducted in a low-risk area (Chow *et al.*, 1993a), a significant increase in risk among smokers and suggestive positive dose-response relationships by duration of smoking and age at starting smoking were found. In another study, conducted in Province of Taiwan, China, an area in which nasopharyngeal cancer area is endemic, a similarly increased risk was found, but it was not statistically significant (Liaw & Chen, 1998). Doll *et al.* (2005) identified a risk only for smokers of more than 25 cigarettes per day, however, this result was based on only four deaths. Friberg *et al.* (2007) in Singapore found statistically significant increased risk of nasopharyngeal cancer only for those smoking for 40 years or more. Hsu *et al.* (2009) in Taiwan, China observed increased statistically significant risks only for those smoking for 30 years or more and those with cumulative exposure of 30 pack-years or more.

(b) Case-control studies

The study designs and the results of the case-control studies on the association of nasopharyngeal carcinoma with cigarette smoking

reported since the previous *IARC Monograph* (IARC, 2004a) are given in Table 2.17 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.17.pdf>) and Table 2.18 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.18.pdf>), one being a nested case–control analysis within a cohort study (Marsh *et al.*, 2007).

In total, 14 informative case–control studies were available. In almost all of these, the risk for nasopharyngeal carcinoma was higher in smokers than in non-smokers. In Taiwan, China (Cheng *et al.*, 1999) high risks were statistically significant only for duration of smoking of 20 years or more. In the five studies conducted in the USA (Mabuchi *et al.*, 1985; Nam *et al.*, 1992; Zhu *et al.*, 1995; Vaughan *et al.*, 1996; Marsh *et al.*, 2007), where the incidence of nasopharyngeal carcinoma is low, the relative risks for current smokers ranged between 2 and 4, but were not statistically significant in the two studies (Mabuchi *et al.*, 1985; Marsh *et al.*, 2007). In a study conducted in Shanghai, an area of China in which nasopharyngeal carcinoma is not endemic (Yuan *et al.*, 2000), the relative risk was just below 2. In one study from the Philippines there was a sevenfold increase in risk after more than 30 years of smoking (West *et al.*, 1993). The four studies (Lin *et al.*, 1973; Yu *et al.*, 1990; Ye *et al.*, 1995; Cao *et al.*, 2000) conducted in areas of China in which nasopharyngeal carcinoma is endemic (Taiwan, China, Guangzhou, and Sihui) found relative risks for ever smoking ranging between 2 and 5. In the study from the North of Africa (Feng *et al.*, 2009) the only statistically significant increased risk was found for differentiated nasopharyngeal cancer in those that had smoked more than 22 cigarettes/day. [The result, based only on three cases, is very unstable (RR, 313; 95%CI: 1.94–50336).]

A statistically significant dose–response relationship was detected in seven studies that evaluated the effects of daily or cumulative exposure to tobacco smoke (Yu *et al.*, 1990; Nam *et al.*, 1992;

Zhu *et al.*, 1995; Vaughan *et al.*, 1996; Cao *et al.*, 2000; Yuan *et al.*, 2000; Feng *et al.*, 2009) and was suggestive in two others (Lin *et al.*, 1973; West *et al.*, 1993). In two studies the risk of nasopharyngeal carcinoma decreased with increasing time since quitting smoking (Nam *et al.*, 1992; Vaughan *et al.*, 1996).

In the remaining studies, six from areas in which nasopharyngeal carcinoma is endemic (Ng, 1986; Yu *et al.*, 1986; Sriamporn *et al.*, 1992; Zheng *et al.*, 1994; Cheng *et al.*, 1999; Feng *et al.*, 2009; Guo *et al.*, 2009) and seven from areas in which it was not endemic (Henderson *et al.*, 1976; Lanier *et al.*, 1980; Mabuchi *et al.*, 1985; Ning *et al.*, 1990; Armstrong *et al.*, 2000; Marsh *et al.*, 2007), the relative risks for nasopharyngeal carcinoma for ever smoking were not significantly increased (Lanier *et al.*, 1980; Mabuchi *et al.*, 1985; Cheng *et al.*, 1999) or were close to 1.0 (Henderson *et al.*, 1976; Ng, 1986; Yu *et al.*, 1986; Ning *et al.*, 1990; Sriamporn *et al.*, 1992; Zheng *et al.*, 1994; Guo *et al.*, 2009).

In the two studies that distinguished between different histological types, relative risks were higher for keratinized (squamous-cell) carcinoma than for unkeratinized carcinoma (Zhu *et al.*, 1995; Vaughan *et al.*, 1996).

In the three studies in which men and women were analysed separately (Lin *et al.*, 1973; Nam *et al.*, 1992; Yuan *et al.*, 2000), the relative risks were found to increase similarly in both sexes in two studies (Nam *et al.*, 1992; Yuan *et al.*, 2000) and were higher among women in the study of Lin *et al.* (1973).

2.3.5 Cancer of the oesophagus

In the previous *IARC Monograph* (IARC, 2004a), both histological subtypes of oesophageal cancer (squamous-cell carcinoma and adenocarcinoma) were considered to be causally related to cigarette smoking. Many more epidemiological studies have since been conducted, and results of these studies further support this conclusion.

(a) *Squamous cell carcinoma and unspecified cancer of the oesophagus*

Since the previous *IARC Monograph* (IARC, 2004a), there have been reports on 9 cohort studies (Table 2.19 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.19.pdf>) and 22 case-control studies (Tables 2.20–2.23; see below), making 30 cohort and 55 case-control studies in all. All showed that the risk of oesophageal squamous cell carcinoma was associated with cigarette smoking. In one study (Li *et al.*, 1989), the elevated risk was observed only in an area with a relatively low incidence of oesophageal cancer. However, two later studies in the same area, Lin County, China, found a twofold increase in risk for oesophageal cancer among smokers (Gao *et al.*, 1994; Lu *et al.*, 2000).

In most cohort studies and in most case-control studies with relatively large sample sizes (IARC, 2004a; Table 2.19 online; Table 2.20 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.20.pdf>; Table 2.21 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.21.pdf>), the risk for oesophageal cancer was shown to increase with increasing duration of smoking (11 cohort and 32 case-control studies) or number of cigarettes smoked daily (18 cohort and 31 case-control studies), and to decrease with increasing age at starting smoking (12 case-control studies). In comparison with pharyngeal and laryngeal cancers, relative risks for oesophageal cancer estimated by duration and by intensity of smoking were somewhat lower (see Sections 2.3.2 and 2.3.6, respectively).

Ten cohort and 20 case-control studies (IARC, 2004a; Table 2.19 online; Table 2.22 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.22.pdf>) investigated the effect of smoking cessation on risk of oesophageal cancer. Although not all studies analysed the trend, all found a decreasing

relative risk with increasing number of years since quitting. In some studies, the risk first started to decrease after 10 years of cessation (Brown *et al.*, 1988; Rolón *et al.*, 1995; Gammon *et al.*, 1997; Castellsagué *et al.*, 1999; Freedman *et al.*, 2007b; Bosetti *et al.*, 2008) or after 30 years of cessation (Pandeya *et al.*, 2008).

When comparing the types of tobacco smoked (Table 2.23 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.23.pdf>), consumption of black tobacco resulted in a higher risk for oesophageal cancer than did consumption of blond tobacco (De Stefani *et al.*, 1990; Rolón *et al.*, 1995; Castellsagué *et al.*, 1999; Launoy *et al.*, 2000; Vioque *et al.*, 2008). Similarly, smoking untipped cigarettes generally resulted in a higher risk than smoking filter-tipped cigarettes (Vaughan *et al.*, 1995; Gammon *et al.*, 1997; Castellsagué *et al.*, 1999).

Two studies from the USA reported risks separately for blacks and whites. After adjustment for alcohol consumption, age and income, risks were very similar for former and current smokers and for the number of cigarettes smoked per day and duration of smoking (Brown *et al.*, 1994a; Brown *et al.*, 2001).

(b) *Adenocarcinoma of the oesophagus*

Two decades ago it was noted that incidence rates for adenocarcinoma of the oesophagus and gastric cardia had increased steadily in the USA, whereas the incidence rate for squamous-cell carcinoma of the oesophagus had remained relatively stable (Blot *et al.*, 1991). An increase in the incidence of adenocarcinoma of the distal oesophagus and cardia was also noted in the United Kingdom (Powell & McConkey, 1990), and in several other countries. Since 1990, several studies have focused on the risk factors for adenocarcinoma of the oesophagus. Since the last evaluation (IARC, 2004a) one cohort study (Freedman *et al.*, 2007b) and three case-control studies (Table 2.24 available at <http://monographs.iarc.fr/ENG/Monographs/>

[vol100E/100E-01-Table2.24.pdf](#); Table 2.25 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.25.pdf>) have been reported, totaling 13 case-control studies on the association of cigarette smoking and adenocarcinoma of the oesophagus.

(i) *Intensity and duration of smoking*

Ten studies, three that included only cases of adenocarcinoma of the oesophagus ([Menke-Pluymers et al., 1993](#); [Gammon et al., 1997](#); [Wu et al., 2001](#)), three that included cases of adenocarcinoma of the oesophagus, gastro-oesophageal junction and gastric cardia combined ([Kabat et al., 1993](#); [Brown et al., 1994b](#); [Vaughan et al., 1995](#)), and four that stratified by histology ([Lindblad et al., 2005](#); [Freedman et al., 2007b](#); [Hashibe et al., 2007a](#); [Pandeya et al., 2008](#)), showed a significant positive association of adenocarcinoma of the oesophagus with cigarette smoking. The relative risks were somewhat lower than those for squamous cell carcinoma of the oesophagus. Three studies, one in China ([Gao et al., 1994](#)), one in Sweden ([Lagergren et al., 2000](#)), and one in the USA ([Zhang et al., 1996](#)), reported similarly elevated relative risks, but some of these risks were not statistically significant, probably because of relatively small numbers of cases.

Of those studies that reported risks adjusted for alcohol consumption, a positive, significant dose-response relationship was found with intensity of smoking ([Kabat et al., 1993](#); [Brown et al., 1994b](#); [Gammon et al., 1997](#); [Hashibe et al., 2007a](#)), duration of smoking ([Gammon et al., 1997](#); [Pandeya et al., 2008](#)) and/or pack-years ([Vaughan et al., 1995](#); [Zhang et al., 1996](#); [Gammon et al., 1997](#); [Pandeya et al., 2008](#)).

(ii) *Cessation of smoking*

Ten studies provided point estimates for former smokers. In eight, relative risks were lower in former smokers than in current smokers, although they remained elevated ([Kabat et al.,](#)

[1993](#); [Gao et al., 1994](#); [Vaughan et al., 1995](#); [Gammon et al., 1997](#); [Wu et al., 2001](#); [Lindblad et al., 2005](#); [Freedman et al., 2007b](#); [Pandeya et al., 2008](#)), and were increased in the other studies ([Lagergren et al., 2000](#); [Hashibe et al., 2007a](#)). The decrease in relative risk associated with years since cessation was weak, but a significant trend was found in two out of six studies ([Gammon et al., 1997](#); [Wu et al., 2001](#)).

(iii) *Confounding*

With the exception of two studies ([Levi et al., 1990](#); [Wu et al., 2001](#)), all studies adjusted for alcohol intake as a potential confounder. Three more recent studies also adjusted for fruit and vegetables intake ([Freedman et al., 2007b](#); [Hashibe et al., 2007a](#); [Pandeya et al., 2008](#)). Ten of these studies were conducted in the USA ([Kabat et al., 1993](#); [Brown et al., 1994b](#); [Vaughan et al., 1995](#); [Zhang et al., 1996](#); [Gammon et al., 1997](#); [Freedman et al., 2007b](#)) the Netherlands ([Menke-Pluymers et al., 1993](#)), the United Kingdom ([Lindblad et al., 2005](#)), central and eastern Europe ([Hashibe et al., 2007a](#)) and Australia ([Pandeya et al., 2008](#)), where chewing of betel quid with tobacco or use of other forms of smokeless tobacco are not likely confounders. One study conducted in Sweden was adjusted for snuff use ([Lagergren et al., 2000](#)).

(iv) *Sex*

[Kabat et al. \(1993\)](#) examined risks for men and women separately and observed similar patterns in both sexes, although risks among current smokers and heavy smokers were somewhat higher for women than for men. [Lindblad et al. \(2005\)](#) also found higher risks in women than in men, but they were not statistically significant.

2.3.6 Cancer of the larynx

Laryngeal cancer is one of the cancers most strongly associated with cigarette smoking ([IARC, 1986, 2004a](#)). Since the previous IARC

Monograph, more epidemiological evidence has become available to strengthen this conclusion.

(a) Potential confounders

Other causes of laryngeal cancer include alcohol consumption, some occupational exposures (e.g. sulphuric acid; [IARC, 2012a](#)) and possibly some dietary habits. In investigating associations between smoking and laryngeal cancer, potential confounding by alcohol consumption has been considered in most of the studies.

(b) Intensity and duration of smoking

Cohort and case-control studies have been carried out in Asia, Europe, North and South America, and South Africa. In all, the risk for laryngeal cancer was consistently higher in smokers, and a positive significant trend was observed with increasing duration and intensity of smoking ([IARC, 2004a](#); Table 2.26 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.26.pdf>; Table 2.27 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.27.pdf>; Table 2.28 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.28.pdf>).

In most case-control studies, the relative risks for laryngeal cancer were near to or greater than 10 for smokers who had smoked for longer than 40 years ([Falk et al., 1989](#); [Zheng et al., 1992b](#)) or had smoked more than 20 cigarettes per day ([Tuyns et al., 1988](#); [Falk et al., 1989](#); [Choi & Kahyo, 1991](#); [Zatonski et al., 1991](#); [Muscat & Wynder, 1992](#); [Zheng et al., 1992b](#); [Hedberg et al., 1994](#); [Sokić et al., 1994](#); [Talamini et al., 2002](#)). Cancer of the larynx in non-smokers is so rare that several studies used as the reference category light smokers ([Herity et al., 1982](#); [Olsen et al., 1985a](#); [De Stefani et al., 1987](#); [Zatonski et al., 1991](#); [López-Abente et al., 1992](#); [Maier & Tisch, 1997](#)), or former smokers ([Hashibe et al., 2007b](#)). Consequently, relative risks were lower

in these studies, although the increases were still statistically significant.

Three case-control studies reported odds ratios for cancer of the larynx that increased with decreasing age of starting smoking ([Franceschi et al., 1990](#); [Zatonski et al., 1991](#); [Talamini et al., 2002](#)).

(c) Cessation of smoking

The risk for cancer of the larynx declines rather rapidly after cessation of smoking ([IARC, 2004a](#); Table 2.29 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.29.pdf>). No detectable higher risk compared with never-smokers was seen among subjects who had quit smoking for at least 10 years ([Franceschi et al., 1990](#); [Ahrens et al., 1991](#); [Schlecht et al., 1999a, b](#); [Bosetti et al., 2006](#); [Hashibe et al., 2007b](#)).

(d) Types of tobacco or of cigarette

Some investigators considered the role of type of tobacco ([IARC, 2004a](#); Table 2.30 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.30.pdf>). An average 2.5-fold higher risk was observed in smokers of black tobacco compared to smokers of blond tobacco ([De Stefani et al., 1987](#); [Tuyns et al., 1988](#); [López-Abente et al., 1992](#)). Smoking untipped cigarettes also led to a higher risk than smoking filter-tipped cigarettes ([Wynder & Stellman, 1979](#); [Tuyns et al., 1988](#); [Falk et al., 1989](#)). Those that smoke cigarettes only had higher risks of larynx cancer than those that smoke cigars only ([Hashibe et al., 2007b](#)).

(e) Subsites

Six studies investigated the risk for glottic and supraglottic cancer separately ([Olsen et al., 1985a](#); [Tuyns et al., 1988](#); [López-Abente et al., 1992](#); [Maier et al., 1992b](#); [Muscat & Wynder, 1992](#); [Sapkota et al., 2007](#)). The cancer risk increased with increasing amount smoked per

day and with cumulative exposure for both subsites (IARC, 2004a; Table 2.28 online). In addition, the observed relative risks were higher for supraglottic cancer than for glottic cancer (Maier *et al.*, 1992b; Sapkota *et al.*, 2007).

(f) Sex

Few studies investigated sex-specific effects. In one cohort study (Raitiola & Pukander, 1997) similar risks were found for men and women, whereas in two case-control studies (Zheng *et al.*, 1992b; Tavani *et al.*, 1994), the relative risks for women were up to 10-fold higher than for the corresponding categories in men, though a small number of cases were involved. However, Freedman *et al.* (2007a) observed higher relative risks in men than women (Table 2.26 online). One study looked at women only and found higher risks of laryngeal cancer in former and current smokers relative to non-smokers, and also according to the number of cigarettes per day with a clear dose-response effect ($P < 0.001$) (Gallus *et al.*, 2003b).

2.3.7 Cancer of the upper aerodigestive tract combined

In epidemiological studies, especially in cohort studies in which there are few cases at some sites, investigators often combine cancers of the oral cavity, pharynx, larynx and oesophagus and term these ‘cancer of the upper aerodigestive tract’. This section summarizes the data from 19 cohort studies (IARC, 2004a; Table 2.31 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.31.pdf>), and 40 case-control studies (IARC, 2004a; Tables 2.32–2.35; see below).

(a) Intensity and duration of smoking

In all but two cohort studies from Japan (Kono *et al.*, 1987; Akiba, 1994), the risk for cancer of the upper aerodigestive tract was strongly associated with cigarette smoking. Relative risks increased

with increasing daily cigarette consumption (Hammond & Horn, 1958; Doll *et al.*, 1980, 1994; Akiba & Hirayama, 1990; Kuller *et al.*, 1991; Chyou *et al.*, 1995; Engeland *et al.*, 1996; Murata *et al.*, 1996; Yuan *et al.*, 1996; Kjaerheim *et al.*, 1998; Liaw & Chen, 1998; Yun *et al.*, 2005; Freedman *et al.*, 2007a), duration of smoking (Chyou *et al.*, 1995; Yun *et al.*, 2005; Friberg *et al.*, 2007) or pack-years (Liaw & Chen, 1998; Freedman *et al.*, 2007a).

The main characteristics and results of the case-control studies are presented in IARC (2004a), and in Table 2.32 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.32.pdf>) and Table 2.33 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.33.pdf>), respectively. Intensity of smoking was measured in most of these studies. The link between duration of smoking and cancer of the upper aerodigestive tract was examined in 20 case-control studies (Blot *et al.*, 1988; Merletti *et al.*, 1989; Barra *et al.*, 1991; De Stefani *et al.*, 1992, 2007; Franceschi *et al.*, 1992; Day *et al.*, 1993; Mashberg *et al.*, 1993; Kabat *et al.*, 1994; Lewin *et al.*, 1998; Bosetti *et al.*, 2000a; Garrote *et al.*, 2001; Gallus *et al.*, 2003a; Lissowska *et al.*, 2003; Znaor *et al.*, 2003; Castellsagué *et al.*, 2004; Menvielle *et al.*, 2004a, b; Rodriguez *et al.*, 2004; Hashibe *et al.*, 2007c; Sapkota *et al.*, 2007). Nine also considered age at starting smoking (Blot *et al.*, 1988; Merletti *et al.*, 1989; Barra *et al.*, 1991; Franceschi *et al.*, 1992; Day *et al.*, 1993; Lewin *et al.*, 1998; Garrote *et al.*, 2001; Lissowska *et al.*, 2003; Menvielle *et al.*, 2004a).

In all but one study (Rao *et al.*, 1999) there was an increased risk for cancer of the upper aerodigestive tract associated with cigarette smoking. A clear dose-response relationship was seen with increasing daily tobacco consumption and duration of smoking as well as with decreasing age at starting smoking in most of the studies examined.

(b) Cessation of smoking

Twelve cohort studies ([Doll et al., 1980, 1994](#); [Tomita et al., 1991](#); [Akiba, 1994](#); [Chyou et al., 1995](#); [Engeland et al., 1996](#); [Nordlund et al., 1997](#); [Kjaerheim et al., 1998](#); [Yun et al., 2005](#); [Freedman et al., 2007a](#); [Friborg et al., 2007](#); [Ide et al., 2008](#)) provided point estimates for former smokers ([IARC 2004a](#); Table 2.31 online). The relative risks for former smokers were always lower than those for current smokers.

In 16 case-control studies the relative risk by years since quitting was examined and generally a statistically significant negative trend was found (Table 2.34 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.34.pdf>).

(c) Types of cigarette

The characteristics studied in several case-control studies included the use of a filter, the type of tobacco, the tar content and whether the product was manufactured or hand-rolled ([IARC, 2004a](#); Table 2.35 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.35.pdf>). Consumption of black tobacco, cigars, untipped cigarettes, hand-rolled cigarettes, or cigarettes with a high-tar yield generally resulted in a higher risk than consumption of blond tobacco ([Merletti et al., 1989](#); [Castellsagué et al., 2004](#); [De Stefani et al., 2007](#)), filter-tipped cigarettes ([Merletti et al., 1989](#); [Mashberg et al., 1993](#); [Kabat et al., 1994](#); [Lissowska et al., 2003](#); [De Stefani et al., 2007](#)), manufactured cigarettes ([De Stefani et al., 1992, 2007](#)) or low-tar cigarettes ([Franceschi et al., 1992](#)). Two studies from India ([Znaor et al., 2003](#); [Sapkota et al., 2007](#)) revealed higher risks of *bidi* smoking related to cigarettes smoking.

(d) Sex

Sex-specific effects were analysed in four cohort studies ([IARC 2004a](#); Table 2.31 online). In three cohort studies ([Hammond & Seidman,](#)

[1980](#); [Akiba & Hirayama, 1990](#); [Freedman et al., 2007a](#)) a higher relative risk was found for male smokers than for female smokers; however, [Ide et al. \(2008\)](#) detected a higher risk among women in a study with a small number of cases.

In three case-control studies ([Blot et al., 1988](#); [Kabat et al., 1994](#); [Muscat et al., 1996](#)) the relative risks were higher for women than for men in all categories of intensity of smoking (number of cigarettes per day), cumulative exposure (cumulative tar consumption, pack-years, duration of smoking) and age at starting smoking, as well as for former smokers. However, the trends in men were always in the same direction and of the same order of magnitude. An exception to the pattern was that in one study ([Merletti et al., 1989](#)) the relative risk for smoking filter-tipped cigarettes was higher than that for smoking untipped cigarettes for women.

Overall, the strength of association by sex was generally similar, especially when taking into account the fact that women generally under-report levels of smoking and that most studies included many fewer women than men.

(e) Ethnicity

Relative risks were reported separately for blacks and whites in a large case-control study from the USA ([Day et al., 1993](#)). Relative risks adjusted for alcohol consumption, sex and other relevant variables were very similar for the number of cigarettes smoked per day, years of cigarette smoking, age at starting smoking and number of years since stopping smoking.

2.4 Cancer of the stomach

2.4.1 Overview of studies

In the previous *IARC Monograph* ([IARC, 2004a](#)) it was concluded that there was *sufficient evidence* that tobacco smoking causes cancer of the stomach. Three meta-analyses have since examined the evidence for gastric cancer in 42

independent cohort studies published between 1958 and July 2007 ([Ladeiras-Lopes et al., 2008](#)), in 46 case–control studies published between 1997 and June 2006 ([La Torre et al., 2009](#)), and in 10 cohort and 16 case–control studies conducted in Japanese populations published between 1966 and March 2005 ([Nishino et al., 2006](#); Table 2.36 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.36.pdf>). For current smokers compared to never smokers, the risk for stomach cancer was found to be statistically significantly increased by 53% ([Ladeiras-Lopes et al., 2008](#)), 56% ([Nishino et al., 2006](#)), and 57% when considering high quality case–control studies ([La Torre et al., 2009](#)), with moderate to high heterogeneity.

Since the previous *IARC Monograph* ([IARC, 2004a](#)), the association between cigarette smoking and stomach cancer risk (15 studies) and mortality (4 studies) has been examined in 19 cohort studies (Table 2.37 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.37.pdf>). Eleven of these were conducted in Asia ([Sasazuki et al., 2002](#); [Jee et al., 2004](#); [Koizumi et al., 2004](#); [Wen et al., 2004](#); [Fujino et al., 2005](#); [Sauvaget et al., 2005](#); [Tran et al., 2005](#); [Kurosawa et al., 2006](#); [Kim et al., 2007](#); [Sung et al., 2007](#); [Shikata et al., 2008](#)), seven in Europe ([Simán et al., 2001](#); [González et al., 2003](#); [Doll et al., 2005](#); [Lindblad et al., 2005](#); [Sjödahl et al., 2007](#); [Batty et al., 2008](#); [Zendehdel et al., 2008](#)) and one in the USA ([Freedman et al., 2007a](#)). Only the updated British Doctors' study ([Doll et al., 2005](#)) and the most recent studies ([Shikata et al., 2008](#); [Zendehdel et al., 2008](#)) were not included in the meta-analysis of cohort studies ([Ladeiras-Lopes et al., 2008](#)). Elevated risks in current smokers were found in all studies. The reported association of current smoking with mortality in the four cohort studies conducted in Taiwan, China ([Wen et al., 2004](#)), Japan ([Kurosawa et al., 2006](#)) and the United Kingdom ([Doll et al., 2005](#); [Batty et al., 2008](#)) was comparable to that with incidence.

In addition, the association between smoking and stomach cancer risk has been reported in 37 case–control studies since the previous *IARC Monograph*, of which 22 are hospital-based and 15 population-based. With the exception of three studies ([Campos et al., 2006](#); [García-González et al., 2007](#); [Suwanrungruang et al., 2008](#); Table 2.38 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.38.pdf>), all these studies were included in the meta-analysis conducted by ([La Torre et al., 2009](#)).

2.4.2 Factors affecting risk

(a) Intensity and duration

Clear evidence has been provided by the meta-analyses as well as by the additional cohort studies that the risk for stomach cancer increases significantly with increasing daily cigarette consumption, duration or pack-years of smoking, although individual studies did not always find statistically significant dose–response relationships. In one meta-analysis based on 21 cohort studies, the risk for stomach cancer increased statistically significantly by 53% with consumption of approximately 20 cigarettes per day ([Ladeiras-Lopes et al., 2008](#)). Using trend estimation analysis as proposed by [Greenland & Longnecker \(1992\)](#), the authors found an increase in relative risk from 1.3 for the lowest consumption to 1.7 for smoking 30 cigarettes per day.

(b) Cessation of smoking

Risk for stomach cancer has been generally found to be lower in former smokers than in current smokers. In six of the cohort studies decreasing risk with increasing years since stopping smoking was found although none found statistically significant dose–response relationships ([González et al., 2003](#); [Koizumi et al., 2004](#); [Sauvaget et al., 2005](#); [Freedman et al., 2007a](#); [Kim et al., 2007](#); [Zendehdel et al., 2008](#)). Risk in former smokers was comparable to never smokers after quitting for 5 years ([Kim et al.,](#)

2007), 10 years ([González et al., 2003](#); [Sauvaget et al., 2005](#); [Freedman et al., 2007a](#)) or 15 years ([Koizumi et al., 2004](#)).

2.4.3 Subsites

The effect of current smoking on the risk for stomach cancer by subsite was assessed in ten cohort studies. Elevated risks were found for both cardia and non-cardia cancers. In six studies higher risks were found for cancer of the gastric cardia than for cancer of the distal stomach ([Simán et al. 2001](#); [González et al., 2003](#); [Freedman et al., 2007a](#); [Sung et al., 2007](#); [Shikata et al., 2008](#); [Zendehdel et al., 2008](#)), three studies found no difference ([Sasazuki et al., 2002](#); [Lindblad et al., 2005](#); [Tran et al., 2005](#)), and in one study higher risk for cancer in the antrum rather than the body or the cardia was found ([Koizumi et al., 2004](#)). A meta-analysis yielded statistically significant summary relative risks of 1.87 for cardia cancers and 1.60 for non-cardia cancers based on nine cohort studies ([Ladeiras-Lopes et al., 2008](#)). However, there was substantial heterogeneity across studies for cardia cancers. For case–controls studies, the corresponding odds ratios were 2.05 (95%CI: 1.50–2.81) and 2.04 (95%CI: 1.66–2.50), respectively, with greater heterogeneity for non-cardia cancers. Criteria for the classification by subsite were not always described ([Simán et al., 2001](#); [Koizumi et al., 2004](#); [Lindblad et al., 2005](#); [Tran et al., 2005](#)) and some studies included tumours located in the upper third of the stomach in the group of cardia cancer ([Sasazuki et al., 2002](#); [Sung et al., 2007](#); [Shikata et al. 2008](#)).

In three studies risk estimates for smoking associated stomach cancer were estimated by histological type ([Sasazuki et al., 2002](#); [Koizumi et al., 2004](#); [Shikata et al., 2008](#)). The relative risks were 2.1 (95%CI: 1.2–3.6), 1.6 (95%CI: 1.1–2.3) and 2.3 (95%CI: 1.3–4.1) for the differentiated type, respectively, and 0.6 (95%CI: 0.3–1.1), 2.1

(95%CI: 1.1–4.1), and 1.3 (95%CI: 0.5–3.5) for the non-differentiated type, respectively.

2.4.4 Population characteristics

In four of the additional cohort studies risk was reported separately for men and women ([González et al., 2003](#); [Jee et al., 2004](#); [Fujino et al., 2005](#); [Kim et al., 2007](#)), in three studies only for men ([Koizumi et al., 2004](#); [Tran et al., 2005](#); [Sung et al., 2007](#)) and in one mortality study for men as well as for women ([Wen et al., 2004](#)). Generally, the relative risks were smaller in women than in men. For all stomach cancers, risk in current smokers compared to never smokers was found to be significantly increased by 62% in men (based on 18 studies) and by 20% in women (based on nine studies) in the meta-analysis of cohort studies ([Ladeiras-Lopes et al., 2008](#)). The men–women differences were independent of exposure level but could be explained by the sex difference in the distribution by histological type and other factors associated with socioeconomic status.

Ethnicity does not appear to modify the effect of smoking on stomach cancer risk. In the meta-analysis of case–control studies risk in current smokers was increased by 78% in Caucasians and by 48% in Asians ([La Torre et al., 2009](#)). The summary risk based on the cohort studies increased by 46% and 47% in Caucasian and Asian studies, respectively. In a meta-regression analysis including the variables sex, population, and fruit and vegetable consumption, sex but not origin of the population showed significant differences in risk estimates ([Ladeiras-Lopes et al., 2008](#)).

2.4.5 Bias and confounding

Generally, most cohort studies have relied on baseline information and did not update the exposure information, possibly leading to misclassification of smoking status. Most of

the recent cohort studies have accounted for confounding by alcohol consumption ([Fujino et al., 2005](#); [Lindblad et al., 2005](#); [Sjödahl et al., 2007](#); [Sung et al., 2007](#)) as well as fruit and vegetable consumption ([González et al., 2003](#); [Koizumi et al., 2004](#); [Freedman et al., 2007a](#)) and still observed significantly increased risk of stomach cancer in current smokers.

2.4.6 *Helicobacter pylori* infection

The association between tobacco smoking and stomach cancer could be confounded or modified by the effect of *H. pylori* infection, an established risk factor for stomach cancer. In three case-control studies ([Zaridze et al., 2000](#); [Brenner et al., 2002](#); [Wu et al., 2003](#)), and two cohort studies ([Simán et al., 2001](#); [Shikata et al., 2008](#)) the joint effects and possible interaction between *H. pylori* status and smoking in relation to risk for stomach cancer was investigated. Among subjects who had *H. pylori* infection, the risk for stomach cancer was higher in current smokers than in non-smokers by 1.6 to 2.7 fold, providing evidence for a causal effect of tobacco smoking independently of *H. pylori* infection. Smoking was associated with risk elevations of the same order of magnitude among subjects without *H. pylori* infection. Smoking and *H. pylori* therefore may act synergistically, leading to very high risks in current smokers with *H. pylori* infection compared to non-smokers without *H. pylori* infection. In one study that examined risk by subsite an effect of smoking independent of *H. pylori* infection for gastric cardia as well as distal gastric cancer was found ([Wu et al., 2003](#)). In none of the studies was there statistically significant evidence for interaction.

2.5 Cancer of the pancreas

2.5.1 Overview of studies

Previous *IARC Monographs* ([IARC, 1986, 2004a](#)) concluded that exposure to tobacco smoke caused cancer of the pancreas. Additional evidence has come from a pooled analysis of eight cohort studies with almost 1500 incident cases of pancreatic cancer and an equal number of controls ([Lynch et al., 2009](#)) as well as a meta-analysis of 82 independent studies (42 case-control studies, 40 cohort studies) published between 1950 and 2007 ([Iodice et al., 2008](#); Table 2.39 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.39.pdf>). In the meta-analysis 74% and 20% significant increased risks for current and former smokers, respectively, were found with significant heterogeneity of effect regarding current smoking across studies. Adjustment for confounders explained some of the heterogeneity ([Iodice et al., 2008](#)). A similar significant risk elevation of 77% for current smokers was found in the pooled analysis, without study heterogeneity ([Lynch et al., 2009](#)). For former smokers, risk was increased non-significantly by 9%.

Since the previous *IARC Monograph* ([IARC, 2004a](#)), a total of 15 cohort studies have reported on the association between cigarette smoking and pancreatic cancer incidence (8 studies) and mortality (5 studies) or both (one study) (Table 2.40 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.40.pdf>), two of which were included in the pooled analysis ([Coughlin et al., 2000](#); [Vrieling et al., 2009](#)). Excluding case-control studies that did not report odds ratios for current smokers, there were three additional case-control studies ([Duell et al., 2002](#); [Inoue et al., 2003](#); [Alguacil & Silverman, 2004](#); Table 2.41 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.41.pdf>). The effect of cigar and pipe smoking on pancreatic cancer was

also examined in the ACS Cancer Prevention Study II regarding mortality ([Shapiro et al., 2000](#); [Henley et al., 2004](#)) and in the Kaiser Permanente Medical Care Program regarding incidence ([Iribarren et al., 1999](#)). All the additional studies showed an increased risk for pancreatic cancer associated with tobacco smoking, generally higher in current than in former smokers. The reported risk estimates were not always statistically significant, predominantly due to the small size of some studies and therefore lack of statistical precision.

2.5.2 Factors affecting risks

(a) Intensity and duration

Clear evidence has been provided by the meta-analysis, the pooled analysis as well as the additional studies that the risk for cancer of the pancreas increases significantly with increasing daily cigarette consumption, duration and pack-years of smoking ([Coughlin et al., 2000](#); [Gapstur et al., 2000](#); [Nilsen & Vatten, 2000](#); [Nilsson et al., 2001](#); [Isaksson et al., 2002](#); [Doll et al., 2005](#); [Yun et al., 2005](#); [Ansary-Moghaddam et al., 2006](#); [Gallicchio et al., 2006](#); [Vrieling et al., 2009](#)). In the meta-analysis risk of pancreatic cancer increased significantly by 62% with an increase of 20 cigarettes per day (based on 45 studies) and by 16% with a 10-year increase in smoking duration (based on 16 studies), but with significant study heterogeneity. In the pooled analysis, the excess odds ratio per pack-years generally declined with increasing smoking intensity ([Lynch et al., 2009](#)).

(b) Cessation of smoking

A reduction in risk in former smokers who had stopped smoking for at least 10 years was found in the meta-analysis ([Iodice et al., 2008](#)) and the pooled study ([Lynch et al., 2009](#)). In some cohort studies risk was already comparable to never smokers five years after quitting ([Boyle et al., 1996](#); [Fuchs et al., 1996](#); [Nilsen & Vatten, 2000](#); [Vrieling et al., 2009](#)).

(c) Types of tobacco

In non-cigarette smokers, mortality from pancreatic cancer was increased although not statistically significantly so in cigar smokers in the CPS-II cohort study ([Shapiro et al., 2000](#)) as well as a large case-control study ([Alguacil & Silverman, 2004](#)) but was less clearly elevated in the smaller Kaiser Permanente cohort study ([Iribarren et al., 1999](#)). There was a significantly increased mortality for current cigar smokers who reported inhaling cigar smoke ([Shapiro et al., 2000](#)). Pipe smoking was also found to be associated with an increased risk of cancer of the pancreas, which was stronger in those who reported that they inhaled the smoke ([Henley et al., 2004](#)). A limitation of the cohort studies is that smoking habits were reported only at baseline, misclassification of smoking exposure is likely to underestimate the associated risks. In the meta-analysis there was a significant increase in risk of 47% associated with current cigar and/or pipe smoking (18 studies) and a non-significant risk elevation of 29% with former cigar and/or pipe smoking (5 studies) ([Iodice et al., 2008](#)).

2.5.3 Population characteristics

The effect of sex on pancreatic cancer risk was investigated in two cohort studies ([Nilsen & Vatten, 2000](#); [Larsson et al., 2005](#)) and on pancreatic cancer mortality in four cohort studies ([Coughlin et al., 2000](#); [Gapstur et al., 2000](#); [Nilsson et al., 2001](#); [Lin et al., 2002a](#)). The relative risks were comparable between men and women and no consistent evidence for an effect modification by sex was observed.

Ethnicity does not appear to modify the association of smoking with pancreatic cancer risk. The roughly twofold elevated risk in current smokers compared to never smokers was observed both in studies of Caucasians ([Lynch et al., 2009](#)) and of Asians ([Lin et al., 2002a](#); [Jee et al., 2004](#); [Yun et al., 2005](#); [Li et al., 2006](#)). In populations of the Asia-Pacific Region, there

was also no difference in the strength of association between Asia and Australia/New Zealand ([Ansary-Moghaddam et al., 2006](#)).

2.5.4 Confounding factors

In two large cohort studies the risk estimates for pancreatic cancer associated with cigarette smoking were not substantially influenced by adjustment for further potential confounding factors, including diabetes, body mass index (BMI), alcohol and dietary intake ([Coughlin et al., 2000](#); [Vrieling et al., 2009](#)).

2.6 Cancer of the colorectum

2.6.1 Overview of studies

In the previous *IARC Monograph* ([IARC, 2004a](#)) it was not possible to conclude that the association between tobacco smoking and colorectal cancer is casual, principally because of concern about confounding by other risk factors. That evaluation was based on a total of 60 epidemiologic studies, although only few were specifically designed to study the effects of smoking. Studies have however shown consistently that cigarette smoking is a risk factor for colorectal adenomatous polyps, which are recognized precursor lesions of colorectal cancer ([Hill, 1978](#)). To explain this discrepancy, [Giovannucci et al. \(1994\)](#) hypothesized that a long induction period is required for tobacco to play a role in colorectal carcinogenesis, which would not be captured by studies with shorter follow-up time.

Four recent meta-analyses consistently showed a strong association between cigarette smoking and colorectal cancer ([Botteri et al., 2008a](#); [Liang et al., 2009](#); [Huxley et al., 2009](#); [Tsoi et al., 2009](#)).

2.6.2 Cohort studies

Since the previous *IARC Monograph* ([IARC, 2004a](#)), 22 additional cohort studies have investigated the association between tobacco smoke and colorectal cancer (Table 2.42 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.42.pdf>). [Studies that did not provide point estimates of risk ([Andersen et al., 2009](#); [Hansen et al., 2009](#); [Murphy et al., 2009](#)) and included prevalent colorectal cancer in patients with other diagnosis ([Chan et al., 2007](#)) are excluded from this review]. Seven of the studies were conducted in Europe, nine in Asia and five in the USA. In eleven studies, risk estimates were reported solely for colorectal cancer ([Tiemersma et al., 2002a](#); [Limburg et al., 2003](#); [Otani et al., 2003](#); [Colangelo et al., 2004](#); [Sanjoaquin et al., 2004](#); [Lüchtenborg et al., 2005a](#); [Kim et al., 2006](#); [Akhter et al., 2007](#); [Huxley, 2007a](#); [Kenfield et al., 2008](#); [Hannan et al., 2009](#)), five studies separately for colon cancer and rectal cancer ([Shimizu et al., 2003](#); [Wakai et al., 2003](#); [Jee et al., 2004](#); [Yun et al., 2005](#); [Batty et al., 2008](#)) and five studies both for colorectal cancer as well as for colon and rectal cancers ([Terry et al., 2002a](#); [van der Hel et al., 2003a](#); [Doll et al., 2005](#); [Paskett et al., 2007](#); [Tsong et al., 2007](#); [Gram et al., 2009](#)). Six studies were restricted to women ([Terry et al., 2002a](#); [Limburg et al., 2003](#); [van der Hel et al., 2003a](#); [Paskett et al., 2007](#); [Kenfield et al., 2008](#); [Gram et al., 2009](#)), and two studies to men ([Doll et al., 2005](#); [Yun et al., 2005](#); [Akhter et al., 2007](#)). One study reported both colorectal incidence and mortality ([Limburg et al., 2003](#)) and three studies only reported colorectal cancer mortality ([Doll et al., 2005](#); [Huxley, 2007a](#); [Batty et al., 2008](#); [Kenfield et al., 2008](#)).

(a) Smoking status

Virtually all studies reported elevated risk associated with smoking, although results were not always statistically significant. The largest meta-analysis based on 36 prospective studies

with data from a total of 3007002 subjects found that compared to never smokers, current smokers had a 15% significantly higher risk of developing colorectal cancer and 27% significantly higher risk of colorectal cancer mortality (Liang *et al.*, 2009; Table 2.43 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.43.pdf>). In former smokers, colorectal cancer risk was also significantly elevated by 20% whereas colorectal cancer mortality was non-significantly increased by 20%. The risk estimates were not significantly different between colon and rectal cancer for current smokers (RR, 1.10 versus 1.19) and for former smokers (RR, 1.10 versus 1.20). There was no heterogeneity among colorectal cancer studies and no evidence for publication bias. Comparable risk elevations in current and former smokers were found in the other meta-analyses. For current smokers, the risk for colorectal cancer increased significantly by 16% when using data from 22 cohort studies (Huxley *et al.*, 2009), by 20% based on 28 cohort studies (Tsoi *et al.*, 2009), and by 7% based on data from 45 cohort and case-control studies (Botteri *et al.*, 2008a). In the latter meta-analysis a 17% significantly higher risk of colorectal cancer in former smokers was found.

(b) Intensity of smoking

All but three of the recent 21 cohort studies (van der Hel *et al.*, 2003a; Jee *et al.*, 2004; Sanjoaquin *et al.*, 2004) investigated dose-response relationships, using at least one of number of cigarettes smoked, duration of smoking, pack-years of smoking, age at smoking initiation, time since smoking cessation. In two further studies (Tiemersma *et al.*, 2002a; Batty *et al.*, 2008) these parameters were examined separately in current and former smokers, as by Chao *et al.* (2000). Statistically significant dose-response trends with amount smoked daily were reported for colorectal cancer (Lüchtenborg *et al.*, 2005a; Akhter *et al.*, 2007; Paskett *et al.*, 2007; Kenfield *et al.*, 2008), for colon cancer (Paskett

et al., 2007), and for rectal cancer (Paskett *et al.*, 2007; Tsong *et al.*, 2007). The dose-response of daily cigarette consumption and colorectal cancer was assessed in two meta-analyses (Liang *et al.*, 2009; Tsoi *et al.*, 2009) and both found statistically significant relationships. Based on eleven studies, Liang *et al.* (2009) found that risk for colorectal cancer increased significantly by 17% with an increase of 20 cigarettes/day and by 38% with an increase of 40 cigarettes/day, while colorectal cancer mortality increased by 41% and 98%, respectively (Table 2.43 online). The risk elevation associated with an increase of 20 cigarettes/day was greater for rectal than for colon cancer (13% versus 3%) but this difference was not statistically significant.

(c) Duration of smoking

In addition to two previously reported studies (Hsing *et al.*, 1998; Chao *et al.*, 2000), thirteen studies have examined duration of smoking and colorectal cancer risk. A statistically significant trend of increasing risk with increasing duration was found for colorectal (Limburg *et al.*, 2003; Kim *et al.*, 2006; Paskett *et al.*, 2007; Gram *et al.*, 2009), for colon cancer (Paskett *et al.*, 2007) and for rectal cancer (Terry *et al.*, 2002a; Paskett *et al.*, 2007; Tsong *et al.*, 2007). In one study, increasing duration of smoking was significantly associated with risk for colorectal cancer solely in former smokers (Tiemersma *et al.*, 2002a). Based on eight studies (Terry *et al.*, 2002a; Tiemersma *et al.*, 2002a; Limburg *et al.*, 2003; Lüchtenborg *et al.*, 2005a; Kim *et al.*, 2006; Akhter *et al.*, 2007; Paskett *et al.*, 2007; Tsong *et al.*, 2007), a meta-analysis for duration of smoking and colorectal cancer incidence yielded highly significant results (Liang *et al.*, 2009). Risk was increased by 9.4% with a 20-year increase in smoking duration and 19.7% with a 40-year increase. Smoking duration was also significantly associated with risk for rectal cancer but not for colon cancer. In another meta-analysis where dose-response relationship was modelled, a nonlinear increase in risk with

increasing duration was observed ([Botteri et al., 2008a](#)). The risk started to increase after approximately 10 years of smoking and reached statistical significance after 30 years.

(d) *Pack-years*

Since the previous *IARC Monograph*, the association of colorectal cancer with pack-years of cigarette smoking has been evaluated in six studies ([Limburg et al., 2003](#); [Otani et al., 2003](#); [Shimizu et al., 2003](#); [Wakai et al., 2003](#); [Kim et al., 2006](#); [Gram et al., 2009](#)). In addition to the previously reported significant results ([Giovannucci et al., 1994](#); [Heineman et al., 1994](#); [Chao et al., 2000](#); [Stürmer et al., 2000](#)), a statistically significant trend of increasing risk with increasing pack-years was found for colorectal cancer in two studies ([Limburg et al., 2003](#); [Gram et al., 2009](#)), and for colon cancer in one study ([Gram et al., 2009](#)). In their dose-response analysis of pack-years and colorectal incidence, [Liang et al. \(2009\)](#) included five studies ([Giovannucci et al., 1994](#); [Stürmer et al., 2000](#); [Limburg et al., 2003](#); [Otani et al., 2003](#); [Kim et al., 2006](#)) and found a statistically significant trend of increasing risk with increasing pack-years of smoking for colorectal cancer but not specifically for colon or rectal cancer. Risk for colorectal cancer increased by 27% for an increase of 35 pack-years and by 50% for an increase of 60 pack-years.

(e) *Age at initiation*

In nine of the cohort studies the age at smoking initiation in relation to colorectal cancer (eight studies) or colon and rectal cancer (four studies) was investigated. In four studies a statistically significant trend of increasing risk with decreasing age at initiation of smoking for colorectal cancer was found ([Limburg et al., 2003](#); [Kim et al., 2006](#); [Akhter et al., 2007](#); [Gram et al., 2009](#)) and for colon cancer ([Gram et al., 2009](#)) and rectal cancer ([Tsong et al., 2007](#)). In one meta-analysis ([Liang et al., 2009](#)), a highly significant association was found for age at

smoking initiation and colorectal cancer incidence based on six studies ([Limburg et al., 2003](#); [Kim et al., 2006](#); [Akhter et al., 2007](#); [Paskett et al., 2007](#); [Tsong et al., 2007](#); [Gram et al., 2009](#)). Risk for colorectal cancer was reduced by 2.2% for a 5-year delay in smoking initiation and by 4.4% for a 10-year delay.

(f) *Smoking cessation*

The effect of smoking cessation by years since stopping was assessed in seven studies, six for colorectal cancer ([Tiemersma et al., 2002a](#); [Lüchtenborg et al., 2005a, 2007](#); [Paskett et al., 2007](#); [Kenfield et al., 2008](#); [Gram et al., 2009](#); [Hannan et al., 2009](#)) and three for colon and/or rectal cancer ([Wakai et al., 2003](#); [Paskett et al., 2007](#); [Gram et al., 2009](#)). In one study a statistically significant trend in risk reduction with years since quitting was found both overall as well as separately for men and for women ([Hannan et al., 2009](#)).

(g) *Population characteristics*

It has been suggested that the association between smoking and colorectal cancer may be stronger in men than in women. In the three recent cohort studies reporting sex-specific results ([Shimizu et al., 2003](#); [Wakai et al., 2003](#); [Colangelo et al., 2004](#)), this was only observed in studies in Japan ([Shimizu et al., 2003](#); [Wakai et al., 2003](#)), but could be attributed to the very low prevalence of smoking in women. The studies restricted to women have generally shown associations with cigarette smoking that were of comparable magnitude to those observed in men ([Terry et al., 2002a](#); [Limburg et al., 2003](#); [van der Hel et al., 2003a](#); [Paskett et al., 2007](#); [Kenfield et al., 2008](#); [Gram et al., 2009](#)).

Recent studies have been carried out either in Europe and in USA, with predominantly Caucasian study subjects, or in Asia, mostly in Japan and in the Republic of Korea. The results from these studies suggest no differences in the association between tobacco smoking and

colorectal cancer between different ethnic groups.

(h) *Subsites*

Smoking and risks for colon cancer and for rectal cancer were investigated in eleven of the 21 additional studies. Risk patterns are generally consistent between colon and rectal cancer ([Otani et al., 2003](#); [van der Hel et al., 2003a](#); [Wakai et al., 2003](#); [Jee et al., 2004](#); [Yun et al., 2005](#); [Batty et al., 2008](#)). In some studies, dose-response relationships were stronger for rectal cancer than for colon cancer ([Terry et al., 2002a](#); [Paskett et al., 2007](#)) or were statistically significant only for rectal cancer ([Shimizu et al., 2003](#); [Doll et al., 2005](#); [Tsong et al., 2007](#)). In a meta-analysis ([Liang et al., 2009](#)) the association was stronger for rectal cancer than for colon cancer in the subset of cohort studies that differentiated cancer by site. Most dose-response variables were not associated with colon cancer incidence whereas associations were stronger for rectal cancer incidence and statistically significant with longer duration of smoking, albeit based only on a small number of studies. In one cohort study the increased risk associated with smoking was more apparent for proximal than for distal colon cancer ([Lüchtenborg et al., 2005a](#)), which was not found in an earlier study ([Heineman et al., 1994](#)).

(i) *Confounding and effect modification*

Smokers have been shown to be more likely than non-smokers to be physically inactive, to use alcohol, to have lower consumption of fruits and vegetables and higher consumption of fat and meat, and they are less likely to be screened for colorectal cancer ([Le Marchand et al., 1997](#); [Ghadirian et al., 1998](#); [Nkondjock & Ghadirian, 2004](#); [Reid et al., 2006b](#); [Mutch et al., 2009](#)).

Few potential confounders were considered in the cohort studies evaluated in the previous IARC Monograph ([IARC, 2004a](#)). Of the cohort studies published since, all except three ([van der Hel et al., 2003a](#); [Jee et al., 2004](#); [Doll et al., 2005](#))

considered two or more potential confounders. In eleven of the recent studies adjustments were made for physical activity, alcohol consumption, overweight/obesity ([Terry et al., 2002a](#); [Limburg et al., 2003](#); [Otani et al., 2003](#); [Wakai et al., 2003](#); [Yun et al., 2005](#); [Akhter et al., 2007](#); [Ashktorab et al., 2007](#); [Paskett et al., 2007](#); [Tsong et al., 2007](#); [Kenfield et al., 2008](#); [Hannan et al., 2009](#)), and seven also adjusted for dietary habits (e.g. intake of fruits and vegetables, dietary fibres, fat, red meat). Among the studies with the latter adjustments, eight ([Giovannucci et al., 1994](#); [Chao et al., 2000](#); [Stürmer et al., 2000](#); [Limburg et al., 2003](#); [Yun et al., 2005](#); [Akhter et al., 2007](#); [Paskett et al., 2007](#); [Hannan et al., 2009](#)) found significant dose-response relationships with at least one of the smoking variables. In two studies a significant association of smoking with colorectal cancer risk was observed after accounting for history of colonoscopy ([Paskett et al., 2007](#); [Hannan et al., 2009](#)). Risk factors in multivariable analyses in several studies were level of education, use of menopausal hormone therapy, family history and regular aspirin use. The association between smoking and colorectal cancer was not modified by these other characteristics, or by alcohol consumption in two studies ([Otani et al., 2003](#); [Tsong et al., 2007](#)). Therefore, confounding factors do not seem to affect the observed significant increase in risk for colorectal cancer associated with tobacco smoking and the dose-response relationships with smoking variables.

When considering other types of smoking, it is generally found that cigar and pipe smoking are less associated with socioeconomic class and other life-style habits than cigarette smoking. Therefore, it is logical to assume that, for these types of smoking, risk associations derived from epidemiologic studies may be less prone to potential confounding. In all the cohort studies reviewed in the previous IARC Monograph ([IARC, 2004a](#)) an elevated, though not always statistically significant, risk was consistently reported for cancers of the colon and the rectum

associated with exclusive pipe and/or cigar smoking.

Infection with JC virus has been proposed as a potential risk factor for colon cancer ([Rollison et al., 2009](#)) but results still need further validation.

Three cohort studies assessed possible modifying effects by genetic susceptibility. Rapid acetylator phenotype (as determined by polymorphisms of the *NAT2* gene involved in metabolism of heterocyclic aromatic amines) was found to increase the risk for colorectal cancer in smokers, in one ([van der Hel et al., 2003a](#)) but not in another study ([Tiemersma et al., 2002a](#)). For genes involved in the metabolism of polycyclic aromatic hydrocarbons such as *GSTM1* or *GSTT1*, no statistical contribution to the risk of colorectal cancer associated with smoking was observed ([Tiemersma et al., 2002a](#); [Lüchtenborg et al., 2005a](#)).

2.6.3 Case-control studies

Thirty-one case-control studies were included in the previous *IARC Monograph* ([IARC, 2004a](#)). Although results were inconsistent with respect to risk association in ever versus former and current smokers, a dose-response relationship with smoking variables was found in some studies. Since then, seventeen case-control studies investigating the association between tobacco smoke and colorectal cancer risk have been published, seven carried out in Asia, four in Europe, five in North America and one in Hawaii (Table 2.44 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.44.pdf>). Six studies reported solely for colorectal cancer ([Ateş et al., 2005](#); [Chia et al., 2006](#); [Verla-Tebit et al., 2006](#); [Lüchtenborg et al., 2007](#); [Steinmetz et al., 2007](#); [Wu et al., 2009b](#)), four separately for colon and rectal cancer ([Ji et al., 2002](#); [Sharpe et al., 2002](#); [Minami & Tateno, 2003](#); [Goy et al., 2008](#)), two for colorectal cancer as well as for colon and rectal cancer ([Ho et al., 2004](#); [Gao](#)

[et al., 2007](#); [Wei et al., 2009](#)), three for colon cancer only ([Diergaarde et al., 2003](#); [Kim et al., 2003](#); [Hu et al., 2007](#)) and one for rectal cancer only ([Slattery et al., 2003](#)). Nine of the studies reported risk estimates separately for men and for women.

(a) Smoking status

Most case-control studies considered the effects of current and former smoking separately. A positive association between smoking and colorectal cancer was found in virtually all the studies, although the results were generally not statistically significant. Statistically significant increased risk was reported in current smokers for colorectal cancer ([Chia et al., 2006](#); [Wu et al., 2009b](#)), for rectal cancer ([Slattery et al., 2003](#); [Ho et al., 2004](#)), and in former smokers for colorectal cancer both in men and women combined ([Chia et al., 2006](#)) and in women only ([Lüchtenborg et al., 2007](#)). Five studies, which did not focus on the main effects of smoking, only evaluated risks for ever smoking ([Diergaarde et al., 2003](#); [Kim et al., 2003](#); [Ateş et al., 2005](#); [Gao et al., 2007](#); [Hu et al., 2007](#)); none of these reported significant risk estimates.

(b) Intensity of smoking

Nine case-control studies investigated dose-response relationships considering at least one smoking variable. Number of cigarettes smoked daily was evaluated in seven studies, three for colorectal cancer ([Verla-Tebit et al., 2006](#); [Lüchtenborg et al., 2007](#); [Wu et al., 2009b](#)), two for colon and rectal cancer ([Ji et al., 2002](#); [Minami & Tateno, 2003](#)), one for rectal cancer ([Slattery et al., 2003](#)) and one for colorectal cancer and both subsites ([Ho et al., 2004](#)). Statistically significant positive trends of increasing risk with increasing number of cigarettes smoked daily were found for colorectal cancer in only one study ([Wu et al., 2009b](#)).

(c) *Duration of smoking, pack-years, age at initiation, smoking cessation*

Duration of smoking was examined in several studies in relation to colorectal cancer ([Ho et al., 2004](#); [Chia et al., 2006](#); [Verla-Tebit et al., 2006](#); [Lüchtenborg et al., 2007](#); [Wu et al., 2009b](#)) and/or to colorectal cancer by subsite ([Ji et al., 2002](#); [Minami & Tatenno, 2003](#); [Ho et al., 2004](#)). A statistically significant trend with increasing number of years smoked was found in two of the five studies of colorectal cancer ([Chia et al., 2006](#); [Wu et al., 2009b](#)). In one study, increasing duration of smoking was significantly associated with risk for rectal cancer in ever smokers but not in current smokers ([Ho et al., 2004](#)). In only one earlier case-control study was a significant association in ever smokers with increasing number of years of smoking for colon as well as rectal cancer found ([Newcomb et al., 1995](#)).

Duration of smoking exposure was assessed by pack-years of smoking in seven studies ([Ji et al., 2002](#); [Slattery et al., 2003](#); [Chia et al., 2006](#); [Verla-Tebit et al., 2006](#); [Lüchtenborg et al., 2007](#); [Goy et al., 2008](#); [Wu et al., 2009b](#)) and by age at smoking initiation in three studies ([Ji et al., 2002](#); [Slattery et al., 2003](#); [Wu et al., 2009b](#)). All four studies that evaluated pack-years of smoking with respect to colorectal cancer risk found statistically significant associations. Two studies found a significant association with increasing pack-years in men and women combined; when investigated separately, the increasing trend was statistically significant only in women ([Verla-Tebit et al., 2006](#)) or only in men ([Wu et al., 2009b](#)). In one study a statistically significant trend with pack-years of smoking in both men and women was found only with non-filtered cigarettes ([Lüchtenborg et al., 2007](#)); the relative risk was significant for colon as well as rectal cancer and was greater for rectal cancer.

In two studies a non-significant trend of decreasing risk with increasing time since

stopped smoking was found ([Verla-Tebit et al., 2006](#); [Lüchtenborg et al., 2007](#)).

(d) *Subsites and molecular subtypes*

A stronger association between tobacco smoking and rectal cancer compared with colon cancer has generally been observed in the studies that reported risk estimates by cancer site. In a recent meta-analysis including both cohort and case-control studies, higher smoking-related risk estimates for rectal cancer were found than for proximal and distal colon cancer ([Botteri et al., 2008a](#)). Stronger relative risk in ever smokers, but not in current smokers, was found for proximal compared to distal tumours in one recent study ([Hu et al., 2007](#)).

Colorectal cancer is a multipathway disease. A molecular approach to its classification utilizes: (1) the type of genetic instability, specifically microsatellite instability, and (2) the presence of DNA methylation or the CpG island methylator phenotype (CIMP) ([Jass, 2007](#)). Smoking has been associated with microsatellite instability in sporadic colon cancer. Higher risk for microsatellite-unstable than for microsatellite-stable tumours was found in four studies ([Slattery et al., 2000](#); [Yang et al., 2000](#); [Chia et al., 2006](#); [Campbell et al., 2009](#)). The observed twofold risk elevation for colorectal cancer showing microsatellite instability is similar in order of magnitude to that found for colorectal polyps. In only one small study similar risk estimates for stable and unstable tumours were found ([Diergaarde et al., 2003](#)). Microsatellite instability is characteristic of hereditary nonpolyposis colorectal cancer syndrome and smoking has been associated with colorectal cancer in patients with this syndrome ([Watson et al., 2004](#); [Diergaarde et al., 2007](#)). Among sporadic colorectal tumours with microsatellite instability, about 11–28% carry somatic genetic mutations. In addition, the association of colon cancer with smoking was increased two to threefold when widespread CIMP and/or *BRAF* mutation, irrespective of microsatellite instability

status, was present ([Samowitz et al., 2006](#)). These data indicate that the association with MSI-high tumours may be attributed to the association of smoking with CIMP and *BRAF* mutation.

(e) *Effect modification*

Effect modification by genetic polymorphisms in enzymes metabolizing tobacco smoke constituents could provide further evidence for a causal association between smoking and colorectal cancer. Most studies that have investigated modification of colorectal cancer risk associated with smoking by genetic polymorphisms of xenobiotic enzymes were too small to be informative ([Inoue et al., 2000](#); [Smits et al., 2003](#); [Jin et al., 2005](#); [Tranah et al., 2005](#); [van den Donk et al., 2005](#); [Tijhuis et al., 2008](#)). Studies on the possible differential effect by acetylation status have reported stronger association of tobacco smoking (in terms of pack-years) with colorectal cancer risk in slow acetylators phenotypes ([Lilla et al., 2006](#)), and with rectal cancer in rapid acetylators phenotypes ([Curtin et al., 2009](#)). Furthermore, *CYP1A1* and *GSTM1* variant alleles were found to greatly affect colon cancer or rectal cancer risk in smokers ([Slattery et al., 2004](#)).

2.6.4 Colorectal polyps

Colorectal adenomas and possibly some hyperplastic polyps are considered precursors of colorectal cancer. The epidemiologic evidence on the relationship between cigarette smoking and colorectal polyps has been generally consistent. Since the previous *IARC Monograph* ([IARC, 2004a](#)), twelve further independent studies have investigated this association (Table 2.45 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.45.pdf>). All studies found a significantly increased risk for polyps in association with one or more smoking variables. A recent meta-analysis including 42 studies reported a statistically significant positive association between smoking and colorectal adenomas

([Botteri et al., 2008b](#)). The meta-analysis, which included several studies that did not explicitly report relative risks for tobacco smoking ([Cardoso et al., 2002](#); [Voskuil et al., 2002](#); [Sparks et al., 2004](#); [Gong et al., 2005](#); [Jiang et al., 2005](#); [Kim et al., 2005](#); [Mitrou et al., 2006](#); [Otani et al., 2006](#); [Skjelbred et al., 2006](#)), found a twofold risk elevation for colorectal adenomas in current smokers and a 50% increase in former smokers. The association had been previously found to be equally strong in men and women. In one of two recent studies, there was no difference in the results for men and women separately ([Tranah et al., 2004](#)) but significantly greater effects in women were found in the other ([Hermann et al., 2009](#)).

Significant positive trends with number of cigarettes per day were found in four ([Ji et al., 2006](#); [Larsen et al., 2006](#); [Stern et al., 2006](#); [Shrubsole et al., 2008](#)) of five studies ([Tiemersma et al., 2004](#)). Dose-response with duration of smoking was assessed in four studies ([Ji et al., 2002](#); [Tiemersma et al., 2004](#); [Stern et al., 2006](#); [Shrubsole et al., 2008](#)) and with pack-years of smoking in five studies ([Hoshiyama et al., 2000](#); [Ulrich et al., 2001](#); [Tranah et al., 2004](#); [Ji et al., 2006](#); [Shrubsole et al., 2008](#); [Omata et al., 2009](#)). All nine studies found statistically significant trends, which were consistent with those for adenomas and hyperplastic polyps when reported separately ([Ulrich et al., 2001](#); [Ji et al., 2006](#); [Shrubsole et al., 2008](#)). Ever smokers were estimated to have a 13% (95%CI: 9–18%) increasing risk of presenting with adenomatous polyps for every additional 10 pack-years smoked in comparison to never smokers, based on data from 19 studies ([Botteri et al., 2008b](#)).

Decreasing risks with years since quitting smoking were found in four studies ([Ulrich et al., 2001](#); [Tiemersma et al., 2004](#); [Ji et al., 2006](#); [Shrubsole et al., 2008](#)), statistically significant so in the latter three studies. In comparison to never smokers, former smokers retained moderately elevated risk for colorectal polyps even 20

years after quitting smoking. One study examined both dose metrics (cigarettes per day, duration, and pack-years) and recency of tobacco use: in subjects who had quit smoking for at least 20 years, only the heaviest users of tobacco still had modest excess risks ([Ji et al., 2006](#)).

It has been proposed that the association between cigarette smoking and polyps may be stronger with non-progressing adenomas, such as those that are smaller and less villous but the hypothesis is not supported in most studies ([Anderson et al., 2003](#); [Toyomura et al., 2004](#); [Ji et al., 2006](#); [Skjelbred et al., 2006](#)). In one study a clearly higher risk for large and multiple adenomas in every anatomic site of the colon was found in a dose-response manner ([Toyomura et al., 2004](#)). A meta-analysis found that the combined risk estimate for high-risk adenomas associated with smoking was greater than that for low-risk adenomas and that the difference was statistically significant for current smokers but not former smokers ([Botteri et al., 2008b](#)). In addition, a stronger association of smoking with hyperplastic polyps than with adenomas was found in some studies ([Ulrich et al., 2001](#); [Ji et al., 2006](#); [Shrubsole et al., 2008](#)) but not in another ([Erhardt et al., 2002](#)). The risk associated with smoking may be even higher in subjects presenting with concurrent benign hyperplastic and adenomatous polyps ([Ji et al., 2006](#); [Shrubsole et al., 2008](#)).

Relative risk estimates for tobacco smoking and polyps generally range between 2 and 3 whereas those for colorectal cancer range between 1.2 and 1.4. One possible explanation is the effect dilution due to the inclusion of a high proportion of individuals with precursor lesions in the unscreened control groups in most colorectal cancer studies ([Terry & Neugut, 1998](#)). Some indirect evidence for this hypothesis is provided by the meta-analysis of colorectal adenomas, which showed that the smoking-associated risk for adenomas was significantly higher in studies including subjects who had undergone complete

colonoscopy in comparison to those in which some or all controls had undergone incomplete examination (i.e. only sigmoidoscopy) ([Abrams et al., 2008](#); [Botteri et al., 2008b](#)).

It is also possible that smoking is associated with a subset of colorectal cancers so that relative risk estimates for colorectal cancer as a whole are diluted. The pattern of risk observed for colorectal cancer by microsatellite instability status and for type of colorectal polyps suggests that the traditional (non-serrated) adenoma-carcinoma sequence may proceed through a hyperplastic polyps-mixed polyps-serrated adenoma progression and that smoking may be more strongly related to the development of these subtypes ([Jass et al., 2000](#); [Hawkins & Ward, 2001](#)). More recently, a *BRAF* mutation was shown to be a specific marker for the serrated polyp neoplasia pathway originating from a hyperplastic polyp, in which the CIMP-high develops early and the microsatellite instability carcinoma develops late ([O'Brien et al., 2006](#)). The findings of strong associations between smoking and colon cancer with CIMP and/or *BRAF* mutation, irrespective of microsatellite status, are compatible with this observation ([Samowitz et al., 2006](#)).

2.7 Hepatocellular carcinoma

2.7.1 Overview of studies

In the previous *IARC Monograph* ([IARC, 2004a](#)), a causal relationship between liver cancer (hepatocellular carcinoma) and smoking was established. Two case-control and one cohort studies have been published since (Table 2.46 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.46.pdf>). Overall, most cohort studies and the largest case-control studies, most notably those that included community controls, showed a moderate association between tobacco smoking and risk for hepatocellular carcinoma.

Confounding from alcohol has been addressed in the best studies. The association between alcohol drinking and hepatocellular carcinoma is strong, and alcohol intake is frequently misclassified, leading to potential residual confounding. However an association with smoking has been demonstrated also among non-drinkers.

A meta-analysis was based on 38 cohort studies and 58 case-control studies ([Lee et al., 2009](#)). Compared to never smokers, the meta-relative risks adjusted for appropriate confounders were 1.51 (95%CI: 1.37–1.67) for current smokers and 1.12 (0.78–1.60) for former smokers. The increased liver cancer risk among current smokers appeared to be consistent in strata of different regions, study designs, study sample sizes, and publication periods. The association with smoking was observed in non-alcohol-drinkers (RR, 1.34; 95%CI: 0.92–1.94 in men and 1.31; 95%CI: 0.70–2.44 in women). Further supportive evidence is provided by the association between smoking and liver cancer observed among Chinese women and Japanese women, in whom alcohol drinking is extremely rare ([Li et al., 2011](#)). One difficulty is that sometimes studies do not specify the histology of liver cancer (hepatocellular versus intra-hepatic biliary tract).

In the update of the Whitehall study ([Batty et al., 2008](#)) (a cohort of 17363 government employees in London, followed-up for 38 years), the hazard ratio for death from liver cancer was 1.03 (0.49–2.16) in former smokers and 1.43 (0.69–2.95) in current smokers (based on 57 deaths). In the 50-year follow-up of the British doctors cohort ([Doll et al., 2005](#)), there were 74 deaths from liver cancer. Death rates per 100000 per year were 4.4 in never smokers, 10.7 in smokers of 1–14 cigarettes/day, 2.6 in smokers of 15–24 cigarettes/day, and 31.3 in smokers of ≥ 25 cigarettes/day.

2.7.2 Factors affecting risks

(a) Dose-response relationship

Most studies, including the recent ones (Table 2.46 online), show a dose-response relationship with the number of cigarettes smoked and with smoking duration, with exceptions such as [Franceschi et al. \(2006\)](#) and some older studies from Asia. Relative risk estimates increased to 2.0 after 20 years of smoking.

(b) Cessation

Though former smokers tend to have lower relative risks than current smokers, there were no consistent patterns of risks after cessation, including in the recent studies (Table 2.46 online).

2.7.3 Interaction with hepatitis B or C

Infection with hepatitis B virus (HBV) is one of the major causes of liver cancer worldwide, whereas hepatitis C virus (HCV) infection causes a large fraction of liver cancer in Japan, Northern Africa and southern Europe. While many studies, most notably from Asia, have found no attenuation of the association between smoking and liver cancer after adjustment/stratification for markers of HBV or HCV infection, an apparent interaction between smoking and HBV or HCV infection has been reported. The increase in risk for liver cancer associated with cigarette smoking appears to be greater among HBV carriers than among uninfected persons in some studies ([Tu et al., 1985](#)), but not in others ([Kuper et al., 2000a](#)). Two recent reports ([Franceschi et al., 2006](#); [Hassan et al., 2008a](#)) studied possible interactions between smoking and hepatitis virus infection and both reported an apparent interaction between smoking and hepatitis C infection. Interactions between smoking and hepatitis B infection were not found among men in one study ([Hassan et al., 2008a](#)) and the rarity of HBsAg prevented the evaluation of HBV and smoking in the other ([Franceschi et al., 2006](#);

Table 2.46 online). In the meta-analysis by [Lee et al. \(2009\)](#) adjustment for HBV reduced the relative risks in both men and women, while adjustment for HCV did not change the risk in women and increased it in men.

2.8 Renal cell carcinoma

2.8.1 Overview of studies

The previous *IARC Monograph* ([IARC, 2004a](#)) concluded that renal-cell carcinoma is associated with tobacco smoking in both men and women. Four case-control studies and no cohort studies have become available since then (Table 2.47 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.47.pdf>). Overall these confirm the previous evidence, though with some conflicting results. In particular, both the study by [Hu et al. \(2005\)](#) in Canada and the multicentre European study by [Brennan et al. \(2008\)](#) do not show a clear effect of smoking. In contrast, the study by [Theis et al. \(2008\)](#) shows an increased risk with smoking duration (irregular, levelling-off after 40 years) and a statistically significant dose-response relationship with pack-years.

In the update of the Whitehall study ([Batty et al., 2008](#)) (a cohort of 17363 government employees in London, followed for 38 years), the hazard ratio for deaths from kidney cancer was 0.64 (0.32–1.26) for former smokers, and 1.29 (0.69–2.41) for current smokers (based on 68 deaths). In the 50-year follow-up of the British doctor cohort ([Doll et al., 2005](#)) there were 140 deaths from kidney cancer. Mortality rates per 100000 per year were 9.3 in never smokers, 16.4 in smokers of 1–14 cigarettes/day, 16.6 in smokers of 15–24 cigarettes/day, and 15.5 in smokers of ≥ 25 cigarettes/day (age-adjusted).

[Hunt et al. \(2005\)](#) performed a meta-analysis based on 19 case-control studies and 5 cohort studies (total 8032 cases in case-control and 1326 in cohort studies). The relative risk for smoking

men was 1.54 (1.42–1.68), and for smoking women was 1.22 (1.09–1.36). A dose-response relationship was found in both men and women. The association observed was more convincing in population-based compared to hospital-based studies.

2.8.2 Confounding

Hypertension is a well established risk factor for kidney cancer but the association with smoking is only indirect. Potential confounding from hypertension was considered only by [Brennan et al. \(2008\)](#).

Other potential confounders such as BMI have been appropriately addressed in most studies.

2.8.3 Cessation

Most studies reviewed in the previous *Monograph* showed a lower risk for former smokers compared to current smokers, with a significant negative trend with increasing number of years since quitting ([IARC, 2004a](#)). In case-control study on smoking cessation and renal-cell carcinoma, the decrease in risk became significant only after 30 years of quitting ([Parker et al., 2003](#)). In the meta-analysis ([Hunt et al., 2005](#)), former smokers were at reduced risk after 10 years or more of quitting. A clear decline in risk after cessation was also reported by [Theis et al. \(2008\)](#). [The Working Group noted the poor quality of the study, considering the low response rate among controls.]

2.9 Cancer of the lower urinary tract (including cancer of the bladder, ureter, and renal pelvis)

2.9.1 Overview of studies

The previous *IARC Monograph* ([IARC, 2004a](#)) clearly identified a causal relationship of smoking with transitional-cell carcinomas and squamous-cell carcinomas of the bladder, ureter and renal pelvis both in men and women. Two new case-control studies ([Cao et al., 2005](#); [Samanic et al., 2006](#); Table 2.48 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.48.pdf>) and two cohort studies ([Bjerregaard et al., 2006](#); [Alberg et al., 2007](#); Table 2.49 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.49.pdf>) have been reported since then in addition to updates of cohort studies with longer follow-up.

In the update of the Whitehall study ([Batty et al., 2008](#)) (a cohort of 17363 government employees in London, followed-up for 38 years), the hazard ratio for death from bladder cancer was 0.98 (0.62–1.54) in former smokers and 1.66 (1.06–2.59) in current smokers (based on 164 deaths). In the 50-year follow-up of the British doctors cohort ([Doll et al., 2005](#)), there were 220 deaths from bladder cancer. Death rates per 100000 per year were 13.7 in never smokers, 37.7 in smokers of 1–14 cigarettes/day, 31.8 in smokers of 15–24 cigarettes/day, and 51.4 in smokers of ≥ 25 cigarettes/day. All the new studies confirm the existence of a dose-response relationship with the number of cigarettes smoked and with duration, and a decline in relative risk with time since quitting smoking, compared to non-quitters.

2.9.2 Types of tobacco

The risk of lower urinary tract cancer was more strongly associated with smoking air-cured (black) tobacco than smoking flue-cured

(blond) tobacco in several studies ([IARC, 2004a](#)). The stronger association with air-cured (black) than blond tobacco among current smokers has not been clearly confirmed in a re-analysis of the Spanish multicentre case-control study ([Samanic et al., 2006](#)). Relative risks in current smokers were 7.3 (4.9–10.9) in black tobacco smokers and 5.8 (3.4–10.0) in blond tobacco smokers; in former smokers, 4.2 (2.9–6.0) for black tobacco and 1.8 (1.0–3.2) for blond tobacco (Table 2.48 online). The effect of cessation was more pronounced in blond tobacco smokers than in black tobacco smokers, suggesting potentially different mechanisms of action of the two types of tobacco. Air-cured (black) tobacco is richer in arylamines.

2.9.3 Gene-environment interactions

A large number of studies have considered gene-environment interactions between tobacco smoking and genetic polymorphisms, including DNA repair genes ([Vineis et al., 2009](#)) and genes involved in carcinogen metabolism ([Malats, 2008](#); [Dong et al., 2008](#)). Overall, there is evidence that the slow acetylator variant of the *NAT2* gene is involved in bladder carcinogenesis and may interact with smoking. The meta-relative risk for *NAT2* slow acetylator and bladder cancer was 1.46 (95%CI: 1.26–1.68; $P = 2.5 \times 10^{-7}$), based on 36 studies and 5747 cases ([Dong et al., 2008](#)). Similar but weaker evidence has been provided for *GSTM1* ([Malats, 2008](#)).

The extent of interaction between *NAT2* variants and smoking is still unclear. In one study the *NAT2* acetylation status was found to modulate the association of bladder cancer and cigarette smoking through smoking intensity and not smoking duration ([Lubin et al., 2007](#)). Studies are not consistent concerning the three-way association between smoking intensity, *NAT2* and bladder cancer. Some studies found greater effects at a lower level of exposure and others the opposite ([Malats, 2008](#)). Genome-wide

association studies have indicated 8q24 as a region that may confer high risk for bladder cancer ([Kiemenev et al., 2008](#)).

2.10 Myeloid leukaemia (acute and chronic)

Myeloid leukaemia in adults was observed to be causally related to cigarette smoking in the previous *IARC Monograph* ([IARC, 2004a](#)). Risk increased with amount of tobacco smoked in a substantial number of adequate studies, with evidence of a dose–response relationship. Biological plausibility for a causal relationship of smoking with myeloid leukaemia is provided by the finding of known leukaemogens in tobacco smoke, one of which (benzene) is present in relatively large amounts. No evidence was found for an association with acute lymphocytic leukaemia.

One recently published cohort study included information on acute and chronic myeloid leukaemias ([Fernberg et al., 2007](#)), based on 372 incident cases. A weak association was found between acute myeloid leukaemia and intensity of smoking, and a statistically significant association with current smoking (RR, 1.5; 95%CI: 1.06–2.11). No association was found with chronic myeloid leukaemia.

In the update of the Whitehall study ([Batty et al., 2008](#)) (a cohort of 17363 government employees in London, followed-up for 38 years), the hazard ratio for mortality from myeloid leukaemias (acute plus chronic) was 5.08 (95%CI: 1.78–14.5) for current smokers, and 3.84 (95%CI: 1.35–11.0) for former smokers (based on 66 deaths). In the 50-year follow-up of the British doctors cohort ([Doll et al., 2005](#)), there were 100 deaths from myeloid leukaemias. The mortality rates per 100000 per year were 6.3 in never smokers, 2.8 in smokers of 1–14 cigarettes/day, 14.0 in smokers of 15–24, and 18.3 in smokers of ≥ 25 cigarettes/day (age-adjusted).

2.11 Other leukaemias and lymphomas

2.11.1 Non-Hodgkin lymphoma

Six cohort studies have been published on the association between non-Hodgkin lymphoma and smoking, all reviewed in the previous *IARC Monograph* ([IARC, 2004a](#)). In five of these, no increased risk among smokers was evident ([Doll et al., 1994](#); [McLaughlin et al., 1995](#); [Adami et al., 1998](#); [Herrinton & Friedman, 1998](#); [Parker et al., 2000](#)). However, in one study, men who had ever smoked cigarettes had a twofold increase in risk for non-Hodgkin lymphoma, and the risk was still higher among the heaviest smokers ([Linnet et al., 1992](#)). Data from case–control studies generally also fail to support an effect of smoking on the incidence of non-Hodgkin lymphoma ([Peach & Barnett, 2001](#); [Stagnaro et al., 2001](#); [Schöllkopf et al., 2005](#); [Bracci & Holly, 2005](#); Table 2.50 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.50.pdf>). Reanalysis of data of an Italian study ([Stagnaro et al., 2004](#)) found a statistically significant association (OR, 1.4; 95%CI: 1.1–1.7) for blond tobacco exposure and non-Hodgkin lymphoma risk.

Three studies and a pooled analysis have examined histological subtypes of non-Hodgkin lymphoma. In one cohort study in women, smoking was associated with increased risk for follicular non-Hodgkin lymphoma ([Parker et al., 2000](#)). Similarly, two other studies reported a weak positive association between smoking and risk for follicular lymphoma, but no effect for other histological types ([Herrinton & Friedman, 1998](#); [Stagnaro et al., 2001](#)). A large pooled analysis based on nine North-American and European case–control studies found an overall odds ratio of 1.07 (95%CI: 1.0–1.15) for smokers; the association was particularly strong for follicular lymphoma (OR, 1.31; 95%CI: 1.12–1.52) ([Morton et al., 2005](#)).

2.11.2 Hodgkin lymphoma

In the previous *IARC Monograph* ([IARC, 2004a](#)) seven studies on the association between Hodgkin lymphoma and smoking were examined and null or weakly positive associations were noted. Among studies published since, a positive association was observed in two case-control ([Willett et al., 2007](#); [Kanda et al., 2009](#)) and three cohort studies ([Nieters et al., 2006](#); [Lim et al., 2007](#); [Nieters et al., 2008](#)), while one study found no clear association ([Monnereau et al., 2008](#)). Several other recent studies also reported a positive association, but with some internal inconsistencies. In a European multicentre case-control study, no association was observed between tobacco and Hodgkin lymphoma for subjects below age 35 years, whereas for older subjects, ever-smokers experienced a doubled risk of Hodgkin lymphoma as compared to never smokers ([Besson et al., 2006](#)). In contrast, a positive association was observed in young adults participating in the International Twin Study ([Cozen et al., 2009](#)). A positive association was observed in a Scandinavian case-control study, but without a clear dose-response ([Hjalgrim et al., 2007](#)). In a case-control study addressing infectious precursors, particularly Epstein-Barr virus (EBV), an increased risk for EBV-positive Hodgkin lymphoma was found among current smokers ([Glaser et al., 2004](#); Table 2.50 online).

Several of the above studies found positive associations for Hodgkin lymphoma while also demonstrating null or inverse associations with non-Hodgkin lymphoma ([Nieters et al., 2006](#); [Lim et al., 2007](#); [Nieters et al., 2008](#); [Kanda et al., 2009](#)).

2.11.3 Multiple myeloma

In the previous *IARC Monograph* ([IARC, 2004a](#)), the large majority of studies on tobacco smoking and risk for multiple myeloma evaluated showed no clear association. More recently,

two case-control studies found a positive association ([Vlajinac et al., 2003](#); [Nieters et al., 2006](#)), whereas no clear association was observed in another case-control study ([Monnereau et al., 2008](#)) or in a cohort study in Sweden ([Fernberg et al., 2007](#); Table 2.51 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.51.pdf>).

2.12 Cancer of the breast

Approximately 150 epidemiological studies have been published on the relationship between breast cancer and active and passive smoking. The results from these studies have been comprehensively examined in peer-reviewed literature ([Palmer & Rosenberg, 1993](#); [Terry et al., 2002a](#); [Johnson et al., 2002](#); [Johnson, 2005](#); [Terry & Goodman, 2006](#); [Miller et al., 2007](#)). The previous *IARC Monograph* ([IARC, 2004a](#)) considered studies conducted through June 2002 and concluded that there is evidence suggesting lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast.

Other consensus reviews have drawn different conclusions, based partly on the availability of new data, and partly on differences in interpretation:

- The 2001 US Surgeon General Report on Women and Smoking (Department of Health & Human Services, 2001) concluded that tobacco smoking does not appear to appreciably affect breast cancer risk overall. However, several issues were not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether exposure to second-hand smoke affects risk.
- The 2004 US Surgeon General report on “The Health Consequences of Smoking” (Department of Health & Human

Services, 2004) concluded the evidence is suggestive of no causal relationship between tobacco smoking and breast cancer.

- The 2009 Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk ([Collishaw et al., 2009](#)) concludes that based on the weight of evidence from epidemiological and toxicological studies and understanding of biological mechanisms, the associations between tobacco smoking and both pre- and post-menopausal breast cancer are consistent with causality.

The lack of agreement in the conclusions from these groups is not surprising, given that the observed associations are weaker and less consistent for breast cancer than for other tobacco-related cancers. Furthermore, several methodological considerations could either obscure a small increase in risk caused by tobacco smoking, or alternatively introduce a spurious association where no causal relationship exists.

2.12.1 Methodological and related issues

The principal concerns about studies of tobacco smoking and breast cancer are the following: timing of exposure, the relevant disease endpoint, the potential for confounding by factors associated with both smoking and the occurrence/detection of breast cancer, the hypothesis that tobacco smoking may have opposing effects on breast cancer risk (protective and detrimental), and the hypothesis that some women may be genetically more susceptible to develop breast cancer from smoking, and that increased risk in these subgroups may be obscured in analyses of average risk in the population.

(a) Misclassification of exposure

Self-reported information on tobacco smoking is generally considered more reliable than questionnaire information on exposure to second-hand tobacco smoke. However, studies of tobacco smoking have not uniformly considered the duration of smoking (years), the average amount smoked (cigarettes/day), or the timing of initiation in relation to first full-term pregnancy. Only one ([Al-Delaimy et al., 2004](#)) of the seven available cohort studies updated the information on smoking behaviour during follow-up. Whereas some exposure variables, such as age at initiation and age at first full-term pregnancy remain constant over time, others, such as smoking status, duration and age at cessation do not. Furthermore, the average age at initiation and duration of smoking are highly correlated with birth cohort and attained age. While the number of years of smoking before first full term pregnancy has been proposed as a potentially relevant measure of exposure, the range of this variable is constrained except among women whose first pregnancy occurs at an older age, which is itself an independent risk factor for breast cancer.

(b) Specificity of disease endpoints

Breast cancer is not a single disease. Accordingly, some researchers have postulated that exposure to tobacco smoke (from tobacco smoking or second-hand tobacco smoke) could differentially affect certain clinical subtypes of breast such as pre- or post-menopausal cancers or tumours with or without hormonal receptors. It is also possible that smoking might affect the survival of women with breast cancer, whether or not it affects incidence rates. Most published studies have measured incidence rates as the endpoint, although some have measured mortality rates or effects on survival.

(c) Confounding

Alcohol consumption is positively correlated with tobacco smoking ([Marshall et al., 1999](#)) and is an established cause of breast cancer ([IARC, 2010a](#); *Monograph on Consumption of Alcoholic Beverages* in this Volume). Most epidemiologic studies attempt to control for alcohol consumption using questionnaire information on usual drinking patterns. This approach is vulnerable to residual confounding, because self-reported data on lifetime alcohol consumption leave room for misclassification. Potential confounding by alcohol consumption is of greater concern for current than for former smokers, since, on average, current smokers drink more than former smokers ([Reynolds et al., 2004a, b](#)). One study by the Collaborative Group on Hormonal Factors and Breast Cancer ([Hamajima et al., 2002](#)) controlled rigorously for alcohol consumption by restricting the analysis of smoking and breast cancer to women who reported drinking no alcohol.

Conversely, mammography screening can be a negative confounder in studies of tobacco smoking and breast cancer incidence. Few studies of tobacco smoking in relation to breast cancer have controlled for mammography screening. Current smokers report a lower frequency of mammographic screening than never-smokers, whereas health conscious former smokers report higher screening rates ([Gross et al., 2006](#)). Mammography screening affects the detection rather than the occurrence of breast cancer; it detects some tumours that might otherwise never have been recognized and allows earlier diagnosis of others, thereby increasing breast cancer incidence in the short-term. The consequence of uncontrolled confounding by mammography screening would be to underestimate an association between current smoking and breast cancer incidence, and to overestimate the association in former smokers. Confounding by screening

would be expected to have the opposite effect in studies of breast cancer mortality.

Other correlates of tobacco smoking might also confound a potential association between tobacco smoking and breast cancer, although their net effect is likely to be smaller and harder to predict than confounding by alcohol and mammography screening. Women who smoke undergo menopause about two to three years earlier than never-smokers ([Baron et al., 1990](#)). The effect of this may be partly or wholly offset by the greater likelihood of girls who experience early menarche to initiate smoking in early adolescence ([Jean et al., 2011](#)). There is no documentation that smokers and never-smokers differ with respect to average years of ovulation. Tobacco smoking also has a complex relationship to body mass index. Post-menopausal women who smoke are less likely to be overweight or obese than former or never smokers, but overweight adolescent girls are more likely to begin smoking for weight control ([Fine et al., 2004](#)). Similarly complex relationships exist between smoking and physical activity. Current smokers report less physical activity than either former or never smokers ([Kaczynski et al., 2008](#); [Troost et al., 2002](#)), but only a small proportion of the population engages in the vigorous physical activity that is needed to protect against breast cancer. The socioeconomic correlates of smoking have changed over time. Women who attended college during the 1960s and 1970s were more likely to initiate smoking than less educated women, but subsequently college-educated women have been more likely to quit. Thus, the potential for confounding by reproductive patterns and use of post-menopausal hormone treatment varies by birth cohort and differs for current and former smokers.

Most epidemiological studies have attempted to control for factors that might confound the relationship between breast cancer and tobacco smoking using questionnaire information collected on these factors. None of the published

studies have been able to control for all of the potential confounders, however. Most studies lack data on screening behaviour and have limited information on alcohol consumption, use of post-menopausal hormones, and physical activity.

(d) *Potential anti-estrogenic effects of tobacco smoking*

Indirect evidence suggests that tobacco smoking may have anti-estrogenic effects that might offset the adverse effects of tobacco smoke carcinogens on breast cancer risk. [Baron et al. \(1990\)](#) pointed to observations suggesting lower estrogen activity levels in women who smoke compared to those who do not. Smokers have lower risk of endometrial cancer (Department of Health & Human Services, 2004), higher risk of osteoporosis ([Jensen et al., 1985](#); [Jensen & Christiansen, 1988](#)), earlier age at natural menopause ([Baron et al., 1990](#)) and lower mammography density ([Roubidoux et al., 2003](#)) than women who do not smoke. Smoking also attenuates the effects of hormone replacement therapy (HRT) on lipid profiles ([Jensen & Christiansen, 1988](#)) and serum estrone ([McDivitt et al., 2008](#)). No difference in serum concentrations of estradiol and estrone between post-menopausal smokers and non-smokers have been reported in several studies ([Cassidenti et al., 1992](#); [Khaw et al., 1988](#); [Berta et al., 1991](#); [Longcope et al., 1986](#); [Berta et al., 1992](#); [Cauley et al., 1989](#); [Friedman et al., 1987](#); [Key et al., 1991](#)). However, smokers have been observed to have higher levels of androgens ([Cassidenti et al., 1992](#)) (specifically androstenedione) ([Khaw et al., 1988](#); [Cauley et al., 1989](#); [Friedman et al., 1987](#); [Key et al., 1991](#)), prolactin ([Berta et al., 1991](#)), and unbound serum estradiol ([Cassidenti et al., 1992](#)).

(e) *Genetically susceptible subgroups*

Certain subgroups of women may have greater risk of breast cancer when exposed to tobacco smoke because of genetic or other factors

affecting cancer susceptibility. Potential interactions between inherited polymorphisms and tobacco smoking have been studied for selected candidate genes that affect carcinogen metabolism, modulation of oxidative damage, immune responses, and DNA repair (see Sections 2.12.4b and 4.2).

2.12.2 Analytical studies

Over 130 epidemiological studies on tobacco smoking and breast cancer were reviewed.

(a) *Incidence in current and former smokers*

Since the previous IARC Monograph ([IARC, 2004a](#)), seven reports on cohort studies ([Al-Delaimy et al., 2004](#); [Reynolds et al., 2004a](#); [Gram et al., 2005](#); [Hanaoka et al., 2005](#); [Olson et al., 2005](#); [Cui et al., 2006](#); [Ha et al., 2007](#)) have been published on breast cancer incidence in relation to tobacco smoking (Table 2.52 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.52.pdf>). Breast cancer incidence was significantly associated with current tobacco smoking in three studies ([Reynolds et al., 2004a](#); [Olson et al., 2005](#); [Cui et al., 2006](#)), with relative risk estimates among the larger studies ranging from 1.12 (95%CI: 0.92–1.37) ([Al-Delaimy et al., 2004](#)) to 1.32 (95%CI: 1.10–1.57) ([Reynolds et al., 2004a](#)). Former smoking was significantly associated with risk in only one cohort ([Al-Delaimy et al., 2004](#)), with relative risk estimates across all of the cohorts ranging from 1.00 (95%CI: 0.93–1.08) ([Cui et al., 2006](#)) to 1.18 (95%CI: 1.02–1.36) ([Al-Delaimy et al., 2004](#)). The association with breast cancer is stronger in current than in former smokers in four of the seven cohort studies ([Reynolds et al., 2004a](#); [Hanaoka et al., 2005](#); [Olson et al., 2005](#); [Cui et al., 2006](#)), although the confidence intervals overlap widely in all but one ([Cui et al., 2006](#)). [The Working group noted that three cohort studies ([Gram et al., 2005](#); [Hanaoka et al., 2005](#); [Olson et al., 2005](#)) provided data on both

the age-adjusted and the multivariate-adjusted risk estimates for current and former smoking. None of these showed attenuation of the estimate associated with current smoking, and two (Hanaoka *et al.*, 2005; Olson *et al.*, 2005) reported somewhat stronger estimates when adjusted for established risk factors besides age. None of the studies adjusted for the frequency of mammography screening. Residual confounding by screening and incomplete control for other risk factors would be expected to cause underestimation of the association with current smoking, and overestimation of the association with former smoking.]

Since the previous *IARC Monograph* (IARC, 2004a), a total of 12 case-control studies on tobacco smoking and breast cancer incidence have been published (Table 2.53 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.53.pdf>). Results from the case-control studies are less consistent than those from the cohort studies. Six studies (Li *et al.*, 2004; Mechanic *et al.*, 2006; Magnusson *et al.*, 2007; Prescott *et al.*, 2007; Roddam *et al.*, 2007; Slattery *et al.*, 2008) differentiated between current and former smokers, while the six other reports (Band *et al.*, 2002; Lash & Aschengrau, 2002; Gammon *et al.*, 2004; Rollison *et al.*, 2008; Ahern *et al.*, 2009; Young *et al.*, 2009) specify only ever or never smokers. Only one study (Li *et al.*, 2004) reported a borderline significant increase in risk associated with current smoking, and two studies (Band *et al.*, 2002; Rollison *et al.*, 2008) with ever smoking.

None of the six case-control studies that presented data on breast cancer incidence separately for current and former smokers found a significant difference in risk between the two smoking categories; the relative risk estimates were higher for former than for current smokers in four of the studies (Mechanic *et al.*, 2006; Prescott *et al.*, 2007; Roddam *et al.*, 2007; Slattery *et al.*, 2008) and identical in the fifth (Magnusson *et al.*, 2007).

(b) *Years of cessation*

When the relative risk for breast cancer incidence in former smokers is examined by years since cessation in cohort studies (Table 2.54 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.54.pdf>), the point estimates do not consistently decrease with longer time since cessation. In none of the four cohort studies (London *et al.*, 1989b; Egan *et al.*, 2002; Reynolds *et al.*, 2004a; Cui *et al.*, 2006) and in only one (Li *et al.*, 2005) of the five case-control studies (Chu *et al.*, 1990; Gammon *et al.*, 1998; Johnson *et al.*, 2000; Kropp & Chang-Claude, 2002; Li *et al.*, 2005) that formally tested for trend (Table 2.55 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.55.pdf>) was there a statistically significant decrease in relative risk observed with longer time since cessation. Only one study has reported data on breast cancer mortality in relation to years since quitting or age at cessation (Calle *et al.*, 1994). A statistically significant inverse trend in the relative risk estimates was reported with both years since quitting (p trend = 0.04) and younger age at cessation (p trend = 0.02). [The Working Group noted that the inverse trends in the relative risk of dying from breast cancer observed in this study are weaker than those observed with most other cancers designated as causally associated with smoking.]

(c) *Duration of smoking and age at initiation*

Tables 2.56–2.61 (see below for links) list the published epidemiologic studies that relate breast cancer incidence to duration of tobacco smoking, age at initiation and/or timing relative to first full term pregnancy.

Longer duration of smoking is associated with higher breast cancer incidence in five of seven cohort studies (Table 2.56 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.56.pdf>). A similar trend is seen inconsistently among the 33 case-control

studies that report relative risk estimates by duration of smoking (Table 2.57 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.57.pdf>). Among the 18 studies that reported a formal test of trend, eight studies (Gammon *et al.*, 1998; Johnson *et al.*, 2000; Reynolds *et al.*, 2004a; Gram *et al.*, 2005; Li *et al.*, 2005; van der Hel *et al.*, 2005; Cui *et al.*, 2006; Mechanic *et al.*, 2006) reported a statistically significant or borderline increase in the relative risk of incident breast cancer with the duration of smoking; seven studies (Ewertz, 1990; Palmer *et al.*, 1991; Egan *et al.*, 2002; Al-Delaimy *et al.*, 2004; Lissowska *et al.*, 2006; Magnusson *et al.*, 2007; Prescott *et al.*, 2007) reported no trend, and one study (Brinton *et al.*, 1986) reported an inverse relationship.

Thirty studies, including cohort (Tables 2.58 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.58.pdf>) and case-control studies (Table 2.59 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.59.pdf>) related breast cancer incidence to age at smoking initiation. Fifteen of these (Chu *et al.*, 1990; Ewertz, 1990; Palmer *et al.*, 1991; Nordlund *et al.*, 1997; Gammon *et al.*, 1998; Johnson *et al.*, 2000; Egan *et al.*, 2002; Kropp & Chang-Claude, 2002; Gram *et al.*, 2005; Cui *et al.*, 2006; Lissowska *et al.*, 2006; Ha *et al.*, 2007; Lissowska *et al.*, 2007; Magnusson *et al.*, 2007; Prescott *et al.*, 2007; Slattery *et al.*, 2008) reported a formal test of trend. Among these, only two (Gram *et al.*, 2005; Ha *et al.*, 2007) found a statistically significant or borderline significantly higher risk in women who began smoking at a younger ages; twelve studies (Chu *et al.*, 1990; Ewertz, 1990; Palmer *et al.*, 1991; Nordlund *et al.*, 1997; Gammon *et al.*, 1998; Johnson *et al.*, 2000; Egan *et al.*, 2002; Cui *et al.*, 2006; Lissowska *et al.*, 2006; Magnusson *et al.*, 2007; Prescott *et al.*, 2007; Slattery *et al.*, 2008) found no relationship with age at initiation, and one (Kropp & Chang-Claude, 2002) reported higher risk among women who began

smoking later. [The Working Group noted that at least two studies (Cui *et al.*, 2006; Slattery *et al.*, 2008) appear to have included never-smokers in the tests of trend and that the categories that define age at initiation differ across studies.]

The relative risk of incident breast cancer according to the timing of smoking initiation relative to first full-term pregnancy was reported in 21 studies, of cohort (Table 2.60 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.60.pdf>) and case-control (Table 2.61 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.61.pdf>) design. For nine studies (Hunter *et al.*, 1997; Egan *et al.*, 2002; Al-Delaimy *et al.*, 2004; Reynolds *et al.*, 2004a; Li *et al.*, 2005; Cui *et al.*, 2006; Prescott *et al.*, 2007; Rollison *et al.*, 2008; Young *et al.*, 2009) categorical data on years of smoking before first pregnancy are presented, whereas for 12 (Lash & Aschengrau, 1999; Innes & Byers, 2001; Band *et al.*, 2002; Kropp & Chang-Claude, 2002; Lash & Aschengrau, 2002; Fink & Lash, 2003; Lawlor *et al.*, 2004; Gram *et al.*, 2005; Olson *et al.*, 2005; Lissowska *et al.*, 2006; Magnusson *et al.*, 2007; Slattery *et al.*, 2008) whether smoking was initiated before or after the initial pregnancy was considered. Breast cancer incidence is consistently higher when smoking began before or during first pregnancy in most (Hunter *et al.*, 1997; Lash & Aschengrau, 1999; Innes & Byers, 2001; Band *et al.*, 2002; Egan *et al.*, 2002; Al-Delaimy *et al.*, 2004; Reynolds *et al.*, 2004a; Gram *et al.*, 2005; Li *et al.*, 2005; Olson *et al.*, 2005; Cui *et al.*, 2006; Slattery *et al.*, 2008; Young *et al.*, 2009) but not all (Kropp & Chang-Claude, 2002; Lash & Aschengrau, 2002; Fink & Lash, 2003; Prescott *et al.*, 2007) studies that tested this. [The Working Group noted that the number of years of smoking before first pregnancy is highly correlated with age at first full-term pregnancy, which is itself an independent risk factor for breast cancer.]

It has been argued that some studies, and especially cohort studies, may underestimate

the true association between tobacco smoking and breast cancer risk by ignoring or underestimating lifetime exposure to second-hand tobacco smoke of those in the referent group ([California Environmental Protection Agency, 2005](#); [Johnson, 2005](#); [Collishaw *et al.*, 2009](#)). This criticism is based on the hypothesis that exposure to second-hand smoke may confer almost the same degree of breast cancer risk as tobacco smoking. Under this hypothesis, the inclusion of women exposed to second-hand smoke in the referent group dilutes the contrast between exposed and unexposed women in studies of tobacco smoking, and causes underestimation of the association between tobacco smoking and breast cancer. In several case-control studies the association between breast cancer and tobacco smoking strengthened when the referent group was defined as women with “never active, never-passive” exposure to tobacco smoke ([Morabia *et al.*, 1996](#); [Lash & Aschengrau, 1999](#); [Johnson *et al.*, 2000](#); [Kropp & Chang-Claude, 2002](#)). In contrast, a stronger association between tobacco smoking and breast cancer risk, when women exposed only to second-hand smoke are excluded from the referent group, has not been observed in cohort studies ([Egan *et al.*, 2002](#); [Reynolds *et al.*, 2004a](#)). Debate continues over whether the case-control studies should be considered “of highest quality” because they provide “lifetime exposure assessment” ([Collishaw *et al.*, 2009](#)) or whether the cohort studies are more credible, because prospectively-collected exposure data are not susceptible to the recall bias that can affect retrospective studies.

(d) *Survival and mortality from breast cancer*

The relationship between smoking and the natural history of breast cancer has been examined in several studies ([Daniell, 1988](#); [Ewertz *et al.*, 1991](#); [Daniell *et al.*, 1993](#); [Scanlon *et al.*, 1995](#); [Yu *et al.*, 1997](#); [Manjer *et al.*, 2000](#); [Murin & Inciardi, 2001](#); [Holmes *et al.*, 2007](#)). In cross-sectional analyses, [Daniell *et al.* \(1993\)](#) found that

smokers with breast cancer had more and larger lymph node metastases than non-smokers, after controlling for primary tumour size and other variables. Further, a case-control study ([Murin & Inciardi, 2001](#)) and a retrospective cohort study ([Scanlon *et al.*, 1995](#)) found smoking to be associated with an increased risk of developing pulmonary metastases from breast cancer. However, these studies could not definitively distinguish lung metastases from primary lung cancers.

Five cohort studies have focused specifically upon the association of tobacco smoking with either breast cancer survival ([Ewertz *et al.*, 1991](#); [Yu *et al.*, 1997](#); [Manjer *et al.*, 2000](#); [Holmes *et al.*, 2007](#)) or breast cancer death rates ([Calle *et al.*, 1994](#)). A study of 1774 Danish women showed no association between smoking and breast cancer survival ([Ewertz *et al.*, 1991](#)), as did a study of 5056 women with breast cancer in the Nurse’s Health Study ([Holmes *et al.*, 2007](#)). In contrast, follow-up of 792 women with in situ or invasive breast cancer detected in a screening study in Malmö, Sweden found a crude relative risk for smokers and ex-smokers, compared to never smokers, of 1.44 (95%CI: 1.01–2.06) and of 1.13 (95%CI: 0.66–1.94), respectively ([Manjer *et al.*, 2000](#)). The relative risk associated with smoking remained significant after adjustment for age and stage at diagnosis (RR, 2.14; 95%CI: 1.47–3.10). A study based on the ACS Cancer Prevention Study II reported an association between current smoking and increased breast cancer death rates after six years of follow-up (Table 2.56 online; [Calle *et al.*, 1994](#)). Risk of death attributed to breast cancer was positively and significantly related to the duration of current smoking reported at the time of enrolment. However, the authors acknowledge that mortality studies cannot exclude biases arising from the effect of smoking on overall death rates, which could increase the potential for prevalent breast cancer to be coded as the underlying cause of death on the death certificate ([Calle *et al.*, 1994](#)).

2.12.3 Subtypes

(a) Pre- versus post-menopausal

Since the previous *IARC Monograph* ([IARC, 2004a](#)), 19 case-control studies have published data on tobacco smoking in relation to pre- and post-menopausal breast cancer (Table 2.62 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.62.pdf>). The results are inconsistent. Of the 12 studies that provide information separately for current smokers ([Schechter et al., 1985](#); [Brinton et al., 1986](#); [Rohan & Baron, 1989](#); [Ewertz, 1990](#); [Baron et al., 1996](#); [Gammon et al., 1998](#); [Millikan et al., 1998](#); [Johnson et al., 2000](#); [Zheng et al., 2002](#); [Magnusson et al., 2007](#); [Slattery et al., 2008](#)), only five ([Schechter et al., 1985](#); [Johnson et al., 2000](#); [Magnusson et al., 2007](#); [Slattery et al., 2008](#)) found a stronger association with pre- than with post-menopausal breast cancer. The other analyses show either similar associations ([Brinton et al., 1986](#); [Ewertz, 1990](#); [Baron et al., 1996](#); [Gammon et al., 1998](#); [Millikan et al., 1998](#); [Zheng et al., 2002](#)) or a stronger association with post-menopausal breast cancer ([Rohan & Baron, 1989](#); [Millikan et al., 1998](#); [Johnson et al., 2000](#); [Zheng et al., 2002](#)).

(b) Hormone receptor status

Two cohort studies ([London et al., 1989a](#); [Manjer et al., 2001](#)), one case-control study ([Morabia et al., 1998](#)) and a case series ([Yoo et al., 1997](#)) have examined the association between quantitative measures of cigarette smoking and breast cancer risk according to estrogen receptor (ER) status. In one of the cohort studies ([Manjer et al., 2001](#)), a statistically significant increased risk (RR, 1.6) of ER negative tumours associated with current smoking was found but no clear association between smoking and ER positive tumours, and no difference in the association with progesterone receptor (PR)-positive and PR-negative tumours. In the other three studies

there was no clear difference in the association related to ER or PR receptor status.

2.12.4 Susceptible populations

More than 30 studies and meta-analyses ([Alberg et al., 2004](#); [Terry & Goodman, 2006](#); [Ambrosone et al., 2008](#); [Collishaw et al., 2009](#)) have evaluated whether a family history of breast cancer and/or inherited polymorphisms in various genes may confer greater susceptibility to develop breast cancer from exposure to tobacco smoke. These are described below in relation to the measure indicating potential susceptibility.

(a) Family history

In two studies, whether a family history of breast cancer modifies susceptibility to develop breast cancer from tobacco smoking has been examined. [Couch et al. \(2001\)](#) measured breast cancer incidence among female family members in a cohort of breast cancer cases diagnosed between 1944 and 1952 at the University of Minnesota. Sisters and daughters in families with at least three breast and/or ovarian cancers were at 2.4 fold higher risk for breast cancer (95%CI: 1.2–5.1) if they smoked compared to never-smokers. No dose-response was observed in relation to pack-years of smoking.

[Suzuki et al. \(2007\)](#) reported a statistically significant interaction between family history of breast cancer and smoking history in a hospital-based case-control study of 3861 breast cancer cases treated at a large cancer centre in Japan between 1988 and 2000. A family history of breast cancer in the absence of smoking was associated with a relative risk of 1.44 (95%CI: 1.21–1.71); the relative risk estimate was 1.95 (95%CI: 1.36–2.81) in women who reported < 30 pack-years of tobacco smoking, and 4.33 (95%CI: 1.65–11.40) in women who reported > 30 pack-years of smoking.

[The Working group noted that Japanese women who smoked during this time period

may have differed from never-smokers in other characteristics related to breast cancer. Besides its strong correlation with female smoking, “Westernization” might be associated with delayed childbearing, smaller families, higher body mass index, and greater use of post-menopausal hormones.]

(b) Genetic polymorphisms

Studies of breast cancer, smoking and low penetrance genetic polymorphisms are summarized in Table 2.63 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.63.pdf>). The candidate genes in these studies are involved in carcinogen metabolism [*N*-acetyltransferases (*NAT1*, *NAT2*), cytochrome P450s (*CYP1A1*, *CYP1B1*, *CYP2E2*), GSTs], host responses to oxidative stress (superoxide dismutase) or to infectious organisms (myeloperoxidase and immunoglobulin binding protein) and DNA repair (*O*⁶-methylguanine DNA methyltransferase, nucleotide excision repair).

The most consistent associations with breast cancer risk have been observed among long-term smokers with the *NAT2* slow acetylation genotype (Terry & Goodman, 2006). *NAT2* slow acetylation genotype is thought to confer less capability to detoxify tobacco smoke carcinogens and is associated with an increase in breast cancer risk (Ambrosone *et al.*, 1996, 2008). Approximately 50–60% of Caucasian women are reported to be slow acetylators.

Table 2.63 (online) lists 15 studies of polymorphisms in *NAT2*, of which 9 were included in a pooled analysis and 13 in a meta-analysis (Ambrosone *et al.*, 2008). [The study by Delfino *et al.* (2000) was excluded from these analyses because cases included women with benign breast disease; the study by Lilla *et al.* (2005) was not considered because it is based on the same population as that by Chang-Claude *et al.* (2002).] The meta-analysis found a statistically significant association between ever tobacco

smoking and breast cancer risk among women with the *NAT2* slow acetylator genotype (meta-RR, 1.27; 95%CI: 1.16–1.40) but not in those with rapid acetylator genotype (meta-RR, 1.05; 95%CI: 0.95–1.17). Pack-years of tobacco smoking was significantly associated with increasing breast cancer risk among women with *NAT2* slow acetylator genotype (meta-RR for ever smokers, 1.44; 95%CI: 1.23–1.68, for > 20 pack-years versus never smokers), but not among rapid acetylators (Ambrosone *et al.*, 2008). No main effect was seen between *NAT2* status and breast cancer risk (meta-RR, 1.0; 95%CI: 0.93–1.07). In contrast to an earlier meta-analysis (Alberg *et al.*, 2004), this study observed no difference in risk for pre- or post-menopausal breast cancer. The pooled analysis of nine studies (Ambrosone *et al.*, 2008) reported pooled risk estimates for pre- and post-menopausal women of 1.49 (95%CI: 1.08–2.04) and 1.42 (95%CI: 1.16–1.74), respectively, among women with slow *NAT2* genotype and at least 20 pack-years of smoking compared to never-smokers. The corresponding values for women with rapid acetylator genotype were 1.29 (95%CI: 0.89–1.86) and 0.88 (95%CI: 0.69–1.13). A statistically significant interaction was observed between pack-years of smoking as a continuous variable and *NAT2* genotype (*p* interaction = 0.03).

A population-based case-control study published after the meta-analysis by Ambrosone *et al.* compared the prevalence of the *NAT2* genotypes and their joint effect with smoking on breast cancer risk in Hispanic and non-Hispanic white women (Baumgartner *et al.*, 2009). Non-Hispanic white women were more likely (*P* < 0.001) than Hispanics to have a slow (41.7% versus 33.5%) or very slow (19.0% versus 11.1%) *NAT2* acetylator status. Breast cancer risk was significantly increased in non-Hispanic smoking white women with a very slow acetylator genotype (RR, 2.46; 95%CI: 1.07–5.65 for current versus never).

[The Working Group noted that publication bias remains a concern in the studies of *NAT2* published to date. All of the studies included in the meta-analysis by Ambrosone *et al.* were published between 1996 and 2006; some among them (Morabia *et al.*, 2000; Sillanpää *et al.*, 2007) reported very strong associations that seem inconsistent with the rest of the data. Because genetic studies often examine multiple genes, it is plausible that studies that find no main effect with *NAT2* have not examined this association or that null results for smoking have not been published.]

Fewer studies with less consistent findings have been published on polymorphisms in other genes such as *NAT1*, *CYP1A1*, *GST*, *NOS3*, *MPO*, *MnSOD2* and various DNA repair genes (Table 2.63 online).

2.12.5 High penetrance genes & prognosis

At least seven studies have examined the hypothesis that tobacco smoking may modify breast cancer risk among women who carry *BRCA1* and *BRCA2* mutations (Brunet *et al.*, 1998; Ghadirian *et al.*, 2004; Colilla *et al.*, 2006; Gronwald *et al.*, 2006; Nkondjock *et al.*, 2006; Breast Cancer Family Registry, 2008; Ginsburg *et al.*, 2009). The results have been inconsistent. A recent case-control study of women under age 50 years who were carriers of mutations in *BRCA1* or *BRCA2* reported increased risk for breast cancer associated with as little as five pack-years of smoking. Compared to non-smokers, the risk associated with five or more pack-years of smoking was 2.3 (95%CI: 1.6–3.5) for *BRCA1* mutation carriers and 2.6 (95%CI: 1.8–3.9) for *BRCA2* mutation carriers (Breast Cancer Family Registry, 2008). In contrast, six other studies reported no increased risk among *BRCA1* or *BRCA2* carriers who smoke. The Canadian Panel review (Collishaw *et al.*, 2009) postulated that the five previous studies (Brunet *et al.*, 1998; Ghadirian *et al.*, 2004; Colilla *et al.*,

2006; Gronwald *et al.*, 2006; Nkondjock *et al.*, 2006) may have failed to observe a relationship because they included prevalent cases. However, a sixth study published since the Canadian panel review is also negative (Ginsburg *et al.*, 2009).

2.13 Cancer of the cervix

The association between smoking and cervical cancer has been examined in many epidemiological studies over the past few decades.

Since the previous *IARC Monograph* (IARC, 2004a), additional epidemiological studies have been published. Study design and results of the case-control studies restricted to HPV positive women or that adjusted for HPV status are presented in Table 2.64 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.64.pdf>) and Table 2.65 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.65.pdf>). Cohort studies and pooled analyses are presented in Table 2.66 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.66.pdf>) and Table 2.67 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.67.pdf>), respectively. Table 2.68 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.68.pdf>) and Table 2.69 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.69.pdf>) present additional cohort studies and pooled analyses on tobacco smoking and cervical, cervical intraepithelia neoplasia and carcinoma in situ, with or without controlling for HPV status, respectively.

2.13.1 Dose-response relationship

A positive association between smoking and incidence of cervical squamous-cell carcinoma, which account for approximately 90% of all cervical cancers, has been shown consistently over several decades in many epidemiological studies

of various designs conducted across different geographic regions. Dose–response associations with smoking intensity and duration were noted in many of the studies where such associations were examined ([Berrington de González et al., 2004](#); [Appleby et al., 2006](#)). Conversely, no clear association was found among former smokers. For adenocarcinoma of the cervix, which usually account for less than 10% of the total of all types of cervical cancer, there appears to be no clear association with smoking ([Berrington de González et al., 2004](#)).

2.13.2 Interaction with HPV positivity

Epidemiological studies of smoking and cervical cancer increasingly have considered the effects of HPV infection, which is recognized as the main etiological factor for invasive and pre-invasive cervical neoplasia worldwide ([IARC, 1995, 2012b](#)). HPV infection has been considered not only with respect to possible effect modification ([Hellberg & Stendahl, 2005](#); [Gunnell et al., 2006](#)), but also to confounding, as both HPV infection and smoking habits are directly associated with number of sexual partners and other indications of high-risk sexual behaviours ([Sikström et al., 1995](#); [Wang et al., 2004](#); [Hellberg & Stendahl, 2005](#); [McIntyre-Seltman et al., 2005](#); [Syrjänen et al., 2007](#)). Although there have been exceptions ([Syrjänen et al., 2007](#)), recent studies have generally continued to show that statistical adjustment for the potential confounding effects of HPV infection, or restricting studies to women with high risk HPV infection ([Plummer et al., 2003](#)), does not appreciably alter the finding of a positive association or its magnitude ([McIntyre-Seltman et al., 2005](#); [Appleby et al., 2006](#); [Tolstrup et al., 2006](#); [Tsai et al., 2007](#); [Nishino et al., 2008](#); [Kapeu et al., 2009](#)).

Statistical adjustment for the potentially confounding effect of HPV infection was usually based on the measured presence of HPV DNA in cervical cells or anti-HPV serum antibodies

in multivariate analytical models; as noted above, studies have also restricted their analyses to HPV-positive cases and controls. As there is currently no reliable marker of persistent HPV infection, case–control studies based on a cross-sectional measurement of HPV cannot distinguish between transient and persistent infections ([Franco et al., 1999](#)). Tobacco smoking is suspected to facilitate acquisition or persistence of an HPV infection through a reduced number of Langerhans cells and CD4 lymphocytes, which are markers of local immune response in the cervix ([Vaccarella et al., 2008](#)). In addition, smoking may affect innate immunity ([Ferson et al., 1979](#)). Current smokers have been shown to have a slightly higher HPV prevalence than non-smokers in a broad range of world populations after adjustment for life-time number of sexual partners (OR, 1.18; 95%CI: 1.01–1.39) ([Vaccarella et al., 2008](#)). Studies have evaluated the effect of smoking on HPV persistence. One study shows lower probability of HPV clearance among ever smokers ([Giuliano et al., 2002](#)) but a few others found no relationship ([Molano et al., 2003](#); [Richardson et al., 2005](#)).

2.14 Cancer of the endometrium

2.14.1 Overview of studies

To date, at least 42 epidemiological studies have examined the association between smoking and endometrial cancer, 25 reviewed in the previous *IARC Monograph* ([IARC, 2004a](#)) and 17 published since then ([Petridou et al., 2002](#); [Folsom et al., 2003](#); [Furberg & Thune, 2003](#); [Newcomb & Trentham-Dietz, 2003](#); [Beral et al., 2005](#); [Matthews et al., 2005](#); [Viswanathan et al., 2005](#); [Okamura et al., 2006](#); [Strom et al., 2006](#); [Trentham-Dietz et al., 2006](#); [Weiss et al., 2006a](#); [Al-Zoughool et al., 2007](#); [Bjørge et al., 2007](#); [Lacey et al., 2007](#); [Loerbroeks et al., 2007](#); [Setiawan et al., 2007](#); [Lindemann et al., 2008](#)). Study design and results of the additional studies

are presented separately for the case-control studies (Table 2.70 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.70.pdf> and Table 2.71 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.71.pdf>, respectively) and for the cohort studies (Table 2.72 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.72.pdf> and Table 2.73 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.73.pdf>, respectively).

(a) Cohort studies

The majority of the 13 cohort studies (Engeland *et al.*, 1996; Terry *et al.*, 1999, 2002b; Folsom *et al.*, 2003; Furberg & Thune 2003; Beral *et al.*, 2005; Viswanathan *et al.*, 2005; Al-Zoughool *et al.*, 2007; Bjørge *et al.*, 2007; Lacey *et al.*, 2007; Loerbroks *et al.*, 2007; Setiawan *et al.*, 2007; Lindemann *et al.*, 2008) suggest a decreased risk among current smokers, including the largest study with over 9000 cases (Bjørge *et al.*, 2007). In five of these studies quantitative smoking measures have been examined in relation to endometrial cancer risk (Terry *et al.*, 1999, 2002b; Viswanathan *et al.*, 2005; Al-Zoughool *et al.*, 2007; Loerbroks *et al.*, 2007). Of these, one (Terry *et al.*, 1999) found a 50% reduced risk among current smokers in the highest level of intensity (11 cigarettes per day or more) compared with non-smokers, but the number of cases was low and the confidence intervals correspondingly wide. A more recent and larger cohort study (Terry *et al.*, 2002b) found a statistically significant 40% reduced risk among current smokers of more than 20 cigarettes per day, but showed somewhat weaker and statistically non-significant reductions in risk with smoking of long duration or high cumulative consumption (i.e. pack-years). In contrast, the risk among former smokers was similar to that among never smokers. The largest of these studies generally showed decreasing risk of endometrial cancer with increasing

smoking intensity, duration, and pack-years of consumption (Viswanathan *et al.*, 2005). Three studies examined the association between time since smoking cessation and endometrial cancer risk. Two of these studies suggested a positive association with time since quitting (compared with non-smokers) (Viswanathan *et al.*, 2005; Loerbroks *et al.*, 2007), whereas one found no association (Terry *et al.*, 2002b).

(b) Case-control studies

The results of 17 population-based case-control studies (Smith *et al.*, 1984; Tyler *et al.*, 1985; Franks *et al.*, 1987; Elliott *et al.*, 1990; Rubin *et al.*, 1990; Brinton *et al.*, 1993; Goodman *et al.*, 1997; Shields *et al.*, 1999; Jain *et al.*, 2000; McCann *et al.*, 2000; Newcomer *et al.*, 2001; Weiderpass & Baron, 2001; Newcomb & Trentham-Dietz, 2003; Matthews *et al.*, 2005; Strom *et al.*, 2006; Trentham-Dietz *et al.*, 2006; Weiss *et al.*, 2006a), that have included between 46 and 1304 endometrial cancer cases, generally have shown reductions in risk among current smokers compared with never smokers (although the magnitude of the reduction in risk has varied somewhat); results among former smokers compared with never smokers were equally variable, albeit somewhat weaker overall. The results of eight hospital-based case-control studies (Kelsey *et al.*, 1982; Lesko *et al.*, 1985; Levi *et al.*, 1987; Stockwell & Lyman, 1987; Koumantaki *et al.*, 1989; Austin *et al.*, 1993; Petridou *et al.*, 2002; Okamura *et al.*, 2006), which included between 83 and 1374 endometrial cancer cases, are somewhat consistent with those of population-based studies. They showed moderate (e.g. 30–40%) reduction in risks among current compared with never smokers, and unaltered risks (or perhaps a small 10–20% reduction in risk) in former compared with never smokers. The largest of the hospital-based studies (Stockwell & Lyman, 1987), with 1374 cases and 3921 controls, found both former and current smokers to be at moderately (approximately 30%) reduced risk

of endometrial cancer. To date, six population-based case-control studies ([Tyler et al., 1985](#); [Lawrence et al., 1987, 1989](#); [Brinton et al., 1993](#); [Newcomer et al., 2001](#); [Weiderpass & Baron, 2001](#)) have examined quantitative measures of smoking in relation to endometrial cancer risk, generally showing inverse associations to be strongest among current smokers of high intensity or long duration.

2.14.2 Confounders

Whereas the majority of these studies adjusted their relative risk estimates for potentially confounding variables, such as BMI, HRT, parity, diabetes, and age at menopause, studies that did not adjust for these variables tended to show similar inverse associations. Within individual studies, statistical adjustment for the effects of BMI and other covariates often made little difference, although some attenuation of relative risk estimates has been noted ([Weiderpass & Baron, 2001](#); [Terry et al., 2002c](#)).

2.14.3 Effect modification

The association between smoking and endometrial cancer risk according to factors that are known determinants of endogenous hormone concentrations, and which may counteract or augment possible tobacco-related hormonal changes, have been examined in several studies. These factors include menopausal status, HRT and BMI. Effect modification can reflect true underlying differences in the association across strata (for example, if cigarette smoking acts to reduce or modify estrogen concentrations differently in one group compared with another), but can also reflect methodological factors, such as differences that occur by chance or through the varying prevalence of confounding variables.

(a) Menopausal status

Although endometrial cancer is rare among pre-menopausal women, several studies have examined the association between cigarette smoking and endometrial cancer risk according to menopausal status, because the effect of smoking (if any) might vary according to the underlying hormonal milieu. The studies have included two cohort studies ([Terry et al., 2002b](#); [Al-Zoughool et al., 2007](#)), five population-based case-control studies ([Smith et al., 1984](#); [Franks et al., 1987](#); [Lawrence et al., 1987](#); [Brinton et al., 1993](#); [Weiderpass & Baron, 2001](#)), and four hospital-based case-control studies ([Lesko et al., 1985](#); [Levi et al., 1987](#); [Stockwell & Lyman, 1987](#); [Koumantaki et al., 1989](#)). In all but one of these studies, a study of early stage endometrial cancer ([Lawrence et al., 1987](#)), the inverse association was (to varying degrees) stronger among post-menopausal than pre-menopausal women. Among pre-menopausal women, the relative risk estimates for cigarette smoking have been inconsistent, sometimes showing increased risks with certain measures of cigarette smoking ([Smith et al., 1984](#); [Stockwell & Lyman, 1987](#); [Koumantaki et al., 1989](#); [Brinton et al., 1993](#); [Al-Zoughool et al., 2007](#)), sometimes showing decreased risks ([Lawrence et al., 1987](#); [Levi et al., 1987](#); [Brinton et al., 1993](#); [Terry et al., 2002b](#)), and sometimes showing practically no association ([Lesko et al., 1985](#); [Weiderpass & Baron, 2001](#); [Al-Zoughool et al., 2007](#)). In analyses limited to post-menopausal women, on the other hand, all showed between 10% and 80% reduced risks of endometrial cancer with the various smoking measures.

(b) Hormone replacement therapy

Given the possibility that cigarette smoking affects hormone concentrations mostly among women who are taking HRT ([Jensen et al., 1985](#); [Jensen & Christiansen, 1988](#); [Cassidenti et al., 1990](#)), the inverse association between tobacco

smoking and endometrial cancer risk might be stronger among HRT users than among non-users. However, the results of studies that have examined the association between smoking and endometrial cancer risk according to HRT use have been equivocal ([Weiss *et al.*, 1980](#); [Franks *et al.*, 1987](#); [Lawrence *et al.*, 1987](#); [Levi *et al.*, 1987](#); [Terry *et al.*, 2002b](#); [Beral *et al.*, 2005](#)). Whereas in two studies ([Franks *et al.*, 1987](#); [Levi *et al.*, 1987](#)) a larger reduction in risk among smokers taking HRT than among smokers not taking HRT was observed, in two other studies ([Lawrence *et al.*, 1987](#); [Terry *et al.*, 2002b](#)) there was no difference in the association according to HRT status. A cohort study that examined associations only among women using HRT showed no clear association among users of continuous combined HRT and cyclic combined HRT, but some suggestion of increased risk among smokers who used tibolone (perhaps more clearly among former smokers) ([Beral *et al.*, 2005](#)). Thus, although effect modification by HRT status is biologically plausible, the available epidemiological evidence is equivocal.

(c) *Relative body weight*

Obesity is an established risk factor for endometrial cancer ([IARC, 2002](#)). Smokers tend to have a lower BMI than non-smokers, although former smokers tend to have a higher BMI than current or never smokers ([Baron *et al.*, 1990](#)). Two case-control studies have examined the association between cigarette smoking and endometrial cancer risk according to BMI, one population-based ([Elliott *et al.*, 1990](#)) and one hospital-based ([Levi *et al.*, 1987](#)). Neither of these studies found clear differences in the association between smoking and endometrial cancer risk according to BMI. In a population-based case-control study of early stage endometrial cancer ([Lawrence *et al.*, 1987](#)), the inverse association with cigarette smoking tended to become stronger with increasing absolute rather than relative body weight.

2.14.4 *Gene polymorphisms*

Cigarette smoking and estrogen are both thought to influence cancer risk through pathways that are under the control of specific genes, such as those involved in the formation of bulky DNA adducts by estrogen metabolites ([Cavalieri *et al.*, 2000](#)) and both bulky and non-bulky adducts formed by carcinogens in tobacco smoke ([Terry & Rohan, 2002](#)). Therefore, studies have been conducted to examine the association between smoking and endometrial cancer risk according to genes that repair these types of DNA damage. In a moderately-sized population-based case-control study no clear effect modification according to certain polymorphisms in the *XPA* and *XPC* genes, both of which are involved in the nucleotide excision repair of bulky DNA adducts and may influence endometrial cancer risk, were found ([Weiss *et al.*, 2005, 2006b](#)). A nested case-control study also showed no clear effect modification according to three polymorphisms in *CYP1A1* ([McGrath *et al.*, 2007](#)), a gene that encodes microsomal *CYP1A1*, which contributes to aryl hydrocarbon hydroxylase activity, catalysing the metabolism of PAHs and other carcinogens found in tobacco smoke ([Masson *et al.*, 2005](#)). In another nested case-control study some evidence was found that the association between smoking and endometrial cancer may vary according to a polymorphism (Ile¹⁴³Val) in *O*⁶-methylguanine DNA methyltransferase (*MGMT*). Overall, studies that address the association between smoking and endometrial cancer risk according to genotype are scarce.

2.15 Cancer of the prostate

Many epidemiological studies have examined the association between cigarette smoking and prostate cancer risk, and most have shown no consistent association ([Hickey *et al.*, 2001](#); [Levi & La Vecchia, 2001](#); [Batty *et al.*, 2008](#); [Butler](#)

et al., 2009; *Huncharek et al.*, 2010; Table 2.74 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.74.pdf>; Table 2.75 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.75.pdf>). However, questions remain regarding whether smoking may alter risk in various population subgroups, for example, those defined by certain genotypes, and whether any association with smoking may be stronger for, or limited to, advanced tumours or prostate cancer mortality. Regarding this latter issue, the majority of epidemiological studies, including several large, long-term cohort studies, have reported a positive association between smoking and prostate cancer mortality (*Rohrmann et al.*, 2007; *Zu & Giovannucci*, 2009). Several studies that examined smoking in relation to both prostate cancer incidence and mortality tend to show positive results only for the latter (*Rohrmann et al.*, 2007; *Zu & Giovannucci*, 2009). Given the largely null results with respect to prostate cancer incidence, the latter findings suggest that smoking is less likely to be a causal agent in prostate cancer initiation than an agent that acts on existing tumours to promote their progression (*Zu & Giovannucci*, 2009).

A recent review of smoking and prostate cancer that focused specifically on aggressive and fatal tumours, considered the findings from 14 cohort studies (*Zu & Giovannucci*, 2009). Nine of these studies showed statistically significant increased risk with at least one smoking measure, and five showed increased risks that were not statistically significant for any measure. Only one study showed no association with any measure of tobacco consumption. Seven studies of various designs examined smoking with respect to indicators of cancer aggressive behaviour at the time of diagnosis. In these studies smoking was associated positively with tumour grade, risk of regional, distant, extraprostatic or metastatic disease, Gleason score, and biochemical outcome (failure) after prostate brachytherapy

and in several dose–response associations with the respective endpoint were demonstrated. In one study smoking cessation was associated with a decline in risk compared with that among current smokers.

The association between smoking and prostate cancer risk according to genotype and other potentially effect-modifying factors have been examined in several studies. For example, in a population-based case–control study tobacco use was a risk factor for prostate cancer primarily among men with high BMI (*Sharpe & Siemiatycki*, 2001). The results of a cohort study in Switzerland suggest that risk of prostate cancer mortality is increased in smokers, particularly those with low plasma vitamin E levels (*Eichholzer et al.*, 1999). These latter associations, as well as those regarding several genotypes that may modify the association (*Mao et al.*, 2004; *Nock et al.*, 2006; *Quiñones et al.*, 2006; *Yang et al.*, 2006; *Iguchi et al.*, 2009; *Kesarwani et al.*, 2009), have yet to be fully clarified.

[The Working Group noted that several of the studies of smoking and prostate cancer mortality did not demonstrate clear dose–response associations with risk, and noted the possibility of bias due to confounding by screening behaviour. However, in the Health Professionals Follow-up Study, screening behaviour was not found to differ appreciably between smokers and non-smokers. In an analysis limited to men with a negative digital rectal examination in the prior two years, stronger associations were found between smoking and metastatic prostate cancer risk among high intensity smokers (RR, 4.2; 95%CI: 1.6–10.9) (*Zu & Giovannucci*, 2009). This finding was evidence against bias from screening behaviour.]

2.16 Cancer of the ovary

2.16.1 Overview of studies

A total of over 30 epidemiological studies have investigated the association between tobacco smoking and ovarian cancer risk. Of these, 24 were case-control studies (IARC, 2004a; Table 2.76 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.76.pdf>; Table 2.77 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.77.pdf>) and six were cohort studies (IARC, 2004a; Table 2.78 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.78.pdf>; Table 2.79 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.79.pdf>). Most studies showed no statistically significant association between a measure of smoking and risk for ovarian cancer overall (Newhouse *et al.*, 1977; Smith *et al.*, 1984; Tzonou *et al.*, 1984; Baron *et al.*, 1986; Stockwell & Lyman, 1987; Whittemore *et al.*, 1988; Hartge *et al.*, 1989; Polychronopoulou *et al.*, 1993; Engeland *et al.*, 1996; Goodman *et al.*, 2001; Goodman & Tung, 2003; Pan *et al.*, 2004; Zhang *et al.*, 2004; Kurian *et al.*, 2005; Niwa *et al.*, 2005; Baker *et al.*, 2006; Huusom *et al.*, 2006; Fujita *et al.*, 2008; Lurie *et al.*, 2008; Nagle *et al.*, 2008; Tworoger *et al.*, 2008); some showed positive associations (Doll *et al.*, 1980; Tverdal *et al.*, 1993; Kuper *et al.*, 2000b; Marchbanks *et al.*, 2000; Green *et al.*, 2001; Modugno *et al.*, 2002; Gram *et al.*, 2008; Rossing *et al.*, 2008) and one (Riman *et al.*, 2004) showed an inverse association.

2.16.2 Histological subtypes

Differences in ovarian cancer risk factor profiles have been observed according to histological type, on the basis of which it has been suggested that mucinous and non-mucinous tumours are etiologically distinct diseases (Risch *et al.*, 1996). Epidemiological studies that have considered histological type tend to support a

positive association primarily between cigarette smoking and mucinous ovarian tumours (Kuper *et al.*, 2000b; Marchbanks *et al.*, 2000; Green *et al.*, 2001; Modugno *et al.*, 2002; Pan *et al.*, 2004; Zhang *et al.*, 2004; Kurian *et al.*, 2005; Tworoger *et al.*, 2008). In contrast, two studies showed no clear association between smoking and risk of mucinous or non-mucinous ovarian tumours (Riman *et al.*, 2004; Baker *et al.*, 2006). In addition, one early case-control study (Newhouse *et al.*, 1977), with 300 ovarian cancer cases and with both population and hospital controls, found no clear association with “ever” compared with “never” smoking, and reported no differences according to histological type.

A pooled analysis of 10 case-control studies (Kurian *et al.*, 2005) with 254 cases of mucinous and 1580 non-mucinous tumours found an increased risk of mucinous tumours among current smokers (RR, 2.4; 95%CI: 1.5–3.8), a positive association that was not observed with other histological types. Former smokers in that analysis did not have an increased risk of any histological type of ovarian cancer. This type of dose-response, whereby current smokers have a higher risk than former smokers, was observed in most, but not all, studies of mucinous ovarian cancer (Tables 2.77 and 2.79 online). Overall, the positive association between cigarette smoking and risk of mucinous ovarian tumours is generally consistent across both case-control and cohort studies conducted among various populations. In contrast, associations with smoking have been mostly null with respect to non-mucinous ovarian tumours, suggesting that recall bias is unlikely to explain the association with mucinous tumours.

[The Working Group considered the possibility that women who smoke may come to medical attention more frequently. This raises the possibility of detection bias, because mucinous tumours, benign or malignant, tend to be quite large and could be more easily detected on routine physical exam or testing. However, the

Working Group felt that detection bias would not account for the association entirely.

2.17 Cancer of the thyroid

The previous *IARC Monograph* ([IARC, 2004a](#)) noted inconsistent associations between smoking and thyroid cancer risk. In 2003, a pooled analysis of 14 case–control studies showed that smoking was inversely associated with thyroid cancer risk ([Mack et al., 2003](#); Table 2.80 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.80.pdf>; Table 2.81 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.81.pdf>). The sample consisted of 2725 thyroid cancer cases (2247 women, 478 men) and 4776 controls (3699 women, 1077 men). The inverse association was stronger among current smokers (RR, 0.6; 9% CI: 0.6–0.7) than former smokers (RR, 0.9; 9% CI: 0.8–1.1) and were similar in both men and women, for both papillary and follicular thyroid cancers, as well as by age and region. An inverse association between smoking and thyroid cancer risk was also found in a subsequent case–control study ([Nagano et al., 2007](#)). In contrast, two case–control studies ([Zivaljevic et al., 2004](#); [Bufalo et al., 2006](#)) reported no clear association between smoking and thyroid cancer risk (no risk ratio estimates were reported; hence, data are not shown in the tables) and a cohort study with 169 incident cases of thyroid cancer, also found no clear association with any qualitative or quantitative smoking measure ([Navarro Silvera et al., 2005](#); Table 2.82 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.82.pdf>; Table 2.83 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.83.pdf>).

2.18 Other cancers

The cancers reviewed in this section generally have low incidence and mortality rates and are not considered to be strongly associated with cigarette smoking. This raises the possibility of preferential reporting of positive associations in epidemiological studies.

2.18.1 Cancer of the salivary gland

Studies of smoking and cancers of the salivary gland reviewed in the previous *IARC Monograph* ([IARC, 2004a](#)) were sparse and their results were inconsistent ([Spitz et al., 1990](#); [Swanson & Burns, 1997](#); [Hayes et al., 1999](#)). A few additional studies also show inconsistent results ([Kotwall, 1992](#); [Pinkston & Cole, 1996](#); [Horn-Ross et al., 1997](#); [Vories & Ramirez, 1997](#); [Muscat & Wynder, 1998](#)). Studies that focused specifically on Warthin's tumour [papillary cystadenoma lymphomatosum or adenolymphoma, a benign tumour of the parotid gland] tend to show strong positive associations with smoking ([Kotwall, 1992](#); [Pinkston & Cole, 1996](#); [Vories & Ramirez, 1997](#)). One study ([Pinkston & Cole, 1996](#)) compared the risk for Warthin's tumour with that for other salivary gland tumours and found that smoking increased risk significantly only for Warthin's tumour.

2.18.2 Cancer of the small intestine

Epidemiological studies (all of case–control design) reviewed in the previous *IARC Monograph* ([IARC, 2004a](#)) have been inconsistent in showing a positive association between smoking and cancers of the small intestine ([Chow et al., 1993b](#); [Chen et al., 1994](#); [Wu et al., 1997](#); [Negri et al., 1999](#); [Kaerlev et al., 2002](#)). A more recent study showed no clear association ([Hassan et al., 2008b](#)).

2.18.3 Cancers of the gallbladder and extra-hepatic bile ducts

Epidemiological studies of smoking and risk of cancers of the gallbladder and extra-hepatic bile ducts reviewed in the previous *IARC Monograph* ([IARC, 2004a](#)) tended to show null, weak, or moderately strong positive associations. More recent studies also tend to show either no clear association with biliary tract carcinoma/extra-hepatic cholangiocarcinoma ([Shaib et al., 2007](#); [Welzel et al., 2007](#)) or suggest positive associations with gallbladder/biliary cancers ([Pandey & Shukla, 2003](#); [Yagyu et al., 2008](#); [Grainge et al., 2009](#)). Attention should be paid to potential confounders, especially BMI, when considering the results of epidemiological studies of risk of cancers of the gallbladder and extra-hepatic bile ducts. Recent studies that statistically adjusted for BMI, on gallbladder disease risk ([Grainge et al., 2009](#)) or on extrahepatic biliary tract carcinoma risk ([Ahrens et al., 2007](#)), showed a positive and null association with smoking, respectively. To date, there are too few studies with adequate control for potentially confounding factors to determine any clear pattern.

2.18.4 Soft-tissue sarcoma

As reported in the previous *IARC Monograph* ([IARC, 2004a](#)), one cohort study found an association between cigarette smoking and mortality from soft-tissue sarcoma after 26 years of follow-up but no dose-response relationship with the number of cigarettes/day, duration of smoking or pack-years ([Zahm et al., 1992](#)). No effect of cigarette smoking was detected in an Italian hospital-based case-control study ([Franceschi & Serraino, 1992](#)).

2.18.5 Cancer of the skin

(a) Melanoma

Several case-control studies found no difference in the prevalence of tobacco smoking between patients with malignant melanoma and controls, and one study found an inverse association ([IARC, 2004a](#)). An inverse association with smoking was also found in the US Radiologic Technologists cohort Study ([Freedman et al., 2003a](#)). In that study, smoking for at least 30 years compared with never smoking was inversely related to melanoma risk (RR, 0.6; 95%CI: 0.3–1.3), though risk was not associated with number of cigarettes/day. An inverse association was also observed in a cohort of Swedish construction workers ([Odenbro et al., 2007](#)). In this study, the risk for malignant melanoma was reduced in a dose-dependant manner for both cigarette and pipe smokers. The possibility that smoking may reduce the risk for melanoma should, therefore, be considered.

(b) Non-melanoma skin cancer

Four studies showed a positive association between smoking and non-melanoma skin cancer risk ([De Stefani et al., 1995](#); [Wojno, 1999](#); [Smith & Randle, 2001](#); [Boyd et al., 2002](#)), and two found no clear association ([van Dam et al., 1999](#); [Corona et al., 2001](#)). When distinguishing between histological subtypes, tobacco smoking was linked to the incidence of squamous-cell carcinoma of the skin in most studies, whereas the results for basal cell carcinoma remain inconsistent ([Zak-Prelich et al., 2004](#)). No clear association between smoking and risk for basal cell carcinoma was found in a cohort study ([Freedman et al., 2003b](#)).

2.18.6 Cancer of the penis

Case-control studies of smoking and penile cancer ([Hellberg et al., 1987](#); [Daling et al., 1992, 2005](#); [Maden et al., 1993](#); [Harish & Ravi, 1995](#);

Table 2.84 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.84.pdf>; Table 2.85 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.85.pdf>) and reviews of studies of smoking and penile cancer and population surveys (Dillner *et al.*, 2000; Favorito *et al.*, 2008; Bleeker *et al.*, 2009; Table 2.86 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.86.pdf>; Table 2.87 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.87.pdf>) consistently showed a positive association. In most studies there was a dose–response relationship, with higher risks among those with increased smoking intensity and/or duration. A study in Brazil showed a positive correlation with penile tumour grade (Favorito *et al.*, 2008). Based on the two reviews (Dillner *et al.*, 2000; Bleeker *et al.*, 2009), relative risks were generally increased twofold to fivefold among smokers.

Most studies did not adjust for HPV infection. In one case–control study (Daling *et al.*, 2005), current smoking was associated with a 160% increased risk of HPV-positive penile cancer ($n = 75$), and a 180% increased risk of HPV-negative penile cancer ($n = 19$), suggesting no important effect modification.

2.18.7 Cancer of the testis

Studies reviewed in the previous IARC Monograph (IARC, 2004a) showed no association between cigarette smoking and risk for testicular cancer. More recently, two case–control studies showed positive associations with smoking, one in Canada (Srivastava & Kreiger, 2004) and one in the Czech Republic (Dusek *et al.*, 2008).

2.18.8 Cancer of the central nervous system

A recent meta-analysis was conducted on smoking in relation to glioma risk (Mandelzweig *et al.*, 2009), which included 17 epidemiological

studies (6 cohort and 11 case–control). It was concluded that smoking is not associated with risk of glioma, despite a small significant increased risk seen in cohort studies. A recent cohort study found no association between smoking and carcinoma of the brain (Batty *et al.*, 2008). There have been no consistent associations of smoking with other CNS tumours (IARC, 2004a). In a population-based case–control study in the USA, smoking was associated with increased risk of intracranial meningioma in men (OR, 2.1; 95%CI: 1.1–4.2) but not in women (Phillips *et al.*, 2005).

2.18.9 Cancer of the adrenal gland

Data on risk factors for adrenal carcinoma are sparse. In the US Veterans' Study there was a fivefold increase in risk among current cigarette smokers during 26 years of follow-up, with risk being particularly high among those who smoked most intensely (Chow *et al.*, 1996). Other forms of tobacco use were associated with a statistically non-significant increase in risk. A case–control study in the USA found a twofold increase in risk for adrenal cancer among heavy smokers in men, but not in women (Hsing *et al.*, 1996).

2.19 Bidi smoking

2.19.1 Cancer of the oral cavity

(a) Overview of studies

The association between cancers of oral cavity and bidi smoking has been examined in 10 case–control studies conducted in India (Sankaranarayanan *et al.*, 1989a, b, 1990a; Rao *et al.*, 1994; Rao & Desai, 1998; Dikshit & Kanhere, 2000; Balaram *et al.*, 2002; Znaor *et al.*, 2003; Subapriya *et al.*, 2007; Muwonge *et al.*, 2008; Table 2.88 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.88.pdf>). In these studies both cases and controls were interviewed and analyses were restricted

to men, except for the studies by [Balaram *et al.* \(2002\)](#) and [Subapriya *et al.* \(2007\)](#), because very few women smoked among study subjects.

Three hospital-based case-control studies considered cancers of subsites of the oral cavity (gingiva, tongue and floor of the mouth, buccal and labial mucosa) ([Sankaranarayanan *et al.*, 1989a, b, 1990a](#)). All three studies showed a higher oral cancer risk for bidi smoking. In one early study an unadjusted relative risk of 1.6 (95%CI: 1.3–2.0) for oral cancer in bidi smokers was reported ([Rao *et al.*, 1994](#)). [The Working Group noted that the study had several deficiencies, particularly in the selection of controls that resulted in cigarette smoking apparently being protective for oral cancer.] In another early study ([Rao & Desai, 1998](#)) relative risks were estimated after stratification by age and place of residence. Bidi smoking was a significant risk factor for cancer of the base of the tongue (RR, 5.9; 95%CI: 4.2–8.2) but not significant for cancer of the anterior tongue. Relative risk for bidi smoking adjusted for alcohol drinking, illiteracy, non-vegetarian diet and tobacco chewing showed significant risk for cancer of the base of the tongue (RR, 4.7; 95%CI: 3.5–6.3) but not for cancer of the anterior tongue. In a population-based case-control study a relative risk of 1.5 (95%CI: 0.9–2.4), adjusted for age and tobacco quid chewing for smokers (bidis and/or cigarettes), was found ([Dikshit & Kanhere, 2000](#)).

Two hospital-based multi centre case-control studies on cancer of the oral cavity were conducted in southern India. One included 309 cases and 292 controls ([Balaram *et al.*, 2002](#)). The risk for oral cavity cancer among those who smoked < 20 bidis per day was 2.0 (95%CI: 1.1–3.8) and 2.5 (95%CI: 1.4–4.4) for ≥ 20 per day. The second study included 1563 cases and 3638 controls and found a risk for bidi smoking only of 2.2 (95%CI: 1.75–2.63) compared to never smokers, adjusted for age, centre, level of education, alcohol consumption and chewing ([Znaor *et al.*, 2003](#)).

In a hospital-based case-control study with 388 oral squamous cell carcinoma cases (202 men and 186 women) and an equal number of age and sex-matched controls the effect of life-style factors (tobacco chewing, smoking and alcohol drinking, diet and dental care) on the risk of oral cancer was evaluated ([Subapriya *et al.*, 2007](#)). Both cases and controls were interviewed using a structured questionnaire. The risk estimate for bidi smoking based on 22 cases (84 cases included in the model) and 22 controls was 4.6 (95%CI not given).

Data from a randomized control trial conducted between 1996 and 2004 in Trivandrum, southern India were used in a nested case-control analysis with 282 (163 men and 119 women) incident oral cancer cases and 1410 matched population controls aged 35 years and over ([Muwonge *et al.*, 2008](#)). Oral cancer risk among men, adjusted for education and religion, was 1.9 (95%CI: 1.1–3.2) for bidi smokers only compared to never smokers. No association was found between mixed smoking of bidi and cigarette and risk of oral cancer.

[Rahman *et al.* \(2003\)](#) performed a meta-analysis to investigate the relationship between bidi smoking and oral cancer. They identified 12 case-control studies published in English during 1996–2002 with quantitative information on bidi smoking and oral cancer. Of these, ten studies were conducted in India, one in Sri Lanka and one in Pakistan. All cases were confirmed histologically and exposure data were collected by direct interview. In these studies ORs were not adjusted for tobacco chewing or alcohol drinking. The OR for bidi smokers compared to never smokers based on random effects model was 3.1 (95%CI: 2.0–5.0). The ORs ranged from 2.0 to 3.6 in different regions of India: studies conducted in Mumbai had an OR of 3.6 (95%CI: 1.6–7.9), in central India 2.7 (95%CI: 1.6–4.6), in Kerala 2.0 (95%CI: 1.5–2.9) and in Bangalore 2.0 (95%CI: 1.1–3.7).

(b) Dose–response evidence

The trends in relative risks by intensity and duration of bidi smoking were both statistically significant in two studies ([Rao et al., 1994](#); [Rao & Desai, 1998](#)). A meta-analysis based on three studies on duration of bidi smoking and on five studies on number of bidi sticks per day, showed a dose–response relationship for duration of bidi smoking but not for number of sticks used per day ([Rahman et al., 2003](#)).

In a nested case–control analysis ([Muwonge et al., 2008](#)) a dose–response relationship was observed for duration of bidi smoking ($P = 0.045$). [It is not clear if the analysis was restricted to bidi smokers only ($n = 40$ men) and if smokers with combined smoking habits (bidi and cigarette) were excluded. Moreover, ORs for the dose–response analysis were not reported.]

2.19.2 Cancer of the pharynx

Five case–control studies, two hospital-based ([Wasnik et al., 1998](#); [Rao et al., 1999](#)), one population-based ([Dikshit & Kanhere, 2000](#)) and two multicentric studies ([Znaor et al., 2003](#); [Sapkota et al., 2007](#)) were conducted on cancers of oropharynx and hypopharynx in India (Table 2.88 online). In all these studies, analyses were restricted to men because very few women smoked among study subjects.

[Wasnik et al. \(1998\)](#) conducted a case–control study on oropharyngeal cancers with cases and controls were matched on age and sex. Odds ratios for tobacco smoking, predominantly in the form of bidi and/or chillum, were 2.3 (95%CI: 1.2–3.7) after adjustment for tobacco chewing and outdoor occupation. [The Working Group noted some problems with the data analysis.]

[Rao et al. \(1999\)](#) reported a relative risk for bidi smoking adjusted for alcohol, illiteracy, diet and tobacco chewing of 4.7 (3.6–6.3) for oropharyngeal cancer and of 2.8 (2.1–3.7) for cancer of the hypopharynx. [Dikshit & Kanhere \(2000\)](#) found

an odds ratio for oropharyngeal cancer among bidi smokers only of 7.9 (95%CI: 5.1–12.4).

[Znaor et al. \(2003\)](#) reported a risk for bidi smoking only for pharyngeal cancer of 4.7 (95%CI: 3.5–6.3) and for combined bidi and cigarette smoking of 3.6 (95%CI: 2.55–4.98). [Sapkota et al. \(2007\)](#) reported an odds ratio for hypopharyngeal cancer of 6.8 (95%CI: 4.6–10.0) for bidi smokers compared to never smokers.

A dose–response relationship was observed for intensity and duration of bidi smoking for both cancers of oropharynx and hypopharynx ([Rao et al., 1999](#); [Dikshit & Kanhere, 2000](#); [Sapkota et al., 2007](#)).

2.19.3 Cancer of the lung

One cohort study ([Jayalekshmy et al., 2008](#)), one population-based case–control study ([Dikshit & Kanhere, 2000](#)) and two hospital-based case–control studies ([Gupta et al., 2001](#); [Gajalakshmi et al., 2003](#)) in India (Table 2.88 online) have investigated the relationship between bidi smoking and lung cancer. In all these studies both cases and controls were interviewed and analyses were restricted to men because very few women smoked among study subjects. One hospital-based case–control study in Chiang Mai, Thailand, looked at the association between lung cancer and *khii yoo*, hand-rolled cigars. The risk for lung cancer for *khii yoo* smoking was 1.2 in men and 1.5 in women, $P > 0.05$ ([Simarak et al., 1977](#)).

In the population based case–control study by [Dikshit & Kanhere \(2000\)](#) the age-adjusted relative risk for lung cancer among bidi smokers only was 11.6 (95%CI: 6.4–21.3).

[Gupta et al. \(2001\)](#) reported an odds ratio for bidi smoking of 5.8 (95%CI: 3.4–9.7) from a hospital-based case–control study of lung cancer conducted in Chandigarh. [Gajalakshmi et al. \(2003\)](#) conducted a case–control study in two centres in which all subjects were interviewed by trained social investigators with standard

questionnaires. Odds ratios were adjusted for age, educational level, centre, chewing and alcohol habit. The odds ratios of lung cancer for former and current bidi smokers were 3.4 (95%CI: 2.1–5.4) and 5.3 (95%CI: 3.8–7.3), respectively. Odds ratios for former and current smokers of cigarette and bidi combined were 4.0 (95%CI: 2.5–6.6) and 9.1 (95%CI: 6.2–13.2), respectively.

Baseline data of a cohort of 359 619 residents in Kerala, India was collected by direct interview using standardized questionnaires during 1990–97 ([Jayalekshmy et al., 2008](#)). After excluding rare earth workers, those who died, were diagnosed with cancer before 1997 or died within three years of interview, there were 65 829 bidi-smoking men aged 30–84 years old. Two hundred and twelve lung cancer cases were identified by the Karunagappally Cancer Registry between 1997 and 2004. The relative risk for lung cancer for current compared to never bidi smokers calculated by Poisson regression analysis and adjusted for age, religion and education was 3.9 (95%CI: 2.6–6.0; $P < 0.001$). The risk was lower among former than among current smokers.

(a) Dose–response evidence

Lung cancer risks increased with increasing bidi smoking intensities. The highest odds ratio was found for 9 pack-years (3.9; 95%CI: 2.1–7.1) ([Gupta et al., 2001](#)). In a cohort study [Jayalekshmy et al. \(2008\)](#) found increased lung cancer incidence with increasing number of bidi sticks smoked per day ($P < 0.001$) and with increasing duration of bidi smoking ($P < 0.001$). [The number of lung cancer cases was small in each category, resulting in wide confidence intervals.] [Gajalakshmi et al. \(2003\)](#) also reported increased risk with duration and intensity of bidi smoking.

(b) Cessation of smoking

In two case–control studies ([Gupta et al., 2001](#); [Gajalakshmi et al., 2003](#)) there was a clear decreasing trend in risk for years since quitting.

[Gajalakshmi et al. \(2003\)](#) reported that lung cancer risk of former bidi smokers fell to 0.4 (0.1–1.2) after quitting for more than 15 years. The cohort study conducted in Kerala did not have the power to assess the risk associated with stopping bidi smoking ([Jayalekshmy et al., 2008](#)).

2.19.4 Cancer of the larynx

Two hospital based case–control studies ([Sankaranarayanan et al., 1990b](#); [Rao et al., 1999](#)) showed a higher risk for bidi smokers (Table 2.88 online). The relative risk was adjusted for age and religion in [Sankaranarayanan et al. \(1990b\)](#) study and for alcohol use, illiteracy, vegetarian/non-vegetarian diet and tobacco chewing in [Rao et al. \(1999\)](#) study. A multicentre case–control study on laryngeal cancer was conducted in four Indian centres using standardized questionnaires adjusting risks for centre, age, socio-economic status, alcohol consumption, tobacco snuffing and tobacco chewing ([Sapkota et al., 2007](#)). Compared to never smokers bidi smokers had a higher risk for cancers of the supraglottis (OR, 7.5; 95%CI: 3.8–14.7), glottis (OR, 5.3; 95%CI: 3.2–8.9) and rest of larynx (OR, 9.6; 95%CI: 5.6–16.4).

All levels of intensity and duration of bidi smoking were associated with significant relative risk estimates and dose–response for laryngeal cancer ([Sankaranarayanan et al., 1990b](#); [Rao et al., 1999](#)). A strong dose–response relationship was observed for duration and frequency of bidi smoking for cancers of supraglottis, glottis and rest of larynx ([Sapkota et al., 2007](#)).

2.19.5 Cancer of the oesophagus

Three hospital-based case–control studies and one multicentre study ([Sankaranarayanan et al., 1991](#); [Nandakumar et al., 1996](#); [Nayar et al., 2000](#); [Znaor et al., 2003](#)) showed increased risk for oesophageal cancer among bidi smokers in India (Table 2.88 online). A significantly elevated

risk for all three segments of the oesophagus was reported (Nandakumar *et al.*, 1996). One study (Nayar *et al.*, 2000) adjusted for chewing of betel leaf with tobacco and low consumption of vegetables other than leafy vegetables. The multicentre case–control study conducted in two centres in South India found an increased risk for oesophageal cancer for bidi smoking only (OR, 3.3; 95%CI: 2.45–4.39) (Znaor *et al.*, 2003). Odds ratios were adjusted for age, centre, level of education, alcohol consumption and chewing. Only men were analysed in all the above studies.

Significant effects were noted in men for all levels of intensity and for duration of more than 20 years of bidi smoking (Sankaranarayanan *et al.*, 1991).

2.19.6 Cancer of the stomach

In a hospital-based case–control study the association between stomach cancer and bidi smoking was analysed as part of a multicentre study (Gajalakshmi & Shanta, 1996). Cases and controls were matched on age, sex, religion and mother tongue. The odds ratio for stomach cancer for current bidi smokers only was 3.2 (95%CI: 1.8–5.7) and for current smokers of any type of tobacco was 2.7 (95%CI: 1.8–4.1).

Table 2.88 (online) summarizes the studies published since the last IARC Monograph (IARC, 2004a). A hospital-based case–control study of stomach cancer included 170 stomach cancer cases (121 men and 49 women) and 2184 controls (1309 men and 875 women) aged 30–75 years (Rao *et al.*, 2002). The association between bidi smoking and stomach cancer was not significant (RR, 0.8; 95%CI: 0.5–1.2) in a univariate analysis. The risk increased with increase in lifetime exposure to bidi smoking and was highly significant ($P < 0.001$).

One study investigated stomach cancer risk in association with smoking of *meiziol*, a local cigarette in Mizoram, India (Phukan *et al.*, 2005). Statistically significant higher risks were seen for

smokers of combined users of tobacco (cigarette and *meiziol*), with an odds ratio of 3.1 (95%CI: 2.0–11.1). Among users of a single type of tobacco, higher risks were seen for *meiziol* smokers (OR, 2.2; 95%CI: 1.3–9.3) in the multivariate model in comparison to cigarette smokers. Overall, the excess risk was limited to smokers of > 10 *meiziols* per day.

2.20 Synergistic effects of tobacco smoking and alcohol drinking

This section addresses the combined effects of smoking and alcohol consumption on cancers of oral cavity, pharynx, larynx and oesophagus, which have been examined extensively. For the purposes of this report interdependence of effects is termed *effect modification*, and *synergism* and *antagonism* are used to describe the consequences of the interdependence of disease risk when both risk factors are present (Rothman & Greenland, 1998). The studies varied in their methods and in the approaches used to assess effect modification, which ranged from descriptive to formal estimation of interaction terms in multivariate models. Study designs of the case–control and cohort studies are presented in Table 2.89 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.89.pdf>) and Table 2.90 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.90.pdf>), respectively; and the results for both study designs are presented in Table 2.91 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.91.pdf>).

2.20.1 Cancers of the upper aerodigestive tract

It was noted in the previous IARC Monograph (IARC, 2004a) with relatively large numbers of cases and controls that the pattern of increasing cancer risk with increasing alcohol consumption is strong (Mashberg *et al.*, 1993; Kabat *et al.*, 1994).

For cancers of the oral cavity, recent evidence comes from seven case-control studies and one cohort study. The pattern of odds ratios for smoking, across categories of alcohol consumption, is consistent with synergism. In four case-control studies with relatively large numbers of cases and controls (more than 200 cases and equivalent number of controls), the pattern of increasing cancer risks with increasing alcohol consumption was strong ([Schlecht *et al.*, 1999b](#); [Znaor *et al.*, 2003](#); [Castellsagué *et al.*, 2004](#); [Hashibe *et al.*, 2009](#)). In the cohort study from Taiwan, China ([Yen *et al.*, 2008](#)) similar strong risks were also observed. In all four case-control studies in which the estimate of formal statistical interaction was examined, the tests were statistically significant ([Schlecht *et al.*, 1999b](#); [Znaor *et al.*, 2003](#); [Castellsagué *et al.*, 2004](#); [Hashibe *et al.*, 2009](#)). In two case-control studies from India ([Znaor *et al.*, 2003](#); [Muwonge *et al.*, 2008](#)) and in the cohort study from Taiwan, China ([Yen *et al.*, 2008](#)) the interaction of tobacco smoking, alcohol and betel quid chewing was examined. In general, the results suggested increasing risks when betel quid chewing was included in the model.

Five case-control studies and one cohort study examined the effect of interaction between tobacco and alcohol in pharyngeal cancer. The results from case-control studies were similar to those observed for oral cancer ([Olsen *et al.*, 1985b](#); [Choi & Kahyo, 1991](#); [Schlecht *et al.*, 1999b](#); [Znaor *et al.*, 2003](#); [Hashibe *et al.*, 2009](#)). In a Singapore cohort study ([Friborg *et al.*, 2007](#)) the pattern of odds ratios for smoking across categories of alcohol consumption was consistent with synergism for oropharyngeal but not for nasopharyngeal cancer.

Two cohort and fourteen case-control studies reported on joint effects of tobacco smoking and alcohol drinking on the risk for oesophageal cancer. Since multiple logistic regression models were used for analysing most of these studies, some of them tested likelihood ratio test

for departure from multiplicativity of the individual effects of tobacco and alcohol. Generally, the positive results were stronger for squamous cell carcinoma. However, these tests for interaction are inadequate to assess synergy. Four studies from India and Taiwan, China, included betel quid chewing to the joint effect analysis of tobacco smoking and alcohol consumption and the results suggested increasing risks of oesophageal cancer.

Most of the twenty case-control studies of laryngeal cancer provided strong evidence for synergism of tobacco smoking and alcohol consumption. Only [Zheng *et al.* \(1992\)](#) did not find consistent evidence with synergism. In several studies, tests for interaction were carried out and reported to be 'non significant.' These were tests for departure from the multiplicative models, typically multiple logistic regression models, used to analyse the case-control data, and not tests for departure from additive model.

Several studies (14 case-control, 3 cohort) reported on cancer of the 'mixed upper aerodigestive tract', comprising studies on squamous cell carcinomas, regardless of specific sites. These studies also provided strong evidence for synergism.

The Working Group considers that there is strong evidence of tobacco smoking and alcohol consumption interaction on the incidence of upper aerodigestive tract cancers, as well as with regard to cancer of specific subsites of this anatomical region.

2.21 Synthesis

2.21.1 Lung

Tobacco smoking is the major cause of lung cancer, primarily from cigarettes. Duration of smoking is the strongest determinant of lung cancer in smokers. Risk also increases in proportion to the number of cigarettes smoked. The strong dose- and duration-response

relationships between lung cancer and tobacco smoking have been confirmed more recently in both questionnaire-based and biomarker-based studies. Tobacco smoking increases the risk of all histological types of lung cancer.

Differences in the intensity and/or duration of tobacco smoking may explain, in part, the lower lung cancer risks in Asian populations relative to whites. However, several studies of genetic polymorphisms among African-American and Caucasian populations provide some preliminary evidence supporting the hypothesis of a racial/ethnic disparity in susceptibility.

The results from observational studies do not provide strong support that a higher intake or a greater circulating concentration of carotenoids reduce lung cancer risk, particular in light of the elevated risk of lung cancer observed in the randomized trials of β -carotene supplementation. Residual confounding from smoking and the possibility that carotenoid measurements are serving as markers for a diet rich in total fruit and vegetables mitigate the likelihood of any protective role for total carotenoids or β -cryptoxanthins.

The specific genes that are responsible for enhanced lung cancer risk remain poorly understood, in spite of hundreds of candidate gene studies. Single-gene studies conducted to date have several limitations which contribute to inconclusive results, including small sample size and associated low power to detect moderate risks when allele frequencies are low.

2.21.2 Upper aerodigestive tract

(a) Oral cavity

Tobacco smoking is causally associated with cancer of the oral cavity in both men and women. Since the previous *Monograph*, additional evidence has accumulated that further confirms the association. Risk increases with duration and intensity of smoking, and decreases after quitting.

(b) Pharynx

Tobacco smoking is an important cause of oropharyngeal and hypopharyngeal cancers. The risk increases with increasing duration and intensity of smoking and decreases with increasing time since quitting.

(c) Nasal cavity and accessory sinuses

The evidence of an association between tobacco smoking and sinonasal cancer is based on the results from case-control studies, each of which may be subject to different sources of bias. However, presence of a dose-response relationship in most studies, the decrease in risk associated with time since quitting, the consistently higher risks for squamous-cell carcinoma than for adenocarcinoma and the lack of potential confounders support the existence of a causal association.

(d) Nasopharynx

Although the interpretation of the results is complicated by small sample sizes in several studies, by different criteria used for the selection of controls and by the control groups in some studies including smoking-related diseases, the combined evidence shows an association between tobacco smoking and nasopharyngeal carcinoma in both endemic and non-endemic areas. Most studies that adjusted for known and suspected causes of nasopharyngeal carcinoma such as intake of Chinese-style salted fish, other dietary factors, alcohol drinking and family history of nasopharyngeal carcinoma, suggested only a limited confounding effect of these factors. Adjustment for infection with Epstein-Barr virus (human herpes virus 4), a major cause of nasopharyngeal carcinoma worldwide, was possible in just one of the available studies. However, it is unlikely that confounding by infection with Epstein-Barr virus would explain the observed association between tobacco smoking and risk for nasopharyngeal carcinoma.

(e) Oesophagus

Several well conducted case-control studies found a statistically significant higher risk for adenocarcinoma of the oesophagus in smokers than in nonsmokers. Positive dose-response relationships obtained using various indicators of amount smoked support a causal association, which is further corroborated by the findings of decreasing risks after smoking cessation. Several of these studies reported relative risks adjusted for alcohol consumption and other potential confounders. Further risk factors, such as chewing betel quid with tobacco or use of other forms of smokeless tobacco, have not been considered in these populations, but are not likely to be strong confounders. Studies from Australia, China and Europe also found increased risks for smokers.

(f) Larynx

Laryngeal cancer is one of the cancers most strongly associated with cigarette smoking. Recent epidemiological evidence strengthens this conclusion.

2.21.3 Stomach

The additional epidemiologic data showing a consistent association of stomach cancer with tobacco smoking in both men and women greatly strengthens the previous conclusion of a causal association. There was insufficient evidence for differential risks between cardia and non-cardia stomach cancer. Confounding and effect modification by *H. pylori* has not been found.

2.21.4 Pancreas

The additional data supports the previous evaluation that cancer of the pancreas is causally associated with tobacco smoking. The risk increases with increasing daily consumption levels and duration of smoking and decreases with increasing time since cessation of smoking.

The risk remains elevated after accounting for potential confounding factors.

2.21.5 Colorectum

At the previous evaluation, there was already some evidence from prospective cohort and case-control studies that the risk of colorectal cancer is increased among tobacco smokers. However, inadequate adjustment for various potential confounders was considered to possibly account for some of the small increase in risk that appears to be associated with smoking. Since then, an appreciable amount of data has accumulated to support a causal association with smoking. In virtually all the cohort studies published since elevated risk associated with smoking was found, although not always statistically significant. More than half of the cohort studies that assessed dose-response relationships found statistically significant increasing risks with increasing daily cigarette consumption, duration of smoking and/or pack-years of smoking. Risk of colorectal cancer decreased with increasing delay in smoking initiation and years since cessation of smoking. A meta-analysis based on 36 cohort studies with data from a total of 3 million subjects found a significantly 15% increased risk of colorectal cancer and 27% higher risk of colorectal cancer mortality in current smokers compared to never smokers. A stronger association with smoking for rectal cancer than for colon cancer was found in the meta-analysis of the subset of cohort studies that differentiated colorectal cancer by site. Risk for colorectal cancer increased significantly by 17% and by 38% with 20 cigarettes and 40 cigarettes/day, respectively, and was elevated by 9.4% and by 19.7% with a 20-year and a 40-year duration of smoking, respectively. While these results are persuasive, this meta-analysis could not correct for the potential confounders in the individual studies. Convincing evidence has been provided by three large cohort studies that adjusted for at

least four important potential confounders (i.e. physical activity, alcohol consumption, body mass index and dietary intake of fruits and vegetables and/or meat); two studies also adjusted for history of colonoscopy. Significant dose–response relationships were found with one or more of the smoking variables, for risk of colorectal cancer and/or colon cancer and/or rectal cancer. Earlier cohort studies may not have been able to establish the association because of insufficient follow-up time and a limited number of cases. Updated results of several large cohort studies, which now show clearly significant increased risk of colorectal cancer associated with smoking, provide support for the lag-time hypothesis for smoking and colorectal risk.

Recent evidence suggests that smoking may be associated with the subtype of colorectal cancer characterized by microsatellite instability, and by CIMP status and BRAF mutation. For this subtype, the magnitude of risk associated with smoking reaches the twofold risk elevation consistently observed for colorectal adenomas and supported by a recent meta-analysis. Smoking has been associated with a stronger risk for hyperplastic polyps than for adenomas. Also, CIMP positivity and BRAF mutations have been associated with hyperplastic polyps, particularly serrated polyps. These data suggest that smoking may be associated primarily with a subtype of colorectal cancer that develops through a hyperplastic (serrated) polyp progression. The association with smoking may therefore be diluted when considering colon cancers overall.

2.21.6 Liver

Recent studies on smoking and hepatocellular carcinoma supports the established causal relationship. Supporting evidence comes from the consistency of the findings across regions (with the best evidence coming from Asian studies), and the observations of an association among non-drinkers and after controlling for hepatitis B or C virus infection.

2.21.7 Kidney

Recent evidence supports a causal association between kidney cancer and smoking. After adjustment for body mass index and hypertension, current and former smokers still had a greater risk for renal-cell cancer. A dose–response relationship with the number of cigarettes smoked has been noted in most studies, and a few also noted a reduction in risk after cessation.

2.21.8 Urinary bladder

Tobacco smoking is causally associated to bladder cancer, based on a large number of case–control and cohort studies that showed statistically significant associations not explained by confounding or bias. Risk increased with the duration of smoking and the number of cigarettes smoked. Also, stopping smoking at any age avoids the further increase in risk incurred by continued smoking. The evidence supporting a modulating role by *NAT2* polymorphisms is convincing.

2.21.9 Myeloid leukaemia

There is evidence for a causal association of tobacco smoking with myeloid leukaemia.

2.21.10 Breast

New evidence from cohort and case–control studies and from meta-analyses of genetic polymorphisms has become available since the previous *IARC Monograph* ([IARC, 2004a](#)). Results from seven new cohort studies consistently show a small overall association between current smoking and breast cancer incidence, with relative risk estimates ranging from 1.1–1.3 in studies with at least 100 exposed cases. The overall association is weaker than that observed with other cancers that have been designated as causally related to smoking, and the dose–response relationships (with years of smoking,

cigarettes smoked per day, age at initiation) are correspondingly small.

Emerging evidence from case-control studies suggests that inherited polymorphisms in the *NAT2* gene, which encode the slow acetylator phenotype, may modify (increase) the association between smoking and breast cancer. The p-value for interaction with pack-years of smoking as a continuous variable is statistically significant ($P = 0.03$) and another small study published since this meta-analysis supports the conclusion. The potential for publication bias remains of concern.

It is biologically plausible that tobacco smoke could be causally related to breast cancer risk. There are multiple chemicals in tobacco smoke that are known to cause mammary cancer in rodents. These substances reach the breast in humans; some are stored in adipose tissue, and some can be detected in nipple aspirate and DNA adducts.

Hypotheses have been proposed to explain why numerous well conducted epidemiological studies have generally not observed strong or consistent associations between tobacco smoking and breast cancer. Underlying all of these is the theory that tobacco smoking may have both protective and detrimental effects on breast cancer risk, which cancel each other out and which could explain the atypical dose-response relationship that has been reported between tobacco smoke and breast cancer from some studies.

2.21.11 Cervix

The largely positive findings observed in studies of cohort design, the relatively high consistency of positive associations found for squamous-cell carcinoma of the cervix (but not adenocarcinomas) across all epidemiological studies, including those with adjustment for a wide range of potentially confounding variables, and the positive associations observed in studies

restricted to HPV-positive individuals, all argue against the observed positive association being due to recall or selection bias or confounding.

2.21.12 Endometrium

The results of epidemiological studies to date, including recent studies, largely show inverse associations of smoking with risk of postmenopausal endometrial cancer. However, the Working Group noted the few studies of premenopausal cancer that were less consistent, as well as indications of an increased risk among smokers in a recent multicentre European study.

2.21.13 Prostate

Many epidemiological studies have examined the association between cigarette smoking and prostate cancer risk, and most have shown no consistent association. The question remains whether smoking may alter risk in various population subgroups.

2.21.14 Ovary

A causal association between cigarette smoking and risk for mucinous ovarian tumours is indicated by 1) the consistency of the positive association across the large majority of ten pooled case-control studies and ten additional independent epidemiological studies of both case-control and cohort design, 2) the relatively strong magnitude of the association (typically greater than a doubling of risk among current smokers), 3) the tendency to show dose-response associations with risk, such that current smokers generally have higher risk than former smokers and the dose-response observed with measures of smoking intensity in some (but not all) studies, and 4) the specificity of the positive association with the mucinous histological type, which argues against recall bias as an explanation of the findings.

2.21.15 Thyroid

A pooled analysis of 14 case–control studies showed that smoking was inversely associated with thyroid cancer risk. Similar inverse associations were also observed in two subsequent case–control studies.

2.21.16 Other sites

There is inconsistent or sparse evidence for an association between tobacco smoking and other cancer sites that were considered by the Working Group.

2.21.17 Bidi smoking

Overall, bidi smoking increases the risk for cancers of the oral cavity, oropharynx, hypopharynx, larynx, lung, oesophagus and stomach.

3. Cancer in Experimental Animals

3.1 Mainstream tobacco smoke

3.1.1 Mouse

There have been multiple studies of the carcinogenic potential of tobacco smoke in mice ([Table 3.1](#)). Lifetime exposure of several mouse strains to cigarette smoke failed to result in the production of lung tumours ([Harris & Negroni, 1967](#); [Otto & Elmenhorst, 1967](#); [Henry & Kouri, 1986](#)). However, studies involving lifetime exposure of C57BL mice to a mixture of flue-cured or air-cured cigarette smoke or to the gas phase of flue-cured cigarette smoke led to significant increases in the number of lung tumours (adenomas) ([Harris *et al.*, 1974](#)). Similarly, lifetime exposure of Snell's mice to the gas phase of cigarette smoke led to an increased incidence of lung adenocarcinomas ([Leuchtenberger & Leuchtenberger, 1970](#)). Exposure of B6C3F₁

female mice to smoke for lifetime led to increased incidence of lung adenomas, bronchiolar papillomas and lung adenocarcinomas in smoke-exposed mice. In addition, the occurrence of squamous cell carcinomas of the nasal cavity in smoke-exposed mice was increased ([Hutt *et al.*, 2005](#)). In a recent study, Swiss mice were exposed whole-body to cigarette smoke for 120 days, starting within 12 hours of the birth. Smoke-exposed mice developed microscopic lung tumours beginning only 75 days after birth and reaching an overall incidence of 78.3% after 181–230 days. The mean lung tumour multiplicity was 6.1 and 13.6 tumours per mouse in males and females, respectively. In addition, malignant tumours, some of which may have had a metastatic origin, were detected in the urinary tract of smoke-exposed mice ([Balansky *et al.*, 2007](#)).

3.1.2 Rat

Several studies have evaluated the carcinogenic potential of mainstream tobacco smoke in rats ([Table 3.1](#)). Exposure of Wistar rats to cigarette smoke for lifetime did not increase the lung tumour incidence ([Davis *et al.*, 1975](#)). In contrast, exposure of Fischer 344 rats to a mixture of non-filter cigarette smoke for 128 weeks resulted in an increased incidence of nasal and lung tumours. There was also an increase in subcutaneous sarcomas at forelimb ulceration sites ([Dalbey *et al.*, 1980](#)). CDF rats were exposed to low-dose cigarette smoke (LCS) or high-dose cigarette smoke (HCS) for 126 weeks. The incidence of lung tumours was significantly higher only in female rats that received HCS ([Finch *et al.*, 1995](#)). In a recent study, Fischer 344 rats received whole body exposure to smoke containing either 100 mg (LCS) or 250 mg (HCS) total particulate matter/m³ for 30 months. This led to significant increases in the incidence of lung and nasal cavity tumours in male rats treated with HCS but not with LCS. In female rats, there were significant increases in the incidence of lung adenomas

in animals treated with HCS and of all lung tumours in animals treated with both LCS and HCS. There was also a significant increase in the occurrence of nasal cavity tumours in female rats treated with HCS ([Mauderly et al., 2004](#)).

3.1.3 Hamster

Four studies have evaluated the ability of mainstream tobacco smoke to induce tumours in hamsters ([Table 3.1](#)). Syrian golden hamsters were exposed to either a mixture of German reference cigarette smoke or of dark air-cured cigarette smoke for lifetime. There were increases in the incidence of laryngeal carcinomas in hamsters exposed to both smoke preparations ([Dontenwill et al., 1973](#)). In a subsequent study, hamsters were exposed to a mixture of German reference cigarette smoke containing 1.5 mg nicotine, 0.173 mg phenol and 12.7 mL carbon monoxide/cigarette for lifetime. The incidence of laryngeal tumours in smoke-exposed hamsters was higher than in controls ([Dontenwill et al., 1977](#)). BIO male hamsters exposed to a mixture of US reference smoke for 100 weeks developed laryngeal and nasopharyngeal tumours ([Bernfeld et al., 1974](#)). In a subsequent study, male BIO hamsters exposed to smoke from commercial British filter cigarettes developed higher incidence of laryngeal tumours than controls ([Bernfeld et al., 1979](#)).

3.2 Co-administration of tobacco smoke with known carcinogens and other agents

Study design and results of the studies on co-administration of tobacco smoke with known carcinogens and other agents are summarized in [Table 3.2](#).

3.2.1 Rat

(a) Benzo[a]pyrene

Wistar rats received a single intratracheal instillation of 2 mg benzo[a]pyrene followed by lifetime exposure to cigarette smoke. This treatment led to a low incidence of lung tumours that was not significantly higher than in controls ([Davis et al., 1975](#)). In another study Wistar rats were given intratracheal instillations of benzo[a]pyrene mixed with ferric oxide and exposed to cigarette smoke either during initiation and post-initiation or only after treatment with benzo[a]pyrene/ferric oxide (post-initiation). Inhalation of cigarette smoke during the initiation and post-initiation phases of carcinogenesis resulted in a higher lung tumour (squamous-cell carcinoma) multiplicity than that seen in rats exposed during the post-initiation phase only ([Gupta et al., 1990](#)).

(b) Radon progeny

Sprague-Dawley rats were exposed to radon progeny at cumulative doses of 4000, 500 or 100 work-level-months (WLM), with or without concurrent exposure to cigarette smoke by inhalation for one year. Rats exposed to 4000 WLM radon progeny, without exposure to smoke, developed lung carcinomas (17/50). Thirty four carcinomas were seen in 50 rats exposed to radon and cigarette smoke. The 500 WLM radon progeny group exposed to radon only had 2/28 lung carcinomas as compared with 8/30 rats exposed to radon and cigarette smoke. No tumours were observed in rats treated with 100 WLM radon and one carcinoma was seen among 30 rats exposed to 100 WLM radon and cigarette smoke. Seventy five percent of the lung tumours were squamous-cell carcinomas, 20% were adenocarcinomas, and the remainder were undifferentiated carcinomas ([Chameaud et al., 1982](#)).

Table 3.1 Carcinogenicity in response to mainstream tobacco smoke in animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, C57BL (M, F) Harris & Negroni (1967)	100 animals/sex/group Nose-only, mixture of fresh non-filter cigarette smoke/ air (1/39, v/v), nicotine, 0.1 mg/mL; CO, 0.064% (v/v), 12 min/every other d; lifetime	Nicotine, 14–17 µg	Alveolar adenocarcinomas: M: 4/100 (alveolar adenocarcinoma) Controls–0/100 F: 4/100 (alveolar adenocarcinoma) Controls–0/100	$P = 0.06$ $P = 0.06$	
Mice, C57BL and BLH (sex, NR) Otto & Elmenhorst (1967)	126 animals/group Whole-body, gas phase of 12 cigarettes puffed 2 sec/ min, concentration (NR), 90 min/d; lifetime (~27 mo)	NR	Lung (adenomas): C57BL–7/126 (5.5%) Controls–3/90 (3%) BLH–40/126 (32%) Controls–19/60 (32%)	NS NS	
Mice, (C57BL/Cum × C3H/ Anf Cum) _{F₁} (F) Henry & Kouri (1986)	2053, 1 014 sham Nose-only, 10% smoke from US reference cigarettes, concentration (NR), smoke 20 sec/min, 6–8 min/d, 5 d/wk for 110 wk; 116 wk	Particulate deposition, 125–200 µg	Alveolar adenocarcinomas: 19/978 (2%) Sham-exposed controls–7/651 (1%)	$P = 0.10$	Shorter latency of tumour occurrence in smoke-exposed group suggested
Mice, C57BL (M, F) Harris et al. (1974)	100 animals/sex/group Nose-only, mixture of fresh flue-cured or air-cured cigarette smoke/air (1/39, v/v), concentration (NR), 12 min/d on alternate d; lifetime	NR	M: 9/162 ^a (5%, flue-cured), 7/189 ^a (4%, air-cured) Controls–3/160 ^a (2%) F: 7/164 ^a (4%, flue-cured), 0/173 (air-cured) Controls–1/159 ^a (1%)	$P = 0.07$, flue-cured $P > 0.05$, air-cured $P = 0.04$, flue-cured	
	Nose-only, gas phase of flue-cured cigarette smoke, concentration (NR), 12 min/d on alternate d; lifetime	NR	M: 3/8 ^a (37%) Controls–3/160 ^a (2%) F: 2/88 ^a (2%) Controls–1/159 ^a (1%)	$P > 0.05$ $P > 0.05$	

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, Snell (M, F) Leuchtenberger & Leuchtenberger (1970)	160 M, 118 F Whole-body, whole fresh cigarette smoke, concentration (NR), 2 puffs, 1 × /d, lifetime (26 mo)	Nicotine, 5 µg	M: Lung A-7/107 (6.5%) Controls-8/106 (7.5%)	NS	
			Lung AdC-11/107 (10%) Controls-5/106 (4.7%)	P = 0.15	
			F: Lung A-2/65 (3%) Controls-1/78 (1.2%)	P = 0.475	
			Lung AdC-5/65 (7.7%) Controls-3/78 (3.8%)	P = 0.035	
	100 M, 89 F Whole-body, gas phase of fresh cigarette smoke, concentration (NR), 2 puffs, 1 × /d, lifetime (26 mo)	NR	M: Lung A-1/44 (2%) Controls-8/106 (7%)	NS	
			Lung AdC-10/44 (23%) Controls-5/106 (5%)	P = 0.005	
			F: Lung A-3/44 (7%) Controls-1/78 (1%)	P = 0.15	
			Lung AdC-5/44 (11%) Controls-3/78 (4%)	P = 0.15	
			Lung A: 93/330 (28%) Sham-exposed controls-22/326 (7%)	P < 0.001 P < 0.007	
			Bronchiolar papillomas: 15/330 (4%) Controls-0/326	P < 0.001	
Mice, B6C3F1 (F) Hutt et al. (2005)	330, 326 controls Whole-body, smoke from Kentucky 2R1 unfiltered reference cigarettes, 250 mg total particulate matter/m ³ , 6 h/d, 5 d/wk for 30 mo; 30 mo or lifetime	NR	Lung AdC: 67/330 (20%) Controls-9/326	P < 0.001	
			All lung tumours: 148/330 (45%) Controls-31/326	P < 0.001 ^b	
			Nasal cavity tumours: 20/330 (6%) Controls-0/326	P = 0.002, one-tailed Fisher	
			Squamous-cell carcinomas: 9/330 (3%) Controls-0/326		

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, Swiss (M, F) Balansky <i>et al.</i> (2007)	38, 36 controls (neonatal mice, 21 h of age) Whole-body, cigarette smoke/air, 818 mg total particulate matter/m ³ , 65 min/d for 120 d	NR	Lung A: 15/38 (19%) Sham-exposed controls–0/36 Lung AdC: 7/38 (18%) Controls–0/38 Kidney A: 6/16 (16%) (F only) Controls–0/21 Liver carcinomas: 2/16 (5%) (F only) Controls–0/21	$P < 0.001$ $P < 0.01$ $P < 0.01$	
Rats, Wistar (F) Davis <i>et al.</i> (1975)	408, 102 untreated, 102 sham Nose-only, mixture of cigarette smoke/air (1/5), concentration (NR), 15 sec/min, 2 × 11 min/d, 5 d/wk, lifetime	NR	4/408 (1%) (1 lung C and 3 lung neoplasms of uncertain malignancy) Controls–0/102 Sham treated controls–0/102	NS	
Rats, F344 (F) Dalbey <i>et al.</i> (1980)	80, 63 untreated, 30 sham Nose-only, mixture of non-filter cigarette smoke/ air (1/10), 18.4 mg smoke particulate and 0.89 mg nicotine/cigarette, 1 cigarette/h, 7 cigarettes/d, 5 d/wk for 128 wk; 160 wk	Particulate deposition, 1.75 mg/d	10/80 (12%) (1 nasal AdC, 1 nasal C, 5 pulmonary A, 1 pulmonary C, 2 alveoleogenic C) Controls–3/93 (3%) Subcutaneous sarcomas at forelimb ulceration sites: 21/80 (26%) Controls–0/93	$P < 0.05$ $P < 0.05$	
Rats, CDF ^a (F344)/CrIBR (M, F) Finch <i>et al.</i> (1995)	2165 animals Whole-body, cigarette smoke/air, 100 mg (LCS) or 250 mg (HCS) total particulate matter/m ³ , 6 h/d, 5 d/ wk for 30 mo; lifetime	NR	Lung tumours: M: LCS 3/173 (2%) HCS 7/78 (9%) Filtered air 3/119 (2%) F: LCS–4/145 (3%) HCS–6/83 (7%) Filtered air–0/113	$P < 0.05$ $P < 0.05$	

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rats, F344 (M, F) Mauderly et al. (2004)	M: 178 LCS, 82 HCS F: 175 LCS, 81 HCS Whole-body, smoke from Kentucky 1R3 unfiltered reference cigarettes, 100 mg (LCS) or 250 mg (HCS) total particulate matter/m ³ , 6 h/d, 5 d/wk for 30 mo; lifetime	NR	<p>M: Lung A– LCS 4/178 (2%) HCS 2/82 (2%) Sham-exposed controls 1/118 (1%)</p> <p>Lung AdC– LCS 1/178 (1%) HCS 5/82 (6%) Controls 3/118 (3%)</p> <p>All lung tumours– LCS 4/178 (2%) HCS 7/82 (8%) Controls 4/118</p> <p>Nasal cavity (all tumour types)– LCS 1/178 (1%) HCS 5/82 (6%) Controls 1/118 (1%)</p> <p>F: Lung A– LCS 7/175 (6%) HCS 7/81 (9%) Sham-exposed controls 0/119</p> <p>AdC– LCS 4/175 (2%) HCS 4/81 (5%) Controls 0/119</p> <p>All lung tumours– LCS 10/175 (6%) HCS 11/81 (13%) Controls 0/119</p> <p>Nasal cavity (all tumour types)– LCS 0/175 HCS 3/81 Controls 0/119</p>	<p>NS</p> <p>NS</p> <p>NS; trend, $P = 0.055$</p> <p>$P = 0.032$ (HCS); trend, $P = 0.010$</p> <p>NS (LCS); $P < 0.001$ (HCS)</p> <p>NS</p> <p>$P = 0.023$ (LCS); $P = 0.001$ (HCS)</p> <p>$P = 0.020$ (HCS); trend, $P = 0.003$</p>	

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Hamsters, Syrian golden (M, F) Dontenwill et al. (1972)	80 animals/sex/group Whole-body, mixture of German reference cigarette smoke/air (1/15), concentration (NR), smoke of 30 cigarettes for 7–10 min; 1, 2 or 3 × /d, 5 d/wk, lifetime	NR	Laryngeal carcinomas: 1/160 (1%), 17/160 (11%) and 11/160 (7%) Controls–0/80		
	Whole-body, mixture of dark air-cured cigarette smoke/air (1/15), concentration (NR), Smoke of 30 cigarettes for 7–10 min; twice/d, 5 d/wk, lifetime	NR	Laryngeal carcinomas: 2/160 (1%) Controls–0/80		
Hamsters, Syrian golden (M, F) Dontenwill et al. (1972)	80 animals/group Whole-body, mixture of German reference cigarette smoke/air (1/15), 1.5 mg nicotine, 0.173 mg phenol and 12.7 mL CO/cigarette, smoke of 30 cigarettes for 7–10 min; 1, 2 or 3 × /d, 5 d/wk, lifetime	NR	M: Laryngeal C–0, 4, 6 and 11%, Controls–0% F: Laryngeal C–0, 1, 2 and 7% Controls–0%		
	102 animals/group Whole-body, mixture of US reference cigarette smoke/ air (1/5), concentration (NR), duration (NR)		Inbred BIO 15.16: Laryngeal tumours–9/84 (10%) Nasopharyngeal tumours–2/84 (2%) Sham-exposed controls 0/42 Controls 0/40 Inbred BIO 87.20: Laryngeal tumours–2/87 (2%) Sham-exposed controls 0/44 Controls 0/48		
Rats, Inbred BIO 15.16 (M) Bernfield et al. (1979)	Number at start (NR) Whole-body, 11 or 22% smoke from commercial British filter cigarettes, concentration (NR), 2 × 12 min/d, 7 d/wk for 35–42 wk; up to 74–80 wk	NR	Laryngeal carcinomas: 11% smoke–3/44 (7%) 22% smoke–27/57 (47%) Sham-exposed controls 0/36; Controls 0/50		

^a Most of these lung tumours are adenomas^b Nasal cavity tumours included 14 squamous cell carcinomas (5 in situ), 5 hemangiomas, and 1 respiratory papilloma
A, adenoma; AdC, adenocarcinoma; C, carcinoma; CO, carbon monoxide; d, day or days; F, female; h, hour or hours; HCS, high cigarette smoke; LCS, low cigarette smoke; M, male;
min, minute or minutes; mo, month or months; NR, not reported; NS, not significant; sec, second or seconds; wk, week or weeks; yr, year or years

Table 3.2 Carcinogenicity in response to exposure to mainstream tobacco smoke in conjunction with exposure to known carcinogens or other agents in animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rats, Wistar (F) Davis et al. (1975)	84 or 408 animals/group A single intratracheal instillation of benzo[a]pyrene (2 mg) + infusine + carbon black followed by British reference cigarette smoke/air (1/5); 1 cigarette, twice/d, 5 d/wk, lifetime	3/84 (4%, lung C), 1/84 (1%, lung C; benzo[a]pyrene alone), 4/408 (1%, 3 A + 1 malignant neoplasm; cigarette smoke only), 0/204 (controls + sham-exposed controls)	NS
Rats, Wistar (M) Gupta et al. (1990)	35 animals/group Cigarette smoke; 5 cigarettes/8.2 L air; 1 h/d during 2nd–24th wk or 10th–24th wk of the study Benzo[a]pyrene (20 mg) + Fe ₂ O ₃ ; intratracheally (3 weekly doses) during 6th–8th wk of the study; 24 wk	Conventional diet: 2nd–24th wk, 2.14 lung C/animal; 10th–24th wk, 1.33 lung C/animal; benzo[a]pyrene control, 1.22 lung C/animal. Vitamin A-deficient diet: 2nd–24th wk, 2.86 lung C/animal; 10th–24th wk, 1.67 lung C/animal; benzo[a]pyrene control, 1.83 lung C/animal	
Rats, Sprague-Dawley, sex NR Chameaud et al. (1982)	28–50 animals/group French reference cigarette smoke (9 cigarettes/500 L air); 10–15 min session, 4 d/wk for 1 yr Radon progeny (4 000, 500 or 100 WLM) Lifetime	4000 WLM: 34/50 (68%, lung C); 17/50 (34%, lung C; radon progeny alone) 500 WLM: 8/30 (27%, lung C); 2/28 (7%, lung C; radon progeny alone) 100 WLM: 1/30 (3%, lung C); 0/50 (radon progeny alone)	P = 0.0015
CDF (F344)/CrIBR (M, F) Finch et al. (1995)	Number at start (NR) Cigarette smoke/air, 100 mg (LCS) or 250 mg (HCS) total particulate matter/m ³ ; 6 h/d, 5 d/wk for 126 wk ²³⁹ PuO ₂ aerosol, 1 wk (6th wk of the study); > 52 wk	49–61% (lung tumours, LCS + ²³⁹ PuO ₂) 72–74% (HCS + ²³⁹ PuO ₂) 20–33% (²³⁹ PuO ₂) 2–3% (LCS) 7–8% (HCS)	
Syrian golden (M, F) Dontenwill et al. (1973)	80 animals/sex/group German reference cigarette smoke/air (1/15); Smoke of 30 cigarettes for 7–10 min; twice/d, 5 d/wk, lifetime DMBA (0.5 mg); intratracheally 10 d before the beginning of smoke exposure	32/160 (20%, laryngeal C), 17/160 (11%, laryngeal C; smoke only), 0/160 (DMBA alone)	

Table 3.2 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Syrian golden, (sex NR) Hoffmann <i>et al.</i> (1979)	20 or 40 animals/group Cigarette smoke/air (1/7); Cigarette smoke 2 × 10 min/d, 5 d/wk, 48 wk DMBA (0.24 mg); intralaryngeally	3/40 (7%, laryngeal C), 0/20 (smoke only), 0/20 (DMBA alone)	
Syrian golden (M) Takahashi <i>et al.</i> (1992)	10 or 30 animals/group Cigarette smoke/air (1/7); Smoke of 30 cigarettes for 9 min; twice/d, 5 d/wk, 12 wk NDEA (100 mg/kg bw); subcutaneously	Non-filter cigarettes (2.10 ± 1.74 P+H/animal) and filter cigarettes (1.93 ± 1.55 P + H/animal) versus sham-exposed (0.97 ± 1.03 P + H/animal)	<i>P</i> < 0.01 <i>P</i> < 0.01
Syrian golden (M) Harada <i>et al.</i> (1985)	30 animals/group Non-filter cigarette smoke/air (1/7); Smoke of 30 cigarettes for 6 min: twice/d, 5 d/wk, 58 wk NDEA (10 mg/hamster); subcutaneously (12 weekly doses)	Nasal cavity tumours 14/30 (47%, smoke + NDEA), 5/30 (17%, NDEA alone)	<i>P</i> < 0.05

A, adenoma; bw, body weight; C, carcinoma; d, day or days; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; h, hour or hours; HCS, high cigarette smoke; LCS, low cigarette smoke; M, male; min, minute or minutes; mo, month or months; NDEA, *N*-nitrosodiethylamine; NR, not reported; NS, not significant; P + H, epithelial hyperplasias and papillomas; sec, second or seconds; wk, week or weeks; WLM, work-level-months; yr, year or years

(c) *Plutonium oxide*

CDF®/CrlBR rats were exposed to either filtered air or mainstream cigarette smoke at concentrations of either 100 or 250 mg total particulate matter/m³ (LCS and HCS groups, respectively). At 12 weeks, rats were removed from smoke chambers and exposed nose-only to plutonium oxide (²³⁹PuO₂) then returned to the smoke chambers one week later for 30 months of continuous exposure to either filtered air or cigarette smoke. The incidence and multiplicity of lung tumours (adenocarcinomas, squamous-cell carcinomas, adenosquamous carcinomas) in animals exposed to both concentrations of cigarette smoke and ²³⁹PuO₂ were higher than those in animals exposed to ²³⁹PuO₂, LCS or HCS alone (Finch *et al.*, 1995).

3.2.2 Hamster

(a) *7,12-Dimethylbenz[a]anthracene*

Groups of 160 Syrian golden hamsters received 7,12-dimethylbenz[a]anthracene (DMBA) intratracheally, followed by cigarette smoke for life, or treated with cigarette smoke or DMBA only. A total of 32 squamous-cell carcinomas of the larynx were observed in animals treated with both DMBA and cigarette smoke, in comparison with 17 in hamsters exposed to cigarette smoke only and none in hamsters treated with DMBA alone (Dontenwill *et al.*, 1973). Similar results were reported from other experiments in which Syrian golden hamsters were exposed to DMBA and cigarette smoke (Hoffmann *et al.*, 1979).

(b) *N-Nitrosodiethylamine*

Groups of hamsters received a single subcutaneous injection of *N*-nitrosodiethylamine (NDEA) and then were exposed to smoke from unfiltered cigarettes, filtered cigarettes and sham smoke. Controls were exposed to either unfiltered cigarette smoke, filtered cigarette smoke or sham smoke. In the NDEA-smoke-treated

groups, epithelial hyperplasias and/or papillomas of the larynx were induced at higher frequency than in controls (Takahashi *et al.*, 1992). Hamsters exposed to cigarette smoke in air also received 12 weekly subcutaneous injections of NDEA (total dose, 10 mg/hamster). Treatment with NDEA only resulted in both benign and malignant tumours of the respiratory tract, and co-exposure to cigarette smoke potentiated the development of tumours in the nasal cavity (Harada *et al.*, 1985).

3.3 Smoke condensates

Study design and results of the studies on administration of tobacco smoke condensates are summarized in Table 3.3.

3.3.1 Skin application

(a) *Mouse*

Cigarette-smoke condensate produces both benign and malignant tumours on mouse skin. The carcinogenic potency of the cigarette-smoke condensate depends upon tobacco variety, composition of cigarette paper and the presence of additives (Wynder *et al.*, 1957; Gargus *et al.*, 1976; Gori, 1976).

(b) *Rabbit*

Cigarette-smoke condensate induced skin papillomas and carcinomas when applied to the ears of rabbits for lifetime (Graham *et al.*, 1957).

3.3.2 Intrapulmonary administration

Injection of 24 mg cigarette-smoke condensate into the lungs of female Osborne Mendel rats led to the development of squamous cell carcinomas (Stanton *et al.*, 1972). These observations were confirmed by Dagle *et al.* (1978) who observed a dose-dependent incidence of lung carcinomas when cigarette-smoke condensate prepared from two types of cigarettes were given.

Table 3.3 Carcinogenicity in response to exposure to cigarette-smoke condensate in animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mice CAF1 (M, F) Wynder et al. (1953)	112, 44 controls Skin painting (dorsal) of CSC, CSC/acetone solution (40 mg CSC/ application), 3 × /wk, lifetime	36/81 (44%, skin epidermoid C), 0/30 (acetone controls)	
Mice ICR Swiss (F) Gargus et al. (1976)	5200 Skin painting (dorsal) of CSC, CSC/acetone solution (150 mg or 300 mg CSC/wk), 6 × /wk, 78 wk	482/5200 (9%, skin C), 3/800 (0.4%, acetone controls) ^a	
Mice ICR Swiss (F) Gori (1976)	4900 Skin painting (dorsal) of CSC, CSC/acetone solution (25 mg or 50 mg CSC/application), 6 × /wk, 78 wk	1157/4900 (24%, skin C), 0/800 (acetone controls)	
Mice, ICR/Ha Swiss (F) Hoffmann & Wynder (1971)	30 animals/group Skin painting (dorsal) with CSC active fraction with or without subsequent painting of the skin with croton oil, CSC active fraction/acetone (2.5 mg of 0.6% CSC/application), 10 times on alternate d Croton oil (2.5%), 3 × /wk, up to 12 mo, 10 d after last CSC active fraction application; 15 mo	After 12 and 15 mo: 4/30 (13%, skin C), 0/65 (croton oil controls)	
Mice, Swiss (F) Wynder & Hoffmann (1961)	30–50 animals/group Skin painting (dorsal) of CSC with or without initiation by DMBA application; DMBA (75 µg); CSC/acetone (75 mg CSC/application, start: 1 wk after DMBA application), 2–3 × /wk, 12 mo; 15 mo	DMBA: 2/30 (7%, skin C) 2 × CSC: 1/40 (3%, skin C) DMBA + 2 × CSC: 8/30 (27%, skin C) 3 × CSC: 11/50 (22%, skin C) DMBA + 3 × CSC: 11/30 (37%, skin C)	
Mice, SENCAR (F) Meckley et al. (2004a)	40 animals/group Skin painting (dorsal) of CSC from Kentucky IR4F reference cigarettes, with or without initiation by DMBA application; DMBA (75 µg) or acetone, 1x. Then starting 1 wk after DMBA or acetone: CSC in acetone, 0, 10, 20 or 40 mg/application, 3 × /wk, 29 wk; 31 wk	Mean mice with tumours/mice per group at 31 wk: No DMBA: 0/40 acetone-acetone, 9/40 (22%) acetone-CSC 40 mg/treatment DMBA/CSC: 0/40, 3/40 (1.0), 16/40 (75 tumours/16 mice = 4.7), 32/40 (200 tumours/32 mice = 6.3)	
Mice, SENCAR (F) Meckley et al. (2004b)	40 animals/group Skin painting (dorsal) of CSC from Kentucky IR4F reference cigarettes or ECLIPSE (non-burned) cigarettes, with or without initiation by DMBA application; DMBA (75 µg) or acetone, 1 × . Then starting 1 wk after DMBA or acetone: CSC in acetone, 0, 10, 20 or 40 mg/application, 3 × /wk, 29 wk; 31 wk	No DMBA: acetone/acetone 0/40 (0); acetone/1R4F CSC 40 mg, 9/40 (1.8); acetone/ECLIPSE CSC 40 mg, 0/40 (0) DMBA/CSC: acetone, 0/40 (0); 1R4F CSC 10 mg, 6/40 (1.8); 1R4F CSC 12 mg, 28/40 (6.6); 1R4F CSC 40 mg, 36/40 (6.8); ECLIPSE CSC, 0/40 (0); ECLIPSE CSC 10 mg, 1/40 (1); ECLIPSE CSC 20 mg, 2/40 (5.5); ECLIPSE CSC 40 mg, 12/40 (2.6)	

Table 3.3 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mice, SENCAR (F) Hayes et al. (2007)	40 or 50 animals/group Skin painting (dorsal) of CSC from heat-exchanged flue cured tobacco (HE; low TSNA) or direct-fire (DF) cured tobacco, with or without initiation by DMBA application; DMBA (75 µg) or acetone, 1 × . Then starting 1 wk after DMBA or acetone: CSC/acetone, 0, 9, 18, or 36 mg/ application, 3 × /wk, 29 wk; 31 wk	No DMBA: acetone/acetone 0/40; acetone/DF CSC 36 mg, 5/50 (1.4); acetone/HE CSC 36 mg, 8/50 (1.3) DMBA/CSC: DF CSC, 0/40, DF CSC 9 mg, 15/40 (5.5); DF CSC 18 mg, 30/40 (10.0); DF CSC 36 mg, 43/50 (8.2); HE CSC, 0/40, HE CSC 9 mg, 17/40 (4.8); HE CSC 18 mg, 32/40 (7.3); HE CSC 36 mg, 42/50 (8.5)	$P < 0.05$ $P < 0.05$ $P < 0.05$
Mice, Swiss albino (M) Pakhale et al. (1988)	20 animals/group Oral gavage of Indian bidi smoke condensate; 1 mg bidi smoke condensate/0.1 mg DMSO, 5 d/wk, 55 wk; 90 wk	4/15 (27%, hepatic haemangiomas); 1/15 (7%, stomach papilloma); 1/15 (7%, stomach carcinoma); 1/15 (7%, oesophageal carcinoma); 0/15 (untreated or DMSO-treated controls)	
Rats, Osborne Mendel (F) Stanton et al. (1972)	Number/group at start (NR) Intrapulmonary administration of CSC pellet; CSC/ beeswax:tricaprylin (24 mg CSC/injection), up to 107 wk after implantation	14/40 ^c (35%, lung squamous-cell C), 0/63 ^c (beeswax:tricaprylin controls)	
Rats, OM/NCR (F) Dagle et al. (1978)	120 ^d Intrapulmonary administration of CSC pellet; CSC/ beeswax:tricaprylin (5, 10, 20 or 67 mg CSC/injection), 120 wk after implantation	4, 10, 20 and 42% pulmonary C prevalence; 0% C prevalence for 3 control groups of about 190 rats each	
Rabbits, Albino New Zealand (M, F) Graham et al. (1957)	38, 7 controls Skin painting of CSC (both ears); CSC/acetone solution (100 mg CSC/ application/ear), 5 × /wk, lifetime (4–6 yr)	4/38 (11%, 2 skin C + 1 skin liposarcoma + 1 skin fibrosarcoma), 0/7 (acetone controls)	

^a Skin papillomas^b Mostly adenomas^c Incidence in animals that died 43–107 weeks after injection^d 4 × 10 rats/group terminated before 120 weeks^e Total visually identified and histologically confirmed skin tumours included mostly squamous papillomas and carcinomas [Tumour incidences and multiplicities estimated from graphs]C, carcinoma; CSC, cigarette-smoke condensate; d, day or days; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMSO, dimethyl sulfoxide; F, female; M, male; NR, not reported; TSNA, tobacco-specific *N*-nitrosamines; wk, week or weeks

3.3.3 Initiation-promotion skin painting studies

Cigarette-smoke condensate and its fractions can act as skin co-carcinogens in Swiss and SENCAR mice when tested in conjunction with croton oil ([Hoffmann & Wynder, 1971](#)) or DMBA ([Wynder & Hoffmann, 1961](#); [Meckley et al., 2004a, b](#); [Hayes et al., 2007](#)).

3.3.4 Bidi smoke

Swiss albino mice administered 1 mg bidi smoke condensate in dimethyl sulfoxide (DMSO) by oral gavage developed haemangiomas (4/15), stomach carcinoma (1/15), and esophageal carcinoma (1/15), whereas no tumours were observed in controls ([Pakhale et al., 1988](#)).

3.4 Synthesis

Mainstream tobacco smoke induced lung tumours in mice, lung and nasal cavity tumours in rats and laryngeal carcinomas in hamsters.

Co-administration of tobacco smoke with benzo[*a*]pyrene, radon progeny and plutonium resulted in higher lung tumour responses in rats than administration of either agent alone. Hamsters exposed to cigarette smoke and either DMBA or NDEA had higher lung tumour responses compared to cigarette smoke, DMBA or NDEA alone.

Topical application of cigarette-smoke condensate led to the development of skin tumours in mice and rabbits; intrapulmonary administration of cigarette-smoke condensate induced squamous cell carcinomas in rat lung.

4. Other Relevant Data

4.1 Overview of the mechanistic evidence for the carcinogenicity of tobacco

4.1.1 Conceptual model of the carcinogenesis of tobacco and tobacco smoke

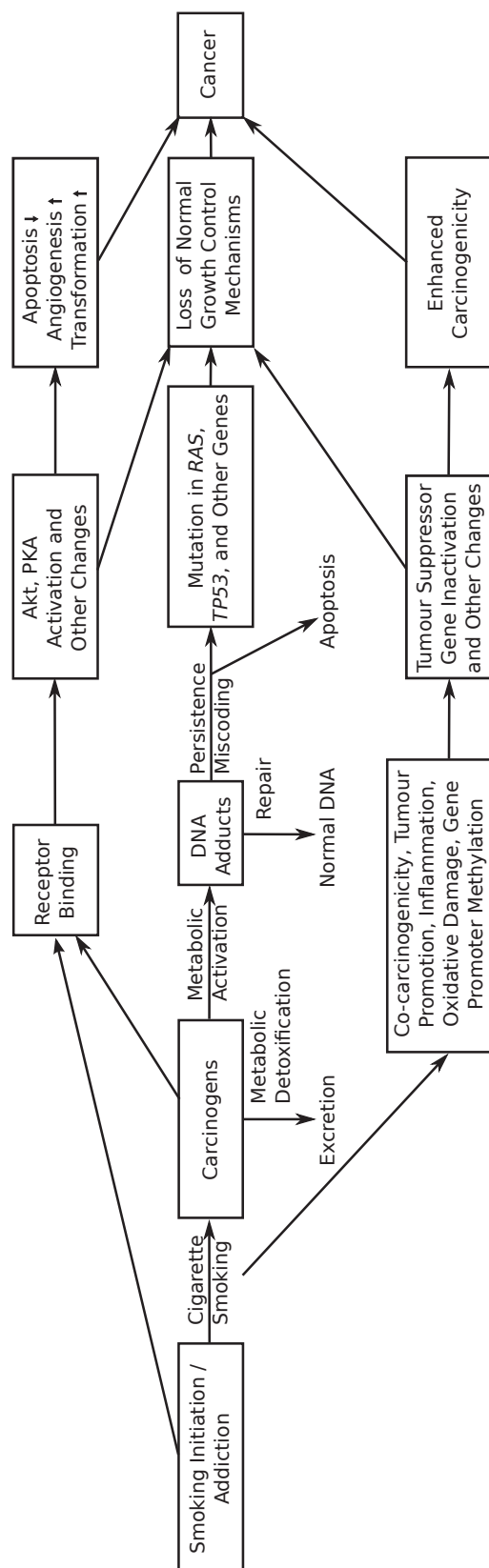
A conceptual model for understanding mechanisms by which tobacco smoke causes cancer is shown in Fig. 4.1 ([Hecht, 1999, 2003](#)). This model also applies to smokeless tobacco and other forms of smoked tobacco and, in theory, to second-hand tobacco smoke since it contains all of the same carcinogens and toxicants as mainstream cigarette smoke, although at lower doses.

The major accepted mechanistic pathway is summarized in the central track of Fig. 4.1. Smokers inhale carcinogens which, either directly or after metabolism, covalently bind to DNA, forming DNA adducts. DNA adducts are central to chemical carcinogenesis because they can cause miscoding and permanent mutations. If these mutations occur in critical regions of oncogenes and tumour suppressor genes, which are essential in growth control, the result can be loss of normal cellular proliferation mechanisms, genomic instability, and cancer. A study that sequenced 623 cancer-related genes in 188 human lung adenocarcinomas validated this premise by finding multiple somatic mutations in critical growth control genes, consistent with the chronic bombardment of cellular DNA by tobacco smoke carcinogens and their metabolically activated forms ([Ding et al., 2008](#)).

Each step of this conceptual model is considered in detail below.

Most people begin smoking cigarettes when they are teenagers, and become addicted to nicotine. Nicotine is not generally considered to be a carcinogen ([Schuller, 2009](#)), but it is accompanied in each puff of each cigarette by a complex

Fig. 4.1 Conceptual model for understanding mechanisms of tobacco carcinogenesis



There may be overlap between these three tracks: e.g. mutation in *TP53* leading to tumour suppressor gene inactivation.

mixture of carcinogens and toxicants. There are over 60 carcinogens in cigarette smoke that have been evaluated in the previous *IARC Monograph* as having *sufficient evidence* for carcinogenicity in laboratory animals ([IARC, 2004a](#)), sixteen of which are considered to be *carcinogenic to humans* (Group 1). There are also many other carcinogens and potential carcinogens in cigarette smoke that have not been evaluated ([Rodgman & Perfetti, 2006](#); see Section 1.1). Structures of tobacco smoke constituents and biomarkers discussed here are presented in Fig. 4.2.

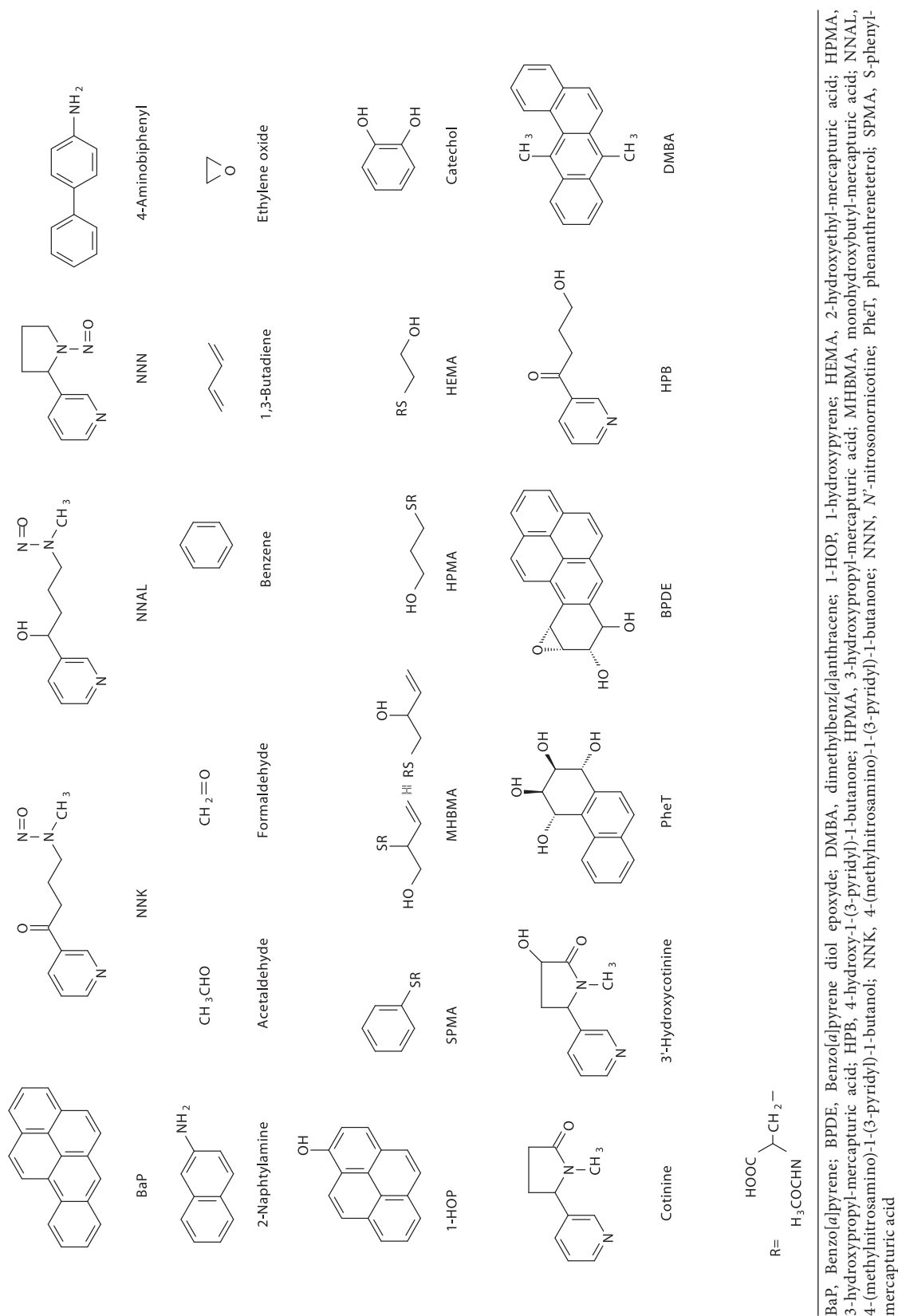
Numerous studies demonstrate the uptake of tobacco smoke carcinogens and toxicants by smokers, and showed higher levels of their metabolites in urine and blood of smokers than non-smokers (Sections 4.1.1 and 4.1.2). There are substantial differences in carcinogen exposure among people because of the number and types of cigarettes they smoke and the ways in which they smoke them. These differences can be monitored in part by biomarkers of exposure such as urinary metabolites or haemoglobin adducts (Section 4.1.2). Haemoglobin adducts of multiple aromatic amines and volatile carcinogens have been demonstrably related to tobacco ([Hatsukami et al., 2006a](#)). There may also be differences in carcinogen exposure due to genetic variations (Section 4.2).

The body's response to cigarette smoke constituents is similar to its response to pharmaceutical agents and other foreign compounds. Drug metabolizing enzymes, most frequently CYPs, convert these compounds to more water soluble forms, facilitating excretion. During this natural protective attempt, some reactive intermediates are formed. These intermediates are frequently electrophilic (electron seeking, or bearing a partial or full positive charge). Electrophilic intermediates may react with water, generally resulting in detoxification, or may covalently bind to nucleophilic (electron rich) sites in DNA, forming DNA adducts ([Guengerich, 2001](#); [Jalas et al., 2005](#)), which are

critical in the carcinogenic process (see Section 4.1.3c). CYP1A1 and CYP1B1, repeatedly shown to be inducible by cigarette smoke via interactions of smoke compounds with the aryl hydrocarbon receptor (AhR), are particularly important in the metabolic activation of PAHs, while CYP2A13 is critical for the metabolism of NNK ([Nebert et al., 2004](#); [Jalas et al., 2005](#)). The inducibility of certain CYPs may be a critical aspect of cancer susceptibility in smokers ([Nebert et al., 2004](#)). CYP1A2, CYP2A6, CYP2E1 and CYP3A4 are also important in the metabolism of cigarette smoke carcinogens to DNA binding intermediates ([Jalas et al., 2005](#)), and aldo-keto reductase enzymes, also induced by tobacco smoke ([Quinn et al., 2008](#)), are involved in the metabolism of NNK, BaP and other tobacco smoke carcinogens. Competing with this process of “metabolic activation” resulting in DNA binding is the intended metabolic detoxification, which leads to harmless excretion of carcinogen metabolites, and is also catalysed by CYPs and a variety of other enzymes including GSTs, uridine diphosphate-glucuronosyl transferases (UGTs), and arylsulfatases. The relative amounts of carcinogen metabolic activation and detoxification differ among individuals. It is widely hypothesized that this balance will affect cancer risk with those having higher activation and lower detoxification capacity being the most susceptible. This premise is supported in part by molecular epidemiologic studies of polymorphisms, or variants in more than 1% of the population, in certain genes coding for these enzymes ([Vineis et al., 2003](#); [Carlsten et al., 2008](#)).

DNA adducts are thought to be a critical lesion in carcinogenesis. Many investigations demonstrate the presence of DNA adducts in human tissues, and some of these are summarized in Section 4.1.2c. There is massive evidence, particularly from studies which use relatively non-specific DNA adduct measurement methods, that DNA adduct levels in the lung and other tissues of smokers are higher than in non-smokers, and some epidemiologic data link

Fig. 4.2 Structures of compounds discussed in the text



BaP, Benzo[a]pyrene; BPDE, Benzo[a]pyrene diol epoxide; DMBA, dimethylbenz[a]anthracene; 1-HOP, 1-hydroxypyrene; HEMA, 2-hydroxyethyl-mercapturic acid; HPMA, 3-hydroxypropyl-mercapturic acid; HPB, 4-hydroxy-1-(3-pyridyl)-1-butanol; HPMA, 3-hydroxypropyl-mercapturic acid; MHBMA, monohydroxybutyl-mercapturic acid; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNN, N'-nitrosonicotine; PheT, phenanthrenetetrol; SPMA, S-phenyl-mercapturic acid

these higher adduct levels to increased cancer risk ([IARC, 2004b](#); [Veglia et al., 2008](#)). However, there is much more limited evidence from studies using specific carcinogen-derived DNA adducts as biomarkers ([Pfeifer et al., 2002](#)). Oxidative DNA damage has also been observed, and this may result partially from exposure to metals in cigarette smoke ([Stavrides, 2006](#)).

Cellular DNA repair systems can excise DNA adducts and restore normal DNA structure ([Christmann et al., 2003](#)). These complex multiple systems include direct base repair by alkyltransferases, removal of DNA damage by base and nucleotide excision repair, mismatch repair, and double strand repair. If these DNA repair systems are unsuccessful in fixing the damage, then the DNA adducts can persist, increasing the probability of a permanent mutation. There are polymorphisms in genes coding for some DNA repair enzymes. If these variants lead to deficient DNA repair, the probability of cancer development can increase ([Vineis et al., 2009](#)).

DNA adducts can cause miscoding during replication when DNA polymerase enzymes misread the DNA adduct and consequently insert the wrong base opposite to it. There is some specificity in the relationship between specific DNA adducts formed from cigarette smoke carcinogens and the types of mutations which they cause. G to T and G to A mutations have often been observed (Section 4.1.3) ([Hecht, 1999](#)). Extensive studies have characterized the mutations which occur because of specific carcinogen-DNA adducts ([Delaney & Essigmann, 2008](#)). Mutations have been reported in the *KRAS* oncogene in lung cancer and in the *TP53* tumour suppressor gene in a variety of cigarette smoke-induced cancers ([Ahrendt et al., 2001](#); [Pfeifer et al., 2002](#); [Ding et al., 2008](#)). The cancer causing role of these genes has been firmly established in animal studies ([Lubet et al., 2000](#); [Johnson et al., 2001](#)). A selection and promotion process may also play a role in the final mutation spectrum seen in genes

in smoking-associated tumours ([Rodin & Rodin, 2005](#); [Sudo et al., 2008](#)).

Urinary mutagenicity, sister chromatid exchanges, micronuclei in buccal cells, and other genetic effects have been consistently observed in smokers at higher levels than in non-smokers ([IARC, 2004a](#); [Proia et al., 2006](#)). In addition to mutations, numerous cytogenetic changes are observed in lung cancer, and chromosome damage throughout the field of the aerodigestive tract is strongly associated with cigarette smoke exposure. Mutations resulting from DNA adducts can cause loss of normal cellular growth control functions, via a complex process of signal transduction pathways, ultimately resulting in genomic instability, cellular proliferation and cancer ([Ding et al., 2008](#)). Apoptosis, or programmed cell death, is a protective process, and can remove cells which have DNA damage, thus serving as a counterbalance to these mutational events. The balance between apoptotic mechanisms and those suppressing apoptosis will have a major impact on tumour growth.

While the central track of Fig. 4.1 is the major pathway by which tobacco smoke carcinogens cause cancer, other mechanisms also contribute, as indicated in the top and bottom tracks ([Hecht, 2003](#)). Nicotine, NNK, and NNN bind to nicotinic and other cellular receptors, resulting in activation of serine/threonine kinase Akt (also known as protein kinase B), protein kinase A, and other changes. Nicotine and NNK increase expression of survivin, an inhibitor of apoptosis in normal human bronchial epithelial cells, and survivin mRNA is detected in bronchial brush samples from heavy smokers ([Jin et al., 2008](#)). This can cause decreased apoptosis, increased angiogenesis, and increased transformation ([Heeschen et al., 2001](#); [West et al., 2003](#)). Thus, although nicotine is not carcinogenic, it may enhance carcinogenicity in various ways ([Schuller, 2009](#)). Cigarette smoke also contains well established oxidants, co-carcinogens, tumour promoting fractions, and inflammatory agents, as well as

cilia-toxic compounds such as acrolein, which impede clearance. Many studies demonstrate the co-carcinogenic and cytotoxic effects of catechol, an important constituent of cigarette smoke. An epigenetic pathway frequently observed in tobacco-induced cancers is enzymatic methylation of promoter regions of genes such as *p16* and *FHIT* [fragile histidine triad gene, a gene coding for a dinucleoside 5', 5'''- P¹, P³-triphosphate hydrolase, a putative tumour suppressor protein] resulting in gene silencing, which are also strongly implicated in tobacco-induced lung cancer (D'Agostini *et al.*, 2006; Bhutani *et al.*, 2008). When this occurs in tumour suppressor genes, the result can be unregulated proliferation (Belinsky, 2005). Inflammation due to smoking is associated with tumour promotion and activation of factors such as NFκB. Inflammation also plays a role in chronic obstructive pulmonary disease (COPD), which in turn is an independent risk factor for lung cancer (Smith *et al.*, 2006; Turner *et al.*, 2007; Lee *et al.*, 2008a).

This conceptual model can be applied to smokeless tobacco products. Smokeless tobacco products have much lower levels of carcinogens and toxicants that result from combustion, so the effects of these agents are not seen to a significant extent. The most prevalent strong carcinogens in smokeless tobacco are the tobacco-specific nitrosamines; other nitrosamines, PAHs, aldehydes and metals are also present, and there are large amounts of some inorganic salts that may contribute to inflammation (IARC, 2007a; Stepanov *et al.*, 2008). An additional factor in carcinogenesis by betel quid with tobacco is the basic pH resulting from addition of slaked lime to the quid, leading to oxidative damage and inflammation (IARC, 2004b).

Multiple studies demonstrate that tobacco-specific nitrosamines are absorbed and metabolised in smokeless tobacco users (IARC, 2007a).

There is evidence for DNA adduct formation in oral tissues of smokeless tobacco users, and sister chromatid exchanges, chromosomal

aberrations, and micronuclei – consequences of DNA adduct formation – have been reported (Proia *et al.*, 2006; Warnakulasuriya & Ralhan, 2007). Many studies have demonstrated RAS and TP53 mutations in smokeless tobacco users (Warnakulasuriya & Ralhan, 2007) consistent with the conceptual framework.

Oxidative stress and reactive oxygen species could play a significant role in cancer induction in smokeless tobacco users, particularly at high pH (Boffetta *et al.*, 2008). Chronic local inflammation and irritation induced by smokeless tobacco and its constituents could have a tumour promoting or co-carcinogenic effect (Boffetta *et al.*, 2008). Upregulation of cyclooxygenase-2, involved in prostaglandin synthesis and inflammation, has been observed in animal studies upon exposure to smokeless tobacco (Boffetta *et al.*, 2008). Smokeless tobacco products have relatively high levels of sodium chloride (NaCl), which could contribute to inflammation, tumour promotion, and co-carcinogenesis. Cancer of the oral cavity is strongly associated with tobacco smoking (IARC, 2004a) or chewing (IARC, 2007a) and alcoholic beverage drinking (IARC, 2010a). However only a fraction of exposed subjects develop tumours, which suggests that other exposures such as HPV may be independently involved or act as cofactors. HPV is known to infect the oral cavity of healthy individuals and several HPV-related lesions have been characterized (IARC, 2007b). Herpes simplex virus has also been shown to enhance the carcinogenicity of smokeless tobacco products in animal studies (Park *et al.*, 1986). These factors may contribute significantly to the local carcinogenic effects characteristic of smokeless tobacco use.

4.1.2 Absorption, distribution, metabolism and excretion

There are examples of toxicant and carcinogen metabolism and excretion for representatives of virtually every major class of compounds;

some of these are summarized in [Table 4.1](#). Nicotine and five of its urinary metabolites – cotinine, 3'-hydroxycotinine and their glucuronides, and nicotine glucuronide – comprise about 73–96% of the nicotine dose ([Hukkanen et al., 2005](#)), and are found in blood, sweat, hair and toenails ([Al Delaimy, 2002](#); [Hukkanen et al., 2005](#); [Stepanov et al., 2007](#); [Al Delaimy & Willett, 2008](#)). Metabolites of various polycyclic aromatic hydrocarbons including pyrene, phenanthrene, fluorene, and benzo[a]pyrene have been quantified in human urine and are higher in smokers than in non-smokers ([Hecht, 2002](#); [Hecht et al., 2005a](#); [Jacob et al., 2007](#); [Hansen et al., 2008](#)). Metabolites of tobacco-specific nitrosamines – NNAL and its glucuronides (total NNAL) from NNK; and NNN and its glucuronides (total NNN) from NNN – are present in human urine ([Hecht, 2002](#); [Stepanov & Hecht, 2005](#); [Hecht et al., 2008a](#); [Stepanov et al., 2008](#)). Total NNAL has also been quantified in blood and toenails ([Hecht et al., 2002](#); [Stepanov et al., 2007](#)). Aromatic amine-haemoglobin adducts have been frequently measured in human blood, and their levels increase with smoking ([Hecht, 2002](#); [Hatsukami et al., 2006a](#)). Mercapturic acids of several tobacco smoke compounds such as benzene, 1,3-butadiene, acrolein, and ethylene oxide are present in human urine and are related to smoking ([Carmella et al., 2009](#)). Haemoglobin adducts of acrylonitrile and related compounds are elevated in smokers' blood, and levels of metals such as Cd are increased in smokers' urine ([Carmella et al., 2002](#); [IARC, 2004b](#)).

All of the metabolites listed in [Table 4.1](#) are elevated in cigarette smokers; in studies of second-hand smoke exposure, only nicotine metabolites and urinary total NNAL are consistently increased in exposed versus non-exposed subjects, although one very large study also observed an increase in PAH metabolites ([Pirkle et al., 2006](#); [Hecht, 2008](#); [Suwan-ampai et al., 2009](#)). Smokeless tobacco users have significantly raised levels of nicotine metabolites

and tobacco-specific nitrosamine metabolites compared to non-tobacco users ([Hecht et al., 2007](#)).

4.1.3 Biomarkers

Tobacco carcinogen biomarkers are quantifiable entities that can be *specifically* related to tobacco carcinogens. Specificity to a given carcinogen is critical because tobacco carcinogens vary widely in their potency and target organs.

Considering the mechanistic framework outlined in Fig. 4.1, one could visualize various types of biomarkers. Currently, biomarkers of carcinogen/toxicant dose, reflecting the second box of the central track of Fig. 4.1, are by far the most extensively used and validated. The second most common are measurements of DNA adducts (or protein adducts as their surrogates), but fewer of these have both practical utility and validation with respect to tobacco carcinogen specificity.

The use of tobacco carcinogen biomarkers bypasses many uncertainties in estimation of dose. The most commonly used estimation of dose is self-reported number of cigarettes/day, but this is not a very good marker. It may not be reported accurately and it provides no information on the way in which the cigarettes were smoked, which is critical when one considers the common phenomenon of smoker's compensation. Brand information together with machine smoking measurements of specific components is another way of obtaining a measure of dose. However, machine smoking measurements are known to have limitations and the application of a given machine smoking protocol to a given smoker requires smoking topography measurements for that smoker. A disadvantage of tobacco carcinogen biomarkers is that they are affected to some extent by individual differences in metabolism, which may complicate interpretation of dose.

Table 4.1 Examples of toxicant or carcinogen metabolites in tobacco users

Toxicant or carcinogen	Examples of metabolites in tobacco users	References
Nicotine	Cotinine, 3'-hydroxycotinine and their glucuronides in urine, blood or saliva; nicotine and cotinine in toenails	Al Delaimy (2002) , Hukkanen et al. (2005) , Al Delaimy & Willett (2008) , Stepanov et al. (2007)
Polycyclic Aromatic Hydrocarbons (PAHs)	1-hydroxypyrene, phenanthrols, phenanthrene tetraols, fluorenols, benzo[a]pyrenols, benzo[a]pyrene tetraols in urine	Hecht (2002) , Hecht et al. (2005a) , Hansen et al. (2008) , Jacob et al. (2007)
Tobacco-specific nitrosamines	NNAL and its glucuronides (total NNAL) in urine or blood, total NNN in urine; NNAL and NNN in toenails	Hecht (2002) , Hecht et al. (2002, 2008a) , Stepanov & Hecht (2005) , Stepanov et al., (2007, 2008)
Aromatic amines	Parent amines in urine and haemoglobin adducts in blood	Hecht (2002) , Hatsukami et al. (2006a)
Volatile hydrocarbons		
Benzene 1,3-Butadiene	Muconic acid and S-phenyl-mercapturic acid (SPMA) in urine; Monohydroxybutyl-mercapturic acid (MHBMA) in urine	Hecht (2002) , Carmella et al. (2009)
Acrolein	3-hydroxypropyl-mercapturic acid (HPMA) in urine	Carmella et al. (2009)
Ethylene oxide	2-hydroxyethyl-mercapturic acid (HEMA) in urine, haemoglobin adducts in blood	Bono et al. (2002) , Carmella et al. (2009)
Acrylonitrile	Haemoglobin adducts in blood	Carmella et al. (2002)
Metals	Cadmium in urine	IARC (2004a)

(a) Urinary biomarkers

Probably the most practical and, to date, the most extensively applied tobacco carcinogen biomarkers are urinary metabolites of tobacco carcinogens, and these have been comprehensively reviewed ([Hecht, 2002](#); [IARC, 2004a](#)). Advantages include the ready availability of samples, and concentrations in urine that are easily quantifiable using modern analytical chemistry methods, most frequently liquid chromatography-tandem mass spectrometry (LC-MS/MS). The urinary metabolites listed in [Table 4.1](#) have all been used as biomarkers and all are validated with respect to exposure in cigarette smokers ([Carmella et al., 2009](#)). Total nicotine equivalents (the sum of nicotine and the five metabolites in [Table 4.1](#)) is a particularly effective way of estimating nicotine dose from tobacco products.

Total NNAL, the sum of NNAL and its glucuronides, is a highly useful biomarker of NNK exposure ([Hecht, 2002, 2003](#); [Hatsukami et al., 2006a](#)). The tobacco-specificity of NNK, and therefore total NNAL, is a key feature of this biomarker because studies in which it is applied are not confounded by other environmental or dietary exposures. It also has a considerably longer half-life than cotinine and several other urinary biomarkers. Total NNAL has been used in numerous studies that estimated uptake of NNK in smokers under varying circumstances. In one example, smokers reduced their number of cigarettes smoked per day, but there was not a corresponding decrease in NNK uptake due to compensation ([Hecht et al., 2004](#)). In another study, NNK and PAH uptake, estimated by total NNAL and 1-hydroxypyrene, respectively, were compared in smokers of regular, light, and ultra-light cigarettes, and found to be similar, consistent with epidemiologic studies that

demonstrate no protection against lung cancer in smokers of light compared to regular cigarettes (Hecht *et al.*, 2005b). Other studies evaluated NNK uptake in smokers who switched from their current cigarette brand to products advertised as being less hazardous, but the results generally did not support these claims (Hatsukami *et al.*, 2004). One of the most useful applications of total NNAL has been in studies of non-smokers exposed to second-hand tobacco smoke (Hecht, 2003). The sensitivity and specificity of this biomarker are ideal for such studies, and it is the most commonly elevated tobacco carcinogen biomarker in non-smokers exposed to second-hand smoke. Total NNAL has also found utility in establishing NNK uptake in smokeless tobacco users (Hecht *et al.*, 2002, 2007, 2008a, b; Hecht, 2008).

The relationship of urinary total NNAL to lung cancer was demonstrated in a study of stored urine samples collected years before diagnosis of lung cancer from smokers in Shanghai, China and Singapore (Yuan *et al.*, 2009). There was a significant relationship between total NNAL and lung cancer incidence, after correction for numbers of cigarettes smoked per day and duration of smoking. An 8.5 fold increased risk for lung cancer was observed for those smokers in the highest tertile of total NNAL and cotinine, relative to smokers with the same smoking history but in the lowest tertiles of total NNAL and cotinine. Urinary biomarkers were also used to demonstrate higher uptake of nicotine and NNK per cigarette in smokers with polymorphisms in the nicotinic acetylcholine genes associated with lung cancer in genome-wide association studies (see Section 4.2; Le Marchand *et al.*, 2008). Collectively, these results indicate that urinary total NNAL is not only a biomarker of exposure, but also a biomarker of risk for lung cancer.

(b) Serum and saliva metabolites

Serum and saliva metabolites have been used as biomarkers much less often than urine metabolites. The most frequently measured tobacco smoke toxicant in serum and saliva is cotinine, documented as a useful biomarker of cigarette smoking in many studies (Lee, 1999; Hukkanen *et al.*, 2005). Total NNAL can be readily quantified in serum and its levels remain relatively constant in a given smoker sampled at bimonthly intervals over a one year period. Consistent with the results described above, one study showed a significant relationship between total NNAL in prospectively collected serum samples from smokers and lung cancer risk (Church *et al.*, 2009). Other biomarkers that have been measured in serum include cadmium, benzene, styrene and *r*-1,*t*-2,3,*c*-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT) (IARC, 2004a; Church *et al.*, 2009).

(c) DNA adducts

Fig. 4.3 presents an overview of metabolism and DNA adduct formation from eight tobacco smoke compounds (clockwise from top left): BaP, NNK, *N*-nitrosodimethylamine (NDMA), NNN, acrolein, ethylene oxide, acetaldehyde and 4-aminobiphenyl. Evidence exists for DNA adduct formation from each of these carcinogens in smokers, based on studies carried out with tissues or blood cells. DNA adduct biomarkers have been applied mainly in studies of smokers, and there is far less evidence from studies of second-hand tobacco smoke or smokeless tobacco use.

The structures of DNA adducts of tobacco smoke carcinogens have been characterized in detail, but a complete description of these structures is beyond the scope of this section. Selected DNA adduct structures are shown in Fig. 4.4. A major DNA adduct of BaP results from *trans*- addition of the benzo[*a*]pyrene diol epoxide (BPDE) to the *N*²-position of dG (Szeliga

Fig. 4.3 Overview of metabolism and DNA adduct formation from eight tobacco smoke constituents

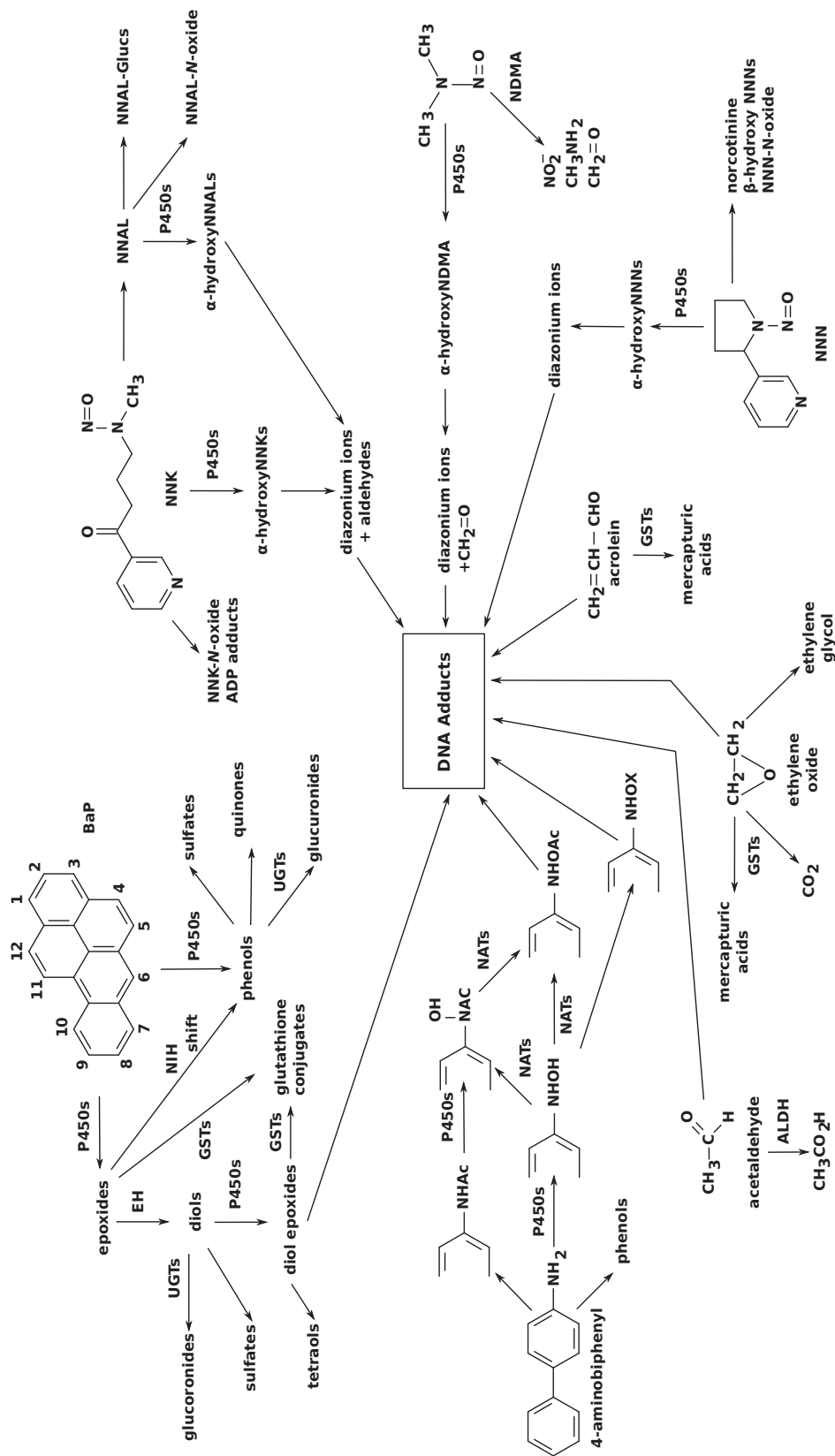
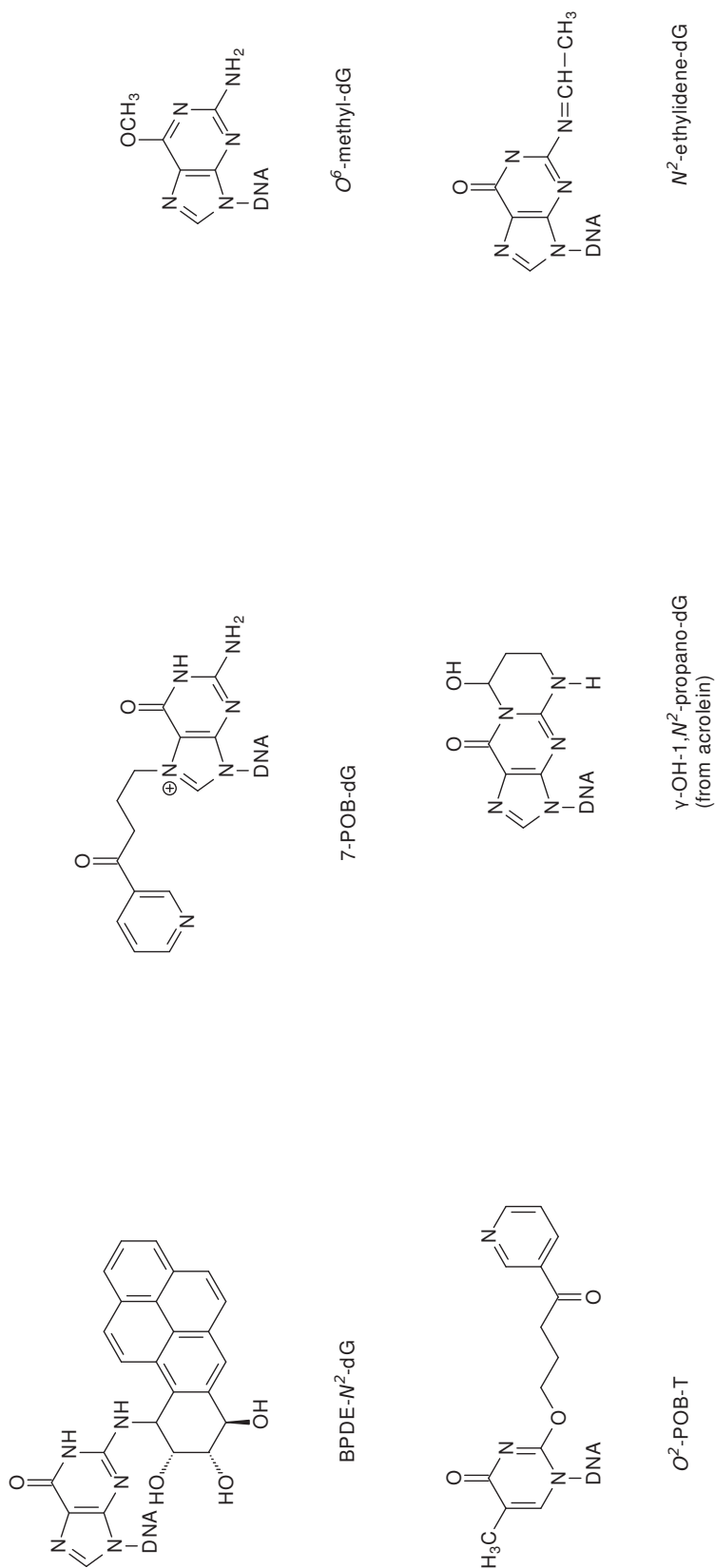


Fig. 4.4 Structures of some DNA adducts of tobacco smoke constituents



BPDE-*N*²-dG, benzo[*a*]pyrene diol epoxide-*N*²-deoxyguanosine; 7-POB-dG, pyridyloxobutyl-deoxyguanosine; *O*²-POB-T, *O*²-pyridyloxobutyl-thymidine

& Dipple, 1998). Pyridyloxobutyl (POB)-DNA adducts of NNK and NNN are formed at the 7- and O^6 -positions of deoxyguanosine dG, the O^2 -position of thymidine, and the O^2 -position of deoxycytidine (Hecht, 2008). They can be measured in part as 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB) released upon hydrolysis. Metabolic activation of NNK also leads to 7-methyl-dG and O^6 -methyl-dG, identical to the DNA adducts formed from NDMA and other DNA methylating agents (Hecht, 2008). Ethylating agents and ethylene oxide in cigarette smoke also alkylate dG (Zhao *et al.*, 1999; Singh *et al.*, 2005). Acrolein and crotonaldehyde react with DNA to produce exocyclic 1, N^2 -dG adducts, while acetaldehyde forms a Schiff base adduct with the exocyclic N^2 amino group of dG. There is evidence for the presence of all these DNA adducts in tissues or blood cells of smokers, but there are also many studies in which these specific adducts have been sought but not found (Boysen & Hecht, 2003).

Measurement of these DNA adducts as biomarkers potentially can provide the most direct link between cellular exposure and cancer, because DNA adducts are so critical in carcinogenesis. However, it is challenging because their levels are extremely low, frequently ranging from 1 per 10^6 to 1 per 10^8 normal bases, and the tissue or blood samples containing them are usually available in only small quantities. Fortunately, the routine detection ofamol levels [attomole, equivalent to 10 moles] of DNA adducts by conventional LC-MS/MS techniques is now feasible (Singh & Farmer, 2006). There are still relatively few examples of quantitation of *specific* DNA adducts of tobacco carcinogens in tissues of smokers using mass spectrometry, high pressure liquid chromatography (HPLC)-fluorescence, HPLC with electrochemical detection, or postlabelling techniques (Pfeifer *et al.*, 2002). A much larger body of work has used the highly sensitive, but relatively non-specific ^{32}P -postlabelling and immunoassay methods of

DNA adduct detection. Although the adducts detected using ^{32}P -postlabelling are often referred to as “aromatic DNA adducts,” there is strong evidence that they are not related to PAHs (Arif *et al.*, 2006). Adduct levels are generally higher in lung tissues of smokers than non-smokers while studies using blood DNA have produced varied results. Adducts have also been detected in the larynx, oral and nasal mucosa, bladder, cervix, breast, pancreas, stomach, placenta, foetal tissue, cardiovascular tissues, sputum, and sperm of smokers (IARC, 2004a). A meta-analysis of the relationship of DNA adduct levels in smokers to cancer, as determined by ^{32}P -postlabelling in the majority of studies or enzyme linked immunosorbent assay (ELISA), demonstrated a positive relationship in current smokers (Veglia *et al.*, 2003; 2008).

(d) Protein adducts

Carcinogen-haemoglobin (Hb) and serum albumin adducts are regarded as surrogates for DNA adduct measurements. Although these proteins are not targets for carcinogenesis, virtually all carcinogens that react with DNA will also react with protein. Advantages of haemoglobin adducts include the ready availability of haemoglobin from blood and the relatively long lifetime of the erythrocyte in humans – 120 days –, which provides an opportunity for adducts to accumulate. Studies on protein adducts in smokers have been comprehensively reviewed (IARC, 2004a).

Haemoglobin adducts of aromatic amines are a highly informative type of carcinogen biomarker, with levels that are consistently higher in smokers than non-smokers, particularly for 3-aminobiphenyl and 4-aminobiphenyl-Hb adducts. Haemoglobin binds aromatic amines efficiently because heme accelerates the rate of nitrosoarene formation from the hydroxylamine, which is produced metabolically from the aromatic amine by CYP1A2 (Fig. 4.3; Skipper & Tannenbaum, 1990). Binding of the nitrosoarene occurs at the β -93 cysteine residue of human

haemoglobin; the adduct is hydrolysed releasing the free amine, which is quantified by GC-MS (Skipper & Tannenbaum, 1990). Adduct levels are clearly related to cigarette smoking (Skipper & Tannenbaum, 1990). Adducts that form at the terminal valine of haemoglobin are also useful biomarkers: examples include those derived from ethylene oxide, acrylonitrile and acrylamide (Bergmark, 1997; Fennell *et al.*, 2000). Ethylated N-terminal valine of haemoglobin is also higher in smokers than in non-smokers (Carmella *et al.*, 2002).

HPB-releasing Hb adducts of NNK and NNN have been quantified in studies of smokers and smokeless tobacco users (IARC, 2004a, 2007a). These adducts are thought to be tobacco-specific, but some studies report their presence in non-smokers (Falter *et al.*, 1994; Schlöbe *et al.*, 2008).

4.1.4 Genetic and related effects

(a) Mutagenicity and cytogenetic effects

Tobacco smoke and its condensates are mutagenic in a wide variety of test systems from bacteria to mammalian cells in culture to rodents and humans (DeMarini, 2004; IARC, 2004a; Husgafvel-Pursiainen, 2004). In bacterial systems, the heterocyclic amines and aromatic amines in condensates account for much of the frameshift mutagenicity, whereas the PAHs and nitrosamines may account for some of the base-substitution mutagenicity (DeMarini *et al.*, 1995). G to T is the predominant class of base-substitution mutation induced by condensates in experimental systems and found in oncogenes and tumour-suppressor genes in smoking-associated lung tumours (IARC, 2004a). The genotoxic potencies of a variety of condensates in several genotoxicity assays likely have only qualitative value with regard to health risk assessment (DeMarini *et al.*, 2008). This is consistent with findings that smokers of low- or high-tar cigarettes have similar urinary levels of lung carcinogens (Hecht *et al.*, 2005b; Hatsukami *et al.*,

2006b) and similar risks for lung cancer (Harris *et al.*, 2004).

In rodents, cigarette smoke induces sister chromatid exchange and micronuclei in bone marrow and lung cells. Human newborns of smoking mothers have increased frequencies of *HPRT* mutations, chromosomal translocations, and DNA strand breaks. Sperm of smokers has increased frequencies of aneuploidy, DNA adducts, strand breaks, and oxidative damage. Cigarette smoke also causes germ-cell mutations in mice (Yauk *et al.*, 2007). Collectively, these data suggest that smoking is likely a germ-cell mutagen in humans. Smoking produces mutagenic urine and somatic-cell mutations in humans, including *HPRT* mutations, sister chromatid exchange, microsatellite instability and DNA damage in a variety of tissues. Genotoxic effects have been found in eight organ sites at which tobacco smoke causes cancer in humans (DeMarini, 2004; IARC, 2004a).

(b) Mutations in *TP53*, *KRAS* and related genes

Gene mutation data from a variety of databases, including the IARC Cancer *TP53* Mutation Database (<http://www-p53.iarc.fr/>), have been collated in the Genetic Alterations in Cancer (GAC) database (<http://dir-apps.niehs.nih.gov/gac/>) so that mutations in a variety of genes in various cancerous tissues can be compared. An assessment of the Gene Alterations in Cancer database showed that at least three genes were mutated more frequently in lung tumours from smokers than non-smokers (Lea *et al.*, 2007): *TP53* (39 versus 26%), *K-RAS* (20 versus 3%), and loss of heterozygosity at *FHIT* (57 versus 27%). Thus, genes in the cell cycle (*TP53*), cell signalling (*KRAS*) and apoptotic (*FHIT*) pathways are mutated more frequently in smoking- rather than in nonsmoking-associated lung tumours. Genomic sequencing of lung tumours has identified other mutated genes that are associated with smoking; ten times more genes are mutated in

lung tumours from smokers compared to non-smokers ([Ding et al., 2008](#)).

GC to TA transversions were the predominant class of base-substitution mutation found in *TP53* and *KRAS* genes in lung tumours from smokers, with the frequency of this mutation in *TP53* being 30% in smokers versus 22% in non-smokers. In smoking-associated oral cancers, the percentage of GC to TA mutations in *TP53* was 15% versus 2%, respectively. This mutation spectrum is consistent with that produced by a variety of known carcinogens present in tobacco smoke ([IARC, 2004a](#)). At the codon level, the most frequently mutated codons in *TP53* in lung tumours of smokers were 157, 175, 245, 248, and 273, all of which occur in the DNA-binding domain of the protein; among these codons, only 273 was mutated in lung tumours from non-smokers. Only three of these codons (157, 245 and 273) were mutated in smoking-associated larynx tumours, and only codon 157 was mutated in smoking-associated oral tumours. Thus, the mutational specificity at *TP53* is different among smoking- and nonsmoking-associated tumours and among smoking-associated tumours at various organs ([Lea et al., 2007](#)). Thus, different pathways are involved in the development of different types of tumours ([Le Calvez et al., 2005](#); [Mounawar et al., 2007](#); [Subramanian & Govindan, 2008](#)).

4.1.5 Effects on gene expression profile

As indicated in a review by [Sen et al. \(2007\)](#) involving microarray analysis of 18 studies in human smokers, 7 in smoke-exposed rodents, and 3 in condensate-exposed mammalian cells, smoking generally upregulated a wide variety of genes, especially those involved in the stress response, phase I metabolism, and immune response. Genes that were consistently expressed differentially in smokers (as assessed in alveolar macrophages, lung cells or peripheral lymphocytes) included metallothioneins, heat-shock

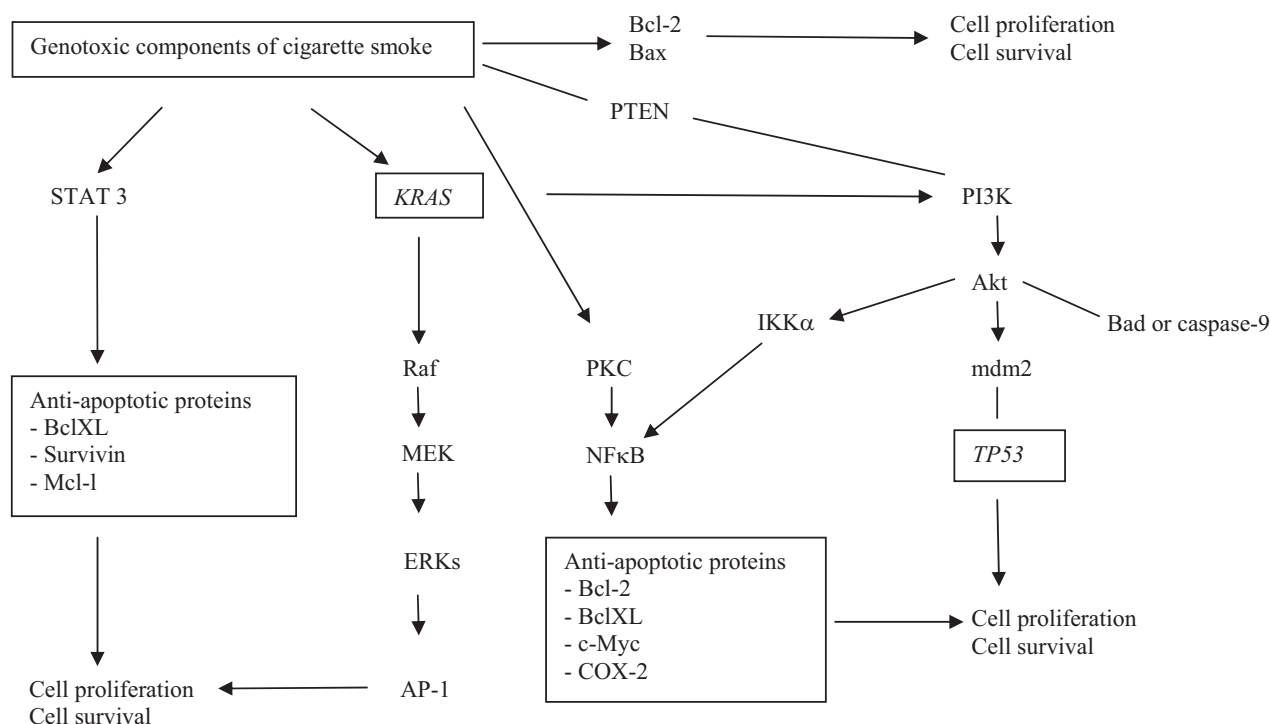
proteins, superoxide dismutase, glutathione transferase, heme oxygenase, *CYP* genes (*1A2*, *1A1* and *1B1*), interleukins and chemokines.

[Spira et al. \(2004\)](#) analysed global gene expression in bronchial epithelial cells and found that the expression levels of metabolizing and antioxidant genes had reverted to control levels after two years of smoking cessation. However, expression of potential oncogenes and tumour-suppressor genes never reverted to never-smoker levels even after years of smoking cessation. Consistently, expression of microRNAs is generally downregulated by cigarette smoke ([Izzotti et al., 2009](#)). As discussed below, smoking also altered methylation patterns and gene expression in smoking-associated tumours.

4.1.6 Other effects associated with carcinogenesis

(a) Proliferation, differentiation, apoptosis, and inflammation

As noted above, the signal-transduction pathways in lung tumours from smokers are distinctly different from those of non-smokers ([Mountzios et al., 2008](#)). Fig 4.5 shows details of signalling pathways that are deregulated by tobacco smoke. The involvement of high frequencies of mutated *K-RAS* and *TP53* genes in smoking-associated lung tumours results in altered regulation of cell proliferation, differentiation, cytoskeletal organization and protein trafficking. Cigarette smoking activates *NF- κ B*, which induces pro-inflammatory cytokine expression and induces growth factors and proliferative signals ([Mountzios et al., 2008](#)). This gene also influences the expression of the anti-apoptotic gene *BCL2* and pro-apoptotic gene *BAX*. Smoking produces chronic inflammation, which promotes cancer ([Walser et al., 2008](#)). Smoking results in high levels of reactive oxygen species, which damage epithelial and endothelial cells and impair their function. In smoking-associated lung cancer, elevated levels of cyclooxygenase-2 (COX-2) and

Fig. 4.5 General scheme of some cell-signalling pathways that are deregulated by tobacco smoke in lung carcinogenesis

Akt, serine/threonine protein kinase; ERKs, extracellular regulated kinases; MEK, mitogen-activated protein kinase; Bad, Bcl2-associated agonist of cell death; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; NF-κB, nuclear factor κB; IKKα, inhibitor of nuclear factor κ-B kinase; PTEN, phosphatase and tensin homologue; STAT3, signal transducer and activator of transcription, COX-2, cyclooxygenase-2

prostaglandin (PGE₂) indicate apoptosis resistance, proliferation, immunosuppression, angiogenesis, invasion, and epithelial-mesenchymal transition ([Walser et al., 2008](#)).

(b) Endogenous nitrosation

Intragastric formation of *N*-nitroso compounds, measured using urinary nitrosamino acids excreted in urine, was increased in smokers compared to non-smokers ([Hoffmann & Brunnemann, 1983](#)). Two recent studies demonstrated that NNN forms endogenously in some users of nicotine replacement therapy products ([Stepanov et al., 2009a, b](#)).

(c) Hormonal changes

These are described in Section 4.3.2a.

4.2 Polymorphisms in carcinogen-metabolizing genes

4.2.1 Introduction

It has been long proposed that the known variation among individuals in their capacity to activate and detoxify carcinogens may be associated with increased susceptibility to cancer, and that polymorphisms of carcinogen-metabolising genes may play a significant role. The most intensively studied genes involved in the metabolism of carcinogens include the various *CYP* genes, the *GST* genes and the *NAT* genes. Other relevant xenobiotic-metabolising genes, such as *EPHX*, sulfotransferase (*SULT*), *UGT*, myeloperoxidase (*MPO*), and NAD(P)H quinone oxidoreductase-1 (*NQO1*) genes, have also been studied. Recently, extensive pooled studies and

reviews have been published on polymorphisms of carcinogen-metabolising genes and their role in cancer susceptibility, especially in tobacco-related lung cancer and cancers at other sites. Similarly, various biomarkers of exposure and genotoxicity that are presumed to provide a mechanistic basis for such associations have been comprehensively investigated in relation to these polymorphisms. A brief overview based largely on reviews and the meta- and pooled analyses is presented here.

4.2.2 Genetic polymorphisms of carcinogen metabolism: some central genes

(a) CYP genes

CYPs comprise the principal enzyme system catalysing various phase I oxidation reactions, including metabolic activation and detoxification of many carcinogenic substances in tobacco smoke such as PAHs. Of the various CYP enzymes expressed in humans, many of those belonging to CYP1 to CYP3 families play a role in carcinogen metabolism, producing highly reactive DNA-damaging metabolites as well as detoxified metabolites ([Guengerich & Shimada, 1998](#); [Lang & Pelkonen, 1999](#); [Ingelman-Sundberg, 2004](#)). CYPs have evolved into a wide superfamily with close to 60 different active genes currently identified; most of these genes exhibit polymorphism (www.cypalleles.ki.se).

(i) CYP1A1

Several allelic variants of the human *CYP1A1* gene are currently known (www.cypalleles.ki.se). The major variant forms of the *CYP1A1* gene (wildtype allele *CYP1A1*1*) mostly frequently studied for association to cancer susceptibility include the following two alleles: (i) *CYP1A1*2A* allele (m1 allele; *Msp* I) and (ii) *CYP1A1*2B* ([Cascorbi et al., 1996](#)) or *CYP1A1*2C* (www.cypalleles.ki.se) allele (m2 allele; Ile⁴⁶²Val). Importantly, the *CYP1A1* m1 allele and m2 allele are in complete linkage disequilibrium in

Caucasians ([Kawajiri, 1999](#); [Bartsch et al., 2000](#)). In addition, *CYP1A1*4* allele (m4; Thr⁴⁶¹Asn) ([Cascorbi et al., 1996](#)), and *CYP1A1*3* (m3) allele found in African-Americans but not in Caucasians or Asians ([Crofts et al., 1993](#)) are included in some studies ([Bartsch et al., 2000](#)).

In smoking-related lung cancer, the various *CYP1A1* polymorphisms as well as the differences in the frequencies of the rare variant alleles between ethnicities contribute to the differences in findings. There are collective analyses of data predominantly indicating an overall mild to moderate effect of *CYP1A1* polymorphisms on lung cancer risk ([Kawajiri, 1999](#); [Bartsch et al., 2000](#); [Houlston, 2000](#); [Le Marchand et al., 2003](#); [Vineis et al., 2003](#); [Vineis et al., 2004](#); [Lee et al., 2008a](#); [Shi et al., 2008](#)). In many reviews and meta- or pooled analyses the increased risk associated with *CYP1A1* polymorphism has most clearly been seen in Asian populations ([Kawajiri, 1999](#); [Le Marchand et al., 2003](#); [Vineis et al., 2003](#); [Lee et al., 2008a](#); [Shi et al., 2008](#)).

Multiple studies have also analysed the gene-gene interactions between *CYP1A1*, *GSTM1* and *GSTT1* polymorphisms and lung cancer ([d'Errico et al., 1999](#); [Houlston, 1999](#); [Benhamou et al., 2002](#); [Bolt & Thier, 2006](#); [Raimondi et al., 2006](#); [Ye et al., 2006](#); [Carlsten et al., 2008](#)). Some of the analyses have indicated that the elevated risk for lung cancer may be more pronounced for some *CYP1A1/GSTM1* null genotype combinations ([Le Marchand et al., 1998](#); [Bartsch et al., 2000](#); [Vineis et al., 2004, 2007](#); [Lee et al., 2008a](#); [Shi et al., 2008](#)).

(ii) CYP1A2

CYP1A2 is highly inducible and metabolises, including deacetylation reactions, many tobacco smoke carcinogens such as aromatic and heterocyclic amines and nitro-aromatic compounds, and tobacco-specific nitrosamines such as NNK ([Nebert et al., 2004](#); [Jalas et al., 2005](#); [IARC, 2007a](#)). A few major variant alleles have been described (www.cypalleles.ki.se), some of which

may have been reported to influence inducibility ([Nakajima et al., 1999](#); [Ingelman-Sundberg et al., 2007](#)). Overall, the phenotype-genotype relations have not been well established for *CYP1A2*, although current evidence points towards contribution of genetic variation ([Murayama et al., 2004](#); [Ingelman-Sundberg et al., 2007](#)); data on possible associations with tobacco related cancer are sparse ([Agundez, 2004](#); [Nebert & Dalton, 2006](#)).

(iii) *CYP2A6*

Several aspects of smoking behaviour are likely to be influenced by *CYP2A6* genetic variation, which influences nicotine metabolism ([Malaiyandi et al., 2005](#); [Mwenifumbo & Tyndale, 2007](#)). The most important functionally altered allele is *CYP2A6*4* (gene deletion), which confers a poor-metabolizer phenotype in homozygous individuals ([Malaiyandi et al., 2005](#); [Ingelman-Sundberg et al., 2007](#); [Mwenifumbo & Tyndale, 2007](#)). In some studies, polymorphic variants of *CYP2A6* gene have been implicated in susceptibility to smoking-related cancers ([Gambier et al., 2005](#); [Malaiyandi et al., 2005](#); [Nakajima, 2007](#)). In line with this, the accumulated data have suggested that *CYP2A6* polymorphism may affect cancer risk in smokers but not in non-smokers ([Tan et al., 2001](#); [Kamatani et al., 2005](#); [Malaiyandi et al., 2005](#); [Canova et al., 2009](#)).

(iv) *CYP2A13*

From human CYPs, *CYP2A13* is the primary form involved in the metabolic activation of the tobacco-specific nitrosamines NNK and NNN ([Jalas et al., 2005](#); [IARC, 2007a](#)). The *CYP2A13* gene exhibits polymorphism in humans ([Zhang et al., 2002](#); [Jalas et al., 2005](#)), and experimental studies suggest that some of the polymorphisms may affect the hydroxylation of NNN and NNK ([Jalas et al., 2005](#); [Schlicht et al., 2007](#)). However, the data on possible effects of these polymorphisms on the risk of tobacco-related cancers in

humans are still limited ([Wang et al., 2003](#); [Song et al., 2009](#); [Timofeeva et al., 2009](#)).

(v) *CYP2D6*

The *CYP2D6* gene shows high variability in expression. The enzyme is not inducible, and therefore genetic variation largely contributes to the interindividual variation in enzyme activity. Currently, more than 100 different functional *CYP2D6* gene variants have been described, and these are divided into alleles causing abolished, decreased, normal, and ultrarapid enzyme activity ([Ingelman-Sundberg, 2005](#); [Ingelman-Sundberg et al., 2007](#)). The most important null alleles leading to poor-metabolizer phenotype are *CYP2D6*4* (splice defect) and *CYP2D6*5* (gene deletion) ([Ingelman-Sundberg, 2005](#); [Ingelman-Sundberg et al., 2007](#)).

A large series of studies have been carried out over the past 20 years on the association between *CYP2D6* polymorphism and susceptibility to lung cancer and to some other tobacco-related cancers ([Wolf & Smith, 1999](#)). Despite some indication of an association between *CYP2D6* poor-metabolizer and decreased risk for lung cancer, no major role for *CYP2D6* in carcinogen metabolism or a molecular basis for such an association have been discovered ([Wolf & Smith, 1999](#); [Ingelman-Sundberg, 2005](#)).

(vi) *Other CYP genes*

CYP1B1 allelic variants that affect the catalytic activity have been described but they have been studied to a lesser extent for the association with susceptibility to smoking-related cancers ([Thier et al., 2003](#)). Some positive findings have been reported on head and neck cancer ([Ko et al., 2001](#)), and lung cancer ([Zienolddiny et al., 2008](#)).

Several polymorphisms have been characterized in the *CYP2E1* gene and several positive associations with the risk of different cancers have been reported, in particular for cancers of the upper aerodigestive tract, lung and gastrointestinal tract (Section 2.19). *CYP2E1* may also

play an important role in the interaction of the carcinogenic effects of alcohol and tobacco (Section 4.4).

From the human *CYP3A* locus (*CYP3A4*, *CYP3A5* and *CYP3A7*), the *CYP3A4*1B* allele has been associated with lung cancer and prostate cancer in some studies but not in all ([Dally et al., 2003](#); [Rodriguez-Antona & Ingelman-Sundberg, 2006](#)). However, the role of these variants in relation to tobacco smoking is unknown.

(b) *GSTM1* and other *GST* genes

Polymorphic *GST* genes have long been proposed to modify susceptibility to lung cancer ([Seidegård et al., 1986](#); [Ketterer et al., 1992](#)). The polymorphic genes encoding the various classes of cytosolic *GST* enzymes include the *GSTM1* and *GSTM3* genes (mu class), the *GSTP1* gene (pi class), and the *GSTT1* gene (theta class). The gene deletion (null) allele of the *GSTM1* gene (*GSTM1*0*) and of the *GSTT1* gene (*GSTT1*0*) have been the most intensively studied polymorphisms in relation to increased susceptibility to cancer ([Strange et al., 2001](#); [Bolt & Thier, 2006](#); [McIlwain et al., 2006](#)). For the *GSTP1* gene, the form most abundantly present in lung tissue, genetic variation in exon 5 (*GSTP1*2*; *Ile¹⁰⁵Val*), in exon 6 (*Ala¹¹⁴Val*), as well as a combination of these, are the variations most frequently studied for cancer susceptibility ([Watson et al., 1998](#); [Cote et al., 2009](#)).

Numerous reviews, meta- and pooled analyses have been published over the past 15 years or so for the *GST* genes with systematic assessments covering altogether tens of thousands of cases and controls. For the *GSTM1* null genotype, such analyses have largely provided negative, suggestive or at most moderately positive results for an association with an increased risk for lung cancer ([d'Errico et al., 1999](#); [Houlston, 1999](#); [Benhamou et al., 2002](#); [Ye et al., 2006](#); [Carlsten et al., 2008](#)). The larger the studies, the less significant the estimates for the role of *GSTM1* emerge in systematic analysis ([Ye et al., 2006](#); [Carlsten](#)

[et al., 2008](#)). Also the varying allele frequencies related to ethnic background affect the findings for *GSTM1* as well as for many other genes ([Garte et al., 2001](#); [Ye et al., 2006](#); [Carlsten et al., 2008](#); [Lee et al., 2008a](#)).

In a meta-analysis of the association between the *GSTT1* gene polymorphism and lung cancer no association between *GSTT1* null genotype and risk for lung cancer in Caucasians was observed, but a positive association was found for Asians ([Raimondi et al., 2006](#)). A significant association for either Caucasians or Asians was also not found in a pooled analysis ([Raimondi et al., 2006](#)). A meta-analysis found no significant association between lung cancer risk and the *GSTP1 Ile¹⁰⁵Val* polymorphism; but the pooled analysis suggested an overall statistically significant mild association between lung cancer and homozygosity or heterozygosity for the *Val¹⁰⁵* allele ([Cote et al., 2009](#)).

A recent body of epidemiologic data suggests an inverse association between cruciferous vegetables/isothiocyanates intake and cancers of the colorectum, lung and breast; the studies also provide evidence that this protective effect is greater among individuals who possess the *GSTM1* or *T1* null genotype, who would be expected to accumulate higher levels of isothiocyanates at the target tissue level, a pre-requisite for their enzyme-inducing effects ([Seow et al., 2005](#)). The association between isothiocyanates and cancer, and its modification by *GSTM1* and *GSTT1* status, is most consistent for lung cancer and appears to be strongest among current smokers who possess the combined *GSTM1* and *GSTT1* null genotypes ([London et al., 2000a](#); [Spitz et al., 2000](#); [Zhao et al., 2001](#); [Brennan et al., 2005](#); [Seow et al., 2005](#)).

(c) *NAT1* and *NAT2* genes

The pooled and meta-analyses carried out on *NAT1* and *NAT2* polymorphisms and bladder cancer risk have consistently reported significantly increased risk for *NAT2* slow acetylators

([Dong et al., 2008](#); [Malats, 2008](#); see also Section 2.9). Data on *NAT1* fast acetylators are inconsistent, as are the studies suggesting an increased risk for *NAT2* rapid acetylator status. Additionally, genotypes for other genes, specially *GSTM1*, have also been implicated ([Vineis et al., 2001](#); [García-Closas et al., 2005](#); [Hein, 2006](#); [Sanderson et al., 2007](#); [Dong et al., 2008](#); [Malats, 2008](#)).

In a recent large study on tobacco-related lung cancer and upper aerodigestive cancers, the *NAT* genes, in particular *NAT*10* haplotype, emerged from a set of 16 genes as involved in the risk ([McKay et al., 2008](#)). When more than one hundred single nucleotide polymorphisms for 31 genes involved in phase I or phase II metabolism or in antioxidant defence were investigated, only four of the previously reported polymorphisms of the *GSTP1*, *EPHX1* and superoxide dismutase *SOD2* genes and the *NAT1* fast acetylator phenotype remained significantly associated with risk of non-small cell lung cancer after correction for multiple testing ([Zienolddiny et al., 2008](#)).

In breast cancer, several recent meta-analyses of epidemiological studies have suggested increased risk among smokers with the *NAT2* slow acetylator genotype; such an association has been observed especially among long-term smokers and post-menopausal women ([Terry & Goodman, 2006](#); [Ambrosone et al., 2008](#); [Ochs-Balcom et al., 2007](#); [Baumgartner et al., 2009](#)).

In all, the role of the *NAT* gene polymorphisms in tobacco-related cancers, with the exceptions of increased risk of bladder cancer and possibly breast cancer in *NAT2* slow acetylators, remains largely open due to the incomplete understanding of phenotype-genotype relationships, and the interplay between these two genes and their polymorphisms ([Hein, 2002, 2006](#)).

(d) Others

Genes coding for *EPHX*, *UGT* and *SULT* enzymes, mainly but not exclusively involved in detoxification reactions, exhibit polymorphisms with numerous gene variants discovered

([Mackenzie et al., 1997](#); [London et al., 2000b](#); [Glatt et al., 2001](#); [Burchell, 2003](#)). Additional polymorphic genes studied for their significance in cancer susceptibility are the *NQO1* and *MPO* genes, with *NQO1* playing a dual role in the detoxification and activation of procarcinogens, and *MPO* converting lipophilic carcinogens into hydrophilic forms ([Nebert et al., 2002](#)). All these genes have been studied for their possible association with tobacco-related cancer risk to a varying extent and with variable outcomes ([London et al., 2000b](#); [Bamber et al., 2001](#); [Garte, 2001](#); [To-Figueras et al., 2001](#); [Tiemersma et al., 2002b](#); [Guillemette, 2003](#); [Wells et al., 2004](#); [Kiyohara et al., 2005](#); [Moreno et al., 2005](#); [Nagar & Remmel, 2006](#); [Gallagher et al., 2007](#)).

4.2.3 Biomarkers of tobacco carcinogenesis and polymorphic genes of carcinogen metabolism

A myriad of studies have investigated association between various biomarkers of tobacco-related carcinogenesis and genetic variation of genes involved in carcinogen metabolism. For involvement in increased cancer susceptibility, a large variety of intermediate biomarkers have been studied, including PAH metabolites in urine, urinary mutagenicity, DNA and protein adducts, cytogenetic alterations, *HPRT* mutant lymphocytes, as well as somatic mutations of the tumour suppressor gene *TP53* and *KRAS* oncogene occurring in cancer tissue.

(a) PAH metabolites and mutagenicity in urine

(i) PAH metabolites in urine

Increased excretion of 1-hydroxypyrene in urine in association with the *GSTM1* null genotype has been reported in many studies on individuals with occupational or environmental exposure to PAHs ([Yang et al., 1999](#); [Alexandrie et al., 2000](#); [Lee et al., 2001](#); [Kuljucka-Rabb et al., 2002](#); [Kato et al., 2004](#)). The associations seen between *GSTM1* polymorphism and the

PAH metabolites are somewhat more variable. Similarly, the joint effect of *GSTM1* and *GSTT1* null genotypes, as well as the effects of some other genes of xenobiotic metabolism, such as *EPHX*, *CYP1A1*, *CYP1A2* and the aryl hydrocarbon receptor (*AhR*) gene have been either positive or negative ([Yang et al., 1999](#); [Alexandrie et al., 2000](#); [Lee et al., 2001](#); [Zhang et al., 2001](#); [Kuljukkka-Rabb et al., 2002](#); [Yang et al., 2003](#); [Chen et al., 2007](#); [Cocco et al., 2007](#); [Bin et al., 2008](#)).

Another PAH metabolite studied in this context is phenanthrene, the simplest PAHs with a bay region, a feature closely associated with carcinogenicity. A study quantified ratios of urinary products of metabolic activation (such as PhET) and detoxification (such as phenanthrols, HOPhe) of phenanthrene in 346 smokers, who were also genotyped for 11 polymorphisms in genes involved in PAHs metabolism, including the *CYP1A1* and *GSTM1* genes. A significant association between the presence of the *CYP1A1* Ile⁴⁶²Val polymorphism and high PhET/3-HOPhe ratios was found, particularly in combination with the *GSTM1* null polymorphism ([Hecht et al., 2006](#)).

Overall, the data on the influence of genetic variation in PAHs metabolism on the levels of the urinary metabolite biomarkers are variable, and currently inconclusive.

(ii) Urinary mutagenicity

One relatively early line of research investigated the relationship between urinary mutagenicity and genetic variation in activation or detoxification genes. These studies, however, have seldom been focused on smokers only but rather on other sources of exposure ([Pavanello & Clonfero, 2000](#)).

In some studies, *NAT2* slow acetylator genotype either alone or in combination with *GSTM1* null genotype has been associated with increased urinary mutagenicity in the *Salmonella* test in individuals with occupational, environmental or

medicinal PAH-related exposure, or in smokers ([Vineis & Malats, 1999](#); [Pavanello & Clonfero, 2000](#)). In another study, *CYP1A2* activity, but not *NAT2*, *GSTM1* or *GSTT1* genotypes influenced urinary mutagen excretion in smokers ([Pavanello et al., 2002](#)). A further study also suggested contribution of the *CYP1A2* gene variation to increased urinary mutagenicity in heavy smokers ([Pavanello et al., 2005](#)). Associations with variants of other xenobiotic-metabolising genes (such as *EPHX1*) have also been reported, with somewhat complex results ([Kuljukkka-Rabb et al., 2002](#)).

(b) DNA adducts

The relationship between the variants of polymorphic genes of carcinogen metabolism and tobacco smoke-related DNA adduct formation has been addressed in an abundant number of studies among smokers, occupationally exposed groups, and patients with smoking-related cancer. In addition, multiple *in vitro* studies on this relationship have been carried out ([Bartsch et al., 2000](#); [Pavanello & Clonfero, 2000](#); [Alexandrov et al., 2002](#); [Wiencke, 2002](#)).

The intensive efforts to study the relationship between *CYP1A1* and *GSTM1* gene polymorphism and the level of aromatic-hydrophobic/bulky PAH-DNA adducts in human lungs have so far provided little evidence for a role of a single metabolic genotype or their combinations on DNA adduct formation, with largely weak, non-significant or contradictory results. However, a trend of increasing adduct levels in subjects with the *CYP1A1**2-*GSTM1**0 genotype combination has been observed, which was reinforced when BPDE-DNA adducts were specifically assessed. These results suggest a gene-gene interaction, supported by biological data from other studies ([Bartsch et al., 2000](#); [Alexandrov et al., 2002](#); [Wiencke, 2002](#)). Such gene-gene interaction lends support to the increased risk for lung cancer found in carriers of these genotypes in Japanese, among whom the frequency of the

variant *CYP1A1* allele is much higher ([Bartsch et al., 2000](#); [Alexandrov et al., 2002](#)).

A wide selection of genes and genotypes included in the various studies have made it difficult to assess the overall role of the polymorphisms of *GSTM1* and other genes alone or in combination. Differences between the studies in the types of adducts determined, the various tissues, cell types and cancers studied, detection methods, variation in sources and types of exposure, sample size, gender differences, and sometimes poor knowledge regarding the alleles, genotypes and haplotypes under study also contribute to the large variability seen in these studies ([d'Errico et al., 1999](#); [Hemminki et al., 2001](#); [Alexandrov et al., 2002](#); [Wiencke, 2002](#)).

(c) Cytogenetic biomarkers of genotoxicity

(i) Chromosome aberrations and sister chromatid exchanges

Early studies investigating whether homozygosity for the *GSTM1* null allele affects prevalence of cytogenetic changes in lymphocytes of smokers reported positive results ([Seidegård et al., 1990](#); [van Poppel et al., 1992](#); [Cheng et al., 1995](#)). Since then, studies have investigated the association between genetic polymorphisms of xenobiotic-metabolising genes and cytogenetic biomarkers in smokers and in some occupational groups ([Rebbeck, 1997](#); [Autrup, 2000](#); [Pavanello & Clonfero, 2000](#); [Norppa, 2003, 2004](#)).

Collectively, the reported findings are in support of increased susceptibility of smokers to chromosomal effects in association with *GSTM1* and *GSTT1* null variants deficient in detoxification of tobacco smoke carcinogens. Exposure to genotoxicants generated from other environmental sources (e.g. polluted air, diet, endogenous sources such as reactive oxygen species) may contribute to the observed associations, and it is likely that other polymorphic metabolic genes such as *NAT2* may be involved ([Pavanello & Clonfero, 2000](#); [Norppa, 2001, 2003](#)).

(ii) Micronucleus induction

The relationship between formation of micronuclei and genetic polymorphisms of carcinogen metabolism has been addressed in a wide range of human population studies ([Norppa, 2003, 2004](#)). Induction of micronuclei in smokers may be little, if at all, affected by *GSTM1*, *GSTT1* or *NAT2* genotypes. In contrast, the *NAT1* rapid genotype appears to show an association with increased susceptibility to smoking-related micronuclei ([Norppa, 2004](#)).

A recent review evaluated more than seventy human studies on genetic polymorphisms and micronucleus frequency detected either in peripheral blood lymphocytes or exfoliated cells in populations exposed to various genotoxic agents. There were no significant genotype effects involved in micronucleus induction in smokers ([Iarmarcovai et al., 2008](#)). The relationship between genetic polymorphisms and micronucleus formation is complex, and is influenced to a variable extent by several genes of xenobiotic metabolism and DNA repair, as well as the variety of chromosomal alterations known to contribute to micronucleus formation ([Iarmarcovai et al., 2008](#)).

(iii) Chromosomal damage induced in vitro

The effects of genotypes or genotype combinations *in vitro* on the induction of various cytogenetic endpoints by tobacco-smoke carcinogens and their metabolites have been studied, initially focused on the *GSTM1* and *GSTT1* null genotypes ([Norppa, 2001, 2004](#)). In a study investigating NNK *in vitro*, lymphocytes from *GSTM1* null donors were more sensitive to induction of chromosomal aberrations and sister chromatid exchanges by NNK than lymphocytes from *GSTM1* positive donors ([Salama et al., 1999](#)).

(d) *Gene mutations*(i) *HPRT mutant lymphocytes*

Associations between the frequencies of *HPRT* mutant T-lymphocytes in populations exposed to genotoxic agents, such as smokers, and the polymorphism of xenobiotic-metabolising genes have been studied. In the early studies, positive, weak, or negative associations were reported for *GSTM1* null genotype, and negative findings were published for *NAT2* slow acetylator genotype in occupationally exposed or non-exposed subjects (Rebbeck, 1997; Vineis & Malats, 1999). When healthy, non-smoking and occupationally non-exposed young adults were studied for *HPRT* mutant frequency and polymorphisms in *CYP1A1*, *GSTM1* and *NAT2* genes, none of these polymorphisms, analysed individually, were found to influence the *HPRT* mutant frequency (Davies *et al.*, 1999). A significant interaction between the *GSTM1* null genotype and *NAT2* slow acetylator was associated with higher mutant frequency, but no other genotype combinations (Davies *et al.*, 1999). Some later studies have reported variable associations between *HPRT* mutant frequency and polymorphisms for either individual genes (*GSTM1*, *GSTT1* or *EPHX1*) or some of the genotypes in combination among exposed (Viezzler *et al.*, 1999; Abdel-Rahman *et al.*, 2001, 2003).

(ii) *Mutations of the TP53 gene and other cancer-related genes*

Whether the frequency of somatic mutations detected in tumour tissue in cancer-related genes, primarily the *TP53* tumour suppressor gene and *KRAS* oncogene, may be modified by polymorphisms in carcinogen metabolizing genes was first investigated assessing the effects of the *GSTM1* genotype, alone or in combination with other genetic polymorphisms. Several, but not all, such studies showed significant association between *GSTM1* null genotype and either the frequency or type of *TP53* mutations in

smoking-induced lung cancer or other cancer type (Rebbeck, 1997; Vineis & Malats, 1999; Autrup, 2000). Fewer studies examined the association between *TP53* mutations and *GSTT1* polymorphism, and some results suggested the involvement of both null genotypes (Vineis & Malats, 1999; Autrup, 2000).

In smokers with non-small cell lung cancer, the risk of mutation was found to be the highest among the homozygous carriers of the *CYP1A1* rare allele *CYP1A1 MspI* (Ile⁴⁶²Val) who also exhibited the *GSTM1* null genotype (Kawajiri *et al.*, 1996). Similarly, positive associations between *K-RAS* mutations and homozygosity for the *CYP1A1* rare allele were observed; the risk of mutation was enhanced when the *CYP1A1* susceptible genotype was combined with *GSTM1* null genotype (Kawajiri *et al.*, 1996). In another study, also carried out in a Japanese study population, *K-RAS* mutations occurred with greater frequency in lung adenocarcinoma smoking patients and of the *GSTM1* null genotype as compared with the *GSTM1* positive genotype (Noda *et al.*, 2004).

Many of the studies that assessed *NAT2* acetylator genotypes have found non-significant associations with the frequency or type of *TP53* mutation in bladder, lung, or other cancers (Vineis & Malats, 1999; Autrup, 2000). A study on bladder cancer did not find an overall association between *TP53* mutation frequency and *GSTM1*, *GSTT1*, *GSTP1* or *NAT2* genotypes. However, among patients with *TP53* mutations, transversion mutations were more frequent in those with *GSTM1* null genotype as compared to those with *GSTM1* positive genotype; no significant associations were found for the *NAT2* gene (Ryk *et al.*, 2005).

In rectal cancer, overall negative results for an association between *TP53* or *KRAS* mutations and *GSTM1* and *NAT2* polymorphisms among smokers and non-smokers exposed to tobacco smoke were found (Curtin *et al.*, 2009). An interaction of second-hand tobacco smoke and *NAT2*

was found in *TP53* mutation positive tumours but not in smokers ([Curtin et al., 2009](#)). Earlier, an increased risk of *TP53* transversion mutations among *GSTM1* positive individuals who smoked cigarettes was found in colon cancer ([Slattery et al., 2002](#)).

A statistically significant association was observed between the *GSTT1* null genotype and *TP53* mutation status of breast tumour in one study ([Gudmundsdottir et al., 2001](#)), while in another larger study none of the genotypes for *CYP1B1*, *GSTM1*, *GSTT1* and *GSTP1* genes alone were associated with somatic *TP53* mutations ([Van Emburgh et al., 2008](#)).

In summary, data from various cancer types on the association between genetic polymorphisms of carcinogen-metabolizing genes and somatic mutations of the *TP53* and *K-RAS* genes vary widely and do not permit to conclude ([Rebbeck, 1997](#); [Vineis & Malats, 1999](#); [Autrup, 2000](#)).

4.3 Site-specific mechanisms of carcinogenicity of tobacco smoke

4.3.1 Sites with sufficient evidence of carcinogenicity of tobacco smoking

(a) Lung

The conceptual model presented in Section 4.1 (Fig. 4.1) depicts the main mechanistic steps by which cigarette smoke causes cancer. Smokers inhale into their lungs carcinogens which, either directly or after metabolism, covalently bind to DNA, forming DNA adducts (see Section 4.1, Fig. 4.3). Tobacco smoke contains multiple strong lung carcinogens such as NNN, NNK, PAHs, 1,3-butadiene and cadmium. Levels of tobacco smoke-related DNA adducts, mainly ³²P-postlabelled aromatic-hydrophobic/PAH-related bulky DNA adducts, in the lung are higher in smokers than in non-smokers ([Phillips, 2002](#); [IARC, 2004a](#); [Hecht, 2008](#)). Higher levels

of DNA adducts have further been linked to increased risk for cancer in pooled and meta-analyses ([IARC, 2004a](#); [Veglia et al., 2008](#)).

Mutations in *TP53* and *K-RAS* genes, two central genes of human carcinogenesis, are more frequently mutated in smokers' lung cancer as compared to lung cancer from non-smokers ([DeMarini, 2004](#); [IARC, 2004a](#); [Lea et al., 2007](#); [Ding et al., 2008](#); see Section 4.1.3). In particular, *TP53* but also to some extent *K-RAS* mutations found in smoking-associated lung tumours exhibit mutational specificity that is consistent with the pattern produced by PAH diol epoxides in experimental studies and different from that observed in non-smokers' lung cancer ([Pfeifer et al., 2002](#); [DeMarini, 2004](#); [IARC, 2004a](#); [Le Calvez et al., 2005](#); Section 4.1.3). Keeping with such exposure-specific mutation profile, lung cancer in non-smokers exposed to second-hand tobacco smoke shows mutational similarity to smokers' lung cancer, although less data are available ([Husgafvel-Pursiainen, 2004](#); [IARC, 2004a](#); [Le Calvez et al., 2005](#); [Subramanian & Govindan, 2008](#)). The different pathways of lung carcinogenesis for smokers and non-smokers are likely to involve somatic mutations and other genetic alterations in a larger set of genes that are critical in controlling normal cellular growth via signal transduction ([Bode & Dong, 2005](#); [Lea et al., 2007](#); [Ding et al., 2008](#)).

Smoking-related lung carcinogenesis also involves a multitude of other alterations influencing the complex pathogenic pathways involved in lung cancer development, such as increased inflammation, aberrant apoptosis, increased angiogenesis, tumour progression and tumour metastasis ([Wolff et al., 1998](#); [Heeschen et al., 2001](#); [Schuller, 2002](#); [West et al., 2003](#); [Smith et al., 2006](#); [Lee et al., 2008b](#); Section 4.1.5). Continued exposure to toxicants, genotoxins, carcinogens, co-carcinogens and tumour promoters present in tobacco smoke has major effects on biological processes at all steps of multistep tumourigenesis of human lung ([Hecht,](#)

2003, 2008; Section 4.1). For example, nicotine in tobacco smoke is currently not described as a full carcinogen, but it exerts its biological effects via binding to nicotinic and other cellular receptors and likely enhances cell transformation and carcinogenicity through mechanisms not yet defined (Heesch *et al.*, 2001; West *et al.*, 2003).

Numerous studies have provided evidence that the human genome may contain one or several loci that confer susceptibility to lung cancer. There are low-penetrance genes involved in the metabolism of tobacco smoke carcinogens, DNA repair and cell cycle control that may influence individual susceptibility to lung cancer (Spitz *et al.*, 2006). The role of the polymorphisms of these various classes of genes in lung carcinogenesis requires a systematic evaluation of the genetic evidence with stringent criteria (Ioannidis, 2008; Risch & Plass, 2008; Vineis *et al.*, 2009; Sections 4.1 and 4.2). Recently, genome-wide association studies have identified a susceptibility locus at chromosome 15q25.1 (Amos *et al.*, 2008; Hung *et al.*, 2008; Thorgeirsson *et al.*, 2008). The identity or function of the gene is not yet known, nor is the mechanism through which it may predispose to lung cancer. It is however likely that lung cancer susceptibility is related to the nicotine receptor gene residing at 15q25.1, and there is some evidence suggesting that it may be related to increased uptake of nicotine and NNK per cigarette (Le Marchand *et al.*, 2008).

In addition to genetic alterations, a growing body of evidence shows that epigenetic mechanisms, such as aberrant DNA methylation, histone modifications and RNA-mediated gene silencing are involved in cancer development (Jones & Baylin, 2007; Cortez & Jones, 2008). In lung carcinogenesis, gene promoter-associated (CpG island-specific) hypermethylation is an early and frequent event causing transcriptional inactivation of genes involved in regulation of cellular growth and differentiation (Belinsky, 2004). For example, several studies have indicated that the tumour suppressor gene *p16*

(*p16^{INK4a/CDKN2A}*), a cell cycle regulator, is among the genes most frequently inactivated by aberrant methylation in lung cancer from smokers (Belinsky, 2004), with differences seen between smokers and never-smokers (Toyooka *et al.*, 2006). Significant associations have been established between smoking and promoter hypermethylation of tumour suppressor genes in lung tumours from smokers, and in plasma, serum or sputum DNA from cancer-free smokers (Belinsky, 2004; Belinsky *et al.*, 2005, 2006; Toyooka *et al.*, 2006).

(b) Oral cavity

PAHs can be carcinogenic at the site of application, which could include the human oral cavity. DMBA, a highly carcinogenic PAH not present in tobacco or tobacco smoke, is a standard model compound for induction of oral tumours in the hamster cheek pouch; less is known about the effects on the oral cavity of PAHs that do occur in tobacco products (Shklar, 1972; Rao, 1984; Vairaktaris *et al.*, 2008). A mixture of NNN and NNK induced oral tumours in rats when applied locally (Hecht *et al.*, 1986), and DNA adduct formation from NNN, NNK and NNAL has been observed in the rat oral cavity (Zhang *et al.*, 2009a, b). HPB-releasing DNA adducts from NNK and/or NNN have been reported in exfoliated oral cells from smokers and smokeless tobacco users (Heling *et al.*, 2008) and HPB-releasing haemoglobin adducts are elevated in smokeless tobacco users (IARC, 2007a). Unidentified DNA adduct levels are consistently elevated in oral cells and tissues from smokers compared to non-smokers (IARC, 2004a). Mutations in the *TP53* gene have been observed in oral tumours from smokers and smokeless tobacco users (IARC, 2006b, 2007a; Warnakulasuriya & Ralhan, 2007). Tobacco-associated genetic mutations including micronuclei, gene mutations, DNA polymorphisms, and chromosomal abnormalities have been reported in studies of buccal cells from smokers and smokeless tobacco users (Proia *et al.*, 2006). The use of lime by betel quid chewers is associated

with enhanced oxidative damage that could play a role in inflammation or tumour promotion ([IARC, 2004b](#)).

(c) *Larynx and nasopharynx*

Hamsters exposed to cigarette smoke by inhalation consistently developed benign and malignant tumours of the larynx; tumours were produced by inhalation of the particulate phase, but not the gas phase of cigarette smoke ([IARC, 1986](#)). In related studies in which hamsters were treated with DMBA by intratracheal instillation followed by exposure to cigarette smoke, a significantly higher incidence of laryngeal tumours was observed than in hamsters exposed only to cigarette smoke or to DMBA ([IARC, 1986](#)). Collectively, these results indicate an initiation-promotion mechanism for the production of laryngeal tumours, and are consistent with the results of experiments in which tobacco smoke condensate is applied to mouse skin ([IARC, 1986](#)). The combined data implicate PAHs and tumour promoters in tobacco smoke as potential etiologic agents for cancer of the larynx in hamsters. Levels of DNA adducts measured by non-specific methods were higher in larynx tissue from smokers than from non-smokers ([IARC, 2004a](#)). Analyses of mutations in the *TP53* gene from tumours of the larynx in smokers show a pattern similar to that observed in lung tumours, and both are consistent with the pattern produced by PAH diol epoxides ([IARC, 2006b](#)). The available data are consistent with the conceptual framework illustrated in Fig. 4.1 ([Szyfter et al., 1999](#)).

Formaldehyde, a constituent of cigarette smoke, causes nasopharyngeal cancer in humans ([IARC, 2006a](#)). A recent study demonstrates a 10-fold higher level of the formaldehyde-DNA adduct *N*⁶-hydroxymethyldeoxyadenosine in leukocytes of smokers compared to non-smokers, suggesting its possible involvement in nasopharyngeal cancer in smokers ([Wang et al., 2009](#)). Acetaldehyde, another carcinogenic constituent of tobacco smoke, which also

forms genotoxic adducts (Section 4.1), may also contribute to the development of these forms of head and neck cancer.

(d) *Oesophagus*

Nitrosamines are probably the most effective oesophageal carcinogens known, with particularly strong activity in the rat ([Lijinsky, 1992](#)). NNN and NDEA are both present in cigarette smoke, and levels of NNN greatly exceed those of NDEA ([IARC, 2004a](#)). NNN is also present in considerable quantities in smokeless tobacco and betel quid containing tobacco ([IARC, 2004a, 2007a](#)). Thus, NNN is a likely candidate as a causative agent for esophageal cancer in smokers, smokeless tobacco users, and chewers of betel-quid with tobacco. While considerable mechanistic data are available from studies of NNN in laboratory animals ([Hecht, 1998](#); [Wong et al., 2005](#); [Lao et al., 2007](#); [Zhang et al., 2009a](#)), there are little comparable data in humans.

Increased acetaldehyde production derived both from tobacco smoke and from microbial alcohol oxidation may play a role in the synergistic carcinogenic action of alcohol and smoking on oesophagus, as well as on other upper aerodigestive locations ([Homann et al., 2000](#); [Salaspuro & Salaspuro, 2004](#); [Lee et al., 2007a](#)).

(e) *Stomach*

Hypermethylation of the E-cadherin 1 gene (*CDH1*) was observed preferentially in gastric tumours from smokers rather than non-smokers ([Poplawski et al., 2008](#)). *CDH1* can act as a tumour-suppressor gene, preventing cells from growing and dividing in an uncontrolled way to form a cancerous tumour. Because the protein encoded by this gene helps cells stick together, altered regulation may lead to metastasis.

[Boccia et al. \(2007\)](#) found an increased risk for stomach cancer among smokers who had the *SULT1A1 His* genotype, and [Lee et al. \(2006\)](#) found an increased risk for those who had the *m2* allelic variant of *CYP1A1*. A nested case-control

study found that smokers had an increased risk of gastric cancer if they carried at least one variant allele A in Ex7+129 C > A (*Thr⁴⁶¹Asn, m4*) of *CYP1A1* ([Agudo et al., 2006](#)). Stomach cancer tissue from smokers had higher levels of stable DNA adducts than did those from non-smokers; however, the number of non-smokers was quite small ([Dyke et al., 1992](#)).

(f) *Pancreas*

NNK and its metabolite NNAL are the only pancreatic carcinogens known to be present in tobacco and tobacco smoke. NNK was detected in the pancreatic juice of 15 of 18 samples from smokers, at levels significantly higher than in non-smokers; NNAL and NNN were also detected in some samples ([Prokopczyk et al., 2002](#)). DNA adducts of NNK and NNAL were present in pancreatic tissue of rats treated with these nitrosamines ([Zhang et al., 2009b](#)), but were not detected in most human pancreatic tissue samples ([Prokopczyk et al., 2005](#)).

(g) *Colorectum*

Tobacco smoke contains heterocyclic amines, such as 2-amino-1-methyl-6-phenylimidazo[4,5,6]pyridine (PhIP), which are intestinal carcinogens in rats and mutate the adenomatous polyposis coli (*Apc*) gene in mice ([Møllersen et al., 2004](#)). The *APC* gene is frequently mutated and has altered expression in human colon cancer ([Samowitz et al., 2007](#); [Samowitz, 2008](#)). A recent model of colon cancer by [Sweeney et al. \(2009\)](#) suggests that this disease can develop via at least three independent mechanistic pathways. One pathway is initiated by methylation of *MINT* (methylation in tumour) markers that proceeds down a pathway predisposing to microsatellite instability, followed by methylation of the mismatch repair gene mutL homologue 1 (*MHL1*) and the tumour-suppressor gene *TP16*, followed by mutation in *BRAF* (a homologue of a viral raf oncogen). A second independent pathway is initiated with a mutation in the *APC*

gene, followed by a mutation in the *TP53* gene. A third independent pathway involves only *KRAS2* mutations. One study found BPDE-DNA adducts at a higher frequency in colon DNA from smokers than from non-smokers ([Alexandrov et al., 1996](#)). Mutations or epigenetic changes in some or all of these genes have been found in smoking-associated colon or colorectal tumours.

Microsatellite instability, which is the expansion or contraction of short nucleotide repeats, occurs in approximately 10–15% of sporadic colorectal cancer, and is usually associated with smoking and hypermethylation of the promoter of the mismatch repair gene *MLH1* ([Samowitz, 2008](#)). Smoking-associated colorectal tumours also have high frequencies of methylation at CpG islands ([Samowitz, 2008](#)).

In a case-control study of colorectal cancer, [Kasahara et al. \(2008\)](#) found that the genetic polymorphism *APEX1/APE1* (apurinic/apyrimidinic endonuclease-1) Asp¹⁴⁸Glu, which is a gene involved in DNA repair, was associated with risk for colorectal cancer among smokers but not non-smokers. Other studies have also found associations between polymorphisms in the DNA repair genes *XRCC1* and smoking and risk for colorectal cancer ([Stern et al., 2007](#); [Campbell et al., 2009](#)).

(h) *Liver*

Tobacco smoke contains liver carcinogens such as furan and certain nitrosamines. Liver tumours exhibit increased expression of *C-MYC*, *P16^{INK4A}*, epidermal growth factor receptor (*EGFR*), telomerase, transforming growth factor- α (*TGF- α*), insulin-like growth factor-2 (*IGF-2*) and *RAF* oncogene ([Abou-Alfa, 2006](#)). Smokers show altered expression of some of these genes or of genes in the same or similar pathways ([Sen et al., 2007](#)). A genome-wide association study found that SNP rs1447295 in the 8q24 chromosome was positively associated with liver cancer among ever-smokers ([Park et al., 2008](#)). Thus, tobacco smoke appears to have epigenetic

effects on the liver that may contribute to hepatocellular carcinoma.

(i) *Urinary bladder*

Tobacco smoke contains aromatic amines such as 4-aminobiphenyl and 2-naphthylamine, which are human bladder carcinogens (see [IARC, 2012a](#)). In bladder tumours, smoking was associated with a more than twofold increase risk of methylation of the promoter region of the *PI6^{INK4A}* gene and of the soluble Frizzled receptor protein (*SFRP*) gene ([Marsit et al., 2006](#)). In addition, [Tang et al. \(2009\)](#) suggested that epigenetic silencing of *Wnt* antagonists through hypermethylation may play a role in smoking-related invasive bladder cancer ([Tang et al., 2009](#)). SNP rs6983267 of the 8q24 chromosome was inversely associated with bladder cancer among ever-smokers ([Park et al., 2008](#)). Smokers generally have mutagenic urine and smoking is associated with specific cytogenetic changes and DNA breaks in bladder tumours ([DeMarini, 2004](#)). Smoking-associated stable DNA adducts have been found in bladder tissue or exfoliated urothelial cells, supporting a role for DNA damage in smoking-associated bladder cancer ([Phillips, 2002](#)).

(j) *Cervix*

The cervical mucus of smokers is more mutagenic than that of non-smokers, and cervical epithelia of smokers have higher frequencies of micronuclei than those of non-smokers ([DeMarini, 2004](#)). Several studies have found increased levels of DNA adducts in cervical tissue from smokers relative to non-smokers, suggesting a role for smoking-associated DNA damage in cervical cancer ([Phillips, 2002](#)).

(k) *Ovary*

It has been observed that the inverse associations reported for serous and endometrioid tumours with respect to parity and oral contraceptives did not hold for the mucinous tumours.

Based on these observations, [Risch et al. \(1996\)](#) suggested that mucinous ovarian tumours may be etiologically unrelated to the other types of epithelial tumours. Whereas mucinous elements such as gastric or intestinal type glands may be seen in mature teratomas, a form of germ cell neoplasia, overall mucinous tumours are classified as surface epithelial tumours because transitions among the subtypes may be observed. The major difference between mucinous and serous tumours is their biologic behaviour. Mucinous carcinomas of the ovary are slow growing tumours that appear to develop from their benign counterparts. The fact that the transitions between the benign, borderline, and malignant form of the disease can be seen in the same tumour suggests that over time, there is a progression from benign to malignant ([Riopel et al., 1999](#)). *K-ras* mutational analysis, for example, demonstrates a heterogeneous distribution of the mutation within different parts of the same neoplasm, suggesting that acquisition of the *K-ras* mutation occurs in malignant transformation ([Mandai et al., 1998](#)). Serous carcinomas seem to develop de novo rather than from a benign pre-existing lesion; alternatively, the rate of progression is rapid and the precursor lesion is obliterated before the detection of the tumour. In some data, current smoking is associated with a shorter interval to detection of mucinous than non-mucinous tumours. Because the mucinous tumour is slow growing, smoking could contribute to the malignant progression of the adenoma-carcinoma sequence, as the benign form of the tumour may have been present for some time.

(l) *Leukaemia*

Tobacco smoke contains known leukaemogens such as benzene, 1,3-butadiene and formaldehyde ([IARC, 2012a](#)). The mechanisms of leukaemogenesis are currently not well understood. Data indicate that leukaemogenic agents, such as benzene, cause toxicity to the

haematopoietic system, as well as genotoxicity at low levels, and that genetic polymorphisms may be involved in these processes ([Aksoy, 1989](#); [Lan et al., 2004](#); [Garte et al., 2008](#); [Hosgood et al., 2009](#); [Lau et al., 2009](#); [Rappaport et al., 2009](#)). Recent studies suggest the importance in carcinogen-related leukaemogenesis of damage to haematopoietic stem/progenitor cells circulating in the peripheral blood, or, alternatively, damage to primitive pluripotent progenitor cells present in other tissues ([Zhang et al., 2009c](#)). In these two models, damaged stem/progenitor cells would then travel to the bone marrow and become initiated leukaemic stem cells. Mechanisms considered central in these models are: disruption of bone marrow DNA, through e.g. formation of DNA adducts, DNA-protein crosslinks, the action of free radicals or active states of oxygen; intercalation of metals within the DNA structure; or inhibition of enzymes involved in cell division ([Zhang et al., 2007, 2009c](#)).

4.3.2 Sites with limited evidence of carcinogenicity or evidence suggesting lack of carcinogenicity

(a) Breast

(i) Carcinogenic pathway

Carcinogens found in tobacco smoke pass through the alveolar membrane and into the blood stream, by means of which they can be transported to the breast via plasma lipoproteins ([Yamasaki & Ames, 1977](#); [Shu & Bymun, 1983](#); [Plant et al., 1985](#)). Tobacco smoke contains known rodent mammary carcinogens, including PAHs and aromatic amines ([IARC, 1986, 2004a](#); [el-Bayoumy, 1992](#); [Ambrosone & Shields, 1999](#); [Ambrosone, 2001](#); [Hoffmann et al., 2001](#)) which, due to their lipophilicity, can be stored in breast adipose tissue ([Obana et al., 1981](#); [Morris & Seifter, 1992](#)) and then metabolized and activated by human mammary epithelial cells ([MacNicoll et al., 1980](#)). Tobacco smoke constituents reach

the breast as demonstrated by the detection of cotinine in breast fluid ([Petrakis et al., 1978](#)). There is evidence suggesting the presence of mutagenic arylamines ([Thompson et al., 2002](#)) and PAHs ([Zanieri et al., 2007](#)) in human breast milk. Cigarette smoke condensate has been shown to transform normal human breast epithelial cells *in vitro* ([Narayan et al., 2004](#)), perhaps by blocking long-patch base excision repair ([Kundu et al., 2007](#)). Transformation and cytogenetic effects have been observed in human mammary epithelial cells after exposure to chemical carcinogens such as PAHs or arylamine ([Mane et al., 1990](#); [Eldridge et al., 1992](#); [Calaf & Russo, 1993](#)).

The formation of specific adducts from PAHs and aromatic amines has been observed in human breast epithelial cells *in vitro*, and unspecified-DNA adducts have been found in exfoliated ductal epithelial cells in human breast milk ([Gorlewska-Roberts et al., 2002](#); [Thompson et al., 2002](#)).

Mutations in the *TP53* tumour suppressor gene have been found in 15–30% of breast cancers ([Goldman & Shields, 1998](#); [Olivier & Hainaut, 2001](#)). An increased prevalence and altered spectrum of *TP53* mutations in breast tumours have been observed among current smokers compared with never smokers ([Conway et al., 2002](#)). The breast tumours with the most pronounced smoking-related mutational pattern (for example, a greater number of G:C→T:A transversions) were from women who had smoked for more than 20 years, although total *TP53* mutations were not associated with smoking duration ([Conway et al., 2002](#)). This increased frequency of G to T transversions in smokers versus non-smokers is also observed in the IARC *TP53* database ([IARC, 2006b](#); [Van Emburgh et al., 2008](#)).

Recent meta-analyses of epidemiological studies tend to show positive associations of breast cancer with long-term smoking among *NAT2* slow acetylators, especially among post-menopausal women (who are more likely than pre-menopausal women to be very long-term

smokers). [Firozi et al. \(2002\)](#) showed that breast tissue from NAT2 slow acetylators had significantly higher levels of the diagonal radioactive zone (smoking-related) DNA adduct pattern than that from fast acetylators.

High rates of breast cancer in women exposed to ionizing radiation during adolescence (aged 10–19 years at exposure) ([Tokunaga et al., 1987](#)) suggested that the adolescent breast may also be sensitive to the DNA-damaging effects of other exposures. This might also be true for the genotoxic compounds contained in tobacco smoke. Although some studies have supported such association, the results have been sparse and mixed. In addition, it is difficult to separate the effects of early life exposure to tobacco and smoking duration ([Terry & Rohan, 2002](#)).

Early age at first full-term pregnancy has been associated with reduced breast cancer risk ([Kelsey et al., 1993](#)), hypothetically due to terminal differentiation of the breast epithelium that occurs late in the first trimester. It has been suggested that in the early stages of pregnancy, when growth-promoting hormone levels are high, but before terminal differentiation ([Montelongo et al., 1992](#)), the breast may be particularly susceptible to the cancer-promoting chemicals in tobacco smoke. Several epidemiological studies compared measures of smoking before and after a first full-term pregnancy. Although suggestive, the data did not consistently show an increased risk for breast cancer among women who smoked before a first full-term pregnancy ([Adami et al., 1988](#); [Hunter et al., 1997](#); [Band et al., 2002](#); [Egan et al., 2003](#); [Gram et al., 2005](#); [Li et al., 2005](#); [Olson et al., 2005](#); [Cui et al., 2006](#)). Smoking was associated with a 50% increased risk among women with slow NAT2 acetylation genotype ([Egan et al., 2003](#)). Overall, studies of risk in association with the timing of smoking relative to a first pregnancy are inconclusive; nevertheless, the breast tissue appears to have a greater susceptibility to the carcinogenic chemicals in tobacco smoke

before compared to after terminal differentiation of breast epithelium.

(ii) Estrogenic pathway

The “anti-estrogenic” mechanism through which tobacco smoking may inhibit breast cancer progression is unclear. Estrogen is a known risk factor for breast cancer and several hypotheses have been proposed: earlier age at menopause among smokers, a reduction in the gastrointestinal absorption or distribution of estrogen, enhanced metabolism of estradiol to inactive catechol estrogens, increased binding of estrogens by serum sex hormone-binding globulin, lowered levels of estrogen derived from adipose tissue ([Baron, 1984](#); [Baron et al., 1990](#); [Terry & Rohan, 2002](#)). Several studies of cigarette smoking and mammographically-defined breast density showed lower measures of breast density in current smokers than in non-smokers ([Sala et al., 2000](#); [Vachon et al., 2000](#); [Warwick et al., 2003](#); [Jeffreys et al., 2004](#); [Modugno et al., 2006](#); [Bremnes et al., 2007](#); [Butler et al., 2008](#)). Since exposure to estrogen has been associated positively with breast density, a strong risk factor for breast cancer ([McCormack & dos Santos Silva, 2006](#)), the results of these studies are consistent with an anti-estrogenic effect of cigarette smoking. Although smokers and non-smokers may have the same concentrations of estrogens overall, it may be the type rather than the absolute levels of circulating estrogens that is important. Smokers might have a lower concentration of more biologically active estrogens, primarily 16- α -hydroxyestrone (16 α -OHE1) ([Michnovicz et al., 1986, 1988](#); [Berta et al., 1992](#); [Berstein et al., 2000](#); [Terry et al., 2002b](#)). Estrogen can be metabolized along three pathways, to 16 α -OHE1 or to 2-OHE1 or to 4-OHE1. 16 α -OHE1 and 4-OHE1 have been observed to increase mammary epithelial cell proliferation rates in experimental studies ([Schütze et al., 1993, 1994](#); [IARC, 2007c](#)). In contrast, 2-OHE1 might decrease epithelial cell proliferation rates ([Bradlow et al., 1996](#);

[Muti et al., 2000](#)). If cigarette smoking increases estradiol 2-hydroxylation, as has been suggested ([Michnovicz et al., 1986](#)), thereby increasing the ratio of 2-OHE1:16 α -OHE1, an inverse association between smoking and breast cancer risk might be observed. However, only one study has directly examined 2-hydroxylation in relation to cigarette smoking ([Michnovicz et al., 1986](#)). Using injected radiolabelled estradiol, a 50% increased estradiol 2-hydroxylation was found in premenopausal women who smoked at least 15 cigarettes/day compared with non-smokers. Two studies of urinary estrogens found increased excretion of 2-OHE1 and decreased excretion of estriol among smokers ([Michnovicz et al., 1988](#); [Berstein et al., 2000](#)), which may also support the hypothesis that smoking decreases the formation of active estrogen metabolites along the 16 α -hydroxylation pathway. However, the ratio of urinary 2-OHE1:16 α -OHE1 was not related to breast cancer risk in the one case-control study that examined the association ([Ursin et al., 1999](#)). The 4-hydroxylation of estrogens is catalysed by CYP1B1, which is induced by tobacco smoke ([Nebert et al., 2004](#)). This has been postulated as an additional pathway that could lead to formation of DNA adducts via catechol estrogen-quinones ([Gaikwad et al., 2008](#)) and oxidative/DNA damage via redox-cycling ([Zhu & Conney, 1998](#)). The ratio of 2-OHE1:4-OHE1 has been studied in relation to breast cancer risk and smoking in one study ([Berstein et al., 2000](#)). Smokers carrying the CYP1B1 Val allele [associated with high hydroxylation activity] had a significantly higher risk for breast cancer compared to never smokers with the Leu/Leu [wildtype] genotype ([Saintot et al., 2003](#)).

(b) Endometrium

Exogenous estrogens unopposed by progesterone have been shown to increase the risk for endometrial cancer through increased mitotic activity of endometrial cells, increased number of DNA replication errors, and somatic mutations

resulting in the malignant phenotype ([IARC, 2007c, 2012c](#)). Hence, factors associated with estrogen absorption or metabolism may alter the risk of this malignancy. Several investigators have hypothesized that cigarette smoking might have anti-estrogenic effects, and through this mechanism reduce the risk of endometrial cancer ([Baron, 1984](#); [Baron et al., 1990](#); [Terry et al., 2002b, 2004a](#)).

Whether mediated through changes in the amount of adipose tissue, altered age at menopause, or anti-estrogenic effects, blood hormone concentrations might be an important link between smoking and the reduced risk of endometrial cancer observed in most epidemiological studies. The estrogens that have typically been studied in relation to cigarette smoking include estrone, sex hormone binding globulin (SHBG)-bound estradiol, and estriol. Blood concentrations of androgens, typically androstenedione and dehydroepiandrosterone sulfate (DHEAS), have also been studied, because these are biological precursors of estrone. Studies that have examined blood concentrations of SHBG are less common, and studies of unbound (free) estradiol are scarce.

Studies of cigarette smoking and blood hormone concentrations have been conducted mostly among post-menopausal women who were not taking HRT. Of these studies, nine examined serum ([Friedman et al., 1987](#); [Cauley et al., 1989](#); [Slemenda et al., 1989](#); [Schlemmer et al., 1990](#); [Cassidenti et al., 1992](#); [Austin et al., 1993](#); [Law et al., 1997](#)) or plasma ([Khaw et al., 1988](#); [Longcope & Johnston, 1988](#)) estrone, ten examined serum ([Friedman et al., 1987](#); [Cauley et al., 1989](#); [Slemenda et al., 1989](#); [Schlemmer et al., 1990](#); [Key et al., 1991](#); [Cassidenti et al., 1992](#); [Austin et al., 1993](#); [Law et al., 1997](#)) or plasma ([Khaw et al., 1988](#); [Longcope & Johnston, 1988](#)) estradiol, and two examined serum ([Cassidenti et al., 1992](#)) or plasma ([Longcope & Johnston, 1988](#)) free estradiol. These studies consistently showed little or no association between smoking

and blood estrogen concentrations among post-menopausal women who were not taking hormone replacement therapy. Among pre-menopausal women, three studies ([Longcope & Johnston, 1988](#); [Key et al., 1991](#); [Berta et al., 1992](#)) found no clear association between cigarette smoking and estrogen concentrations. Studies that adjusted hormone measurements for the effects of BMI (and other covariates) showed similar results to those that did not, suggesting that BMI is not a strong confounder of this association.

In two studies the association between cigarette smoking and blood estrogen concentrations after randomization of women to groups receiving either estradiol or placebo were examined ([Jensen & Christiansen, 1988](#); [Cassidenti et al., 1990](#)). In a small study of 25 post-menopausal women, unbound estradiol was significantly lower among smokers than non-smokers both at baseline and shortly after taking micronized estradiol orally ([Cassidenti et al., 1990](#)). No important differences were observed between smokers and non-smokers in serum concentrations of either estrone or bound estradiol. In contrast, in a study in which 110 post-menopausal women were randomized to take hormones (either orally or percutaneously) or a placebo ([Jensen & Christiansen, 1988](#)), smokers had lower concentrations of both estrone and bound estradiol than non-smokers after oral (but not percutaneous) hormone treatment for at least one year (concentrations of free estrogens were not examined). These results indicate that smoking might affect the absorption or metabolism of hormones used in replacement therapy.

Of the five studies that have examined the association between cigarette smoking and serum ([Lapidus et al., 1986](#); [Cassidenti et al., 1992](#); [Law et al., 1997](#)) or plasma ([Khaw et al., 1988](#); [Longcope & Johnston, 1988](#)) SHBG, none found any clear association. However, one of these studies ([Khaw et al., 1988](#)) found an inverse association between smoking and the ratio of bound estradiol to SHBG, a measure of estrogen

activity. In this context, [Cassidenti et al. \(1990\)](#) found unbound (but not SHBG-bound) estradiol was significantly lower among smokers than non-smokers both at baseline and after taking oral estradiol, suggesting an increased SHBG-binding capacity in the women who smoked.

In post-menopausal women, androgens are the major source of estrone, converted through aromatization in fat deposits. Thus, adiposity is positively correlated with estrogen concentrations in post-menopausal women. Of the nine studies in which blood concentrations of androstenedione were examined in smokers ([Friedman et al., 1987](#); [Khaw et al., 1988](#); [Longcope & Johnston, 1988](#); [Cauley et al., 1989](#); [Slemenda et al., 1989](#); [Schlemmer et al., 1990](#); [Cassidenti et al., 1992](#); [Austin et al., 1993](#); [Law et al., 1997](#)), higher circulating concentrations were found among current than among never or former smokers in all studies. However, there was no clear variation in blood estrone concentrations by smoking status, suggesting a reduced conversion of androstenedione to estrone among smokers. Of the five studies where cigarette smoking and DHEAS concentrations were examined, three ([Khaw et al., 1988](#); [Cassidenti et al., 1992](#); [Law et al., 1997](#)) found increased blood concentrations among current smokers, one ([Friedman et al., 1987](#)) found also an increase that was not statistically significant, whereas another ([Key et al., 1991](#)) found no clear differences according to smoking status.

Cigarette smoking and urinary estrogen concentrations have been examined in seven studies ([MacMahon et al., 1982](#); [Michnovicz et al., 1986](#); [Trichopoulos et al., 1987](#); [Michnovicz et al., 1988](#); [Berta et al., 1992](#); [Key et al., 1996](#); [Berstein et al., 2000](#)). Of these, three found no major differences according to smoking status ([Trichopoulos et al., 1987](#); [Michnovicz et al., 1988](#); [Berta et al., 1992](#)). The remaining four studies all showed lower urinary estriol concentrations among smokers than among non-smokers, but mixed results for urinary estrone and estradiol.

Two of these studies ([Michnovicz et al., 1988](#); [Berstein et al., 2000](#)) showed higher concentrations of 2-hydroxyestrone among smokers, than non-smokers but only after estrogen treatment in [Berstein et al. \(2000\)](#).

Age at natural menopause varies substantially under the influence of genetic and environmental factors ([McKinlay, 1996](#)). A relatively early age at menopause has been associated with reduced risk of endometrial cancer ([Kelsey et al., 1982](#); [Baron, 1984](#); [Baron et al., 1990](#); [Akhmedkhanov et al., 2001](#)). A one year decrease in age at menopause has been associated approximately with a 7% decrease in risk ([Kelsey et al., 1982](#)). It has been proposed that cigarette smoking decreases the age at natural menopause ([Baron et al., 1990](#)), more clearly with qualitative than quantitative smoking measures ([Parente et al., 2008](#)), and thus might reduce endometrial cancer risk through reduced exposure to endogenous estrogens. On average, smokers have menopause approximately 1 to 1.5 years earlier than non-smokers ([Terry et al., 2002b, 2004a](#)). Adjustment for obesity and other covariates did not alter the results ([Terry et al., 2002b](#)).

4.4 Mechanistic considerations of the interaction of ethanol and tobacco carcinogens

The combined effects of alcoholic beverages and tobacco on the risk for cancer incidence and mortality have been widely studied in human populations. When tested for multiplicative and additive interactions, synergistic effects of alcoholic beverages and tobacco have been found, especially for oropharyngeal and oesophageal cancers ([Homann et al., 2000](#); [Castellsagué et al., 2004](#); [Salaspuro & Salaspuro, 2004](#); [Lee et al., 2005a](#); [Lee et al., 2007b](#)).

Data support at least four possible mechanisms for the modifying effects of alcoholic beverages on cancer risk due to tobacco.

1. Alcohol may have a local permeabilizing effect on penetration of the oral mucosa by tobacco carcinogens ([Du et al., 2000](#)), particularly important in the case of oropharyngeal and oesophageal cancer.
2. CYP2E1 and other CYPs may both activate and detoxify carcinogens present in tobacco smoke, including NDMA, NDEA, NNK, benzene and other tobacco-derived carcinogens in two ways: CYP induction increases metabolic activation of tobacco carcinogens leading to enhanced formation of proximate reactive chemical species at target sites; and alteration of phase II conjugation/detoxification enzymes by ethanol may also occur, changing the effective dose at the target site.
3. Competitive inhibition of CYP metabolism leads to reduced central hepatic and gastrointestinal clearance thus increasing dose delivery of carcinogens to peripheral target tissues (reviewed in [Meskar et al., 2001](#)).
4. Effects of acetaldehyde derived by microbial alcohol oxidation and from the tobacco smoke ([Homann et al., 2000](#); [Salaspuro & Salaspuro, 2004](#)).

Supportive evidence for ii) and iii) is briefly presented below.

4.4.1 Effects of induction of CYPs by ethanol

(a) CYP2E1

Ethanol induces CYP2E1 in the human liver and in all species tested. Over 70 substrates of CYP2E1 have been compiled ([Raucy & Carpenter, 1993](#); [Guengerich et al., 1994](#); [Djordjević et al., 1998](#); [Klotz & Ammon, 1998](#); [Cederbaum, 2006](#)). Among those are tobacco carcinogens such as benzene, vinyl chloride, NDMA, NDEA and *N*-nitrosopyrrolidine, as well as many low-molecular-weight compounds. Induction of CYP2E1 by ethanol generated increased levels of toxic metabolites from the metabolism of many of these chemicals ([Novak & Woodcroft, 2000](#)). Pyridine, a constituent of tobacco smoke and

substrate of CYP2E1, generates DNA damaging products by redox-cycling ([Kim & Novak, 1990](#)).

In humans, in addition to the prominent CYP2E1 expression in the centrilobular regions of the liver, the enzyme is also detectable in the kidney cortex and, at lower levels, in organs such as the oropharynx, nasal mucosa, ovary, testis, small intestine, colon and pancreas ([Ingelman-Sundberg et al., 1994](#); [Lieber, 1999, 2004](#)).

In rats, ethanol induced CYP2E1 in epithelia of the cheek, tongue and oesophagus ([Shimizu et al., 1990](#)). As a result of CYP2E1 induction by ethanol in the upper respiratory tract and possibly of inhibition of carcinogen clearance, hamsters had a significant increase of nasal cavity and tracheal tumours after intraperitoneal injection of *N*-nitrosopyrrolidine ([McCoy et al., 1981](#)). Thus, induction of CYP2E1 by ethanol may participate in the genesis of cancers at several sites via metabolic activation of tobacco carcinogens into reactive species in target tissues.

(b) Other xenobiotic-activating CYPs

In addition to CYP2E1, several CYPs, including CYP3A4 and probably CYP1A2 in humans, and CYP1A1, 2B1 and 3A in rat liver, may be induced by ethanol. Of particular interest are members of the CYP3A family, which have wide substrate specificity and have been implicated in the activation of several known or suspected human carcinogens, including those derived from tobacco ([Wojnowski & Kamdem, 2006](#)). Both CYP3A4 and CYP1A2 metabolize NNK ([Jalas et al., 2005](#)). Based on the Michaelis constant (K_m) data ([IARC, 2007a](#)), the relative efficiencies in NNK metabolism by human CYP are (from greatest catalyst to least): 2A13 > 2B6 > 2A6 > 1A2 ~1A1 > 2D6 ~2E1 ~3A4. As the amount of CYP enzymes with overlapping substrate specificity that participate in nitrosamine metabolism varies according to organ and species, it is difficult to determine their individual contribution at target sites.

4.4.2 Effects of inhibition of CYPs by ethanol

Ethanol is a competitive inhibitor of CYP2E1 (reviewed in [Anderson, 1992](#)). It also inhibits the activities of CYP1A1, 2B6 and 2C19 but not those of CYP1A2.

Direct inhibition of CYPs by ethanol in target tissues may reduce metabolic activation of xenobiotics and hence local toxic and tumorigenic effects. Thus CYP inhibition in the liver could increase extrahepatic exposure to genotoxic metabolites from tobacco carcinogens that are substrates for these CYP enzymes. This mechanism is supported by several studies.

Ethanol caused a fivefold increase in oesophageal DNA adducts in rats induced by NDEA ([Swann, 1984](#)). In monkeys, *O*⁶-methylguanine-DNA adducts after an oral dose of NDMA with or without ethanol were increased by co-exposure to ethanol in all tissues except the liver ([Anderson et al., 1996](#)). Effects were seen in the oesophagus (17-fold increase), colonic mucosa (12-fold), pancreas (sixfold), urinary bladder (11-fold), ovary (ninefold), uterus (eightfold), brain (ninefold), spleen (13-fold) and nasal mucosa (fivefold). In these studies, ethanol treatment was acute, so that enzyme induction was improbable, and the oesophagus was not directly exposed to either ethanol or carcinogen. This indicates that a systemic interaction, most likely inhibition of hepatic carcinogen clearance, was responsible for the observed effects in the oesophagus and other extrahepatic tissues. The 17-fold increase in DNA adducts in the monkey oesophagus is similar to the 18-fold increased risk for human oesophageal cancers in tobacco smokers combined with heavy alcohol drinking ([Tuyns et al., 1977](#)).

The relevance of increased genotoxic effects in extrahepatic target sites by ethanol is confirmed by many rodent experiments. Oral dosing of mice with NDMA in ethanol resulted in nasal cavity tumours (olfactory neuroblastoma) that were not seen with NDMA or ethanol alone ([Griciute](#)

[et al., 1981](#)). Ethanol in the drinking-water led to a ninefold increase in oesophageal tumours in rats induced by NDEA ([Aze et al., 1993](#)). Ethanol given by gavage to nursing dams together with NDMA or NNK ([Chhabra et al., 2000](#)) increased O⁶-methylguanine-DNA adducts in maternal mammary glands, by 10-fold with NDMA and to a lesser extent with NNK. In the suckling infants, DNA adducts were detected in the lungs and kidneys after maternal exposure to NDMA and increased about fourfold after maternal co-treatment with ethanol. In mice, ethanol given with NDMA in the drinking-water resulted in a fourfold increase in lung tumours, but had no significant effect when NDMA was given intragastrically, intraperitoneally, subcutaneously or intravenously ([Anderson, 1992](#)). These negative findings support that direct inhibition of hepatic carcinogen clearance by ethanol is the main operative mechanism.

There is indirect evidence that ethanol can inhibit the *in vivo* clearance of the carcinogen NDMA in humans: individuals with chronic renal failure showed detectable blood and urine levels of NDMA, which were increased by consumption of ethanol ([Dunn et al., 1990](#)). Other studies that involved sources of NDMA from tobacco smoke, diet or pharmaceuticals are consistent with ethanol reducing its clearance rate in humans ([Anderson, 1992](#)).

Other possible modifying effects of ethanol in tobacco-related tumorigenesis are presented in Section 4 of the *Monograph on Consumption of Alcoholic Beverages* in this Volume.

4.5 Synthesis

4.5.1 Mechanisms of tobacco-related carcinogenesis

The pathways by which tobacco products cause cancer essentially recapitulate established mechanisms of carcinogenesis by individual compounds, which were elaborated by landmark

studies during the second half of the 20th century. These studies demonstrate that most carcinogens, either directly or after metabolism catalyzed by multiple cytochrome P450 enzymes, react with nucleophilic sites in DNA to form covalent binding products called adducts (a contraction for “addition products”). These DNA adducts, if left unrepaired by cellular DNA repair enzymes, persist and cause mistakes during DNA replication leading to incorporation of the wrong base in a DNA strand and consequent permanent mutations. If these permanent mutations occur in important regions of critical growth control genes such as the oncogene *KRAS* or the tumor suppressor gene *p53*, cellular growth processes can become severely unregulated and cancer can result. Multiple studies of mutations in *KRAS*, *p53*, and other growth control genes in lung tumours from smokers, some of which report thousands of mutations, are fully consistent with this overall concept.

It is the complexity of tobacco carcinogenesis which challenges investigators to identify specific mechanisms that fully explain the ways in which tobacco products cause each type of cancer. There are over 70 established carcinogens in cigarette smoke, and analyses of smokers’ urine and blood clearly demonstrate higher uptake of these compounds in smokers than in non-smokers. The urine of smokers is consistently mutagenic. Similar considerations apply to smokeless tobacco users, although there are fewer identified carcinogens. Multiple DNA adducts are present in the lungs and other tissues of smokers, and sister chromatid exchanges as well as other genetic effects are consistently observed. But much less is known about the specifics of the process. Only relatively few DNA adducts in smokers’ lungs have been structurally characterized and the relationship between specific adducts and the consequent mutations in critical genes is still somewhat unsettled.

There are other processes which contribute to cancer induction by tobacco products, based on

multiple studies in both laboratory animals and humans. These include inflammation, tumor promotion, oxidative damage, co-carcinogenesis, and direct activation of cellular growth pathways by constituents of smoke. Many studies demonstrate the involvement of these processes in tobacco carcinogenesis but the details by which they interact with the DNA damage pathways and their roles in specific cancers caused by tobacco products are still not fully understood.

4.5.2 Genetic polymorphisms

Multiple studies have been carried out on the role of genetic polymorphisms of xenobiotic metabolism in smoking-related carcinogenesis in humans. These studies have covered various cancer types, with lung cancer representing one of the most intensively studied. The polymorphic genes, their variant forms, and the genotype combinations investigated in these studies have similarly been numerous. In addition to the associations with increased risk of cancer, much data have accumulated on relationships between the polymorphisms and the various biomarkers of tobacco carcinogenesis in non-cancer control populations, whether smokers or non-smokers, in subjects with work-related exposure or in patients with other cancers.

Despite the massive body of research, many observations remain ambiguous. Some associations between genetic polymorphism and increased risk for cancer, such as for the *GSTM1* null genotype, alone or in combination with *CYP1A1* polymorphism, in lung cancer, or the *NAT2* slow acetylator genotype in bladder cancer and breast cancer appear stronger and more consistent, but not without controversies. Similarly, the data on the various biomarkers of tobacco-related carcinogenesis exhibit inconsistencies.

The variability in the data is at least partially likely due to differences between the studies in the genes and gene variants included (many of

which are still of unknown functional or regulatory consequence), in the types of cancer studied, in levels and sources of exposure, in ethnic backgrounds, in sex, in histological types and in the features of the genome such as haplotype blocks and copy number variation resulting in linkage disequilibrium. In addition, gene-gene interactions and gene-environment interactions are likely to contribute to the discrepancies in current data. Mechanisms of tobacco-related carcinogenesis also involve genes from numerous other classes, such as those encoding for DNA repair proteins and many other regulators of cell cycle and growth. In addition; there are well described mechanistic pathways of carcinogenesis mediated via epigenetic alterations and genetic instability, to mention a few.

4.5.3 Site-specific mechanisms

The Working Group reviewed the mechanistic evidence relative to specific target sites for which there is sufficient evidence of carcinogenicity in humans, i.e. lung, oral cavity, oesophagus, larynx and nasopharynx, pancreas, stomach, liver, urinary bladder, leukaemia, cervix and ovary. Genotoxic effects have been found in eight organ sites at which tobacco smoke causes cancer in humans ([DeMarini, 2004](#)).

Sites with limited evidence of carcinogenicity or evidence suggesting lack of carcinogenicity in humans include the breast and the endothelium and relevant mechanisms are presented below.

Breast — There are several plausible mechanisms by which smoking may increase breast cancer risk, and some data support such an effect, including the increased risk among long-term smokers with *NAT2* slow genotype. Despite the overall lack of clear association in epidemiological studies, and the potential anti-estrogenic effects of smoking, the possibility that smoking increases breast cancer risk is biologically plausible.

Endothelium — The mechanisms by which cigarette smoking reduces the risk for endometrial cancer among current smokers, mainly among postmenopausal, remain unclear.

4.5.4 Interaction of ethanol and tobacco carcinogens

Data in rodents and non-human primates on the relationships between a) inhibition of hepatic clearance of nitrosamines by ethanol, b) the formation of promutagenic DNA adducts and c) tumours in extra-hepatic targets, likely also pertain in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of tobacco smoking.

Tobacco smoking causes cancers of the lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and accessory sinuses, larynx, oesophagus, stomach, pancreas, colorectum, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and ovary (mucinous), and myeloid leukaemia. Also, a positive association has been observed between tobacco smoking and cancer of the female breast. For cancers of the endometrium (post-menopausal) and of the thyroid, there is *evidence suggesting lack of carcinogenicity*.

There is *sufficient evidence* in humans for the carcinogenicity of parental smoking. Parental smoking causes hepatoblastoma in children. Also, a positive association has been observed between parental smoking and childhood leukaemia (particularly acute lymphocytic leukaemia).

There is *sufficient evidence* in experimental animals for the carcinogenicity of tobacco smoke and of tobacco smoke condensates.

Tobacco smoking is *carcinogenic to humans* (Group 1).

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SECOND-HAND TOBACCO SMOKE

Second-hand tobacco smoke was considered by a previous IARC Working Group in 2002 as “involuntary smoking” ([IARC, 2004](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Second-hand tobacco smoke comprises the smoke released from the burning tip of a cigarette (or other burned tobacco product) between puffs (called sidestream smoke (SM)) and the smoke exhaled by the smoker (exhaled mainstream smoke (MS)). Small additional amounts are contributed from the tip of the cigarette and through the cigarette paper during a puff, and through the paper and from the mouth end of the cigarette between puffs ([Jenkins *et al.*, 2000](#)).

Second-hand tobacco smoke is also referred as ‘environmental tobacco smoke’, ‘passive smoking’ or ‘involuntary smoking’ ([IARC, 2004](#)). The terms ‘passive smoking’ or ‘involuntary smoking’ suggest that while involuntary or passive smoking is not acceptable, voluntary or active smoking is acceptable. In this document, we use the term second-hand tobacco smoke ([WHO, 2010](#)).

1.1 Chemical composition

Many studies have examined the concentrations of cigarette smoke constituents in mainstream and sidestream smoke. The composition

of mainstream and sidestream smoke is qualitatively similar but quantitatively different. The ratios of sidestream to mainstream smoke vary greatly depending on the constituent. Some representative SS:MS ratios are: nicotine, 7.1; carbon monoxide, 4.8; ammonia, 455; formaldehyde, 36.5; acrolein, 18.6; benzo[*a*]pyrene, 16.0; *N*′-nitrosonornicotine (NNN), 0.43; (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 0.40 ([Jenkins *et al.*, 2000](#); [IARC, 2004](#)).

The physicochemical properties of second-hand tobacco smoke are different from those of mainstream smoke and sidestream smoke because of its rapid dilution and dispersion into the indoor environment ([IARC, 2004](#)). Concentrations of individual constituents in second-hand tobacco smoke can vary with time and environmental conditions. Field studies of these constituents and representative data have been extensively summarized ([Jenkins *et al.*, 2000](#); [IARC, 2004](#)). Some representative data are presented in [Table 1.1](#) ([Jenkins *et al.*, 2000](#); [IARC, 2004](#); [US Department of Health and Human Services, 2006](#)).

Table 1.1 Concentration of selected constituents in second-hand tobacco smoke

Constituent	Concentration
Nicotine	10–100 µg/m ³
Carbon monoxide	5–20 ppm
Benzene	15–30 µg/m ³
Formaldehyde	100–140 µg/m ³
Acetaldehyde	200–300 µg/m ³
1,3-Butadiene	20–40 µg/m ³
Benzo[a]pyrene	0.37–1.7 ng/m ³
NNK	0.2–29.3 ng/m ³
NNN	0.7–23 ng/m ³

1.2 Sources of exposure

Second-hand tobacco smoke is present in virtually all places where smoking takes place ([Navas-Acien *et al.*, 2004](#)): at home, in the workplace, in bars, restaurants, public buildings, hospitals, public transport and educational institutions. The setting that represents the most important source of exposure differs depending on the population. For example in children, the home environment may constitute a significant source of exposure, while other sources that may contribute are schools and public transportation. Likewise, for most women, the home environment is the primary source of second-hand tobacco smoke, which may be enhanced by exposure at the workplace.

Biomarker studies have evaluated carcinogen uptake in non-smokers to second-hand tobacco smoke. The NNK metabolites NNAL and its glucuronides (total NNAL) are consistently elevated in non-smokers exposed to second-hand tobacco smoke, in studies conducted in various living and occupational environments, and from infancy through adulthood ([Hecht *et al.*, 2006](#); [Hecht, 2008](#)). Levels of the biomarker of PAHs, urinary 1-hydroxypyrene, were significantly elevated in a large study of non-smokers exposed to second-hand tobacco smoke ([Suwan-ampai *et al.*, 2009](#)).

1.3 Measures of exposure

A conceptual framework for considering exposure to second-hand tobacco smoke is the “microenvironmental model,” which takes the weighted sum of the concentrations of second-hand tobacco smoke in the microenvironments where time is spent, with the weights the time spent in each, as a measure of personal exposure ([Jaakkola & Jaakkola, 1997](#)). Direct measures of exposure use concentrations of second-hand tobacco smoke components in the air in the home, workplace, or other environments, combined with information on the time spent in the microenvironments where exposure took place. Measurements of tobacco smoke biomarker(s) in biological specimens also represent a direct measure of exposure to second-hand smoke ([Samet & Yang, 2001](#); [Table 1.2](#)). Indirect measures are generally obtained by survey questionnaires. These include self-reported exposure and descriptions of the source of second-hand tobacco smoke in relevant microenvironments, most often the home and workplace ([Samet & Yang, 2001](#)).

One useful surrogate measure, and the only available in many countries, is the prevalence of smoking among men and women. It provides a measure of the likelihood of exposure. In most countries in Asia and the Middle East,

Table 1.2 Types of indicators measuring exposure to second-hand tobacco smoke

Measure	Suggested indicators
Direct	Concentration of second-hand tobacco smoke components in the air: <ul style="list-style-type: none"> - Nicotine - Respirable particles - Other markers Biomarker concentrations: <ul style="list-style-type: none"> - Cotinine - Carboxyhaemoglobin
Indirect	Report of second-hand tobacco smoke exposure at: <u>Home</u> <ul style="list-style-type: none"> - Number of smokers - Smoking of parents - Intensity (number of cigarettes smoked) <u>Workplace</u> <ul style="list-style-type: none"> - Presence of second-hand tobacco smoke - Number of smokers
Surrogate	Prevalence of smoking tobacco in men and in women Self-reported smoking habits of parents Nicotine concentration in house dust

From [Samet & Yang \(2001\)](#) and [Whitehead *et al.* \(2009\)](#)

for example, the very high prevalence of smoking among men combined with the low prevalence among women would imply that most women are exposed to second-hand tobacco smoke at home ([Samet & Yang, 2001](#)).

To measure exposure to second-hand tobacco smoke in children, self-reported smoking habits of their parents are used as a surrogate ([US Department of Health and Human Services, 2006](#)). More recently, other surrogate measures such as nicotine concentrations in house dust have been considered less biased than parental smoking as they reflect cumulative smoking habits and long-term exposure rather than current patterns of smoking ([Whitehead *et al.*, 2009](#)).

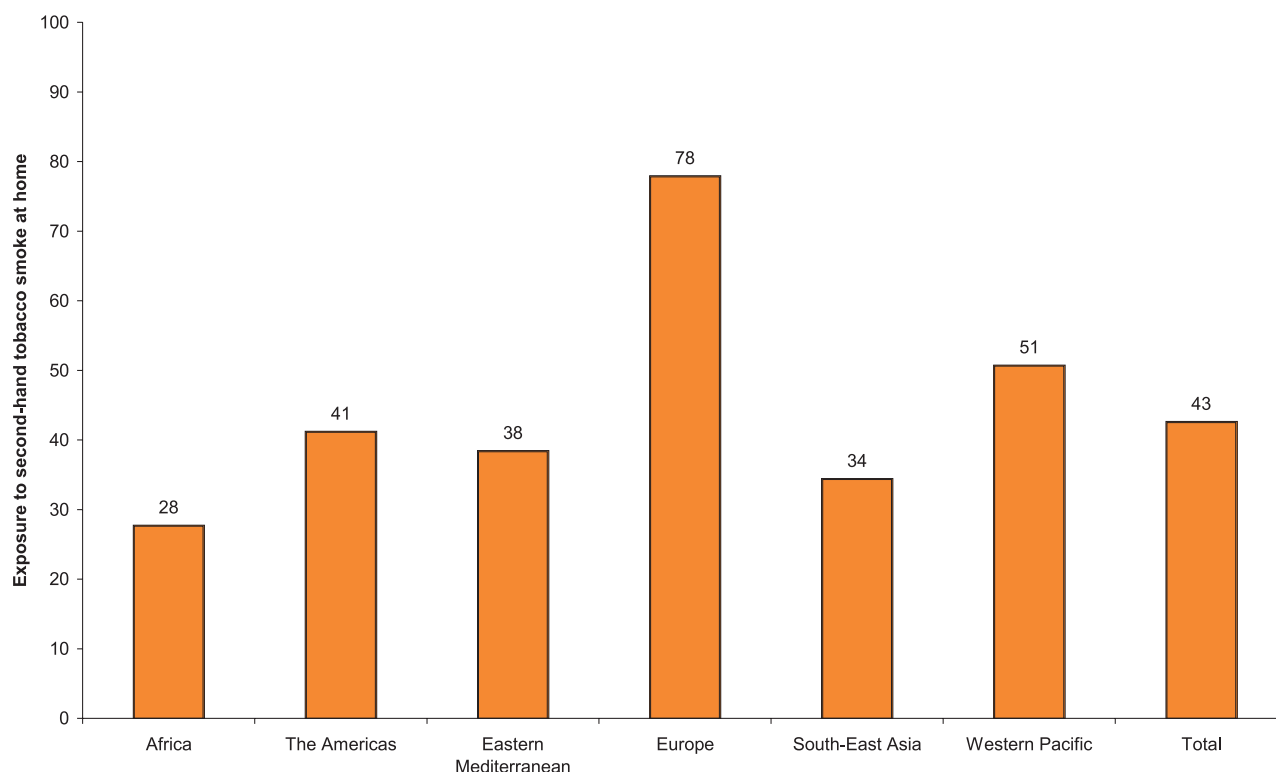
1.4 Prevalence of exposure

1.4.1 Exposure among children

(a) Overview

The most extensive population-based data on exposure to second-hand tobacco smoke among children are available through the Global Youth Tobacco Survey (GYTS) ([CDC/WHO, 2009](#)). GYTS is part of the Global Tobacco Surveillance System (GTSS), developed by the WHO and the United States' Centers for Disease Control and Prevention (CDC) in 1998. The GYTS is a school-based survey designed to measure tobacco use and some key tobacco control measures among youth (13–15 years) using a common methodology and core questionnaire. While most GYTS are national surveys, in some countries they are limited to subnational locations. Further, countries conduct the GYTS in different years, rendering comparison across countries for the same year difficult. The GYTS questionnaire

Fig. 1.1 Average prevalence (in%) of 13–15 year old children living in a home where others smoke, by WHO region, 2007



From [CDC \(2008\)](#)

asks about children's exposure to second-hand tobacco smoke in their home or in other places in the last 7 days preceding the survey. Since its inception in 1999, over 2 million students in 160 countries representing all six WHO regions have participated in the GYTS ([WHO, 2008, 2009a](#)).

Country-level estimates on second-hand tobacco smoke exposure at home and in public places among youth are available in the WHO Reports on the global tobacco epidemic ([WHO, 2008, 2009a, 2011](#)).

(b) *Exposure at home*

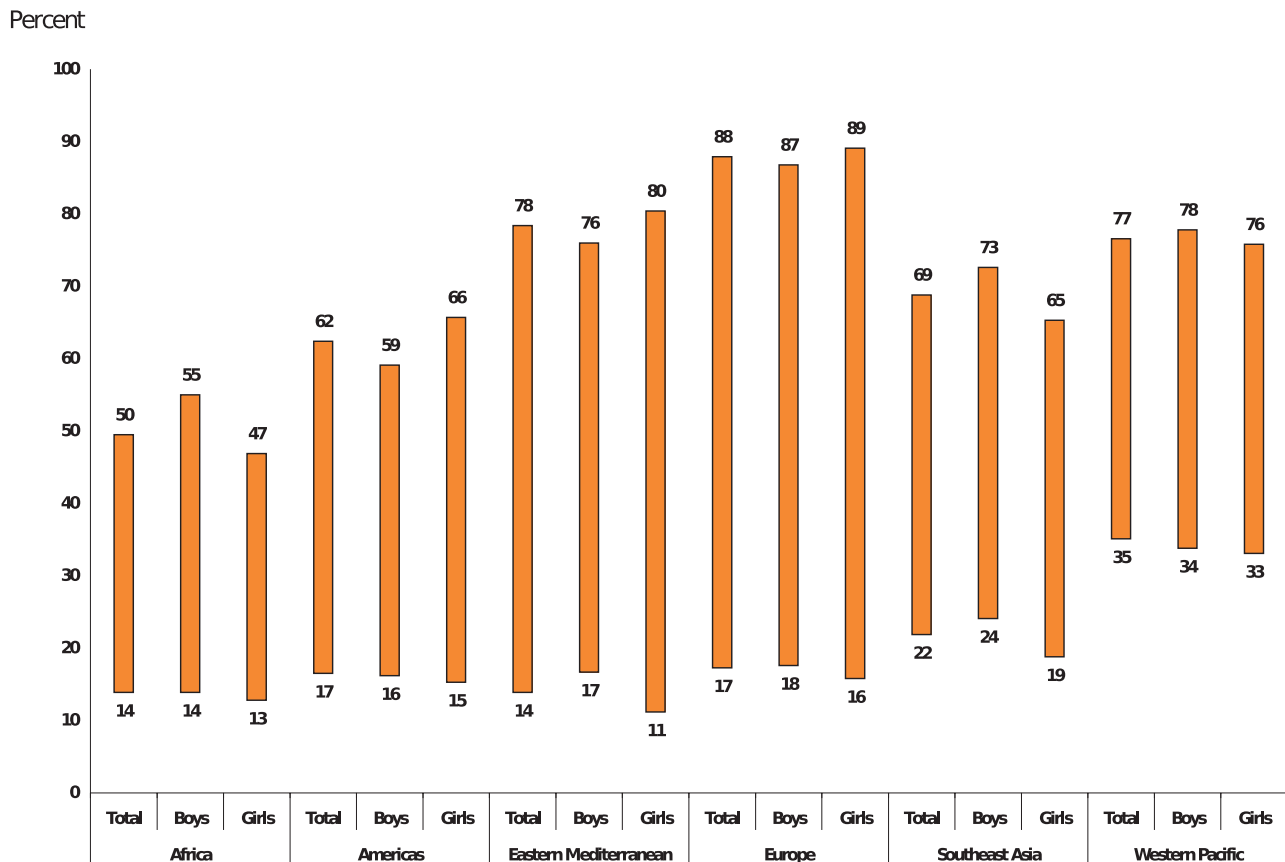
Nearly half of youth aged 13–15 years are exposed to second-hand tobacco smoke in their homes (Fig. 1.1; [CDC, 2008](#)). Among the six WHO regions, exposure to second-hand tobacco smoke at home was highest in the European Region

(77.8%) and lowest in the African region (27.6%). In the other four regions, exposure to second-hand tobacco smoke at home ranged from 50.6% in the Western Pacific Region to 34.3% in the South East Asian Region.

Fig. 1.2 shows the range of exposure to second-hand tobacco smoke at home by WHO region for boys and girls and for both sexes combined. The largest variations are observed in the Eastern Mediterranean Region and the European Region irrespective of sex. These variations are predominantly due to differences in parental smoking prevalence between countries, as well as the impact of the smoke-free places campaigns in place in various countries.

Country-level estimates from the Global Youth Tobacco Survey (1999–2009) are presented in [Table 1.3](#).

Fig. 1.2 Range of prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke at home, by WHO region, 2009



From [CDC/WHO \(2009\)](#)

Öberg and colleagues have estimated the worldwide exposure to second-hand tobacco smoke among children by using parent's current smoking status as an indicator of exposure among children ([WHO, 2010](#)). Four out of ten children (approximately 700 million children globally) have at least one parent who currently smokes, predisposing them to exposure to second-hand tobacco smoke at home ([Table 1.4](#)). Children in the Western Pacific Region had the highest level of potential exposure (68%) while Africa had the lowest, with about 13% of children having at least one parent who smoked. In the 2010 WHO Report on global estimate of the burden of disease from second-hand smoke ([WHO,](#)

[2010](#)), country-level estimates were collected or modelled from various sources. [Data partially overlap with those of the Global Youth Tobacco Survey].

(c) *Exposure outside home*

Similar to second-hand tobacco smoke exposure at home, almost half of the youth are exposed to second-hand tobacco smoke in public places, according to estimates from the Global Youth Tobacco Survey (Fig. 1.3; [CDC, 2008](#)). Exposure was highest in Europe (86.1%); for the other five regions, exposure to second-hand tobacco smoke in public places ranged from 64.1% in the Western Pacific to 43.7% in Africa.

Table 1.3 Prevalence of exposure to second-hand tobacco smoke at home and outside home among 13–15 year olds, by country and sex, from the Global Youth Tobacco Survey (participating countries only) — 1999–2009

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home		Exposed to second-hand tobacco smoke outside their homes			
				Total	Boys	Girls	Total	Boys	Girls
Afghanistan	EMRO	Kabul	2004	38.8	43.4	33.3	45.0	60.2	23.6
Albania	EURO	National	2009	49.7	48.6	50.9	64.5	65.3	63.9
Algeria	AFRO	Constantine	2007	38.7	39.8	37.9	60.2	66.0	56.2
Antigua and Barbuda	AMRO	National	2009	26.7	22.5	29.7	47.5	45.0	49.6
Argentina	AMRO	National	2007	54.7	51.7	57.7	68.6	66.4	70.7
Armenia	EURO	National	2009	70.6	69.2	71.6	78.3	80.7	76.4
Bahamas	AMRO	National	2009	25.1	23.4	27.0	51.0	50.8	52.7
Bahrain	EMRO	National	2002	38.7	37.2	39.5	45.3	49.7	40.9
Bangladesh	SEARO	National	2007	34.7	37.8	32.4	42.2	47.1	38.7
Barbados	AMRO	National	2007	25.9	25.9	26.0	59.6	59.7	59.6
Belize	AMRO	National	2008	25.7	26.2	25.1	50.4	52.1	48.6
Benin	AFRO	Atlantique Littoral	2003	21.5	23.7	18.3	38.0	41.3	33.5
Bhutan	SEARO	National	2009	29.5	29.2	29.5	59.4	58.6	59.7
The Plurinational State of Bolivia	AMRO	La Paz	2003	34.3	34.3	34.4	52.9	54.4	51.4
Bosnia and Herzegovina	EURO	National	2008	77.3	74.0	80.3	84.0	82.3	85.6
Botswana	AFRO	National	2008	38.5	38.2	38.6	62.1	60.0	63.7
Brazil	AMRO	São Paulo	2009	35.5	31.9	38.7	51.3	48.2	54.1
Bulgaria	EURO	National	2008	63.9	61.5	66.3	70.1	66.7	73.7
Burkina Faso	AFRO	Ouagadougou	2009	29.2	28.9	29.2	47.5	53.5	42.2
Burundi	AFRO	National	2008	33.9	35.2	31.7	49.3	54.0	45.3
Cambodia	WPRO	National	2003	47.0	48.9	44.5	58.5	60.6	56.5
Cameroon	AFRO	Yaounde	2008	21.7	25.0	19.1	45.8	49.3	42.4
Cape Verde	AFRO	National	2007	13.9	13.9	13.7	25.4	27.0	24.2
Central African Republic	AFRO	Bangui	2008	35.2	29.9	40.7	52.4	49.9	53.8
Chad	AFRO	National	2008	33.9	34.1	31.2	55.1	54.0	56.2
Chile	AMRO	Santiago	2008	51.7	48.9	54.4	68.3	63.4	73.0
China	WPRO	Shanghai	2005	47.0	46.6	47.4	35.2	34.2	36.2
Colombia	AMRO	Bogota	2007	26.2	25.3	27.0	56.1	55.1	56.9
Comoros	AFRO	National	2007	35.2	35.7	34.9	58.3	66.7	52.9
Congo	AFRO	National	2009	22.3	24.7	19.6	44.4	46.8	41.5
Cook Islands	WPRO	National	2008	61.9	58.8	64.5	73.8	70.3	76.8

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home		Exposed to second-hand tobacco smoke outside their homes			
				Total	Boys	Girls	Total	Boys	Girls
Costa Rica	AMRO	National	2008	21.6	20.8	22.1	41.5	40.0	42.8
Côte d'Ivoire	AFRO	National	2009	33.1	33.1	33.0	74.4	75.9	72.3
Croatia	EURO	National	2007	73.4	71.4	75.7	82.5	81.2	84.2
Cuba	AMRO	Havana	2004	62.4	59.1	65.7	65.0	64.6	65.8
Cyprus	EURO	National	2005	87.9	86.8	89.1	87.8	85.4	90.4
Czech Republic	EURO	National	2007	38.0	37.3	38.9	75.2	71.6	79.5
Democratic Republic of the Congo	AFRO	Kinshasa	2008	30.2	32.5	27.0	36.8	37.4	34.7
Djibouti	EMRO	National	2009	36.0	36.2	35.3	44.7	44.8	44.8
Dominica	AMRO	National	2009	26.9	25.2	27.4	62.3	61.4	62.5
Dominican Republic	AMRO	National	2004	33.1	31.1	34.5	41.9	38.5	44.9
Ecuador	AMRO	Quito	2007	28.9	27.5	30.2	52.5	49.5	54.6
Egypt	EMRO	National	2009	47.6	50.1	45.9	52.2	57.7	47.5
El Salvador	AMRO	National	2009	17.9	19.3	16.5	33.7	36.7	30.7
Equatorial Guinea	AFRO	National	2008	47.5	47.8	45.8	61.7	64.0	59.8
Eritrea	AFRO	National	2006	18.4	20.4	14.8	37.3	40.4	32.3
Estonia	EURO	National	2007	41.1	39.3	42.8	68.5	68.2	68.7
Ethiopia	AFRO	Addis Ababa	2003	14.9	15.5	12.8	41.2	45.1	37.4
Fiji	WPRO	National	2009	42.1	45.4	39.6	55.1	55.2	54.9
Gambia	AFRO	Banjul	2008	45.8	45.8	44.4	59.2	61.6	57.2
Georgia	EURO	National	2008	62.7	62.4	62.8	74.4	75.5	73.4
Ghana	AFRO	National	2009	19.1	19.6	17.9	32.3	33.9	30.4
Greece	EURO	National	2005
Grenada	AMRO	National	2009	27.3	24.9	29.7	53.1	50.5	55.7
Guatemala	AMRO	National	2008	23.1	23.9	22.1	40.8	43.8	37.9
Guinea	AFRO	National	2008	27.7	27.6	28.1	52.3	57.0	48.1
Guinea-Bissau	AFRO	Bissau	2008	31.0	32.1	29.7	35.3	36.6	34.1
Guyana	AMRO	National	2004	33.4	36.6	30.6	61.1	62.9	59.1
Haiti	AMRO	Port-au-Prince	2005	32.3	34.7	29.6	43.2	46.2	40.4
Honduras	AMRO	Tegucigalpa	2003	29.6	26.2	31.6	42.2	46.9	38.4
Hungary	EURO	National	2008	43.0	39.9	45.3	72.6	70.0	74.7
India	SEARO	National	2009	21.9	24.1	18.8	36.6	39.0	33.1
Indonesia	SEARO	National	2009	68.8	72.6	65.3	78.1	83.7	73.1

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Islamic Republic of Iran	EMRO	National	2007	35.4	38.1	32.7	44.8	49.8	39.6
Iraq	EMRO	Baghdad	2008	32.3	30.3	34.4	29.2	27.8	30.7
Jamaica	AMRO	National	2006	32.5	32.2	32.5	60.5	59.9	61.6
Jordan	EMRO	National	2009	53.6	50.6	55.5	50.5	50.6	49.7
Kenya	AFRO	National	2007	24.7	25.4	23.6	48.2	48.6	47.6
Kiribati	WPRO	National	2009	68.3	68.7	68.3	65.8	67.9	64.0
Kuwait	EMRO	National	2009	49.8	46.9	52.0	53.3	54.3	52.4
Kyrgyzstan	EURO	National	2008	33.4	35.1	31.9	57.7	58.7	56.8
Lao People's Democratic Republic	WPRO	Vientiane Capital	2007	40.3	41.2	39.5	55.4	57.7	53.2
Latvia	EURO	National	2007	55.2	55.1	55.1	72.7	73.2	72.3
Lebanon	EMRO	National	2005	78.4	76.0	80.4	74.4	73.9	74.7
Lesotho	AFRO	National	2008	36.9	34.2	37.3	52.6	50.2	53.2
Liberia	AFRO	Monrovia	2008	23.6	22.2	24.5	45.5	45.1	45.4
Lithuania	EURO	National	2009	38.3	34.1	42.6	64.9	66.5	63.3
Madagascar	AFRO	National	2008	49.5	55.0	44.9	62.9	69.5	57.5
Malawi	AFRO	National	2009	19.7	25.0	14.0	29.5	32.9	26.1
Malaysia	WPRO	National	2009	48.7	49.6	47.6	64.1	67.7	60.2
Maldives	SEARO	National	2007	48.3	49.4	47.1	68.0	70.6	65.4
Mali	AFRO	National	2008	48.5	50.1	46.9	81.4	83.1	79.2
Marshall Islands	WPRO	National	2009	52.1	54.7	50.5	59.7	60.5	60.6
Mauritania	AFRO	National	2009	37.5	39.8	35.0	50.9	55.4	47.1
Mauritius	AFRO	National	2008	36.1	38.5	34.1	73.6	77.2	70.7
Mexico	AMRO	Mexico City	2006	46.2	46.3	45.5	60.2	61.6	59.0
Federated States of Micronesia	WPRO	National	2007	60.7	60.4	59.6	71.3	73.3	68.7
Mongolia	WPRO	National	2007	54.4	53.7	54.3	55.5	60.7	50.7
Montenegro	EURO	National	2008	76.8	73.5	79.9	69.9	68.8	70.8
Morocco	EMRO	National	2006	27.1	24.7	29.2	41.1	41.1	40.9
Mozambique	AFRO	Maputo	2007	22.5	25.2	19.6	26.2	28.6	23.0
Myanmar	SEARO	National	2007	34.1	38.8	29.4	46.4	51.2	42.1
Namibia	AFRO	National	2008	38.1	38.0	37.9	49.9	47.7	51.5
Nepal	SEARO	National	2007	35.3	38.5	31.7	47.3	49.5	44.7
New Zealand	WPRO	National	2008	36.0	38.5	33.1	67.2	63.3	71.3

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Nicaragua	AMRO	Centro Managua	2003	43.7	43.9	43.2	54.1	56.4	51.9
Niger	AFRO	National	2009	24.1	28.1	20.4	54.3	58.8	50.2
Nigeria	AFRO	Abuja	2008	21.7	29.2	12.8	39.7	43.6	36.0
Oman	EMRO	National	2007	13.9	16.7	11.2	27.4	29.8	25.2
Pakistan	EMRO	Islamabad	2003	26.6	32.1	21.7	33.9	42.5	26.4
Palau	WPRO	National	2009	79.2	70.4	85.3
Panama	AMRO	National	2008	21.9	22.2	21.5	40.3	38.9	41.4
Papua New Guinea	WPRO	National	2007	73.9	75.4	72.2	86.4	87.0	85.6
Paraguay	AMRO	National	2008	32.5	35.1	30.1	55.3	57.3	53.4
Peru	AMRO	National	2007	25.5	26.2	24.2	46.8	46.9	46.4
Philippines	WPRO	National	2007	54.5	55.7	53.1	64.8	67.2	62.8
Poland	EURO	Warsaw	2009	49.1	42.8	54.6	76.8	75.5	77.8
Qatar	EMRO	National	2007	35.7	36.3	35.2	45.9	52.1	42.8
Republic of Korea	WPRO	National	2008	37.6	33.8	41.6	70.8	67.3	74.8
Republic of Moldova	EURO	National	2008	20.3	20.6	20.1	57.0	59.4	54.8
Romania	EURO	National	2009	52.8	50.0	55.4	59.1	57.1	61.3
Russian Federation	EURO	National	2004	76.4	74.3	78.5	89.4	89.0	89.9
Rwanda	AFRO	National	2008	19.2	19.9	18.0
Saint Kitts and Nevis	AMRO	National	2002	16.5	16.2	15.3	48.8	48.0	49.0
Saint Lucia	AMRO	National	2007	25.2	28.4	22.6	64.0	61.1	65.7
Saint Vincent and the Grenadines	AMRO	National	2007	31.5	31.7	30.9	59.7	56.5	61.8
Samoa	WPRO	National	2007	59.1	60.8	56.4	62.8	64.8	60.5
San Marino	EURO	National	2009	32.9	31.8	34.0	65.8	62.8	69.3
Saudi Arabia	EMRO	National	2007	27.9	28.9	26.4	38.2	45.1	31.6
Senegal	AFRO	National	2007	47.6	49.9	42.5	48.3	48.3	45.0
Serbia	EURO	National	2008	76.9	73.4	80.0	71.9	68.1	74.8
Seychelles	AFRO	National	2007	42.3	38.2	46.1	57.1	54.3	60.6
Sierra Leone	AFRO	National	2008	44.2	46.3	42.9	56.5	59.9	53.4
Singapore	WPRO	National	2000	35.1	34.8	35.2	65.1	64.0	66.0
Slovakia	EURO	National	2007	44.9	42.4	46.9	69.3	68.0	70.5
Somalia	EMRO	Somaliland	2007	29.1	30.8	21.9	48.7	50.2	41.8
South Africa	AFRO	National	2008	32.1	32.7	31.5	41.1	43.5	39.4

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Sri Lanka	SEARO	National	2007	35.4	37.6	33.4	65.9	66.5	65.1
Sudan	EMRO	National	2009	27.6	26.0	28.7	33.1	33.8	32.0
Suriname	AMRO	National	2009	46.6	44.2	47.7	53.3	51.4	53.8
Swaziland	AFRO	National	2009	23.3	21.8	24.3	55.6	52.1	58.0
Syrian Arab Republic	EMRO	National	2010	60.1	58.7	61.7	58.4	61.1	55.7
Thailand	SEARO	National	2009	45.7	46.6	44.7	67.6	68.0	67.1
The former Yugoslav Republic of Macedonia	EURO	National	2008	67.5	64.7	70.5	66.0	63.7	68.3
Timor-Leste	SEARO	National	2009	59.4	66.7	52.1	61.3	66.7	56.0
Togo	AFRO	National	2007	20.2	23.5	15.7	41.6	45.1	36.7
Trinidad and Tobago	AMRO	National	2007	40.1	36.3	43.6	64.2	62.8	65.9
Tunisia	EMRO	National	2007	51.9	53.1	50.6	65.2	69.7	61.0
Turkey	EURO	National	2009	48.6	43.8	53.0	79.9	80.1	79.6
Tuvalu	WPRO	National	2006	76.6	77.8	75.8	76.7	72.0	79.3
Uganda	AFRO	National	2007	20.0	20.7	18.8	45.6	46.1	45.2
United Arab Emirates	EMRO	National	2005	25.3	24.3	25.4	31.6	34.3	28.4
United Republic of Tanzania	AFRO	Arusha	2008	15.7	16.4	14.9	34.7	35.2	33.9
United States of America	AMRO	National	2009	35.7	35.3	36.1	42.8	38.2	47.6
Uruguay	AMRO	National	2007	50.5	47.6	52.5	68.6	64.0	72.1
Uzbekistan	EURO	Tashkent	2008	17.3	17.6	15.8	46.7	47.5	42.4
Vanuatu	WPRO	National	2007	59.3	62.8	56.7	75.9	78.7	73.9
Venezuela (Bolivarian Republic of)	AMRO	National	1999	43.5	40.7	45.3	47.8	47.0	48.4
Viet Nam	WPRO	National	2007	58.5	59.0	58.0	71.2	71.4	71.0
West Bank*	EMRO	West Bank	2009	63.0	61.6	64.4	61.6	67.6	55.8
Gaza Strip*	EMRO	Gaza Strip	2005	47.4	48.0	46.5	46.1	51.9	40.6
Yemen	EMRO	National	2008	44.9	48.2	37.8	42.7	49.8	30.7
Zambia	AFRO	Lusaka	2007	23.1	21.2	24.3	45.5	43.2	47.1
Zimbabwe	AFRO	Harare	2008	20.9	22.0	19.4	40.1	40.5	39.5

* Refers to a territory
From [WHO \(2008, 2009a\)](#)

Table 1.4 Proportion of children under 15 years with one or more parent who smokes, by WHO subregion (based on survey data and modeling)

Subregion	Parental smoking (%)
Africa (D)	13
Africa (E)	13
The Americas (A)	25
The Americas (B)	29
The Americas (D)	22
Eastern Mediterranean (B)	37
Eastern Mediterranean (D)	34
Europe (A)	51
Europe (B)	61
Europe (C)	61
South-eastern Asia (B)	53
South-eastern Asia (D)	36
Western Pacific (A)	51
Western Pacific (B)	68
GLOBAL	41

WHO subregional country grouping (adapted from [WHO, 2002](#)):

Africa. **Region D:** Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo; **Region E:** Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe

The Americas. **Region A:** Canada, Cuba, USA; **Region B:** Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela; **Region D:** Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru

Eastern Mediterranean. **Region B:** Bahrain, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates; **Region D:** Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen

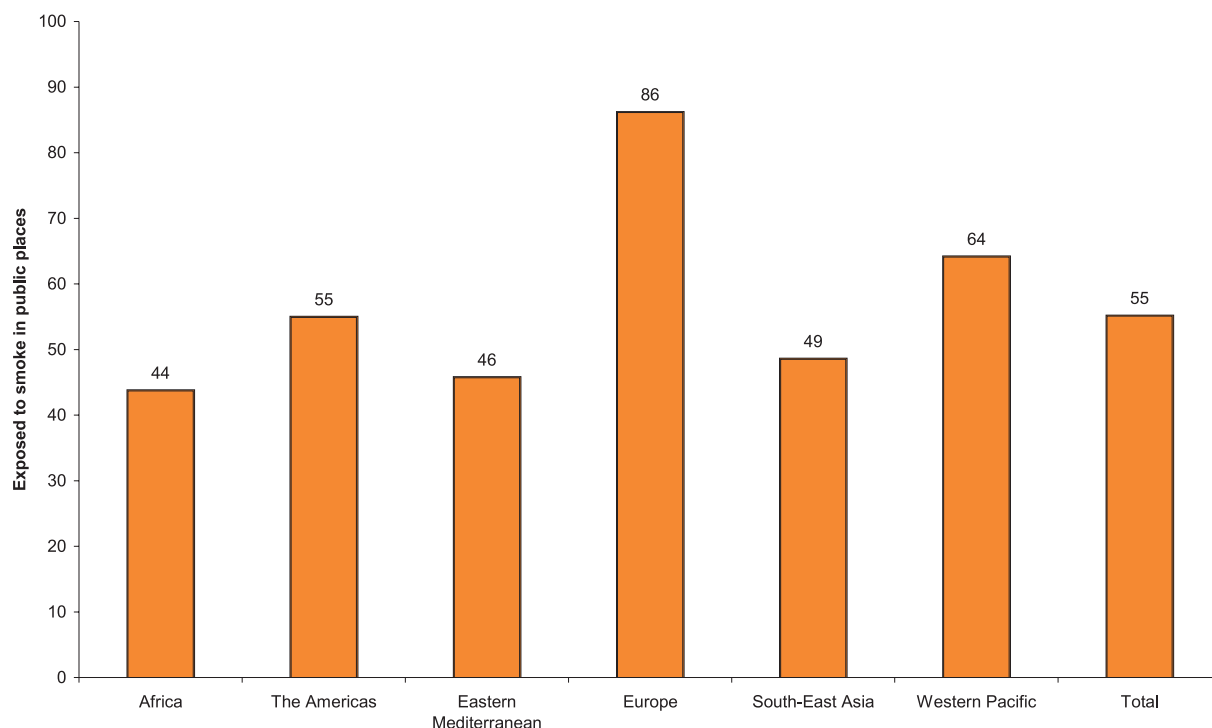
Europe. **Region A:** Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom; **Region B:** Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Serbia and Montenegro, Slovakia, Tajikistan, Former Yugoslav Republic of The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan; **Region C:** Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of the Republic of Moldova, Russian Federation, Ukraine

South-eastern Asia. **Region B:** Indonesia, Sri Lanka, Thailand; **Region D:** Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar (Burma), Nepal, Timor-Leste

Western Pacific. **Region A:** Australia, Brunei Darussalam, Japan, New Zealand, Singapore; **Region B:** Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

Regions are categorized as follows (WHO-approved classifications): A = very low child mortality and very low adult mortality; B = low child mortality and low adult mortality; C = low child mortality and high adult mortality; D = high child mortality and high adult mortality; E = high child mortality and very high adult mortality.

Fig. 1.3 Average prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke in public places, by WHO region, 2007



From [CDC \(2008\)](#)

Fig. 1.4 presents the range of exposure to second-hand tobacco smoke outside home by WHO region for boys and girls and for both sexes combined. There are wide variations in second-hand tobacco smoke exposure outside home within each region. The largest variations are observed in the African region and the Western Pacific region irrespective of sex. This is largely influenced by the presence of smoke-free legislation for public places in the countries, as well as levels of enforcement and public's compliance with these laws.

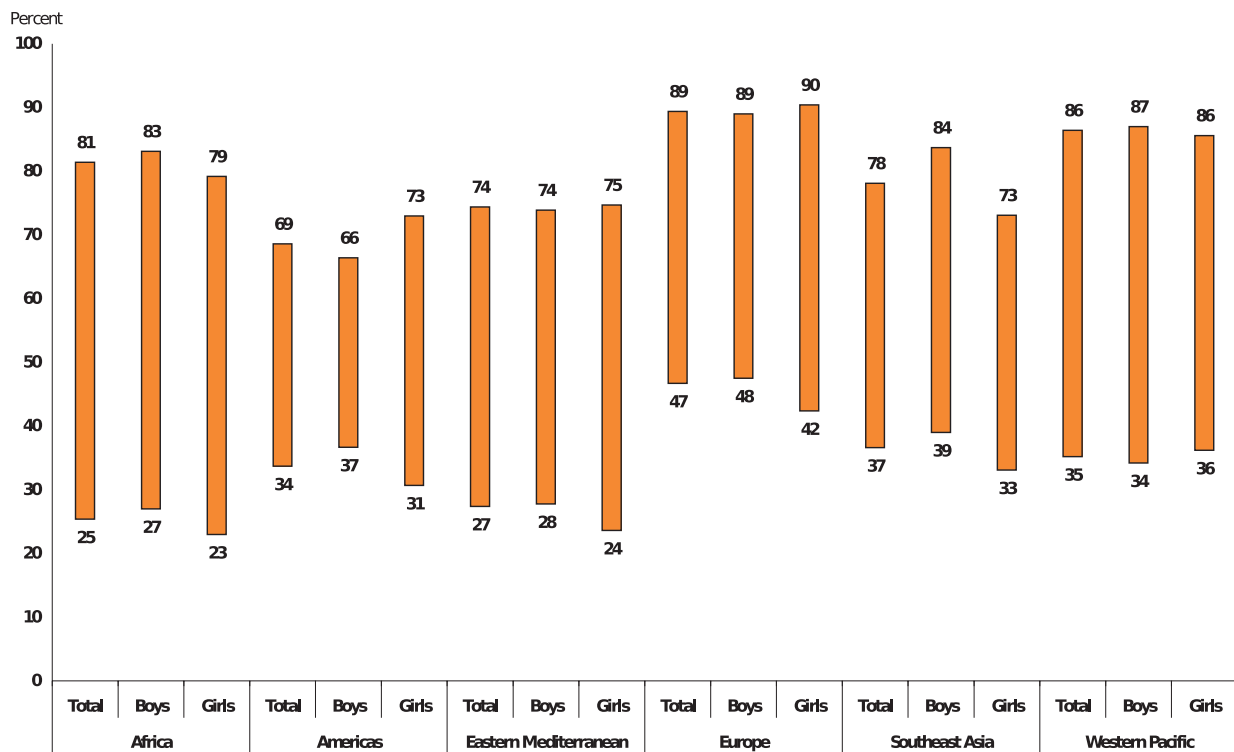
1.4.2. Exposure among adults

(a) Overview

While the GYTS offers a valuable global source for estimating exposure to second-hand tobacco smoke among children, there is no such extensive source of data for adults. Estimates of second-hand tobacco smoke exposure among adults have used the definitions of exposure based on having a spouse who smokes or exposure to tobacco smoke at work. For the countries lacking such data, exposure was estimated using a model based on smoking prevalence among men from the WHO Global InfoBase.

About one third of adults worldwide are regularly exposed to second-hand tobacco smoke ([Table 1.5](#)). The highest exposure was estimated in European Region C with 66% of the population

Fig. 1.4 Range of prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke outside their home, by WHO region, 2009



From [CDC/WHO \(2009\)](#)

being regularly exposed to second-hand tobacco smoke. The lowest regional exposure was estimated in the African region (4%). Differences between men and women were generally small, except in Eastern Mediterranean Region D and South East Asia Region B.

(b) Exposure at home

The Global Tobacco Surveillance System, through its adult household survey “Global Adult Tobacco Survey” (GATS), collects information on key tobacco control indicators including information on second-hand tobacco smoke exposure at home, at work and several public places ([WHO, 2009b](#)). GATS is a nationally representative survey conducted among persons aged ≥ 15 years using a standardized questionnaire, sample design, data

collection method, and analysis protocol. GATS results are available from 14 countries with a high tobacco burden. Additionally since 2008, The WHO STEPwise approach to surveillance (STEPS) surveys have started to collect information on exposure to second-hand tobacco smoke at home and at work, now available for 7 countries ([WHO, 2009c](#)).

In the 21 countries that have reported data on exposure to second-hand tobacco smoke, large numbers of people are exposed at home (Fig. 1.5). Exposure was highest in Sierra Leone (74%) and lowest in the British Virgin Islands (3%). Overall, differences between men and women were relatively small in most countries; in China, Cambodia and Mongolia, more women reported being exposed to second-hand tobacco smoke

Table 1.5 Proportion of non-smoking adults exposed regularly to second-hand tobacco smoke, by WHO region (based on survey data and modeling)

WHO Subregion	Exposure in men	Exposure in women
	(%)	(%)
Africa (D)	7	11
Africa (E)	4	9
The Americas (A)	16	16
The Americas (B)	13	21
The Americas (D)	15	18
Eastern Mediterranean (B)	24	22
Eastern Mediterranean (D)	21	34
Europe (A)	34	32
Europe (B)	52	53
Europe (C)	66	66
South-eastern Asia (B)	58	41
South-eastern Asia (D)	23	18
Western Pacific (A)	50	54
Western Pacific (B)	53	51
GLOBAL	33	31

From [WHO \(2010\)](#)

For the WHO subregional country grouping, see footnote of [Table 1.4](#).

in their homes then men. This lack of difference implies that even when prevalence of smoking among women is low, they are exposed to second-hand tobacco smoke at home as much as men.

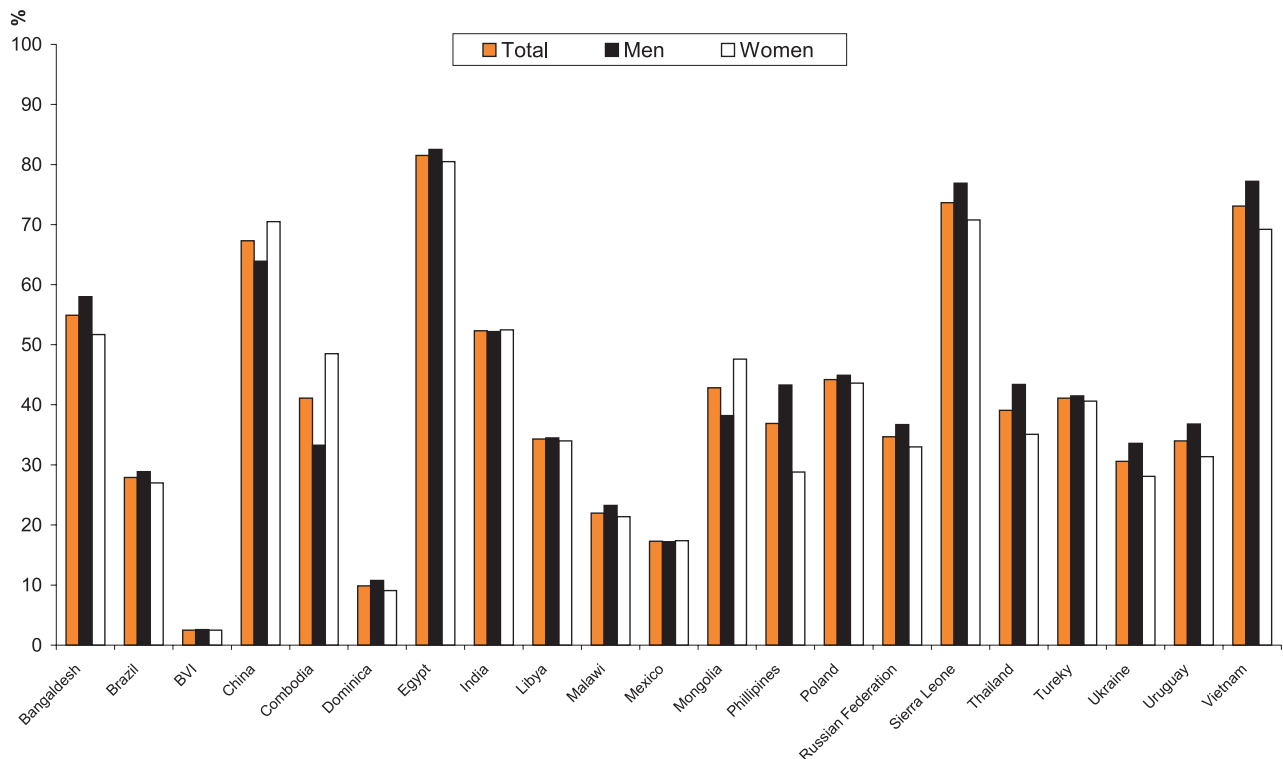
(c) Exposure at the workplace

The same magnitude of second-hand tobacco smoke exposure at the workplace was reported as at home (Fig. 1.6). Exposure to second-hand tobacco smoke at the workplace was highest in Sierra Leone (74%) and lowest in the British Virgin Islands (3%). However, more men reported being exposed to others' smoke at their workplace as compared to women in all countries. This difference was most significant in Libyan Arab Jamahiriya and Bangladesh. These differences could be explained by the fact that women either tend to work in places where smoking is banned, such as education or health facilities, or work predominantly with other women.

1.5 Regulations

The World Health Organization's Framework Convention on Tobacco Control (WHO FCTC) is a multilateral treaty with legally binding obligations for its 174 Parties (as of November 2011) ([WHO, 2003](#)). This comprehensive treaty contains supply and demand reduction measures available to countries to counter the tobacco epidemic. Article 8 of the Treaty specifically addresses the need for protection from second-hand tobacco smoke, and articulates the "adoption and implementation of effective legislative, executive, administrative and /or other measures" by Parties to the Convention to this effect. Guidelines to Article 8 specify key elements needed in legislation to help countries meet the highest standards of protection from second-hand tobacco smoke and provide a clear timeline for Parties to adopt appropriate measures (within five years after entry into Force of the WHO FCTC) ([WHO, 2007](#)).

Fig. 1.5 Prevalence of adults exposed to second-hand tobacco smoke in their homes, in the countries that completed the Global Adult Tobacco Survey (GATS) and WHO STEPwise approach to surveillance (STEPS) surveys, 2008–2009



From [WHO \(2009b, c\)](#)

GATS defines second-hand tobacco smoke exposure at home as reporting that smoking inside their home occurs daily, weekly, or monthly. STEPS defines second-hand tobacco smoke exposure at home as reporting exposure in the home on one or more days in the past 7 days.

All countries, regardless of their FCTC ratification status, are taking steps to reduce second-hand tobacco smoke in public places, through either planning the steps to or implementing national smoke-free laws for public places or workplaces. In 2008, approximately 5% of the world's population (354 million) had national smoke-free laws. Fig. 1.7 provides details on the number of public places with national smoke-free legislation for all WHO Member States.

As of December 2008, fifteen countries across the globe have legislation that provide the highest level of protection against second-hand tobacco smoke exposure. These include: Albania, Australia, Bhutan, Canada, Colombia, Guatemala, Islamic Republic of Iran, Ireland,

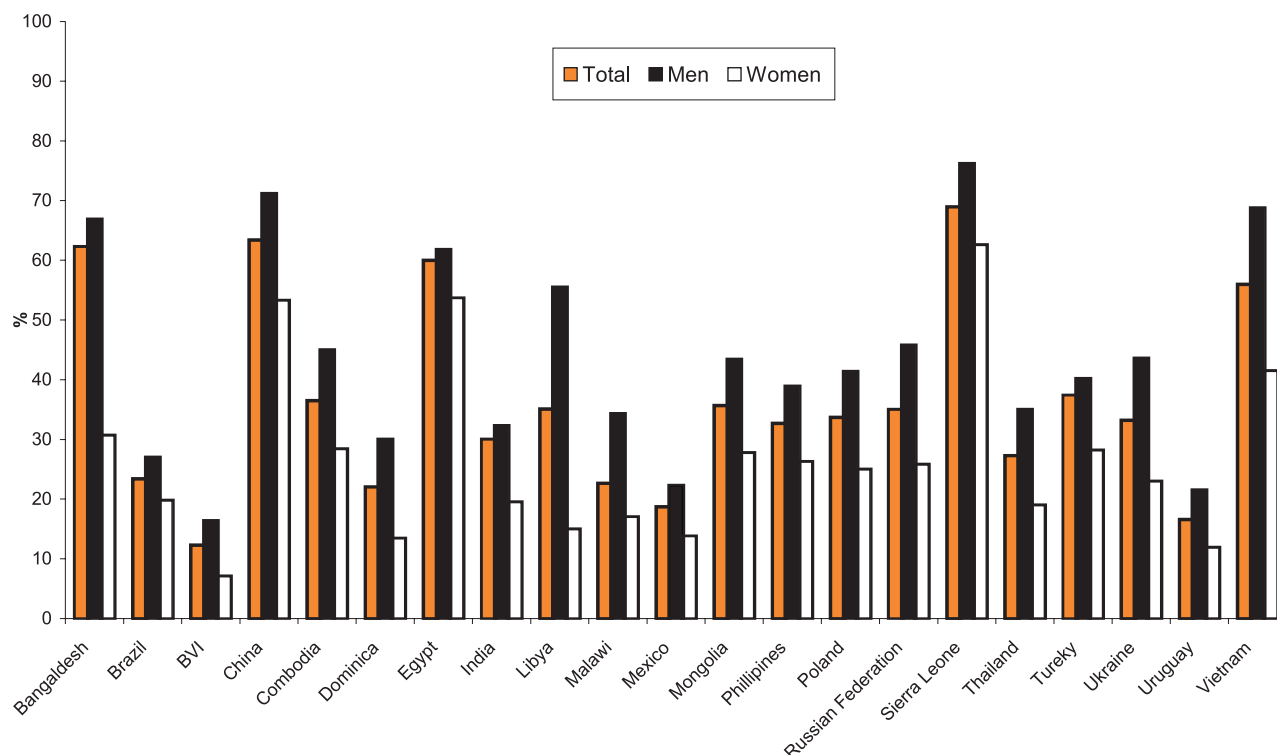
Marshall Islands, New Zealand, Panama, Turkey, Turkmenistan, United Kingdom of Great Britain and Northern Ireland and Uruguay.

2 Cancer in Humans

2.1 Cancer of the lung

More than 50 epidemiological studies since 1981 have examined the association between second-hand tobacco smoke and lung cancer resulting in the conclusion that exposure of non-smokers to second-hand tobacco smoke is causally associated with lung cancer risk ([IARC, 2004](#)). Many studies previously

Fig. 1.6 Prevalence of adults exposed to second-hand tobacco smoke in their workplaces, in the countries that completed the Global Adult Tobacco Survey and WHO STEPwise approach to surveillance (STEPS) surveys, 2008–2009



GATS defines second-hand tobacco smoke exposure at work as indoor workers who were exposed at work in the past 30 days.

STEPS defines second-hand tobacco smoke exposure at work as reporting exposure in the workplace on one or more days in the past 7 days

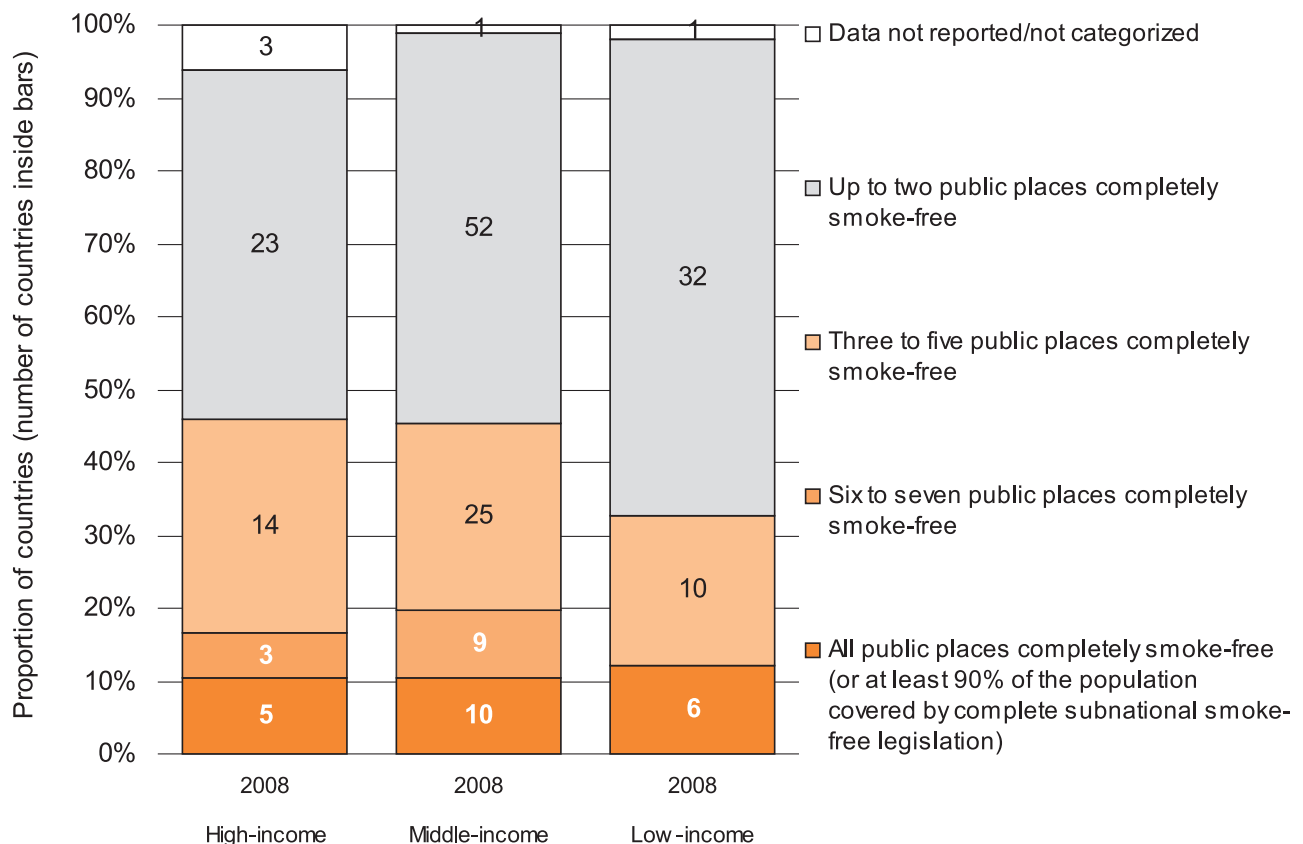
From [WHO \(2009b, c\)](#)

available assessed the lung cancer risk among the nonsmoking spouses of smokers since it is one of the sources of adult exposure to second-hand tobacco smoke that is less likely to be subject to exposure misclassification or other bias. Several important new, cohort, case-control studies and meta-analyses have been published since 2004 that provide additional evidence confirming the causal association (Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.1.pdf>, Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.2.pdf>, and Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.3.pdf>). These new studies also expand our assessment of

the effect of second-hand tobacco smoke in the workplace allowing for more refined estimates of lung cancer risk. Preliminary data also suggest significant interactions between several genetic polymorphisms, second-hand tobacco smoke and lung cancer risk.

In a meta-analysis of 55 studies, including 7 cohort, 25 population based case-control studies and 23 hospital based case-control studies the pooled relative risk (RR) for lung cancer for never smoking women exposed to second-hand tobacco smoke from spouses was 1.27 (95%CI: 1.17–1.37). The relative risk for studies in North America was 1.15 (95%CI: 1.03–1.28), in Asia 1.31 (95%CI: 1.16–1.48) and Europe 1.31 (1.24–1.52) ([Taylor et al., 2007](#)).

Fig. 1.7 Number and percentage of countries with number of public places covered by smoke free legislations, by income status (as of 31 December 2008)



From [WHO \(2009a\)](#)

In a meta-analysis of 22 studies that assessed the effect of second-hand tobacco smoke exposures at work, the relative risk for lung cancer among exposed non-smokers was 1.24 (95%CI: 1.18–1.29) and among those workers classified as highly exposed to second-hand tobacco smoke at work 2.01 (95%CI: 1.33–2.60) compared to those with no exposure at work ([Stayner et al., 2007](#)).

In a large cohort study conducted in 10 European countries (European Prospective Investigation into Cancer and Nutrition, EPIC), it was estimated that the hazard ratio (HR) for lung cancer risk from second-hand tobacco smoke exposure at home and/or at work for never smokers and ex-smokers (at least 10 years)

was 1.34 (0.85–2.13) ([Vineis et al., 2007a](#)). The main component of this risk was attributable to exposure at the workplace, resulting in a hazard ratio of 1.65 (1.04–2.63). The overall hazard ratio between childhood exposure and the risk of lung cancer in adulthood was 2.00 (0.94–4.28); among children with daily exposure for many hours each day the hazard ratio was 3.63 (1.19–11.12). In a separate analysis of workplace exposure to second-hand tobacco smoke in this cohort women were observed to have a lung cancer hazard ratio of 2.13 (1.6–3.4) ([Veglia et al., 2007](#)).

In a large population-based cohort study conducted in Japan, findings confirmed that exposure to second-hand tobacco smoke is

a risk factor for lung cancer among Japanese women ([Kurahashi et al., 2008](#)). Compared with women married to never smokers, the hazard ratio for all lung cancer incidence was 1.34 (95%CI:0.81–2.21) and for adenocarcinoma 2.03 (95%CI:1.07–3.86). For adenocarcinoma dose–response relationships were seen for both intensity (P for trend = 0.02) and total amount (P for trend = 0.03) of the husband’s smoking. Exposure to second-hand tobacco smoke at the workplace also increased the risk of lung cancer (HR, 1.32; 95%CI: 0.85–2.04).

Data from a cohort study of women from Shanghai, China also found that exposure to second-hand tobacco smoke is associated with lung cancer mortality. Exposure to second-hand tobacco smoke at work was associated with a significantly increased mortality to lung cancer (HR 1.79, 95%CI: 1.09–2.93) but the risk was not significant for exposure to husband’s second-hand tobacco smoke (HR 1.09, 95%CI: 0.74–1.61) ([Wen et al., 2006](#)). In a case–control study of lung cancer among lifetime non-smoking Chinese men living in Hong Kong Special Administrative Region a non-significant association between all lung cancer and ever being exposed to household and/or workplace second-hand tobacco smoke was observed (OR, 1.11, 95%CI: 0.74–1.67) but a significant increase was observed for adenocarcinoma (OR, 1.68, 95%CI: 1.00–2.38) ([Tse et al., 2009](#)).

In a long-term case–control study of lung cancer cases at the Massachusetts General Hospital, study participants exposed to second-hand tobacco smoke at work and at leisure were at a significantly greater risk (OR, 1.30, 95%CI: 1.08–1.57) if the exposure occurred between birth and 25 years of age. If the exposures occurred after the age of 25 years the risk was not elevated (OR, 0.66, 95%CI: 0.21–1.57) but the confidence limits are wide for this subgroup analysis ([Asomaning et al., 2008](#)).

In two other cohort studies, one conducted in California ([Enstrom & Kabat, 2003](#)) and

another in New Zealand ([Hill et al., 2007](#)) no excess risk was observed among lifelong non-smokers exposed to second-hand tobacco smoke. In the California study the relative risk was 0.99 (95%CI: 0.72–1.37) based on 126 lung cancer cases. [The confidence intervals in this study are relatively wide and they include the current IARC estimate of lung cancer risk from second-hand tobacco smoke exposure. In addition the opportunity for substantial misclassification of second-hand tobacco smoke exposure is great because exposures outside the home were not assessed and the second-hand tobacco smoke exposures were not re-evaluated after enrollment into the study.] [Hill et al. \(2007\)](#) observed no association between second-hand tobacco smoke exposure in a census enumeration of current second-hand tobacco smoke exposure at home and linkage to cancer registries three years later. The authors suggest that this may be a result of either the misclassification of total second-hand tobacco smoke exposure since exposures outside the home were not assessed and/or the fact that a 3-year follow-up after exposure ascertainment may have been too short to capture important exposures before the diagnosis of lung cancer.

One case–control study ([Wenzlaff et al., 2005](#)) and one case-only study ([Bonner et al., 2006](#)) assessed lung cancer risk associated with second-hand tobacco smoke exposure and several polymorphisms. In the case–control study, individuals were stratified by household second-hand tobacco smoke exposure (yes/no), those with *CYP1B1* *Leu*⁴³²*Val* genotype alone or in combination with Phase II enzyme polymorphisms were more strongly associated with lung cancer risk if they also were exposed to at least some household second-hand tobacco smoke exposure compared to those that had no exposure. In the case-only study a significant interaction was observed between lung cancer risk, second-hand tobacco smoke and a GSTM1 (null) genotype (OR, 2.28, 95%CI:1.15–4.51).

2.2 Cancer of the breast

2.2.1 Overview of studies

The relationship between exposure to second-hand tobacco smoke and breast cancer has been comprehensively reviewed in the peer reviewed literature ([Johnson, 2005](#); [Miller *et al.*, 2007](#)) and in reports from national and international committees ([IARC, 2004, 2009](#); [California Environmental Protection Agency, 2005](#); [US. Department of Health and Human Services, 2006](#); [Collishaw *et al.*, 2009](#)). These reviews have drawn different conclusions. [IARC \(2004\)](#) characterized the evidence as “inconsistent,” based on studies published or in press by June, 2002. A US Surgeon General Report (2006) concluded that the evidence was “suggestive but not sufficient” to infer a causal relationship between second-hand tobacco smoke and breast cancer, whereas reviews by the California Environmental Protection Agency (CalEPA) in 2005 and by a panel of researchers in this area convened in Canada ([Collishaw *et al.*, 2009](#)) designated the evidence for second-hand tobacco smoke as “consistent with a causal association in younger primarily premenopausal women.”

A total of 16 new studies have been published since the previous *IARC Monograph* ([IARC, 2004](#)). These include three cohort studies ([Reynolds *et al.*, 2004](#); [Hanaoka *et al.*, 2005](#); [Pirie *et al.*, 2008](#)) (Table 2.4 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.4.pdf>), and 13 new case-control studies ([Lash & Aschengrau, 2002](#); [Alberg *et al.*, 2004](#); [Gammon *et al.*, 2004](#); [Shrubsole *et al.*, 2004](#); [Bonner *et al.*, 2005](#); [Sillanpää *et al.*, 2005](#); [Lissowska *et al.*, 2006](#); [Mechanic *et al.*, 2006](#); [Roddam *et al.*, 2007](#); [Rollison *et al.*, 2008](#); [Slattery *et al.*, 2008](#); [Ahern *et al.*, 2009](#); [Young *et al.*, 2009](#)) (Table 2.5 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.5.pdf>). Table 2.5 also presents two case-control studies not discussed previously

([Zhao *et al.*, 1999](#); [Liu *et al.*, 2000](#)). Several meta-analyses have also been published as new data became available ([California Environmental Protection Agency, 2005](#); [Johnson, 2005](#); [US. Department of Health and Human Services, 2006](#); [Pirie *et al.*, 2008](#); [IARC, 2009](#)).

The largest of the cohort studies, identified 2518 incident breast cancers among 224917 never smokers followed for an average of 3.5 years in the British Million Women Study ([Pirie *et al.*, 2008](#)). The cohort was drawn from women, age 50–64 years, participating in mammography screening programmes. Nearly all cases were post-menopausal and the overall analyses pertain to postmenopausal breast cancer. No relationship was observed between breast cancer risk and smoking by a parent at the time of birth and/or age 10 years (HR, 0.98; 95%CI: 0.88–1.08); the results were also null for smoking by a current partner (HR, 1.02; 95%CI: 0.89–1.16) or exposure to the combination of parental and spousal smoking (HR, 1.03; 95%CI: 0.90–1.19). [Pirie *et al.* \(2008\)](#) also present a meta-analysis of studies of second-hand smoke and breast cancer risk, separating studies by cohort or case-control design. No overall association was observed in the cohort studies. These largely represent post-menopausal breast cancer, so the analysis was not stratified by menopausal status. An overall association was seen in the case-control studies, similar to the findings of other meta-analyses ([California Environmental Protection Agency, 2005](#); [US. Department of Health and Human Services, 2006](#); [IARC, 2009](#)). [[Pirie *et al.* \(2008\)](#) focus on the discrepancy between the cohort and case-control results and propose that the associations observed in early case-control studies can likely be explained by recall bias. The study has been criticized for the lack of information on occupational exposures to second-hand smoke ([Collishaw *et al.*, 2009](#)).]

A second large cohort study ([Reynolds *et al.*, 2004](#)) identified 1998 women diagnosed with breast cancer during five years of follow-up of the

California Teachers Study. Analyses were based on 433 women with pre/peri-menopausal breast cancer and 1361 women with postmenopausal breast cancer. No association was observed between post-menopausal breast cancer and residential exposure to second-hand tobacco smoke in childhood or adulthood. No association was initially reported with pre/peri-menopausal breast cancer in analyses based on menopausal status at enrollment (RR 0.93, 95%CI: 0.71–1.22). When menopausal status was defined by age at diagnosis rather than by age at enrollment, the hazard ratio for premenopausal breast cancer among women exposed in both childhood and adulthood increased to 1.27 (95%CI: 0.84–1.92) ([Reynolds et al., 2006](#)).

[Hanaoka et al. \(2005\)](#) identified 162 incident breast cancer cases during a nine-year follow-up of 20169 Japanese women, age 40–59 years, who reported no history of active smoking when enrolled in the Japan Public Health Center (JPHC) study in 1990. Nearly three quarters (72%) of the women reported exposure to second-hand tobacco smoke. About half of the women were premenopausal when enrolled in the study, although there were only nine unexposed cases among the pre-menopausal women. The multivariate-adjusted relative risk for breast cancer among all exposed women irrespective of menopausal status was 1.1 (95%CI: 0.8–1.6) compared to those classified as unexposed. The corresponding relative risks for women who were pre- or postmenopausal at baseline were 2.6 (95%CI: 1.3–5.2) and 0.7 (95%CI: 0.4–1.0), respectively.

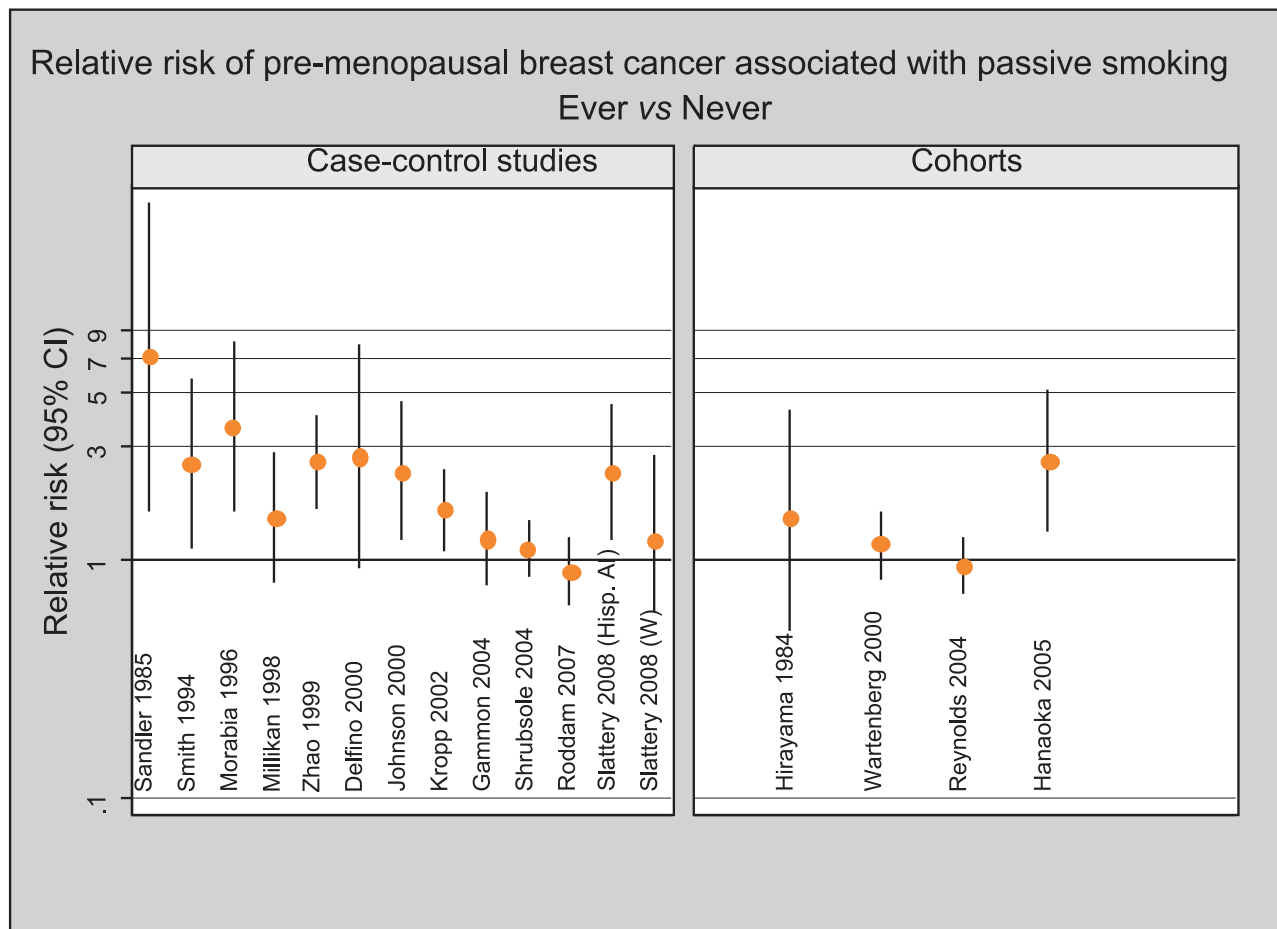
Six of the 13 new population-based case-control studies included more than 1000 cases each ([Shrubsole et al., 2004](#); [Bonner et al., 2005](#); [Lissowska et al., 2006](#); [Mechanic et al., 2006](#); [Slattery et al., 2008](#); [Young et al., 2009](#); Table 2.5 on-line). None of these 13 studies showed an overall increase in breast cancer risk associated with second-hand tobacco smoke exposure in Caucasians. The incidence of premenopausal breast cancer was associated with one or more

indices of second-hand tobacco smoke exposure in all four studies that stratified the results by menopausal status ([Gammon et al., 2004](#); [Shrubsole et al., 2004](#); [Bonner et al., 2005](#); [Slattery et al., 2008](#)) although the association was not always statistically significant ([Gammon et al., 2004](#); [Bonner et al., 2005](#); Fig. 2.1). Associations were also reported between second-hand tobacco smoke exposure and overall breast cancer risk in African Americans ([Mechanic et al., 2006](#)) and with premenopausal breast cancer in Hispanics/American Indians ([Slattery et al., 2008](#)). The associations observed in these case-control studies are generally weaker than those reported in earlier case-control studies. Whereas the relative risk estimates reported in the earlier studies often equalled or exceeded 2.0 ([Sandler et al., 1985a](#); [Lash & Aschengrau, 1999](#); [Zhao et al., 1999](#); [Johnson & Repace, 2000](#); [Liu et al., 2000](#)) or 3.0 ([Smith et al., 1984](#); [Morabia et al., 1996](#); [Liu et al., 2000](#); [Morabia et al., 2000](#)), the estimates in the later studies were mostly under 1.5, even in studies that reported positive associations.

2.2.2 Issues affecting the interpretation of studies

One important consideration in evaluating these data has been the lack of a strong and convincing relationship between active smoking and breast cancer. Several theories have been advanced to explain why second-hand tobacco smoke might have a stronger effect on breast cancer than active smoking ([California Environmental Protection Agency, 2005](#); [Johnson, 2005](#); [Collishaw et al., 2009](#)). Central to these is the hypothesis that active smoking may have counterbalancing protective and detrimental effects on breast cancer risk that, in combination, produce little or no overall association, whereas second-hand tobacco smoke may have only an adverse effect on risk. The weakness of this theory is that there is little direct evidence (see Section 4) identifying the

Fig. 2.1 Relative risk of pre-menopausal breast cancer associated with second-hand tobacco smoke. Ever versus never.



Study sorted by calendar year

mechanism by which active smoking may cause the proposed [protective] antiestrogenic effects. Without knowing the mechanism, it has been impossible to prove that active smoking has this effect but exposure to second-hand tobacco smoke does not. A second hypothesis that has been advanced is that second-hand tobacco smoke may have a greater effect on pre- than on postmenopausal breast cancer. This theory was proposed by CalEPA in 2005 ([Johnson & Glantz, 2008](#)) based on analyses of studies available at the time, and was subsequently questioned by some ([US. Department of Health and Human](#)

[Services, 2006](#)) but not all ([Collishaw *et al.*, 2009](#)) subsequent reviews. [Because this arose as an a posteriori observation rather than as an a priori hypothesis, it must be confirmed by independent studies.] The strongest support for the hypothesis comes from a cohort study in Japan ([Hanaoka *et al.*, 2005](#)), which reported significantly increased risk (RR 2.6, 95%CI: 1.3–5.2) of premenopausal breast cancer in women who previously reported having ever lived with a regular smoker or ever being exposed to second-hand tobacco smoke for at least one hour per day in settings outside the home. However, the

referent group in this analysis included only nine unexposed cases. No associations were observed with post-menopausal breast cancer. A weak association between second-hand tobacco smoke exposure and premenopausal breast cancer was reported in the California Teachers cohort, when menopausal status was defined by age at diagnosis rather than age at entry into the study ([Reynolds et al., 2006](#)). In case-control studies published since the CalEPA review ([California Environmental Protection Agency, 2005](#)) that reported results stratified by menopausal status, [Bonner et al. \(2005\)](#) and [Slattery et al. \(2008\)](#) reported stronger associations with pre- than with post-menopausal breast cancer, although the only statistically significant association with premenopausal breast cancer was in Hispanic or American Indian women who had second-hand tobacco smoke exposure of more than ten hours per week (OR, 2.3, 95%CI:1.2–4.5) ([Slattery et al., 2008](#)). In a case-control study of breast cancer in women age 36–45 years [Roddam et al. \(2007\)](#) observed no increased risk in premenopausal women who, since age 16, were married to or lived with a boyfriend who smoked for at least one year.

Two other explanations for inconsistencies in the evidence relate to the fundamental design differences between cohort and case-control studies. A critical advantage of cohort studies is that they collect information on exposures before the disease of interest is diagnosed, thus preventing knowledge of disease status influencing how participants recall and/or report their exposures. Recall bias is especially challenging in case-control studies of exposures that are difficult to measure, when recollection of the frequency and intensity of exposure is necessarily subjective. In counterpart, an important advantage of case-control studies is that they can collect more detailed information on the exposure of interest than is usually possible in cohort studies. Together, these factors create what has been described as “a tension” between the potential for

recall or selection bias in case-control studies, and the reduced possibility of collecting full “lifetime exposure histories” in cohort studies ([Collishaw et al., 2009](#)). The discrepancy in the results from case-control and cohort studies is seen especially in the earlier case-control studies, which found much stronger associations than those observed in most recent studies. Five studies in particular ([Smith et al., 1984](#); [Morabia et al., 1996](#); [Zhao et al., 1999](#); [Johnson & Repace, 2000](#); [Kropp & Chang-Claude, 2002](#)) were considered by [Collishaw et al. \(2009\)](#) as having the most complete information on lifetime exposure to second-hand tobacco smoke from all sources. At the same time, these studies are among the most susceptible to recall bias for two reasons. The first is a general problem of case-control studies, in that cases are more likely to remember and report potentially hazardous exposures than controls. Second, recall bias is potentially more problematic when subjective considerations can influence reporting. It is easier to report smoking by a parent or spouse than it is to remember exposures from other sources that possibly occurred many years ago in daily life. Exposure to second-hand tobacco smoke was highly prevalent in the decades following World War II in Europe and North America. It would be unusual for someone not to be exposed. The studies that the [California Environmental Protection Agency \(2005\)](#) considered to have the best information on exposure to second-hand tobacco smoke are also those which rely more heavily on recall of past exposures outside the home. Moreover, inclusion in the referent group in these studies is also vulnerable to recall bias. Previous reviews by [IARC \(2004\)](#) and the US Surgeon General ([US Department of Health and Human Services, 2006](#)) have expressed concern about potential biases that may be introduced by relying on a small and unusual subgroup (the unexposed to active smoking and second-hand tobacco smoke) as the referent category in these studies. Recall bias remains a plausible explanation for why the

association with second-hand tobacco smoke is stronger in studies that collect “lifetime exposure histories” than in those that rely on parental or spousal smoking. In addition, publication bias cannot be ruled out because the reporting of association limited by subgroup (pre-menopausal) could have been selective.

[The Working Group noted that adjustment for potential confounders using the questionnaire data on other established risk factors for breast cancer did not eliminate the association with second-hand tobacco smoke in these studies. However, this does not resolve concerns about the possibility of recall or publication bias.]

Several meta-analyses have been published, largely showing similar results but leading to substantially different interpretations of the evidence ([California Environmental Protection Agency, 2005](#); [US Department of Health and Human Services, 2006](#); [Johnson, 2007](#); [IARC, 2009](#)). The [California Environmental Protection Agency \(2005\)](#) calculated a pooled estimate for second-hand tobacco smoke and breast cancer risk of 1.11 (95%CI: 1.04–1.19) in all women and 1.38 (95%CI: 1.21–1.56) in premenopausal women, based on 19 studies and a fixed effects model. These estimates increased to 1.89 (95%CI: 1.57–2.27) for all women and 2.18 (95%CI: 1.70–2.79) in premenopausal women when the analysis was restricted to the subset of studies considered to have the best exposure data.

Based on these analyses, the [California Environmental Protection Agency \(2005\)](#) and [Collishaw et al. \(2009\)](#) emphasized the positive association with premenopausal breast cancer in their conclusion that the evidence is “consistent with a causal relationship” whereas the US Surgeon General ([US Department of Health and Human Services, 2006](#)) was more cautious in characterizing the evidence as “suggestive but not sufficient.”

[The Working Group noted that the criterion used by IARC specifies “sufficient evidence of carcinogenicity in which chance, bias and

confounding could be ruled out with reasonable confidence.” This is a more stringent definition than “consistent with a causal relationship.”]

2.3 Cancers of the upper aerodigestive tract

2.3.1 Upper aerodigestive tract combined

Cancers of the upper aerodigestive tract traditionally comprise cancers of the oral cavity, pharynx, larynx and oesophagus. However, some epidemiological studies have examined only head and neck cancers restricted to tumours of the oral cavity, pharynx and larynx. Four case-control studies ([Tan et al., 1997](#); [Zhang et al., 2000](#); [Lee et al., 2008](#); [Ramroth et al., 2008](#)) assessed the effects of second-hand tobacco smoke on head and neck cancers combined and separately for oral cavity, oropharynx or larynx cancers (Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.6.pdf>).

In a hospital-based case-control study in the USA, including only non smoking cases and controls, [Tan et al. \(1997\)](#) detected high risk of head and neck cancer among those ever exposed to second-hand tobacco smoke at home or at work. Women presented higher risk at home (OR, 7.3; $P < 0.001$) than men (OR, 1.1; $P < 0.79$). On the other hand, men showed higher risk at work (OR, 11.6; $P < 0.001$) than women (OR, 8.9; $P < 0.002$). [The authors did not provide the percentages of the telephone interviews done with the spouses of cases and controls. Probably, this is the main weakness of this study and differential misclassification of exposure to second-hand tobacco smoke could not be excluded. The analysis was performed without adjustment for potential confounding variables.] In a study in the USA, [Zhang et al. \(2000\)](#) observed an increased risk (OR, 2.4; 95%CI: 0.9–6.8) with lifetime second-hand tobacco smoke exposure (ever/never) for head and neck cancers, adjusted for age, sex, ethnicity, education, alcohol drinking,

pack-years of cigarette smoking, and marijuana consumption.

[Lee et al. \(2008\)](#) pooled the data from several studies including cases of head and neck cancers and controls (population and hospital) from central Europe, Latin America and United States. Two groups were examined separately, never tobacco users and never tobacco and alcohol users. Among never tobacco users, no association was observed between ever exposure to second-hand tobacco smoke at home or at work and the risk for head and neck cancers. Among never tobacco and alcohol users, a non-statistically significant risk (OR 1.30; 95%CI: 0.94–1.81) was observed. When considering specific anatomical sites, only laryngeal cancer risk was increased when ever exposed to second-hand tobacco smoke in a lifetime, detected among never tobacco users (OR, 1.71; 95%CI: 0.98–3.00) and among never tobacco and alcohol users (OR, 2.90; 95%CI: 1.09–7.73).

In Germany, in a population-based case-control study on laryngeal cancer, [Ramroth et al. \(2008\)](#) observed a non-statistically significant risk (OR, 2.0; 95%CI: 0.39–10.7) for exposure to second-hand tobacco smoke (ever/never) at home and in workplaces among nonsmokers.

(a) Evidence of a dose-response

[Zhang et al. \(2000\)](#) observed a dose-response relationship with the intensity of exposure to second-hand tobacco smoke (never, moderate and heavy) on head and neck cancers ($P = 0.025$); those at heavy level of exposure at home or at work showed highest risk for head and neck cancer (OR, 3.6; 95%CI: 1.1–11.5). However, the classification of exposure to second-hand tobacco smoke at work as never, occasionally or regularly did not show any dose-response effect; and the risk for the groups of occasionally or regularly exposed at home were similar and non statistically significant.

[Lee et al. \(2008\)](#) explored the intensity and duration of exposure to second-hand tobacco

smoke. For intensity the number of hours of exposure per day was considered at home (0–3 hours, > 3 hours) or at the workplace (never, 1–3 hours and > 3 hours). Among both groups of never tobacco users and never tobacco and alcohol users non-statistically significant risks of head and neck cancers were observed for those exposed for > 3 hours per day at home or at work. For duration the number of years of exposure at home and at work was considered (never, 1–15 years, and > 15 years). Among never tobacco users, there was a trend of increase in risk for head and neck cancers with greater number of years of exposure at home, but not at work. Among never tobacco and alcohol users, the duration of exposure showed a trend for exposure both at work or at home.

Considering specific anatomical sites, for cancer of the oral cavity no dose-response effect was observed with increasing number of years of exposure to second-hand tobacco smoke at home or at work. For cancer of the pharynx, a dose-response effect was observed with increasing number of years of exposure to second-hand tobacco smoke with only at home, in both never tobacco users and never tobacco and alcohol users. For cancer of the larynx, a dose-response effect was noted with increasing number of years of exposure to second-hand tobacco smoke at home among never tobacco users and at work among never tobacco and alcohol users. Among never tobacco and alcohol users, all the odd ratios (OR) were statistically significantly elevated for > 15 years of exposure at home or at work for head and neck cancers overall and separately for cancer of the pharynx, and only at work for cancer of the larynx.

2.3.2 Cancers of the nasopharynx, and nasal cavity and sinonasal cavity

The relationship between exposure to second-hand tobacco smoke and risk for these rare cancers of the upper respiratory tract has

been examined in one cohort study ([Hirayama, 1984](#); Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.7.pdf>) and five case–controls studies ([Fukuda & Shibata, 1990](#); [Yu *et al.*, 1990](#); [Zheng *et al.*, 1993](#); [Cheng *et al.*, 1999](#); [Yuan *et al.*, 2000](#); Table 2.6 on-line). A positive association was found in most of these studies.

[Hirayama \(1984\)](#) found an increased risk of sinonasal cancer in women (histology not noted) associated with increasing numbers of cigarettes smoked by husbands of nonsmoking women. When compared with nonsmoking women married to nonsmokers, wives whose husbands smoked had a relative risk of 1.7 (95%CI: 0.7–4.2) for 1–14 cigarettes per day, 2.0 (95%CI: 0.6–6.3) for 15–19 cigarettes per day and 2.55 (95%CI: 1.0–6.3) for ≥ 20 cigarettes per day (P for trend = 0.03).

[Fukuda & Shibata \(1990\)](#) reported the results of a Japanese case–control study based on 169 cases of squamous-cell carcinoma of the maxillary sinus and 338 controls matched on sex, age and residence in Hokkaido, Japan. Among nonsmoking women, a relative risk of 5.4 ($P < 0.05$) was associated with exposure in the household to second-hand tobacco smoke from one or more smokers. Active smoking was associated with an increased risk for squamous-cell carcinoma of the maxillary sinus in men in the same study.

[Zheng *et al.* \(1993\)](#) used data from the 1986 US National Mortality Followback Survey to assess risk for cancer of the nasal cavity and sinuses in relation to exposure to second-hand tobacco smoke in white men. A total of 147 deaths from cancer of the nasal cavity and sinuses was compared to 449 controls who had died from other causes (excluding any causes strongly linked to alcohol and/or tobacco use). Data were obtained from postal questionnaires completed by next-of-kins. Among nonsmokers, patients with nasal cancer were more likely to have a spouse who smoked cigarettes (RR, 3.0; 95%CI:

1.0–8.9) after adjustment for age and alcohol use. When the analysis of cases was restricted to those with cancer of the maxillary sinus, the risk was somewhat higher (RR 4.8; 95%CI: 0.9–24.7). The risks reported for active smoking and exposure to second-hand tobacco smoke were of similar magnitude in this study.

Neither second-hand tobacco smoke exposure during childhood nor exposure during adulthood were positively associated with an increased risk for nasopharyngeal cancer in a study in Taiwan, China ([Cheng *et al.*, 1999](#)). Although histological type was not specified, all cases were histologically confirmed. Among never-smokers, the risk estimates for cumulative exposure to second-hand tobacco smoke (pack-person-years) in childhood declined as exposure increased (P for trend = 0.05); a similar but non-significant inverse relationship was found for exposure during adulthood. Significant elevations in risk for nasopharyngeal cancer were observed for active smokers in this study. [The Working Group noted that the exposure assessment was relatively detailed and that the estimates of relative risk were adjusted for age, sex, education and family history of nasopharyngeal cancer.]

A large population-based case–control study conducted in Shanghai, China, included 935 cases of nasopharyngeal carcinoma and 1032 population controls randomly selected from a population-registry and frequency-matched by sex and 5-year age group ([Yuan *et al.*, 2000](#)). All cases were histologically confirmed, but the cell type was not specified. The study subjects were interviewed face to face, and the response rates were 84% for cases and 99% for controls. In female never-smokers, a consistent increase in risk related to exposure to second-hand tobacco smoke during childhood was noted. The relative risk was 3.4 (95%CI: 1.4–8.1) if the mother smoked; 3.0 (95%CI: 1.4–6.2) if the father smoked; 2.7 (95%CI: 1.1–6.9) if another household member smoked and 3.0 (95%CI: 1.4–6.2)

if any household member smoked. Risks associated with exposure to second-hand tobacco smoke during adulthood in women were also statistically significantly increased. For male never-smokers, the associations were weaker and were not statistically significantly elevated for exposure during childhood and adulthood. [The Working Group noted that this was a large, well conducted study that included a detailed exposure assessment and adjustment for numerous potential confounders.]

2.4 Leukaemia and lymphomas

[Kasim et al. \(2005\)](#) analysed the risk of leukaemia in adults after exposure to second-hand tobacco smoke (Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.8.pdf>). This case-control study was based on postal questionnaires. There was a slightly increased risk (P for trend = 0.001) with increasing duration of exposure to second-hand tobacco smoke. The association was limited to chronic lymphocytic leukaemia and was stronger for occupational exposures to second-hand tobacco smoke.

2.5 Other cancers in adults

2.5.1 All cancer combined

[Hirayama \(1984\)](#), [Sandler et al. \(1985b\)](#), and [Miller \(1990\)](#) observed a significant association between exposure to second-hand tobacco smoke and overall cancer incidence or mortality. [Nishino et al. \(2001\)](#) also studied all cancers combined and reported a relative risk of 1.1 (95%CI: 0.92–1.4) associated with husband's smoking.

2.5.2 Cancers of the gastrointestinal tract

In addition to the studies reviewed previously ([Sandler et al. 1988](#); [Gerhardsson de Verdier et al., 1992](#); [Mao et al., 2002](#)), ten new studies

have been identified: two cohort ([Nishino et al., 2001](#); [Hooker et al., 2008](#); Table 2.13 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.13.pdf>); seven case-control ([Sandler et al., 1985a, b](#); [Slattery et al., 2003](#); [Lilla et al., 2006](#); [Wang et al., 2006](#); [Duan et al., 2009](#); [Verla-Tebit et al., 2009](#); Table 2.14 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.14.pdf>) and one case-only study ([Peppone et al., 2008](#); Table 2.15 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.15.pdf>). Two studies ([Sandler et al., 1985a](#); [Wang et al., 2006](#)) did not provide risk estimates of gastrointestinal cancers for never smokers and are not discussed further. [No data for these studies are included in the tables.]

[Sandler et al. \(1985b\)](#) observed a relative risk of 0.7 and 1.3 for cancer of the digestive system from exposure to maternal and paternal passive smoke, respectively. [No CIs were provided and the numbers of never smokers exposed were small.] [Verla-Tebit et al. \(2009\)](#) found no evidence of an increased risk for colorectal cancer associated with exposure to second-hand tobacco smoke overall.

(a) Cancer of the colorectum

[Nishino et al. \(2001\)](#) observed no association with husband's smoking for cancer of the colon (RR 1.3; CI: 0.65–2.4) or of the rectum (RR 1.8; 0.85–3.9).

Four studies investigated risk for cancer of the colon and/or rectum by sex. [Sandler et al. \(1988\)](#) reported an increased risk for colorectal cancer in men (RR 3.0; 95%CI: 1.8–5.0) but a protective effect in women (RR 0.7; 95%CI: 0.6–1.0). [Slattery et al. \(2003\)](#) noted that rectal cancer was significantly associated with exposure to second-hand tobacco smoke in men (OR, 1.5; 95%CI: 1.1–2.2 for never smokers) but not in women. [Hooker et al. \(2008\)](#) reported an effect among men only, with a significantly increased risk for rectal cancer in the 1963 cohort (RR 5.8, 95%CI: 1.8–18.4) but not

the 1975 cohort. [Gerhardsson de Verdier et al. \(1992\)](#) found an increased risk for rectal cancer in men (RR 1.9; 95%CI: 1.0–3) and for colon cancer in women (RR 1.8; 95%CI: 1.2–2.8). [The Working Group noted that it is unclear whether the analysis was restricted to never-smokers.]

When analysing different sources of exposure to second-hand tobacco smoke, [Verla-Tebit et al. \(2009\)](#) found no evidence of an increased risk for cancer of the colorectum associated with exposure to second-hand tobacco smoke specifically during childhood or at work, but observed a significant increase in risk associated with spousal exposure.

[Peppone et al. \(2008\)](#) noted that considerable exposure to second-hand tobacco smoke, especially during childhood, was more likely to lead to an earlier-age diagnosis of cancer of the colorectum.

In exploring the association of cancer of the colorectum with exposure to second-hand tobacco smoke and NAT1 and NAT2 status, [Lilla et al. \(2006\)](#) noted that risk may only be relevant among genetically susceptible (NAT1 and NAT2 status) individuals.

(b) Cancer of the stomach

[Nishino et al. \(2001\)](#) observed no association with husband's smoking for cancer of the stomach (RR, 0.95; 95%CI: 0.58–1.6).

The two studies on the association of exposure to second-hand tobacco smoke with stomach cancer by subsite (cardia versus distal) gave contradictory results. In one study ([Mao et al., 2002](#)) a positive trend ($P = 0.03$) in risk for cancer of the gastric cardia was associated with lifetime exposure to second-hand tobacco smoke (residential plus occupational) in never smoking men, with a relative risk of 5.8 (95%CI: 1.2–27.5) at the highest level of exposure (≥ 43 years); no increased risks or trends were observed for distal gastric cancer. In the other study, [Duan et al. \(2009\)](#) an increased risk for distal gastric cancer

was found, but not for gastric cardia [Data were not analysed by sex due to small sample size].

2.5.3 Cancer of the pancreas

Six studies have been identified on the association of exposure to second-hand tobacco smoke with cancer of the pancreas: three cohort ([Nishino et al., 2001](#); [Gallicchio et al., 2006](#); [Bao et al., 2009](#); the latter two are summarized in Table 2.17 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.17.pdf>) and three case-control ([Villeneuve et al., 2004](#); [Hassan et al., 2007](#); [Lo et al., 2007](#); the former two studies are summarized in Table 2.18 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.18.pdf>).

(a) Exposure in adulthood

Data from the majority of the studies ([Nishino et al., 2001](#); [Villeneuve et al., 2004](#); [Gallicchio et al., 2006](#); [Hassan et al., 2007](#); [Bao et al., 2009](#)) suggested lack of an association of cancer of the pancreas with never smokers exposed to second-hand tobacco smoke in adulthood at home or at work. (RR 1.2 (95%CI: 0.45–3.1) and 1.21 (95%CI: 0.60–2.44) respectively).

[Lo et al. \(2007\)](#) reported an odd ratio of 6.0 (95%CI: 2.4–14.8) for never smokers (both sexes combined) exposed to second-hand tobacco smoke in Egypt. [The Working Group noted the small numbers of cases, the use of hospital controls and the small proportion of the cases (35%) with histopathological confirmation. Data are not included in Table 2.18 on-line].

(b) Exposure during childhood

In the Nurses' Health Study, [Bao et al. \(2009\)](#) noted an increased risk for cancer of the pancreas (RR 1.42; 95%CI: 1.07–1.89) for maternal but not for paternal smoking (RR 0.97; 95%CI: 0.77–1.21) during childhood.

2.5.4 Cancer of the kidney (renal cell carcinoma)

Two case-control studies have been published on the association of exposure to second-hand tobacco smoke with cancer of the kidney (specifically renal cell carcinoma) since IARC (2004) (Hu *et al.*, 2005; Theis *et al.*, 2008; Table 2.19 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.19.pdf>). In both studies a significantly increased risk associated with exposure to second-hand tobacco smoke among never smokers was reported.

2.5.5 Cancer of the urinary bladder

A total of seven studies and one meta-analysis have considered the association between exposure to second-hand tobacco smoke and cancer of the urinary bladder: three cohort studies (Zeegers *et al.*, 2002; Bjerregaard *et al.*, 2006; Alberg *et al.*, 2007; Table 2.9, available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.9.pdf>), four case-control studies (Burch *et al.*, 1989; Chen *et al.*, 2005a; Samanic *et al.*, 2006; Jiang *et al.*, 2007; Table 2.10 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.10.pdf>), and one meta-analysis (Van Hemelrijck *et al.*, 2009).

(a) Population-based exposure-response relationship

Burch *et al.* (1989) and Zeegers *et al.* (2002) reported no increased risk for cancer of the urinary bladder [Data are not included in the Tables]. Van Hemelrijck *et al.* (2009) reported a meta-relative risk of 0.99 (95%CI: 0.86–1.14) for never smokers exposed to second-hand tobacco smoke. [Data not included in Table. The Working Group noted the marked variation in risk in the analyses by sex and by timing of exposure to second-hand tobacco smoke during adulthood or childhood].

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study,

Bjerregaard *et al.* (2006) compared ever versus never exposed to second-hand tobacco smoke as an adult or a child: the risk for cancer of the urinary bladder increased for exposures during childhood (OR, 1.38; 95%CI: 1.00–1.90), and was stronger for never-smokers (OR, 2.02; 95%CI: 0.94–4.35).

Alberg *et al.* (2007) analysed data from two cohorts of non-smoking women in the USA exposed to second-hand smoke at home. An association with exposure to second-hand tobacco smoke was found in the 1963 cohort (RR, 2.3; 95%CI: 1.0–5.4) but not in the 1975 cohort (RR, 0.9; 95%CI: 0.4–2.3). [The Working Group noted the small number of cases available for some of the risk estimates.]

In a study assessing occupational exposure to second-hand tobacco smoke (Samanic *et al.*, 2006), the risk for cancer of the urinary bladder was increased in the highest exposure category among women (RR, 3.3; 95%CI: 1.1–9.5) but not among men (RR, 0.6; 95%CI: 0.2–1.4).

(b) Molecular-based exposure-response relationship

4-aminobiphenyl (4-ABP) can form DNA adducts and induce mutations, and cigarette smoke is the most prominent source of exposure to 4-aminobiphenyl in humans (see Section 4). Jiang *et al.* (2007) used variation in 4-ABP-haemoglobin adducts level to assess exposure to second-hand tobacco smoke and reported a significantly increased risk with increasing lifetime exposure among never-smoking women exposed in adulthood or childhood.

Chen *et al.* (2005a) hypothesized that the ability to detoxify arsenic (a risk factor urinary bladder cancer) through methylation may modify risk related to second-hand tobacco smoke exposure. Results of the adjusted analyses show that a high primary methylation index associates with lower risk of cancer of the urinary bladder (OR, 0.37; 95%CI: 0.14–0.96, *p* interaction = 0.11) in second-hand tobacco smoke exposed subjects

compared to unexposed. In endemic area the ability to methylate arsenic may play a role in reducing the risk of cancer of the urinary bladder associated with second-hand tobacco smoke exposure. [The Working Group noted that the small number of cases and the use of hospital controls limit the validity of inferences from this study].

Using case-control data for never and former smokers nested within the EPIC study [Vineis et al. \(2007b\)](#) examined susceptibility in genes involved in oxidative stress (such as *NQO1*, *MPO*, *COMT*, *MnSOD*), in phase I (such as *CYP1A1* and *CYP1B1*) and phase II (such as *GSTM1*, and *GSTT1*) metabolizing genes, and in methylene-tetrahydrofolate (*MTHFR*). *GSTM1* deletion was strongly associated with risk for urinary bladder cancer in never smokers (OR, 1.75; 95%CI: 0.89–3.43), and a similar association was noted for former smokers and for men.

2.5.6 Cancer of the cervix

The cohort studies evaluated previously ([Hirayama, 1984](#); [Jee et al., 1999](#); [Nishino et al., 2001](#)) consistently indicated the lack of association between exposure to second-hand tobacco smoke and cancer of the uterine cervix, while the informative case-control studies ([Sandler et al., 1985b](#); [Slattery et al., 1989](#); [Scholes et al., 1999](#)) suggested a non-statistically significant increase in risk.

A total of 10 new studies have been identified: one cohort study (Table 2.11 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.11.pdf>) and nine case-control studies ([Buckley et al., 1981](#); [Brown et al., 1982](#); [Hellberg et al., 1986](#); [Hirose et al., 1996](#); [Coker et al., 2002](#); [Wu et al., 2003](#); [Tay & Tay, 2004](#); [Sobti et al., 2006](#); [Tsai et al., 2007](#); Table 2.12 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.12.pdf>). Three early case-control studies ([Buckley et al., 1981](#); [Brown et al., 1982](#); [Hellberg et al.,](#)

[1986](#)) did not look at risk of exposure to second-hand tobacco smoke in never smoking women, and are not further discussed.

(a) Squamous cell carcinoma of the cervix

A significant increase risk for invasive cancer of the uterine cervix associated with exposure to second-hand tobacco smoke during adulthood was found in three case-control studies ([Hirose et al., 1996](#); [Wu et al., 2003](#); [Tay & Tay, 2004](#)) and one cohort study ([Trimble et al., 2005](#)).

(b) Cervical intraepithelial lesions and neoplasia

An earlier case-control study ([Coker et al., 1992](#)) found no statistically significant association between exposure to second-hand tobacco smoke and CIN II/III in non-smokers, after adjustment for age, race, education, number of partners, contraceptive use, history of sexually transmitted disease and history of Pap smear. A later study ([Coker et al., 2002](#)) looked at risk of low grade and high grade cervical squamous intraepithelial lesions (LSIL and HSIL, respectively) in HPV positive never-smokers and reported a significant association with exposure to second-hand tobacco smoke. In a community-based case-control study, [Tsai et al. \(2007\)](#) observed a markedly increased risk for both CIN1 and CIN2 in both HPV-positive and HPV-negative women exposed to second-hand tobacco smoke. Only [Coker et al. \(2002\)](#) and [Tsai et al. \(2007\)](#) controlled for HPV status in women.

[Sobti et al. \(2006\)](#) reported that cervical cancer risk is increased in individuals exposed to second-hand tobacco smoke with *GSTM1* (null), *GSTT1* (null) and *GSTP1* (Ile¹⁰⁵Val) genotypes, with odd ratios ranging from 6.4 to 10.2.

2.5.7 Cancer of the ovary

One cohort study ([Nishino et al., 2001](#)) and two case-control studies ([Goodman & Tung, 2003](#); [Baker et al., 2006](#); Table 2.16 available at <http://monographs.iarc.fr/ENG/Monographs/>

[vol100E/100E-02-Table2.16.pdf](#)) have been published on the association of exposure to second-hand tobacco smoke with cancer of the ovary. In all three studies a null or inverse association of cancer of the ovary for never smokers exposed to second-hand tobacco smoke was found. [Nishino *et al.* \(2001\)](#) observed no association with husband's smoking (RR 1.7; 95%CI: 0.6– 5.2). [Goodman & Tung \(2003\)](#) reported no association of exposure to second-hand tobacco smoke during childhood with risk of cancer of the ovary. [Baker *et al.* \(2006\)](#) reported a decreased risk of cancer of the ovary for never smokers exposed to second-hand tobacco smoke (OR, 0.68; 95%CI: 0.46–0.99), with similar findings for former and current smokers.

2.5.8 Tumours of the brain and CNS

A total of three case–control studies ([Ryan *et al.*, 1992](#); [Hurley *et al.*, 1996](#); [Phillips *et al.*, 2005](#)) have considered the association of second-hand tobacco smoke and cancers of the brain and central nervous system. [Ryan *et al.* \(1992\)](#) reported an increased risk of meningioma associated with spousal exposure, particularly among women (RR 2.7; 95%CI: 1.2–6.1). In a case–control study of gliomas in Australia no association was found for exposure to second-hand tobacco smoke in never smokers (RR 0.97, 95%CI: 0.61–1.53) (both sexes combined) ([Hurley *et al.*, 1996](#)). However [Phillips *et al.* \(2005\)](#) found that spousal smoking was associated with an increased risk for intracranial meningioma in both sexes combined (OR, 2.0; 95%CI: 1.1–3.5), the risk increased with increasing duration of exposure (P for trend = 0.02).

2.5.9 Other cancers

One case–control study on hepatocellular cancer ([Hassan *et al.*, 2008](#)) and one on cancer of the testis ([McGlynn *et al.*, 2006](#)) were published since [IARC \(2004\)](#). [Hassan *et al.* \(2008\)](#) did not

find an association with exposure to second-hand tobacco smoke and hepatocellular cancer, while that of [McGlynn *et al.* \(2006\)](#) did not support the hypothesis that maternal smoking is related to the development of cancer of the testis (Table 2.20 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.20.pdf>). However, these studies provide limited information on the association of exposure to second-hand tobacco smoke with the risk of these cancers.

2.6 Parental tobacco smoking and childhood cancers

2.6.1. Overview

A large number of studies have evaluated the association of cancer risk in childhood with exposure to parental smoking. However, childhood cancers are extremely heterogeneous, both between major cancer sites and within subtypes. In addition, given the rarity of childhood cancers, studies of specific cancer sites and subtypes that have adequate sample sizes and detailed exposure assessments are difficult to achieve.

(a) Smoking exposure assessment

Parental smoking before and during pregnancy exposes germ cells (spermatozoa and ova) and/or the fetus to the same chemical mixture and levels of tobacco smoke as during active smoking, while post-natal exposure to parental tobacco smoking exposes the offspring to second-hand tobacco smoke. Some studies distinguish whether exposure to parental smoking was preconceptional, *in utero* or postnatal. Even when a study reports only on one time period, exposure may have occurred at all three periods. Exposures to tobacco smoking during each of these periods tend to correlate, in particular, paternal smoking is less likely to change during and after pregnancy. In addition, paternal and

maternal smoking habits are highly correlated (Boffetta *et al.*, 2000).

Most studies assessed the number of cigarettes smoked per day (e.g. 0–10, 11–20, 20+) and, when data were available, some assessed continuous consumption of cigarettes per day. One study reported exposure in pack-years (Lee *et al.*, 2009). The SEARC international case–control study assessed polycyclic aromatic hydrocarbons (PAHs) as the main exposure of interest and obtained information on both tobacco smoke and occupational exposures (Cordier *et al.*, 2004).

(b) Bias and confounding

Whitehead *et al.* (2009) evaluated the adequacy of self-reported smoking histories on 469 homes of leukaemia cases and controls and found that nicotine concentrations derived from interview responses to a structured questionnaire strongly correlated to measured levels in dust samples.

The major confounders for the relationship between parental smoking and childhood cancers were markers of socioeconomic status, race or ethnicity, birth weight or gestational age, parental age, sex and age of the case child. In most studies matching or adjusting for these confounders was performed as appropriate. In some studies matching was performed for birth order and centre of diagnosis.

2.6.2 All childhood cancers combined

In addition to the four cohort and 10 case–control studies reviewed by IARC (2004), three case–control studies have examined the role of second-hand tobacco smoke in relation to risk for all childhood cancers combined (Sorahan *et al.*, 2001; Pang *et al.*, 2003; Sorahan & Lancashire, 2004; Table 2.21 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.21.pdf>).

(a) Intensity and timing of parental smoking

In a follow-up of the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) by McKinney *et al.* (1987), a statistically significant positive trend with daily paternal smoking before pregnancy was observed when cases were compared with controls selected from General Practitioners' (GPs') lists, but not from hospitals; an inverse trend was noted for maternal smoking before pregnancy when cases were compared with hospital, but not with General Practitioners, controls (Sorahan *et al.*, 2001).

In the United Kingdom Childhood Cancer Study (UKCCS), Pang *et al.* (2003) observed a similar pattern of increasing risk with increasing intensity of paternal preconception smoking, and of decreasing risk for increasing maternal smoking before and during pregnancy for all diagnoses combined, and for most individual diagnostic groups.

In the most recent report from the Oxford Survey of Childhood Cancers (OSCC), the risk of death from all childhood cancers combined was not associated with maternal smoking, but was consistently associated with paternal smoking alone or in combination with maternal smoking, in both adjusted and unadjusted analyses [Ex-smokers of more than 2 years before birth of the survey child were assimilated to non-smokers] (Sorahan & Lancashire, 2004).

(b) Bias and confounding

The significant trends observed by Sorahan *et al.* (2001) and Pang & Birch (2003) did not diminish when adjusted for potential confounding covariates or with simultaneous analysis of parental smoking habits. The relationship between maternal smoking and birth weight reported by Sorahan *et al.* (2001) suggested that self-reported maternal smoking was equally reliable for cases and for controls. However, comparisons of smoking patterns with national data suggested that control parents in this study were heavier smokers.

2.6.3 Leukaemias and lymphomas

Since [IARC \(2004\)](#), one cohort study ([Mucci et al., 2004](#)) (Table 2.22 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.22.pdf>), eleven case-control studies (Table 2.23 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.23.pdf>), and one meta-analysis ([Lee et al., 2009](#)) (Table 2.24 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.24.pdf>) have evaluated the association of parental tobacco smoking with the risk for lymphatic and haematopoietic cancers.

(a) Duration and intensity of exposure

From a meta-analysis of 30 studies published before 1999 [Boffetta et al. \(2000\)](#) reported no statistically significant association for all lymphatic and haematopoietic neoplasms and noted evidence of publication bias for the available data.

[Lee et al. \(2009\)](#) performed a meta-analysis of twelve studies on paternal smoking and risk of childhood leukaemia. Paternal smoking before conception of the index child was significantly associated with the risk for acute leukaemia (AL) and acute lymphoblastic leukaemia (ALL) (Fig. 2.2).

In a cohort study, maternal smoking was associated with a lower risk of acute lymphoblastic leukaemia, a higher risk of acute myeloid leukaemia (AML) particularly among heavy smokers, and a slight excess risk for non-Hodgkin lymphoma (NHL) ([Mucci et al., 2004](#)).

Because of the diversity of types of exposure (paternal, maternal, parental), of timing of exposure (preconception, *in utero*, post-natally) and of the outcome, the case-control studies are briefly summarized individually.

[Schüz et al. \(1999\)](#) showed that the risk for acute childhood leukaemias was inversely related to maternal smoking during pregnancy. Paternal smoking before pregnancy showed no

association with leukaemia risk for any smoking category. [Sorahan et al. \(2001\)](#) reported a non-significant positive association between risk for acute lymphoblastic leukaemia and daily cigarette smoking by fathers before pregnancy, and a non-significant inverse association between risk for acute lymphoblastic leukaemia and daily smoking by mothers before pregnancy. Down Syndrome children are highly susceptible to the development of acute leukaemia. In a case-control study of 27 children with acute leukaemia and Down Syndrome compared with 58 Down Syndrome children without acute leukaemia [Mejía-Aranguré et al. \(2003\)](#) found that paternal smoking of more than 10 cigarettes/day, both preconception and after birth of the index child was associated with acute leukaemia. In the UKCC case-control study ([Pang et al., 2003](#)), paternal but not maternal preconception tobacco smoking of 1–19 cigarettes/day was associated with an increased risk of leukaemia, and a similar pattern was reported for lymphoma. [Menegaux et al. \(2005\)](#) reported no increased risk of acute lymphoblastic leukaemia or acute nonlymphocytic leukaemia (ANLL) associated with any category of post-natal exposure to tobacco smoking (i.e. maternal smoking during breastfeeding or after, paternal smoking after birth, other smokers at home), except for an increased risk of acute nonlymphocytic leukaemia with paternal smoking. In a later study, ([Menegaux et al., 2007](#)) reported no association between acute and parental smoking, by subtype (acute myeloid leukaemia or acute lymphoblastic leukaemia) or by time of exposure, with the exception of an increased risk of acute lymphoblastic leukaemia associated with maternal smoking during pregnancy. [Chang et al. \(2006\)](#) reported no risk for acute leukaemia, acute lymphoblastic leukaemia or acute myeloid leukaemia associated with maternal smoking either by period of smoking (preconception, during pregnancy, post-natally) or by amount smoked. Paternal preconception smoking was strongly associated

Fig. 2.2 Meta-analysis of the association between paternal smoking and childhood leukaemia**(A) Overall paternal smoking status**

Author	Year	Country	Cases
Sorahan	1997	UK	2254
Ji	1997	China	151
Brondum	1999	CCG	1618
Chang	2006	US	228
MacArthur	2008	Canada	388
Our study		Korea	164
All Leukemia (N=6)			
			4830
ALL (N=5)			
			2865

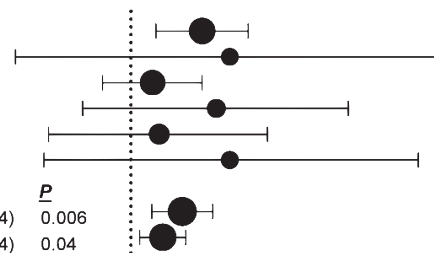
OR 95% CI**P**

1.13 (1.04-1.24)

0.006

1.07 (1.00-1.14)

0.04

**(B) Paternal smoking status before pregnancy of the child**

Author	Year	Country	Cases
Magnani	1990	Italy	138
John	1991	US	47
Ji	1997	China	136
Brondum	1999	CCG	1618
Schuz	1999	Germany	955
Sorahan	2001	UK	139
Pang	2003	UK	1308
Chang	2006	US	227
Menegaux	2007	France	415
MacArthur	2008	Canada	386
Our study		Korea	148
All Leukemia (N=11)			
			5540
ALL (N=9)			
			3073

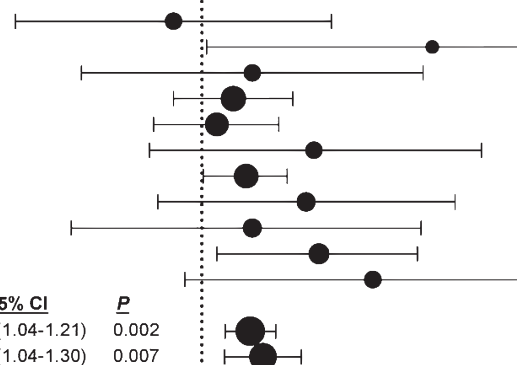
OR 95% CI**P**

1.12 (1.04-1.21)

0.002

1.17 (1.04-1.30)

0.007

**(C) Paternal smoking status after birth of the child**

Author	Year	Country	Cases
Ji	1997	China	164
Infante-Rivard	2000	Canada	486
Menegaux	2007	France	472
Our study		Korea	158
All Leukemia (N=4)			
			1280
ALL (N=4)			
			1111

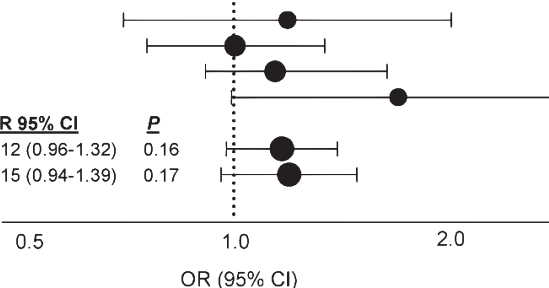
OR 95% CI**P**

1.12 (0.96-1.32)

0.16

1.15 (0.94-1.39)

0.17



with risk for acute myeloid leukaemia both by period and intensity of smoking. When both paternal preconception smoking and maternal postnatal smoking were considered, the risk for acute lymphoblastic leukaemia was stronger. [Rudant et al. \(2008\)](#) reported a significant positive association between paternal smoking and acute lymphoblastic leukaemia, acute myeloid leukaemia, Burkitt lymphoma, and anaplastic large cell non-Hodgkin lymphoma, with increasing relative risks (RR) with increasing

number of cigarettes smoked. No associations with Hodgkin lymphoma or other types of non-Hodgkin lymphoma were observed. Non-significantly elevated risks were observed for maternal smoking during pregnancy for acute lymphoblastic leukaemia and non-Hodgkin lymphoma, but not in the highest category of 10 or more cigarettes/day. [MacArthur et al. \(2008\)](#) reported non-significantly elevated risk estimates for acute lymphoblastic leukaemia and acute myeloid leukaemia with maternal smoking, but

not with paternal smoking, before and during pregnancy. [Lee et al. \(2009\)](#) in Seoul, Republic of Korea, reported that paternal smoking was associated with a significantly increased risk of acute leukaemia and acute lymphoblastic leukaemia in a dose–response manner. The proportion of mothers who smoked was too low (6.1% in controls) to analyse risk in association with maternal smoking.

(b) Potential confounders

In the study of Down Syndrome children ([Mejía-Aranguré et al., 2003](#)), the adjustment models did not show any interaction between paternal alcoholism and smoking. [Menegaux et al. \(2005\)](#) examined the association of parental smoking and maternal alcohol and coffee intake during pregnancy with the risk for childhood leukaemia. They found no association of acute lymphoblastic leukaemia or acute nonlymphocytic leukaemia with maternal smoking during pregnancy but an association with maternal alcohol and coffee consumption.

(c) Effect modification

Cigarette smoke is a known germ-cell mutagen in mice ([Yauk et al., 2007](#)), a likely germ-cell mutagen in humans (see Section 4.1.3a) and alters gene expression (see Section 4.1.4). [Infante-Rivard et al. \(2000\)](#) first assessed the role of parental smoking and *CYP1A1* genetic polymorphisms with leukaemia and reported no statistically significant association with leukaemia overall. However, a case-only subanalysis suggested that the effect of parental smoking may be modified by variant alleles in the *CYP1A1* gene: *CYP1A1*2B* tended to decrease risks and *CYP1A1*2A* and *CYP1A1*4* increased the risks associated with smoking in the second and third trimesters of pregnancy. [Clavel et al. \(2005\)](#) examined the role of metabolic polymorphisms in the *CYP1A1*, *GSTM1*, *GSTP1*, *GSTT1* and *NQO1* genes. The slow *EPHX1* allele (exon 3 homozygous genotype) was negatively associated with leukaemia,

in particular acute lymphoblastic leukaemia, whereas the fast *EPHX1* allele (exon 4 homozygous genotype) was positively associated with leukaemia overall. A non-significant association with acute lymphoblastic leukaemia was noted for the homozygous *NQO1*2* genotype. There was a significant interaction of the *CYP1A1*2A* allele with smoking in the case-only analysis and a not significant interaction, but similar in magnitude, in the case–control analysis. A significant interaction was also observed with the *GSTM1* deletion in the case-only analysis, but not in the case–control analysis. [Lee et al. \(2009\)](#) genotyped five single-nucleotide *CYP1A1* polymorphisms: acute lymphoblastic leukaemia risk was significantly increased for cases without the CGACC haplotype and with paternal smoking or the presence of at least one smoker in the home.

RAS is the second most mutated gene in smoking-associated lung tumours (Section 4.1.3b). *RAS* mutations have been consistently correlated with myeloid leukaemias in adults and children, in particular with occupationally-associated adult myeloid leukemias ([Taylor et al., 1992](#); [Barletta et al., 2004](#)). [Wiemels et al. \(2005\)](#) studied the relationship of *RAS* mutations, hyperdiploidy (> 50 chromosomes) and smoking in a case series of 191 acute leukaemia. Smoking was negatively associated with hyperdiploidy (possibly due to the sensitivity of the hyperdiploid clone and consequent differential survival) and hyperdiploid acute leukaemia cases had the highest rates of *RAS* mutations. [Paternal smoking in the three months before pregnancy was less frequent among hyperdiploids than among non-hyperdiploids.]

2.6.4 Cancers of the brain and central nervous system

Since [IARC \(2004\)](#), the association of exposure to parental smoking and risk for childhood brain and central nervous system (CNS) tumours has been examined in one cohort study ([Brooks](#)

et al., 2004; Table 2.25 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.25.pdf>), six case-control studies (*Schüz et al.*, 1999; *Sorahan et al.*, 2001; *Filippini et al.*, 2002; *Pang et al.*, 2003; *Cordier et al.*, 2004; *Plichart et al.*, 2008; Table 2.26 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.26.pdf>), and one meta-analysis (*Huncharek et al.*, 2002; Table 2.27 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.27.pdf>).

A meta-analysis of 30 studies published before 1999 indicated no significant increase in risk for CNS tumours associated with maternal smoking during pregnancy and an increased risk for brain tumours with paternal smoking (*Boffetta et al.*, 2000).

Huncharek et al. (2002) included one cohort and eleven case-control studies in a meta-analysis and found no clear association of maternal smoking during pregnancy with risk for childhood brain tumours, and a null risk estimate for all CNS tumours (even when the analysis was restricted to astrocytomas, the main brain tumour type). The results were comparable and consistently null for all sensitivity analyses conducted (Table 2.27 on-line).

Brooks et al. (2004) analysing the Swedish birth cohort study observed that children, in particular those aged 2–4 years, whose mother smoked during pregnancy, had an increased incidence of childhood brain tumours; the increase in risk was similar for benign and malignant brain tumours and most apparent for astrocytomas (Table 2.25 on-line).

Schüz et al. (1999) evaluated parental smoking and CNS tumour risk in children < 15 years from the German Childhood Cancer Registry (see Table 2.26 on-line). No association with risk of CNS tumours was observed for either maternal smoking during pregnancy or paternal smoking before pregnancy. *Sorahan et al.* (2001) found no significant association or trends of risk of CNS tumours with either paternal or maternal

smoking, except for low level of maternal exposure [the latter analysis is based on only eleven exposed cases and one control, yielding a very wide confidence interval]. *Filippini et al.* (2002) observed no association between risk of childhood brain tumours and parental smoking before pregnancy, maternal smoking, regular maternal exposure to second-hand tobacco smoke during pregnancy, or exposure of the child to second-hand tobacco smoke during its first year of life. The results did not vary by child's age at diagnosis, type of CNS tumour or study centre. *Plichart et al.* (2008) reported no association for maternal smoking during pregnancy with CNS tumours, while paternal smoking preconception showed a significant association, especially for astrocytomas. When assessing parental exposure to PAHs, *Cordier et al.* (2004) observed an association of paternal exposure to occupational PAHs preconception with all childhood brain tumours and with astroglial tumours, but no trend of increasing risk with increased exposure. Paternal smoking alone was associated with a risk for astroglial tumours when compared with non-smoking, non-occupationally-exposed fathers. *Pang et al.* (2003) found a decreased CNS risk with maternal smoking of more than 20 cigarettes/day preconception, in both unadjusted and adjusted analyses. In the analyses by histological subgroups a statistically significant decreased risk was associated with maternal smoking during pregnancy for primitive neuroectodermal tumours.

2.6.5 Hepatoblastoma

Hepatoblastoma is an embryonal tumour presumably of fetal origin and prenatal exposures are likely more important than post-natal. In some children, a diagnosis of hepatoblastoma is evident at birth or shortly thereafter, with a median age at diagnosis of 12 months. The ability of hepatoblastoma tumour cells to synthesize α -fetoprotein (AFP), a major serum protein

synthesized by fetal liver cells, also suggests a fetal origin. Also, hepatoblastomas, like many other embryonal tumours, are associated with Beckwith-Wiedemann syndrome and hemihypertrophy, further suggesting a gestational oncogenic event (DeBaun & Tucker, 1998). Data were available for both maternal and paternal exposures from two studies (Pang *et al.*, 2003; Sorahan & Lancashire, 2004) while two other studies (McLaughlin *et al.*, 2006; Pu *et al.*, 2009) were limited to data on maternal smoking, available from birth certificates and medical records, respectively (Table 2.28). Most of these studies had limited sample sizes given the extreme rarity of these tumours.

(a) Parental smoking exposure

After adjustment for relevant covariates, Pang *et al.* (2003) observed a statistically significant increased risk of hepatoblastoma in association with maternal preconception smoking (OR, 2.68; 95%CI: 1.16–6.21, $P = 0.02$) in a somewhat dose-dependent manner ($P = 0.058$). The association with parental smoking was strongest (relative to neither parent smoking) when both parents smoked (OR, 4.74; 95%CI: 1.68–13.35, $P = 0.003$). Sorahan & Lancashire (2004) found no increased risk associated with maternal or paternal smoking alone compared to non-smokers, in both adjusted and unadjusted analyses. In contrast, parental smoking (paternal and maternal smoking combined) was strongly and consistently associated with an increased risk for hepatoblastoma in both adjusted and unadjusted analyses.

In a record-based case-cohort study only maternal smoking was examined (McLaughlin *et al.*, 2006). Extremely low birth weight (< 1000 g) was strongly associated with hepatoblastoma. After adjustment for birth weight, a statistically significant elevated risk for hepatoblastoma was found with maternal smoking (RR 2.1; 95%CI: 1.0–4.2). The increased risk was stronger for children diagnosed at the age of two years or

older (RR 6.0 versus 1.4). Also, the relative risk for maternal smoking and hepatoblastoma was stronger for children with normal birth weight [> 2500 g] than for low birth weight children. For cases of hepatoblastoma diagnosed after the age of two years, the relative risk for maternal smoking among children with normal birth weight was also stronger than that among children with low birth weight.

Another study on maternal smoking only was conducted in Chonquing, China (Pu *et al.*, 2009). After adjustment for birth weight, a significantly increased risk for hepatoblastoma was found for maternal smoking (RR 2.9; 95%CI: 1.1–4.2). Adjustments for maternal age, maternal body mass index and sex of the baby did not change the odd ratios. When analyses were stratified by birth weight, the odd ratio associated with maternal smoking for children with a birth weight greater than 2500 g was increased almost fourfold. Stratification by age at diagnosis showed that the risk increased almost fivefold with diagnosis at the age of two years or over. [The Working Group noted that since information regarding mother's smoking status for both cases and controls was obtained before diagnosis the potential for biased recall of maternal exposures during pregnancy is reduced].

(b) Bias and confounding

The known risk factors for hepatoblastoma include low and very low birth weights (< 2000 g and < 1000 g, respectively), maternal age and use of assisted reproductive technologies. All studies adjusted for maternal age, and low birth weight was addressed in three of them (Pang & Birch, 2003; McLaughlin *et al.*, 2006; Pu *et al.*, 2009). Assisted reproductive technologies were not considered to be an important potential confounder of these studies.

Spector & Ross (2003) argued that the association of hepatoblastoma with parental smoking observed by Pang *et al.* (2003) might be confounded by birth weight. In their response,

Table 2.28 Studies of parental tobacco smoking and childhood hepatoblastoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories (case/control)	(Cases/controls)	OR (95% CI)* * $P < 0.05$ ** $P < 0.01$	Adjustment for potential confounders	Comments
Pang et al. (2003) United Kingdom	3838 childhood cancer cases, of which 28 hepatoblastoma; Hospital based; < 15 yr of age; 1991–94 in Scotland; 1992–94 in England and Wales	7581 controls; matched for sex, date of birth and geographical area of residence at diagnosis; randomly selected from Family Health Services Authorities in England and Wales and Health boards in Scotland	Face-to-face structured interviews; Computerized self-administered questionnaires to parents of index child	<i>Parental smoking</i> Neither parent Mother only Father only Both parents <i>Paternal preconception smoking (cigarettes per d)</i> 0 1–19 20+ Trend P <i>Maternal preconception smoking (cigarettes per d)</i> 0 1–19 20+ P for trend	(8/3142) (2/574) (3/1008) (10/1249) **	1.00 (ref) 2.02 (0.40–10.2) 1.86 (0.46–7.55) 4.74 (1.68–13.35)	Deprivation and parental age at birth of index child	Underreporting of smoking by case mothers
Pang & Birch (2003) United Kingdom	Birch and Kelsey diagnostic subgroups, which group biologically similar tumours together (UKCCS Investigators, 2000) excluding diagnostic subgroups with less than 10 cases			<i>Maternal preconception smoking</i> <i>Both parents preconception smoking</i> § <i>Maternal preconception smoking</i> § <i>Both parents preconception smoking</i>	(10/3916) (9/1490) (4/882) 0.058 (28/7581) (27/6987)	1 (ref) 2.99 (1.15–7.76)* 2.17 (0.65–7.20) 2.68 (1.16–6.21)* 4.74** 2.50* 4.97**	§ As above, additionally adjusted for birth weight	

Table 2.28 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories (case/control)	(Cases/controls)	OR (95% CI)* * $P < 0.05$ ** $P < 0.01$	Adjustment for potential confounders	Comments
Sorahan & Lancashire (2004) United Kingdom, 1953–84	43 deaths from hepatoblastoma < 16 yr of age	5777 matched controls, (analysed as unmatched series)	Parental smoking during yr 1953–55, 1971–76, 1977–81	<i>Maternal cigarette smoking</i>			Sex, age at death, yr of death, social class, sibship position, age of mother	
				Non-smoker	(19/3191)	1 (ref)		
				Smoker	(24/2524)	1.73 (0.93–3.21)		
				<i>Paternal cigarette smoking</i>				
				Non-smoker	(12/2267)	1 (ref)		and father at birth of child,
				Smoker	(28/3359)	2.10 (1.03–4.25)*		obstetric radiography
				<i>Parental cigarette smoking</i>				
McLaughlin et al. (2006) , New York, USA, 1985–2001	58 cases of hepatoblastoma, identified from New York State Cancer Registry for 1985–2001 from New York State	Matched on yr of birth, electronic birth records for 1985–2001 from New York State	Routinely recorded data on birth certificate	Neither parent	(9/1601)	1.0 (ref)		
				Mother only	(3/662)	0.85 (0.23–3.19)		
				Father only	(8/1545)	1.23 (0.46–3.28)		
				Both parents	(20/1800)	2.69 (1.18–6.13)*		
				<i>Maternal smoking</i>				
				Non-smoker	(36/3439)	1 (ref)		Association of maternal smoking was stronger in children with birth weights over 2.5kg.
				Smoker	(12/742)	2.1 (1.0–4.2) 2.7 (1.2–5.5) 5.8 (1.4–25.1)		
Pu et al. (2009) , Chongqing China, 1990–97	58 cases	92 controls, appendicitis patients, matched on age, sex, yr	Medical record of mother or follow-up interviews as needed	Birth weight > 2500 g and age > 2 yr				
				<i>Maternal smoking</i>				
				Non-smoker	(43/84)	1 (ref)		Birth weight
				Smoker	(15/8)	2.9 (1.1–4.2)		

d, day or days; yr, year or years

[Pang & Birch \(2003\)](#) showed evidence supporting their initial conclusion: the comparable results for maternal smoking, smoking by both parents and maternal smoking for cases diagnosed at an older age, i.e. one year or older, before and after adjustment for birth weight, appear to rule out low birth weight as an explanation for the association.

Also, both later studies ([McLaughlin et al., 2006](#); [Pu et al., 2009](#)) reported higher relative risks for children with normal birth weight compared to those with low birth weight, particularly in cases diagnosed after the age of two years.

2.6.6 Other childhood cancers

Several other childhood cancers have been studied in relation to parental tobacco smoke exposures, namely neuroblastoma, nephroblastoma, bone tumours, Wilms tumour, soft tissue sarcomas, other neoplasms of the reticuloendothelial system, and childhood germ cell tumours. The data are few and inconsistent ([Schüz et al., 1999](#); [Sorahan et al., 2001](#); [Chen et al., 2005b](#); [Table 2.28](#)).

2.7 Synthesis

2.7.1 Lung

The totality of evidence available to date firmly establishes that exposure to second-hand tobacco smoke at home and at the workplace is causally associated with lung cancer risk in both men and women. This association has been observed in studies from North America, Europe, and Asia. Emerging evidence is also suggesting that exposure to second-hand tobacco smoke among children significantly enhances the risk of lung cancer in adulthood.

2.7.2 Breast

A large number of cohort studies, case-control studies and meta-analyses have assessed the association between exposure to second-hand tobacco smoke and breast cancer. Recent large cohort studies in Europe and North America showed no association between second-hand tobacco smoke and breast cancer. Positive associations in one or more subgroups were reported from some case-control studies; however, these associations were weaker in more recent studies compared with earlier studies.

Explorative analyses focusing on premenopausal breast cancer have suggested that second-hand tobacco smoke may preferentially cause premenopausal breast cancer. Positive associations were largely reported from case-control studies, in which both recall and publication bias cannot be ruled out. Case-control studies that collect a lifetime exposure history are particularly vulnerable to subjective and differential reporting of exposures that occurred long in the past from sources that are difficult to quantify. Overall, the results for an association with premenopausal breast cancer are also inconsistent.

2.7.3 Upper aerodigestive tract combined

Most evidence of the association between second-hand tobacco smoke and upper aerodigestive tract cancers, and the subsites of the oral cavity, pharynx and larynx, comes from a pooled analysis. Overall, the association between second-hand tobacco smoke exposure and cancers of the larynx and pharynx is less than causal.

2.7.4 Nasopharynx, and nasal cavity and accessory sinuses

There is some evidence from a cohort and case-control study that exposure to second-hand tobacco smoke increases the risk of sinonasal cancer; for cancer of the nasopharynx, the evidence is contradictory.

2.7.5 *Others sites*

Overall, data are conflicting and sparse for the association of exposure to second-hand tobacco smoke with all cancers combined, cancers of the gastrointestinal tract combined, and cancers of the stomach, colon, rectum, pancreas, liver (hepatocellular carcinoma), kidney (renal cell carcinoma), urinary bladder, cervix, ovary, testes, and brain and central nervous system.

2.7.6 *Childhood cancers*

(a) *All childhood cancers combined*

Four cohort studies, 13 case-control studies and one meta-analysis have assessed the association of parental tobacco smoking with childhood cancers, all sites combined, in offspring. Most of the early studies only assessed the contribution of maternal smoking, whereas recent studies generally assessed both paternal and maternal smoking, and at various time periods (preconception, during pregnancy, post-natally). Overall, the evidence for an association between parental smoking and childhood cancer (all sites combined) remains inconsistent and may be subject to bias. Nevertheless, a fairly consistent association of paternal tobacco smoking with childhood cancers is beginning to emerge, which is stronger in studies with more specific exposure assessments.

(b) *Leukaemias and lymphomas*

Two cohort studies, 27 case-control studies and 2 meta-analyses have examined the association of childhood haematopoietic malignancies (leukaemia and lymphoma) with exposure to parental smoking (paternal, maternal or both). All studies examined leukaemia, and a large number of these addressed non-Hodgkin lymphoma.

The body of evidence suggests a consistent association of leukaemia (and lymphoma) with paternal smoking preconception and with

combined parental smoking, with risk ratios ranging from 1.5 to 4.0. Maternal tobacco smoking during pregnancy generally showed modest increases in risk, or null or inverse relationships. The combined effects of preconception and post-conception exposures to tobacco smoke were highly significant.

Several studies on lymphoma risk associated with parental smoking showed significantly elevated risks associated with paternal tobacco smoking preconception. The analyses had small samples sizes, and biases due to participation, recall and response, especially related to exposure, cannot be ruled out.

(c) *Brain and central nervous system*

The association of childhood tumours of the brain and central nervous system with parental smoking was assessed in two cohort studies, 21 case-control studies and 2 meta-analyses. Overall these studies do not show an association with either paternal smoking, largely preconception, or maternal smoking prior, during or after pregnancy, or by CNS types, gliomas and primitive neuroectodermal tumours. The strongly positive associations noted in some studies for paternal tobacco smoking with astrocytomas are offset by the lack of association with childhood brain tumours reported by the large UK Childhood Cancer Study.

(d) *Hepatoblastoma*

Four informative case-control studies provided data on the association between parental smoking and hepatoblastomas. Two studies reported on both maternal and paternal smoking, while the two others assessed only maternal smoking. In one study where a large number of categories of childhood cancers ($n = 25$) were assessed, the only childhood cancer that showed an association with parental smoking was hepatoblastoma. This original observation was confirmed in three later studies, with relative risks ranging from 2.0 to 5.5. Chance, bias and

confounding were adequately addressed in the data from the studies available. The evidence for the association of parental smoking with hepatoblastoma is convincing, with an emphasis on prenatal exposures.

(e) *Other childhood cancers*

Most of the associations reported for the other childhood cancers, notably soft tissue sarcomas, rhabdomyosarcomas, Ewing's sarcoma, neuroblastoma, Wilms tumour, reticuloendothelial sarcomas and germ cell tumours were null, with a few isolated and inconsistent positive observations.

3. Cancer in Experimental Animals

3.1 Simulated second-hand tobacco smoke

Simulated second-hand tobacco smoke, frequently a mixture of 89% sidestream and 11% mainstream smoke, generated from cigarettes by smoking machines ([Teague et al., 1994](#)) has been tested for carcinogenicity in adult mice of strains that are genetically susceptible to induction of lung tumours ([Malkinson, 1992](#)). Mice were exposed in inhalation chambers. Several studies reported no increase in lung tumour incidence or multiplicity in mice exposed to simulated second-hand tobacco smoke for 5–9 months and killed immediately thereafter ([Witschi et al., 1995, 1997a](#); [Finch et al., 1996](#)). It was suggested that the lack of tumour response in simulated second-hand tobacco smoke-exposed mice might be due to treatment-induced stress (as determined by the increased plasma corticosterone level) that has been shown to attenuate lung tumorigenesis ([Stinn et al., 2005a](#)).

In subsequent studies from several laboratories ([Table 3.1](#)), an increased multiplicity and often increased incidence of lung tumours was

reported in male and female A/J mice exposed for five months and kept in filtered air for another four months ([Witschi et al., 1997a, b, 1998, 1999](#); [D'Agostini et al., 2001](#)) or longer ([Witschi et al., 2006](#)) before the mice were killed. Similar results were obtained with Swiss albino mice ([Witschi et al., 2002](#)). In these studies, no nasal tumours were observed in smoke-exposed mice.

In one study, male and female transgenic mice with a dominant negative *p53* mutation on an A/J background were exposed to simulated second-hand tobacco smoke for 9.5 continuous months or for 5 months followed by recovery in air for 4.5 months. Transgenic mice exposed by either regimen developed significantly higher incidence and multiplicity of lung tumours than sham-exposed control transgenic mice ([DeFlora et al., 2003](#)). Neither lung tumour incidence nor multiplicity was increased in smoke-exposed wild-type control mice in this study.

In one study, male and female rats exposed to room-aged sidestream cigarette smoke by nose-only inhalation for 24 months and then killed had no increased incidence of lung or other tumours in comparison with fresh-air controls. Lung tumours were not significantly increased in rats exposed for 24 months and kept until 30 months of age ([Stinn et al., 2005b](#)).

3.2 Sidestream smoke condensate

In one study, sidestream cigarette smoke condensate applied to the shaved skin of female NMRI mice lower back, at total weekly doses of 5, 10 and 15 mg, for 3 months caused benign and malignant skin tumours and mammary carcinomas in mice observed for their lifespan and was more potently carcinogenic in this assay than mainstream smoke condensate. No cutaneous or subcutaneous tumours developed in any of three control groups ($P < 0.001$) ([Mohtashamipur et al., 1990](#)). In one study, fractionated sidestream cigarette smoke condensates were implanted into the lungs of female rats. The fraction containing

Table 3.1 Carcinogenicity studies of inhalation exposure to simulated second-hand tobacco smoke^a in A/J mice, transgenic mice with a dominant negative *p53* mutation, and Wistar rats as a function of length of the post-exposure recovery period

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, A/J (M) Witschi et al. (1997a)	48 animals/group Chamber concentration, 0 or 87 mg/m ³ total suspended particulates; 6 h/d, 5 d/wk for 5 mo followed by 0 or 4 mo post-exposure recovery 9 mo	5 mo: 2/24 (8%, 0.1 ± 0.1); 6/24 (25%, 0.3 ± 0.1) 9 mo: 9/24 (38%, 0.5 ± 0.2); 20/24 (83%, 1.4 ± 0.2)	NS Incidence: <i>P</i> < 0.05 Multiplicity: <i>P</i> < 0.05	> 80% of tumours were adenomas; the rest were adenocarcinomas
Mice, A/J (F) D'Agostini et al. (2001)	20 animals/group Chamber concentration, 0 or 120 mg/m ³ total suspended particulates; 6 h/d, 5 d/wk, for 5 mo followed by 4 mo post-exposure recovery 9 mo	5/20 (25%, 0.25 ± 0.10); 15/20 (75%, 1.05 ± 0.17)	Incidence: <i>P</i> < 0.01 Multiplicity: <i>P</i> < 0.01	
A/J mice (sex NR) Witschi et al. (2006)	24, 25 controls (12 mo) 19, 17 controls (24 mo) Chamber concentration, 0 (control) or 158 mg/m ³ total suspended particulates; 6 h/d, 5 d/wk, for 6 mo followed by 4 or 16 mo post-exposure recovery 24 mo	12 mo: 13/24 (54%, 0.9 ± 0.2); 24/25 (96%, 1.8 ± 0.2) 24 mo: 8/9 (89%, 2.1 ± 0.5); 10/10 (100%, 4.3 ± 0.7)	Incidence: <i>P</i> < 0.05 Multiplicity: <i>P</i> < 0.05 Incidence: NS Multiplicity: <i>P</i> < 0.05	80% of tumours were adenomas
(UL53-3xΔJ)F ₁ , Transgenic mice (M, F) De Flora et al. (2003)	222 (108; 114 controls) Chamber concentration, 0 (control) or 113 mg/m ³ total suspended particulates; 6 h/d for 5 mo or 9.5 mo followed by 0 or 4.5 mo post-exposure recovery 9.5 mo	No recovery: NR; 17/30 (57%, 0.93 ± 0.18) With recovery: 5/26 (19%, 0.27 ± 0.10); 15/23 (65%, 0.74 ± 0.11)	Incidence: <i>P</i> < 0.01 Multiplicity: <i>P</i> < 0.01 Incidence: <i>P</i> < 0.01 Multiplicity: <i>P</i> < 0.01	
Wistar rats (M, F) Stinn et al. (2005b)	99 rats/group Nose-only exposure; concentration, 0 (controls) or low dose 3 mg/m ³ or high dose 10 mg/m ³ ; 6 h/d, 7 d/wk, 24 mo followed by 0 or 6 mo post-exposure recovery 30 mo	24 mo: controls–0/16 Low dose–0/16 High dose–0/16 30 mo: controls–2/99 (2%) Low dose–4/98 (4%) High dose–5/94 (5%)	NS	

^a Simulated second-hand tobacco smoke: 89% sidestream and 11% mainstream smoke from Kentucky 1R4F or 2R1 reference cigarettes d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

PAHs with four and more rings (dose, 1.06 mg/rat) induced 5 lung carcinomas in 35 treated rats; fractions containing no PAHs or PAHs with two or three rings (16 mg/rat) had little or no carcinogenic effect ([Grimmer et al., 1988](#)).

3.3 Observational studies of companion animals

In one study, sinonasal cancers occurred more frequently in pet dogs of long-nosed breeds which lived in homes with at least one smoker ([Reif et al., 1998](#)), but no such excess risk was seen in a second study ([Bukowski et al., 1998](#)). A marginal excess risk of lung cancer was observed in dogs aged 10 years or less and exposed to household tobacco smoke in one study ([Reif et al., 1992](#)). Risk of bladder cancer in dogs was not related to exposure to household cigarette smoke in another study ([Glickman et al., 1989](#)).

Risk of malignant lymphoma was increased in pet cats exposed to household tobacco smoke in one study ([Bertone et al., 2002](#)), but the conclusion that this association was causal has been questioned ([Denson, 2003](#)). In another study by the same group ([Bertone et al., 2003](#)), exposure of pet cats to household tobacco smoke was also associated with a non-significant 2-fold increase in risk of oral squamous cell carcinoma.

3.4 Synthesis

Several studies showed consistent increases in lung tumour multiplicity and often lung tumour incidence in inbred strain A/J mice and in transgenic mice with a dominant negative *p53* tumour suppressor gene exposed by inhalation. In addition, in one report, skin and mammary tumours were induced in NMRI mice exposed to sidestream cigarette smoke condensate applied topically to the skin.

4. Other Relevant Data

See Section 4 of the *Monograph on Tobacco Smoking* in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of second-hand tobacco smoke. Second-hand tobacco smoke causes cancer of the lung. Also, a positive association has been observed between exposure to second-hand tobacco smoke and cancers of the larynx and the pharynx.

There is *sufficient evidence* in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke.

There is *sufficient evidence* in experimental animals for the carcinogenicity of sidestream tobacco smoke condensates.

Second-hand tobacco smoke is *carcinogenic to humans* (Group 1).

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* Exceptionally, the most recent updates of well-established ongoing surveys and reports, published after the meeting, were included in this Monograph. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.

SMOKELESS TOBACCO

Smokeless tobacco was considered by a previous IARC Working Group in 2004 ([IARC, 2007a](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Smokeless tobacco products

The term smokeless tobacco implies use of unburned tobacco in the finished products. A variety of smokeless tobacco products are available, for oral or nasal use. Products intended for oral use are sucked, chewed (dipped), gargled or applied to the gums or teeth, while fine tobacco mixtures are usually inhaled into the nostrils.

[Table 1.1](#) summarizes for each smokeless tobacco product its mode of use, the main ingredients included, the WHO regions in which the product is used, and some specification of the countries in which the product is used most commonly or specifically ([DHHS, 2001](#); [IARC, 2007a](#); [European Commission, 2008](#)). Smokeless tobacco products that contain areca nut are commonly used in India, other countries in South Asia, and in migrant populations from these countries. These products may be mentioned here for comparison but are reviewed in the *Monograph* on Betel Quid and Areca Nut in this volume.

1.2 Chemical composition of smokeless tobacco

The tobacco used in a particular product has a decisive influence on its chemical composition, and varies with tobacco species, growing, curing, processing and storage. During product manufacture, tobacco is blended to achieve a specific nicotine content and pH. The pH strongly influences the concentration of unprotonated nicotine, the bioavailable form of nicotine, while the nitrite/nitrate content strongly influences the levels of carcinogenic nitrosamines in the product. Other tobacco components are alkaloids which include nicotine (85–95% of total alkaloids), terpenes, polyphenols, phytosterols, carboxylic acids, aromatic hydrocarbons, aldehydes, ketones, amines, nitriles, *N*- and *O*-heterocyclic hydrocarbons, pesticides, and metallic compounds. Flavour-type additives are also present ([Bates et al., 1999](#)). Ammonia, ammonium carbonate and sodium carbonate are applied to control nicotine delivery by raising pH and subsequently the level of unprotonated nicotine which is most readily absorbed through the mouth into the bloodstream ([Djordjevic et al., 1995](#)).

Table 1.1 Smokeless tobacco products, ingredients, and use by WHO region

Tobacco product	Mode of use	Ingredients	WHO Region					
			AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Oral use								
Betel quid with tobacco ^a	Chewing	Betel leaf, areca nut, slaked lime, tobacco in various forms			X		X	X
<i>Chimó</i>	Sucking	Paste of crushed and boiled tobacco leaves, sodium bicarbonate, sugar, wood ash, flavourings		X ^b				
Chewing tobacco	Chewing	See Tobacco chewing gum						
Chewing tobacco twist/roll	Chewing	Dark, air- or fire-cured tobacco leaves treated with tobacco extract, flavourings		X ^c				
Creamy snuff	Other	Finely ground tobacco with aromatic substances (manufactured commercially)					X	
Dry snuff	Sucking	Fire- or air-cured, fermented powdered tobacco	X ^d	X ^c	X ^e	X ^f	X ^g	
<i>Gudhaku</i>	Other	Paste of powdered tobacco and molasses					X ^g	
<i>Gul</i>	Other	Powdered tobacco, molasses and other ingredients					X ^g	
<i>Gutka</i> ^a	Sucking	Sun-dried finely chopped tobacco, areca nut, slaked lime, catechu, flavourings, sweeteners (manufactured commercially)					X	
<i>Iq'mik</i>	Chewing	Fire-cured tobacco leaves with punk ash		X ^h				
<i>Khaini</i>	Sucking	Sun-dried or fermented coarsely crushed tobacco leaves					X ⁱ	
<i>Khiwam</i>	Chewing	Paste of tobacco extract, spices, additives					X ⁱ	
<i>Loose leaf</i>	Chewing	Small strips of air-cured, shredded cigar tobacco leaves (manufactured commercially)		X ^c	X			
<i>Maraş</i>	Sucking	Sun-dried powdered tobacco leaves, wood ash, water				X ^k		
<i>Mawa</i> ^a	Chewing	Sun-cured areca nut, crushed tobacco leaves, slaked lime					X ⁱ	
<i>Mishri</i>	Sucking	Tobacco toasted on hot metal plate and powdered					X ^g	
Moist snuff	Sucking	Air- or fire-cured tobacco, processed into fine particles (fine-cut) or strips (long-cut), with stem and seeds		X ^c		X ^l		
<i>Naswar/nass</i>	Sucking	Sun-dried, powdered tobacco, ash, oil, flavourings, colourings, slaked lime (optional)	X ^d		X ^m	X		
Plug chewing tobacco	Chewing	Heavy-grade or cigar tobacco top leaves immersed in liquorice or sugar, pressed into a plug		X ^c				
Red tooth powder	Other	Fine tobacco powder, many additional ingredients (manufactured commercially)					X	
<i>Shammah</i>	Sucking	Powdered tobacco, lime, ash, black pepper, oils, flavourings			X ⁿ	X		
<i>Snus</i>	-	See moist stuff		X ^c		X ^l		

Table 1.1 (continued)

Tobacco product	Mode of use	Ingredients	WHO Region				
			AFRO	AMRO	EMRO	EURO	WPRO
<i>Saffa</i>	-	<i>Toombak</i> rolled into a ball	X ^q				
Tobacco tablet	Sucking	Compressed powdered tobacco, mint, eucalyptus		X ^c			
<i>Toombak</i>	Sucking	Dried, fermented, ground and matured tobacco leaves, sodium bicarbonate	X ^q				
<i>Tuibur</i>	Other	Tobacco water				X ^r	
<i>Zarda</i>	Chewing	Tobacco leaves boiled with lime and spices until dry, colourings; chewed with areca nut and spices		X		X	
Nasal use							
Dry snuff	Sniffing	Fire-cured, fermented and powdered tobacco	X ^s		X	X ^t	X
Liquid snuff	Sniffing	Powered tobacco mixed with ash from plants, oil, lemon juice, herbs	X ^u				

^a These products contain areca nut and are reviewed in the *Monograph on Betel Quid and Areca Nut* in this volume.

^b Specific to Venezuela, used by young boys and urban teenagers

^c Used in the USA

^d Used principally in South Africa; dry snuff is mostly inhaled.

^e Common in North Africa, notably in Tunisia as *sniffa*

^f Used in Germany, Georgia and the United Kingdom

^g Used as dentifrice, mostly by women, in various parts of India

^h Specific to native American tribes of North-West Alaska

ⁱ Used in India, Bangladesh and Nepal

^j Specific to India

^k Specific to remote regions of Turkey

^l Used in Sweden, Norway and Finland

^m Common in Afghanistan, Islamic Republic of Iran, Pakistan and central Asia

ⁿ Common in the Middle East, particularly in Saudi Arabia and Yemen

^o Used in Sweden and Denmark

^p Specific to Japan (new product)

^q Specific to Sudan, used by men

^r Specific to eastern States of India

^s Used by several tribes in South Africa, namely Bantus

^t Used in the United Kingdom

^u Specific to tribes in East Africa

AFRO, African Region; AMRO, Regions of the Americas; EMRO, Eastern Mediterranean Region; EURO, European Region; SEARO, South East Asian Region, WPRO, Western Pacific Region; the countries included in each region are available at <http://www.who.int/about/regions/en/>

1.2.1 Nicotine content in smokeless tobacco

The majority of commercial tobacco products are made from *N. tabacum* species, grown throughout the world with an alkaloid content that varies greatly. In randomly cultivated varieties examined, the alkaloid content ranged between 0.17 and 4.93%.

N. rustica species is cultivated in eastern Europe, Asia Minor and Africa, and the cured leaves may contain up to 12% nicotine. *Toombak* from Sudan, which contains *N. rustica* tobacco, had the highest reported levels of nicotine ([Idris et al., 1991](#); [Prokopczyk et al., 1995](#)). In 17 brands of moist snuff from the USA, the nicotine content ranged from 0.47 to 3.43%. The nicotine content of Swedish snus ranges from 0.5–1.7% ([Idris et al., 1998](#); [Stepanov et al., 2008](#)).

1.2.2 Carcinogenic compounds in smokeless tobacco

Multiple carcinogens have been identified in smokeless tobacco ([IARC, 2007a](#)) including:

(a) Tobacco-specific *N*-nitrosamines

Tobacco-specific *N*-nitrosamines include the carcinogens *N*'-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

Tobacco-specific *N*-nitrosamines are formed from tobacco alkaloids (nicotine, nornicotine, anatabine, anabasine, and nitrite) primarily during tobacco curing, fermentation and ageing. The nitrate or nitrite content, the mode of curing and the various steps of processing are the main determining factors for the yields of tobacco-specific *N*-nitrosamines in tobacco.

[IARC \(2007a\)](#) compiled an international comparison of the concentrations of NNN and NNK in smokeless tobacco products. The ranges vary widely and are product- and country-specific. In some moist snuff brands in the USA, the highest concentrations of NNN and NNK

measured were 135 and 17.8 µg/g tobacco, respectively. In home-made *toombak* from Sudan, values as high as 3085 and 7870 µg/g dry wt tobacco, respectively, have been reported ([Idris et al., 1991](#); [Prokopczyk et al., 1995](#)).

(b) *N*-Nitrosamino acids

The amino acids present in tobacco, and probably also the proteins with secondary amino groups, are amenable to *N*-nitrosation. Since 1985, numerous studies have reported the presence of *N*-nitrosamino acids in smokeless tobacco products ([IARC, 2007a](#)).

To date, 11 *N*-nitrosamino acids have been identified in smokeless tobacco: *N*-nitrososarcosine (NSAR), *N*-nitrosoazetidine-4-carboxylic acid (NAzCA), 3-(methylnitrosamino)propionic acid (MNPA), 4-(methylnitrosamino)butyric acid (MNBA), *N*-nitrosoproline (NPRO), *N*-nitrosohydroxyproline (NHPRO), *N*-nitrosopipericolic acid (NPIC), *N*-nitrosothiazolidine-4-carboxylic acid (NTCA), *N*-nitroso-2-methylthiazolidine-4-carboxylic acid (MNTCA), 4-(methylnitrosamino)-4-(3-pyridyl)butyric acid (*iso*-NNAC) and 2-(methylnitrosamino)-3-phenylpropionic acid (MNPhPA) ([Ohshima et al., 1985](#); [Tricker & Preussmann, 1988](#); [Hoffmann et al., 1995](#)). Of these, NSAR, MNPA, MNBA and NAzCA have been established as carcinogens in experimental animals.

The concentration of *N*-nitrosamino acids depends on the nitrate or nitrite content of tobacco; they are formed during prolonged storage, particularly under adverse conditions of temperature and relative humidity. The concentrations reported in USA moist snuff samples were in the range of 5.7 to 13.45 µg/g dry wt. Highest amounts of MNPA were found in Indian *zarda* (up to 18 µg/g) and in moist snuff (up to 70 µg/g).

Table 1.2 PAHs in moist snuff brands marketed in the USA

Compound	Mean \pm SD of 23 brands (ng/g dry weight)
Naphthalene	1726 \pm 392.3
Acenaphthylene	110.5 \pm 42.9
Acenaphthene	105.1 \pm 53.8
Fluorene	826.5 \pm 287.0
Phenanthrene	4700 \pm 1571
Anthracene	844.2 \pm 277.8
Fluoranthene	1404 \pm 537.4
Pyrene	1292 \pm 428.5
Benz[a]anthracene	193.6 \pm 71.3
Chrysene	232.1 \pm 109.8
Methylchrysenes	92.6 \pm 35.0
Benzo[b]fluoranthene + Benzo[f]fluoranthene	107.0 \pm 69.5
Benzo[k]fluoranthene	19.6 \pm 6.6
Benzo[e]pyrene	52.4 \pm 23.8
Benzo[a]pyrene	55.8 \pm 21.5
Indeno[1,2,3-cd]pyrene	20.5 \pm 12.1
Benzo[ghi]perylene	18.0 \pm 8.3
Dibenz[a,h]anthracene	7.5 \pm 1.9

From [Stepanov et al. \(2010\)](#)

(c) Volatile N-nitrosamines

These include N-nitrosodimethylamine (NDMA), N-nitrosopyrrolidine (NPYR) and N-nitrosopiperidine (NPIP).

Levels of volatile N-nitrosamines formed from volatile amines and nitrosating agents in smokeless tobacco products worldwide have been summarized ([IARC, 2007a](#)). The highest amounts were found in moist snuff (NDMA up to 265 ng/g dry wt and NPYR up to 860 ng/g dry wt).

(d) PAHs

These include benzo[a]pyrene, benz[a]anthracene, chrysene, benzo[a]fluoranthene, and dibenz[a,h]anthracene.

Levels of various PAHs in 23 moist snuff brands marketed in the USA were determined by [Stepanov et al. \(2010\)](#) and are summarized in [Table 1.2](#).

(e) Other carcinogenic compounds and constituents

Levels of the volatile aldehydes formaldehyde, acetaldehyde, acrolein and crotonaldehyde in smokeless tobacco products ranged from 0.207–10.6, 0.97–72.3, 0.27–7.85, and 0.55–19.4 μ g/g dry weight tobacco, respectively ([Stepanov et al., 2010](#)).

Uranium was reported in Indian snuff at a concentration of about 3 pCi/g tobacco ([Sharma et al., 1985](#)). Levels of polonium-210 in commercial moist and dry snuff in the USA were reported to be 0.16–1.22 and 0.23–0.39 pCi/g, respectively.

In several parts of the world, smokeless tobacco is invariably chewed with lime which is responsible for highly alkaline pH ([Nair et al., 1990, 1992](#)), facilitating absorption of nicotine in the oral mucosa.

1.2.3 Comparison of new and traditional smokeless tobacco products

Newer types of smokeless tobacco products are appearing on the market. These products are sold as small pouches and do not require spitting. Similar to Swedish snus, they have been manufactured with additional controls to inhibit nitrosamine formation, and are being promoted as reduced risk products. Levels of carcinogens in these newer products are compared to those in traditional products in [Table 1.3](#) ([Stepanov et al., 2008](#)).

1.3 Prevalence of use

1.3.1 Prevalence of smokeless tobacco use among adults

Several surveys have evaluated the prevalence of smokeless tobacco use at different times and targeting different populations in the WHO regions (AFRO, African Region; AMRO, Region of the Americas; EURO, European Region; EMRO, Eastern Mediterranean Region; SEARO,

Table 1.3 Mean levels of selected carcinogens in newer and traditional smokeless tobacco products

	Newer products (n = 12)	Traditional products (n = 5)
NNN (µg/g dry weight)	2.05	4.41
NNK (µg/g dry weight)	0.231	1.20
Benzo[a]pyrene (ng/g dry weight)	3.12	38.2
Fluoranthene	10.0	400
Benzo[b]fluoranthene + Benzo[k]fluoranthene (ng/g dry weight)	2.76	38.3
Formaldehyde (µg/g dry weight)	3.23	8.43
Acetaldehyde (µg/g dry weight)	6.16	35.7
Crotonaldehyde (µg/g dry weight)	9.12	2.98

NNN, *N*'-nitrosornnicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

From [Stepanov et al. \(2008\)](#)

South-East Asian Region; WPRO, Western Pacific Region). The major surveys that form the basis of this report are ([Table 1.4](#)):

- the Global Adult Tobacco Survey conducted during 2009–10 among adults aged 15 years or more in 14 middle and low-income countries in AMRO, SEARO, EURO, EMRO and WPRO;
- the national level STEPS noncommunicable risk factor survey (2006–09) was conducted in 8 countries in AFRO, and a few countries in SEARO, EURO (Georgia), EMRO and WPRO (Mongolia), in adults aged 15–64 years, except for AFRO (age group, 25–64 years);
- the Demographic and Health Surveys (2003–10) provide prevalence on smokeless tobacco use among adults aged 15–49 years in countries in AFRO (16), EURO (4), EMRO (2), WPRO (8);
- some other surveys such as the Behavioural Risk Factor Survey, the National Smoking/Tobacco/Drug use Survey, health cost studies, and national health, public health or morbidity surveys.

The prevalence of smokeless tobacco use reported in the various surveys are not directly comparable because of the different methodologies

and time periods; however, they provide a snapshot of the global smokeless tobacco burden. Large variations are observed between countries ([Table 1.5](#)), between sex within a country, and sometimes within a country ([Table 1.6](#)). Those countries with a high prevalence ($\geq 10\%$) represent about 25% of the global adult population. They include, by WHO region:

- in AFRO: Benin (men, 13%), Madagascar (men 23%; women, 20%), Mauritania (women, 28%), South Africa (women, 11%);
- in EMRO: Yemen (men, 15%);
- in EURO: Norway (men, 17.0%; women, 5.0%), Sweden (men, 26%), Uzbekistan (men, 22.5%);
- in SEARO: Bangladesh (men, 26%; women, 28%), India (men, 33%; women 11–18%), Myanmar (men, 51.4%; women, 16.1%), Nepal (men, 31%), Sri Lanka (men, 24.9%);
- in WPRO: Cambodia (women, 12.7%).

A few countries have medium prevalence (between 5% and 10%); these include:

- in AFRO: Benin, Cape Verde, Malawi in women; Lesotho, Mali, Mauritania, Swaziland, Zimbabwe in men;
- in AMRO: USA in men;

- in EMRO: Tunisia in men; Yemen in women;
- in EURO: Finland, Iceland and Kyrgyzstan in men; Norway and Sweden in women;
- in SEARO: Sri Lanka and Thailand in women.

In most countries, current prevalence of smokeless tobacco use is higher among men than among women. Some exceptions are found at all levels of prevalence (in women and men, respectively): Bangladesh (27.9, 26.9), Barbados (0.6, 0), Cambodia (12.7, 0.7), Cape Verde (5.8, 3.5), Malaysia (3.1, 0.5), Mauritania (28.3, 5.7), South Africa (10.9, 2.4), Thailand (6.3, 1.3) and Viet Nam (2.3, 0.3).

Demographic health survey data indicate that in countries in AFRO and SEARO smokeless tobacco is more prevalent in rural compared to urban areas, and higher among low-income compared to high-income groups. Also, prevalence generally increases with increasing age.

Some countries warrant more detailed information of their pattern of smokeless tobacco use, and are presented below.

1.3.2 Country specific data

(a) India

The India Global Adult Tobacco Survey (2009–10) revealed that 26% of all adults use smokeless tobacco in some form, 21.4% daily and 4.5% occasionally. Prevalence in men (32.9%) is higher than in women (18.4%), and is higher in rural (29.3%) than urban areas (17.7%). Large variations are observed between States, from around 5% in Himachal Pradesh, Goa and Chandigarh to 49% in Bihar (India GATS Report, 2009–10).

Khaini is the most commonly used smokeless tobacco product (11.6%), followed by *gutka* (8.2%). Prevalence of *khaini* chewing is significantly higher among men (18%) than among women (5%); 13.1% men and 2.9% women chew *gutka*; 6.2% (7.5% men, 4.9% women) of adults use betel quid with tobacco; 4.7% (3.3% men, 6.3%

women) use tobacco products such as *mishri*, *gul*, *gudakhu* for oral application (dentifrice); and 4.4% uses some other products, such as snuff for nasal application and some local products. The pattern of use of smokeless tobacco products also varies widely in different States of India ([Table 1.6](#)) (India GATS Report, 2009–10).

Proportion of dual tobacco users (smoking+smokeless) is 19.4% among men and 5.3% among women ([Sinha et al., 2011](#)).

(b) Bangladesh

In Bangladesh the most prevalent form of smokeless tobacco is betel quid with tobacco (24.3%), followed by *gul* (5.3%), *sada pata* (1.8%), *khaini* (1.5%) and others (1.4%) (BAN GATS Report, 2009). Use decreases with increasing education and socioeconomic level in both men and women, by a steeper rate among women compared to men. Among current users, those with the highest prevalence of use of *gul* and *khaini* were labourers among men (7.5% and 2.8%, respectively) and homemaker among women (5.7% and 1.4%, respectively) (BAN GATS Report, 2009).

Proportion of dual tobacco users (smoking+smokeless) is 22.5% among men and 2.5% among women ([Sinha et al., 2011](#)).

(c) Canada

Unchanged from surveys conducted in 2008 and 2009, 8% of Canadians aged 15 years and older reported having ever tried smokeless tobacco products in 2010. In 2009, 11% of young adults aged 20 to 24 years reported ever using smokeless tobacco and 1% having used it within the past 30 days. There has been a shift in the distribution of past-30-day smokeless tobacco users from youth towards older adults: in 2003, 23% of users were aged 15–19 years and 14% were older than 45 years, whereas in 2009, 16% of smokeless tobacco users were 15 to 19 years old and 33% were aged 45 and older.

Table 1.4 Surveys and articles used to compile the information presented*

Bangladesh GATS report Government of the People's Republic of Bangladesh, Ministry of Health and Family Welfare; World Health Organization, Country Office for Bangladesh. Global Adult Tobacco Survey: Bangladesh Report 2009. Dhaka, 2009. http://www.searo.who.int/LinkFiles/Regional_Tobacco_Surveillance_System_GATSBAN_FullReport2009.pdf
Canada CTUMS Canadian Tobacco Use Monitoring Survey (CTUMS) 2010, http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_2010/ann_summary-sommaire-eng.php
Central Statistical Office (CSO) [Swaziland], and Macro International Inc. 2008. <i>Swaziland Demographic and Health Survey 2006–07</i> . Mbabane, Swaziland: Central Statistical Office and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR202/FR202.pdf
Central Statistical Office (CSO) [Zimbabwe] and Macro International Inc. 2007. <i>Zimbabwe Demographic and Health Survey 2005–06</i> . Calverton, Maryland: CSO and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR186/FR186.pdf
Central Statistical Office (CSO), Ministry of Health (health ministry), Tropical Diseases Research Centre (TDRC), University of Zambia, and Macro International Inc. 2009. <i>Zambia Demographic and Health Survey 2007</i> . Calverton, Maryland, USA: CSO and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR211/FR211[revised-05-12-2009].pdf
Department of Health, Medical Research Council, OrcMacro. 2007. <i>South Africa Demographic and Health Survey 2003</i> . Pretoria: Department of Health. http://www.measuredhs.com/pubs/pdf/FR206/FR206.pdf
Ghana Statistical Service (GSS), Ghana Health Service (GHS), and ICF Macro. 2009. <i>Ghana Demographic and Health Survey 2008</i> . Accra, Ghana: GSS, GHS, and ICF Macro. http://www.measuredhs.com/publications/publication-FR221-DHS-Final-Reports.cfm
Global Tobacco epidemic report World Health Organization. World Report on the Global Tobacco Epidemic, 2009: Implementing Smoke-Free Environments. Geneva: WHO, 2009.
Global Tobacco epidemic report World Health Organization. World Report on the Global Tobacco Epidemic, 2011. Geneva: WHO, 2011.
India GATS report Government of India, Ministry of Health and Family Welfare. Global Adult Tobacco Survey: GATS India 2009–2010. Mumbai, 2010. http://www.searo.who.int/LinkFiles/Regional_Tobacco_Surveillance_System_GATS_India.pdf
Institut National de la Statistique (INSTAT) et ICF Macro. 2010. <i>Enquête Démographique et de Santé de Madagascar 2008–2009</i> . Antananarivo, Madagascar: INSTAT et ICF Macro. http://www.measuredhs.com/pubs/pdf/FR236/FR236.pdf
Institut National de la Statistique et de l'Analyse Économique (INSAE) [Bénin] et Macro International Inc. 2007. <i>Enquête Démographique et de Santé (EDSB-III) – Bénin 2006</i> . Calverton, Maryland, USA: Institut National de la Statistique et de l'Analyse Économique et Macro International Inc. http://www.measuredhs.com/publications/publication-FR197-DHS-Final-Reports.cfm
Kenya National Bureau of Statistics (KNBS) and ICF Macro. 2010. <i>Kenya Demographic and Health Survey 2008–09</i> . Calverton, Maryland: KNBS and ICF Macro. http://www.measuredhs.com/publications/publication-FR229-DHS-Final-Reports.cfm
Liberia Institute of Statistics and Geo-Information Services (LISGIS) [Liberia], Ministry of Health and Social Welfare [Liberia], National AIDS Control Program [Liberia], and Macro International Inc. 2008. <i>Liberia Demographic and Health Survey 2007</i> . Monrovia, Liberia: Liberia Institute of Statistics and Geo-Information Services (LISGIS) and Macro International Inc. http://www.measuredhs.com/publications/publication-FR201-DHS-Final-Reports.cfm
Lund M, Lindbak R. <i>Norwegian Tobacco Statistics 1973–2006</i> . Oslo: Norwegian Institute for Alcohol and Drug Research; 2007. Sirus skrifter No. 3/2007.
Lundqvist G, Sandström H, Ohman A, Weinehall L. Patterns of tobacco use: a 10-yr follow-up study of smoking and snus habits in a middle-aged Swedish population, Scand J Public Health. 2009, 37:161–7
Ministry of Health and Social Services (MoHSS) [Namibia] and Macro International Inc. 2008. <i>Namibia Demographic and Health Survey 2006–07</i> . Windhoek, Namibia and Calverton, Maryland, USA: MoHSS and Macro International Inc. http://www.measuredhs.com/publications/publication-FR204-DHS-Final-Reports.cfm
Ministry of Health and Social Welfare (MOHSW) [Lesotho] and ICF Macro. 2010. <i>Lesotho Demographic and Health Survey 2009</i> . Maseru, Lesotho: MOHSW and ICF Macro. http://www.measuredhs.com/publications/publication-FR241-DHS-Final-Reports.cfm

Table 1.4 (continued)

MMWR August 27, 2010, 59(33), 487–92, Tobacco use among Middle and High school students – USA 2000–2009
MMWR August 6, 2010/59(30);946–950, Any tobacco use in 13 states–Behavioural Risk factor Surveillance System 2008
National Bureau of Statistics (NBS) [United Republic of Tanzania] and ICF Macro. 2011. <i>United Republic of Tanzania Demographic and Health Survey 2010</i> . Dar es Salaam, United Republic of Tanzania: NBS and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR243/FR243[24June2011].pdf
National Institute of Population Research and Training (NIPORT), Mitra and Associates, and Macro International. 2009. <i>Bangladesh Demographic and Health Survey 2007</i> . Dhaka, Bangladesh and Calverton, Maryland, USA: National Institute of Population Research and Training, Mitra and Associates, and Macro International. http://www.measuredhs.com/pubs/pdf/FR207/FR207[April-10-2009].pdf
National Population Commission (NPC) [Nigeria] and ICF Macro. 2009. <i>Nigeria Demographic and Health Survey 2008</i> . Abuja, Nigeria: National Population Commission and ICF Macro. http://www.measuredhs.com/publications/publication-FR222-DHS-Final-Reports.cfm
National Statistics Directorate (NSD) [Timor-Leste], Ministry of Finance [Timor-Leste], and ICF Macro. 2010. <i>Timor-Leste Demographic and Health Survey 2009–10</i> . Dili, Timor-Leste: NSD [Timor-Leste] and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR235/FR235.pdf
Sinha DN, Palipudi KM, Rolle I <i>et al.</i> (2011). Tobacco use among youth and adults in member countries of South-East Asia region: Review of findings from surveys under the global tobacco surveillance system. <i>Indian J Public Health</i> , 55:169–176. PMID:22089684
Statistics Indonesia (Badan Pusat Statistik—BPS) and Macro International. 2008. <i>Indonesia Demographic and Health Survey 2007</i> . Calverton, Maryland, USA: BPS and Macro International. http://www.measuredhs.com/pubs/pdf/FR218/FR218[27August2010].pdf
Statistics Sierra Leone (SSL) and ICF Macro. 2009. <i>Sierra Leone Demographic and Health Survey 2008</i> . Calverton, Maryland, USA: Statistics Sierra Leone (SSL) and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR225/FR225.pdf
Uganda Bureau of Statistics (UBOS) and Macro International Inc. 2007. <i>Uganda Demographic and Health Survey 2006</i> . Calverton, Maryland, USA: UBOS and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR194/FR194.pdf

*, Exceptionally, the most recent updates of well established ongoing surveys and reports, published after the meeting, were included in this *Monograph*. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.

Table 1.5 Highest and lowest prevalence of smokeless tobacco use by WHO regions and by sex

WHO region	Men		Women	
	Lowest	Highest	Lowest	Highest
AFRO	0.8% in Gambia	22.6% in Madagascar	0.2% in Ghana	28.3% in Mauritania
AMRO	0.0% in Barbados	6.9% in USA	0.2% in Guyana & Dominican Republic	0.6% in Barbados
EMRO	1.3% in Saudi Arabia	15.1% in Yemen	0.1% in Libyan	6.2% in Yemen
EURO	0.2% in Switzerland & Latvia	26.0% in Sweden	0% in Switzerland & Ukraine	5% in Kyrgyzstan
SEARO	1.3% in Thailand	51.4% in Myanmar	0.3% in Indonesia	27.9% in Bangladesh
WPRO	0.3% in Viet Nam	2.8% in Mongolia & Philippines	0.1% in the People's Republic of China	12.7% in Cambodia

(d) USA

According to the Behavioural Risk Factor Surveillance System survey (2008), conducted in 13 States, prevalence varied from 0.5% (New Jersey) to 8.8% (West Virginia). Dual use of cigarette and smokeless tobacco products varied from 0.2% (Delaware) to 1.8% (West Virginia).

In an overall analysis of users' demographic characteristics, prevalence of smokeless tobacco use was higher among men (6.3%) than women (0.3%); more prevalent among non-Hispanic whites (4.1%) compared to other ethnic groups; highest in the youngest age group (18–24 years) and decreased steadily with age. Users of smokeless tobacco were almost equally distributed between the sextiles of annual income (3.0 to 3.8%).

(e) Europe

In Europe, countries with a high prevalence of smokeless tobacco use are Norway, Sweden and Uzbekistan.

In Sweden, a 10-year follow-up study of smoking and snus [Swedish moist snuff] habits in a middle-aged Swedish population showed that use of snus increased from 3.1% to 6.0% among women and from 24.6% to 26.3% among men. The number of people who used both snus and cigarettes was stable: 0.5% to 0.8% from baseline

to follow-up for women and 4.1% to 3.3% for men. Whereas nearly all snus users in Sweden are daily users, almost half of snus users in Norway use it only occasionally.

1.3.3 Prevalence of smokeless tobacco use among youth

The Global Youth Tobacco Survey (GYTS) is a school-based survey of students aged 13–15 years that uses a two-stage sampling design. In a first stage, schools are selected based on the probability proportional to the enrolment of students in schools. In a second stage, classes are selected randomly. It uses standard questionnaire, field methodology and analysis. The Survey has core questions that spans seven thematic areas pertinent to tobacco. In addition, countries can include country-specific questions that allow assessment of tobacco unique to the country [smokeless tobacco use may include betel quid with tobacco.]

In AFRO, all countries surveyed reported a prevalence of smokeless tobacco use among youth above 5%, ranging from 5.4% in Swaziland to 16.4% in Congo. Among boys, it varied from 5.2% in Seychelles to 18.3% in Congo, whereas among girls, from 4.8% in Togo to 15.8% in Namibia. Prevalence was higher among boys than girls in most countries, except in Uganda where

Table 1.6 Highest and lowest prevalence of use of selected smokeless tobacco products in India, by State

	Lowest	Highest
Betel quid	0.5% in Punjab, Himachal Pradesh, Chandigarh and Uttrakhand	32.8% in Tripura
Dentifrice	0.4% in Tripura	28.35 in Chattishgarh
<i>Khaini</i>	0.5% in Tamil Nadu	32.6% in Jharkhand
<i>Gutka</i>	0.6% in Puducherry	17.0% in Madhya Pradesh

it was higher among girls (9.6% versus 8.6%) ([Asma et al., 2011](#)). Four countries (Botswana, Congo, Lesotho and Namibia) are particularly noteworthy: these countries reported the highest prevalence in both sexes (11.3–16.4%), the highest prevalence in boys (11.3–18.3%), the highest prevalence in girls (11.4–15.8%), and similar prevalence in boys and girls.

In AMRO, prevalence of smokeless tobacco use among youth varied from 3.5% in Panama to 9.8% in Barbados. Among boys, it varied from 3.8% in Panama to 11.5% in Barbados, whereas among girls, it varies from 2.6% in Venezuela to 8.5% in Jamaica. Most notably, smokeless tobacco use among boys was above 10% in Barbados, Dominican Republic and Grenada. Girls in most countries used less smokeless tobacco than boys, except in Jamaica (8.5% for both) and Peru (boys, 4.3%; girls, 4.8%) where boys and girls had comparable prevalence ([Asma et al., 2011](#)).

In SEARO, all countries surveyed reported a prevalence of smokeless tobacco use among youth above 5%, ranging from 4.9% in Bangladesh to 9.4% in Bhutan. Among boys, it ranged from 5.8% in Bangladesh to 14.1% in Bhutan whereas among girls, it varies from 2.7% in Myanmar to 6% in India. In all countries more boys than girls used smokeless tobacco products ([Asma et al., 2011](#)).

In EURO, prevalence of smokeless tobacco use among youth is lower than in other WHO regions, ranging from 1.1% in Montenegro to 6.9% in Estonia. While it ranged from 1.1% in Montenegro to 9.4% in Estonia among boys, it varied from 0.7% in Serbia to 4.5% in Estonia among girls. Except for Estonia (6.9%), all countries reported a prevalence among youth below 5%. Also, in all countries boys used more smokeless tobacco than girls ([Asma et al., 2011](#)).

In EMRO, prevalence of smokeless tobacco use among youth varied from 1.6% in Oman to 12.6% Djibouti. Among boys, it varied from 2% in Libyan Arab Jamahiriya to 15.2% in Djibouti, whereas among girls, it varied from 0.9% in Oman and Tunisia to 9% in Djibouti. Prevalence of smokeless tobacco use among youth was highest in Djibouti (12.6%), where it is also highest among boys and girls separately. Boys generally used more smokeless tobacco than girls, except in Libyan Arab Jamahiriya and Yemen where girl users slightly outnumbered boy users ([Asma et al., 2011](#)).

In WPRO, prevalence of smokeless tobacco use among youth varies from 2.1% in Macau to 8.7% in Cook Islands. Among boys, it varies from 2.2% in Macau to 10.5% in Cook Islands, whereas among girls, it varies from 2.1% in Macau to 7.3% in Cook Islands. Prevalence of smokeless tobacco use among youth in Cook Island and Republic of Korea is above 5% for boys and girls combined, as well as separately for boys and girls. Prevalence among boys was generally higher than among girls ([Asma et al., 2011](#)).

In summary, among the countries included in the GYTS survey 2007–2010, the prevalence of smokeless tobacco use among youth aged 13–15 years exceeds 5% in all or most countries in AFRO, AMRO and SEARO, in Djibouti, Islamic Republic of Iran, Qatar, Syrian Arab Republic and Yemen in EMRO, and in the Cook Islands and Republic of Korea in WPRO ([Asma et al., 2011](#)).

In general, prevalence among boys was higher than among girls, although in several countries prevalence was similar, or higher among girls.

In several countries, smokeless tobacco use among 13 to 15 year-old men is higher than that among adult men (aged 15 years or more). These include Albania, Argentina, Brazil, the Dominican Republic, Guyana, Lesotho, Mexico, Namibia, Saudi Arabia, Tunisia and Uganda. Similarly, in Albania, Argentina, Barbados, Brazil, Dominican Republic, Guyana, Kyrgyzstan, Libyan Arab Jamahiriya, Mexico, Saudi Arabia, Swaziland, Uganda and Yemen, smokeless tobacco use among 13–15 year women is higher than that in adult women.

2. Cancer in Humans

2.1 Oral use

2.1.1 Cancers of the oral cavity and pharynx

(a) Overview of studies

Studies of smokeless tobacco and oral and pharyngeal cancer have been conducted in North and South America, Europe, Asia, and Africa. All of the studies reported here examined oral cancer risks associated with use of unsmoked tobacco that was not part of a betel quid. Evidence regarding betel quid is presented in the *Monograph* on Betel Quid in this volume. This section focuses on the predominant smokeless tobacco products and behaviours in the countries in which the studies were conducted, for example on chewing tobacco and snuff in North America, snus in northern Europe, *shammah* in Saudi Arabia and Yemen, *toombak* in Sudan, and a variety of types in South Asia (see [Table 1.1](#) for their mode of use, ingredients and region of use). The studies typically examine cancers arising in intra-oral sites, which are predominantly squamous cell in origin ([Canto & Devesa, 2002](#)), but some include other sites as well, such as the

oropharynx, hypopharynx, or larynx. Studies involving smokeless tobacco and nasopharyngeal cancer are discussed in another chapter.

The previous *Monograph* ([IARC, 2007a](#)) concluded that there was *sufficient evidence* in humans that smokeless tobacco causes cancer of the oral cavity. Studies published since include updates on mortality and incidence for one of the cohorts reviewed previously ([Accortt et al., 2002, 2005](#)), two new cohort studies ([Luo et al., 2007](#); [Roosaar et al., 2008](#)); case-control studies from Sweden ([Rosenquist, 2005](#); [Rosenquist et al., 2005](#)) and India ([Sapkota et al., 2007](#)); and three meta-analyses ([Weitkunat et al., 2007](#); [Boffetta et al., 2008](#); [Lee & Hamling, 2009](#)).

Because tobacco smoking is a risk factor for oral and pharyngeal cancers ([IARC, 2004](#)), and tobacco smoking is often positively correlated with smokeless tobacco use ([Tomar, 2002](#)), addressing confounding by smoking is important in the examination of causality related to smokeless tobacco. Heavy alcohol use is another important risk factor and can potentially confound the relationship between tobacco use and risk of oral and pharyngeal cancer ([IARC, 2010, 2012](#)).

While analysis restricted to non-smokers and non-alcohol drinkers eliminates the possibility of confounding due to smoking and alcohol drinking, the sample sizes can be small in study populations in regions where these behaviours are common. Adjusting statistically for smoking and alcohol can alternatively be used to address confounding by these factors in populations where these behaviours are common and can provide unbiased estimates that may be more stable if there is no residual confounding within smoking/drinking categories used in the adjustment. There is *sufficient evidence* that human papillomavirus (HPV) 16 causes oral cancer in humans ([IARC, 2007b](#)). Studies have shown that the prevalence of HPV DNA is negatively correlated with tobacco smoking and alcoholic beverage consumption ([Gillison et al., 2000](#)), suggesting that positive confounding by HPV is

not likely to account for a spurious association between smokeless tobacco and oral cancer.

The specific name of the smokeless tobacco product will be used whenever available. In the USA, where moist snuff and chewing tobacco are both common, the term “smokeless tobacco” refers to use of either. Most publications provide data on “ever” versus “never” use of these products, usually defined as using the product or not for some minimal length of time such as a year. Due to the large body of evidence, this *Monograph* will focus on studies published since [IARC \(2007a\)](#).

(i) Cohort studies

Ever lifetime use or ever daily use of smokeless tobacco and risk of oral and pharyngeal cancers was examined in six cohort studies conducted in the USA ([Zahm et al., 1992](#); [Accortt et al., 2002, 2005](#); [Henley et al., 2005](#)), Sweden ([Luo et al., 2007](#); [Roosaar et al., 2008](#)), and Norway ([Boffetta et al., 2005](#)). Mortality data were analysed in four studies ([Zahm et al., 1992](#); [Accortt et al., 2002](#); [Henley et al., 2005](#); [Roosaar et al., 2008](#)), four ([Accortt et al., 2005](#); [Boffetta et al., 2005](#); [Luo et al., 2007](#); [Roosaar et al., 2008](#)) analysed cancer incidence. None of the studies excluded persons diagnosed in the first 1 or 2 years of follow-up nor did they collect information on changes in behaviours, such as smokeless tobacco or smoking cessation or initiation, after the baseline (Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.1.pdf>).

Ever use of smokeless tobacco was associated with a statistically significant threefold increased risk of death from oral cancer and an 8.7 fold increased risk of death from pharyngeal cancer in one study from the USA ([Zahm et al., 1992](#)). Risks were greater among those with more frequent use, but adjustment was not performed for tobacco smoking and therefore this study will not be considered further in this section.

Ever use of smokeless tobacco was not associated with risk for cancer in four cohorts ([Accortt et al., 2005](#); [Boffetta et al., 2005](#); [Henley et al., 2005](#); [Luo et al., 2007](#)). In one cohort the age-adjusted standardized mortality ratio for oral cancer associated with ever smokeless tobacco use was not elevated ([Accortt et al., 2002](#)) and the age-adjusted standardized incidence ratio for smokeless tobacco use and oral cancer was statistically lower than expected ([Accortt et al., 2005](#)). The expected number of oral cancer deaths among ever smokeless tobacco users in this cohort was zero, suggesting limited statistical power to detect elevated risks.

In the Cancer Prevention Study I and II cohorts ([Henley et al., 2005](#); CPS-I and CPS-II, respectively), the hazard ratio (HR) for death from oral and pharyngeal cancer in CPS-I for current use of smokeless tobacco versus never use among men who never used any other form of tobacco was 2.0 (95%CI: 0.5–7.7), based on four deaths adjusting for alcohol consumption, fruit/vegetable intake and other factors. The corresponding HR in CPS-II was 0.9 (95%CI: 0.1–6.7), based on one death adjusting for similar factors as CPS-I.

In the Norwegian cohort ([Boffetta et al., 2005](#)), the HR for ever use of smokeless tobacco was 1.1 (95%CI: 0.5–2.4), for oral, pharynx or salivary gland cancer after adjusting for age and smoking. Among non-smokers in a cohort of 280 000 Swedish male construction workers, the relative risk of developing oral cancer was 0.8 (95%CI: 0.4–1.7), adjusting for attained age and body mass index (BMI) ([Luo et al., 2007](#)).

One cohort study in Sweden involved 9 860 men who participated in an oral examination ([Roosaar et al., 2008](#)). An elevated relative risk (RR) of 3.1 (95%CI: 1.5–6.6) was found for ever daily use of snus compared to never daily use of snus controlling for calendar period, area of residence, alcohol consumption, smoking, and an interaction variable for age and smoking. Among

the never-smokers in the cohort, the relative risk for ever daily use of snus was 2.3 (95%CI: 0.7–8.3).

All cohort studies had at least 12 years of follow-up. No increased risk of oral cancer was observed for the three cohorts with 12–26 years of follow-up ([Accortt et al., 2002, 2005](#); [Henley et al., 2005](#); [Luo et al., 2007](#)). One study with 35 years follow-up found no association of smokeless tobacco and oral cancer risk ([Boffetta et al., 2005](#)) and another study with 27–29 years follow-up had significant positive findings among smokers only ([Roosaar et al., 2008](#)).

(ii) Case-control studies

Many case-control studies examined smokeless tobacco and oral and pharyngeal cancer ([Broders, 1920](#); [Moore et al., 1953](#); [Wynder & Bross, 1957](#); [Wynder et al., 1957a, b](#); [Peacock et al., 1960](#); [Chandra, 1962](#); [Vogler et al., 1962](#); [Vincent & Marchetta, 1963](#); [Martinez, 1969](#); [Keller, 1970](#); [Browne et al., 1977](#); [Jafarey et al., 1977](#); [Williams & Horm, 1977](#); [Wynder & Stellman, 1977](#); [Westbrook, 1980](#); [Winn et al., 1981a](#); [Wynder et al., 1983](#); [Stockwell & Lyman, 1986](#); [Young et al., 1986](#); [Blot et al., 1988](#); [Spitz et al., 1988](#); [Franco et al., 1989](#); [Goud et al., 1990](#); [Blomqvist et al., 1991](#); [Maden et al., 1992](#); [Marshall et al., 1992](#); [Mashberg et al., 1993](#); [Spitz et al., 1993](#); [Kabat et al., 1994](#); [Bundgaard et al., 1995](#); [Idris et al., 1995a](#); [Muscat et al., 1996](#); [Lewin et al., 1998](#); [Muscat & Wynder, 1998](#); [Schildt et al., 1998](#); [Schwartz et al., 1998](#); [Wasnik et al., 1998](#); [Chelleng et al., 2000](#); [Merchant et al., 2000](#); [Rosenquist et al., 2005](#); [Rosenquist, 2005](#); [Sapkota et al., 2007](#)). Two studies were of cancer of the salivary gland ([Keller, 1969](#); [Muscat & Wynder, 1998](#)), one reported on hypopharyngeal cancer ([Sapkota et al., 2007](#)), and one on nasopharyngeal cancer ([Chelleng et al., 2000](#)). The same study was reported on twice in two instances ([Wynder & Bross, 1957](#); [Wynder et al., 1957a](#); [Rosenquist, 2005](#); [Rosenquist et al., 2005](#)). Additionally, one cross-sectional study was conducted, but the comparability of the two surveys analysed to

yield risk estimates was uncertain ([Sterling et al., 1992](#)).

Nearly half the studies addressed potential confounding by tobacco smoking. In three ([Broders, 1920](#); [Stockwell & Lyman, 1986](#); [Keller, 1970](#)), smokeless tobacco information was probably obtained from medical records and, if ascertainment of smokeless tobacco use was more likely from cases than from controls, measurement error might account for the findings and these studies will not be considered further. The remaining 15 studies were conducted in the USA ([Vogler et al., 1962](#); [Martinez, 1969](#); [Williams & Horm, 1977](#); [Winn et al., 1981a](#); [Blot et al., 1988](#); [Mashberg et al., 1993](#); [Kabat et al., 1994](#)), Sweden ([Lewin et al., 1998](#); [Schildt et al., 1998](#); [Rosenquist, 2005](#); [Rosenquist et al., 2005](#)), India ([Chandra, 1962](#); [Wasnik et al., 1998](#); [Sapkota et al., 2007](#)), Pakistan ([Merchant et al., 2000](#)), and Sudan ([Idris et al., 1995a](#)) (Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.2.pdf>).

Five studies were population-based ([Williams & Horm, 1977](#); [Blot et al., 1988](#); [Lewin et al., 1998](#); [Schildt et al., 1998](#); [Rosenquist et al., 2005](#)); positive findings were observed in the majority of them ([Williams & Horm, 1977](#); [Blot et al., 1988](#); [Lewin et al., 1998](#)) and in all of the hospital-based studies except one ([Mashberg et al., 1993](#)). One study ([Winn et al., 1981a](#)) also included death certificate cases and controls.

Several case-control studies of oral cancer addressed potential confounding by tobacco smoking either by statistically controlling for tobacco smoking or by restricting to non-smokers. Odds ratios (OR) for ever versus never use of smokeless tobacco overall, or for at least one of the major cancer subtypes, was statistically significantly elevated in eight studies, with odds ratios for oral cavity cancer ranging from 3.9 to 34.5 ([Vogler et al., 1962](#); [Martinez, 1969](#); [Williams & Horm, 1977](#); [Winn et al., 1981a](#); [Blot et al., 1988](#); [Kabat et al., 1994](#); [Idris et al., 1995a](#); [Wasnik et al., 1998](#); [Merchant et al., 2000](#)) and

in one study of hypopharyngeal cancer in India ([Sapkota et al., 2007](#)). In case-control studies conducted in Sweden, there was no association with use of smokeless tobacco in 2 studies ([Schildt et al., 1998](#); [Rosenquist, 2005](#)) or in another study ([Lewin et al., 1998](#)) that controlled for smoking and alcohol intake. However, when Lewin *et al.*, 1998 restricted the analysis to non-smokers the odds ratio for head and neck cancer associated with ever use of smokeless tobacco was 4.7 (95%CI: 1.6–13.8). [[Rosenquist \(2005\)](#) was based on a relatively small sample size of 132 cases and 320 controls.]

In one case-control study conducted in the USA ([Vogler et al., 1962](#)) and another of *toombak* users in Sudan ([Idris et al., 1995a](#)), neither statistical adjustment for tobacco smoking nor restriction to non-smokers was done. However, confounding by smoking was not likely to have a major effect on the risk estimates from these studies. The proportions of smokers in the case and control groups were low in the rural women in the study of [Vogler et al. \(1962\)](#) among whom positive findings were found. In the study in Sudan less than 10–12% of the two case groups and in a hospital-based control groups smoked; in the population-based control group 21% were smokers, but most had smoked for less than one year ([Idris et al., 1995a](#)).

In a meta-analysis [Boffetta et al. \(2008\)](#) included studies published through 2007 that provided information about non-smokers and studies that adjusted for tobacco smoking. The summary estimate for the 11 studies of oral cancer (6 of them also including pharyngeal cancer) was 1.8 (95%CI: 1.1–2.9) overall. For the USA, it was 2.6 (95%CI: 1.3–5.2) and for northern European countries, 1.0 (95%CI: 0.7–1.3) (Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.3.pdf>).

Another meta-analysis included 40 studies published through May 2008 (Table 2.4 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.4.pdf>) but excluded

studies in Asian or African populations ([Lee & Hamling, 2009](#)). In addition to the studies in the meta-analysis by [Boffetta et al. \(2008\)](#), 15 other studies were included: ([Moore et al., 1953](#); [Wynder & Bross, 1957](#); [Wynder et al., 1957, 1983](#); [Peacock et al., 1960](#); [Vincent & Marchetta, 1963](#); [Martinez, 1969](#); [Keller, 1970](#); [Browne et al., 1977](#); [Wynder & Stellman, 1977](#); [Young et al., 1986](#); [Spitz et al., 1988](#); [Franco et al., 1989](#); [Blomqvist et al., 1991](#); [Maden et al., 1992](#); [Marshall et al., 1992](#); [Sterling et al., 1992](#); [Zahm et al., 1992](#); [Spitz et al., 1993](#); [Bundgaard et al., 1995](#); [Muscat et al., 1996](#); [Schwartz et al., 1998](#)) and one unpublished study by Perry and colleagues in 1993. Among never-smokers the odds ratio was 1.72 (95%CI: 1.01–2.94) based on 9 studies; further adjustment for alcohol in the three studies where this was possible yielded an odds ratio among never-smokers of 1.87 (95%CI: 0.82–4.27). The estimate for never-smokers among the studies conducted in the USA was 3.33 (95%CI: 1.76–6.32), and decreased with additional adjustment for alcohol drinking (1.58; 95%CI: 0.52–4.81), based on two studies among never-smokers. Corresponding estimates for snuff use in never-smokers in Scandinavia were 1.01 (95%CI: 0.71–1.45; 4 studies) and 2.30 (95%CI: 0.67–7.92; 1 study) adjusted for alcohol drinking. For studies published since 1990, the corresponding estimates were 1.24 (95%CI: 0.80–1.90; 7 studies) in never-smokers and 1.87 (95%CI: 0.82–4.27; 3 studies) adjusted for alcohol drinking.

[Lee & Hamling \(2009\)](#) updated an earlier meta-analysis ([Weitkunat et al., 2007](#)) of 32 studies through 2005, excluding studies conducted in Asian populations. [Weitkunat et al. \(2007\)](#) did not include three studies ([Rosenquist et al., 2005](#); [Luo et al., 2007](#); [Roosaar et al., 2008](#)), but provided sex- and tobacco type- specific estimates not reported by [Lee & Hamling \(2009\)](#). For smokeless tobacco, the overall smoking-adjusted relative risk was 1.35 (95%CI: 1.04–1.76), and for chewing tobacco and snuff, the estimates were 1.42 (95%CI: 0.99–2.03; 6 studies) and

1.28 (95%CI: 0.76–2.14; 7 studies). For men the smoking-adjusted estimate was 1.15 (95%CI: 0.97–1.37) and for women 2.51 (95%CI: 1.73–3.64). For case–control studies with hospital-based controls, the estimates were 1.41 (95%CI: 1.18–1.68) and for studies with population-based controls 0.99 (95%CI: 0.69–1.42). Smoking-adjusted relative risks for smokeless tobacco were elevated only for studies conducted before 1980: 2.02 (95%CI: 1.28–3.20) for earlier than 1969, 2.67 (95%CI: 1.83–3.90) for 1970–1979, compared with 0.97 (95%CI: 0.71–1.31) for 1980–1989, and 1.10 (95%CI: 0.88–1.37) for 1990 or later.

(b) Dose–response evidence

In this and subsequent sections, the relative risks and odds ratios are either among non-smokers or are adjusted for tobacco smoking. Dose–response relationships were observed in several studies.

(i) Duration and intensity

[Williams & Horm \(1977\)](#) found that the odds ratio for oral cavity cancers in men associated with heavy use of smokeless tobacco was higher than for moderate use. [Lewin et al. \(1998\)](#) also reported relative risks for head and neck cancer that increased with increasing intensity of oral snuff use. Of the case–control studies that examined duration, higher risks of oral cancer with greater numbers of years of snuff use were noted for cancers of the gum/buccal mucosa, but not for other cancers of the mouth/pharynx category ([Winn et al., 1981a](#)). No increase with years of snus use was observed in two Swedish case–control studies ([Lewin et al., 1998](#); [Rosenquist et al., 2005](#)). In a study in Sudan ([Idris et al., 1995a](#)), the odds ratio for use of *toombak* for more than 11 years was greater than that for fewer years of use.

(ii) Cessation

In two cohort ([Boffetta et al., 2005](#); [Luo et al., 2007](#)) and three case–control studies ([Lewin et al., 1998](#); [Schildt et al., 1998](#); [Rosenquist et al.,](#)

[2005](#)), risks were not significantly elevated in either current or former smokeless tobacco users. No studies provided information on time since stopping.

(c) Comparison of types of smokeless tobacco by geographical location

(i) Northern Europe

Four studies from this area found no overall association between use of snus and oral cancer ([Lewin et al., 1998](#); [Schildt et al., 1998](#); [Boffetta et al., 2005](#); [Rosenquist, 2005](#)). One case–control study ([Rosenquist, 2005](#)) examined users of fermented and not fermented snuff and observed no risk for either type. In Sweden before 1983, snuff was fermented as part of the manufacturing process, and this process is conducive to formation of tobacco-specific *N*-nitrosamines. In one cohort study ([Roosaar et al., 2008](#)) the relative risk for ever daily use of snus was 3.1 (95%CI: 1.5–6.6, adjusted for smoking, calendar period, area of residence, alcohol consumption and a variable to account for the interaction between age and smoking) and 2.3 (95%CI: 0.7–8.3) among non-smokers with adjustment for calendar period, area of residence and alcohol consumption. In a case–control study, among non-smokers, the odds ratio for cancers of the oral cavity, pharynx and oesophagus combined was 4.7 (95%CI: 1.6–13.8) ([Lewin et al., 1998](#)).

(ii) USA

In the USA chewing tobacco and moist snuff are the predominant forms of smokeless tobacco. In five case–control studies of oral cancer, the odds ratio for ever use of smokeless tobacco were statistically significantly elevated overall for use of one or other type, ranging from 4.2 to 34.5 ([Martinez, 1969](#); [Williams & Horm, 1977](#); [Williams et al., 1977](#); [Winn et al., 1981a](#); [Blot et al., 1988](#); [Kabat et al., 1994](#)). No association with use of either of these products was observed in 2 cohort studies ([Accortt et al., 2002](#); [2005](#);

[Henley et al., 2005](#)) and one case-control study ([Mashberg et al., 1993](#)).

The odds ratio for chewing tobacco was not statistically significantly elevated in two studies ([Mashberg et al., 1993](#); [Kabat et al., 1994](#)); but was in a third ([Martinez, 1969](#)). For snuff, one study found no association ([Mashberg et al., 1993](#)) and in three others statistically significant elevated risks were observed, ranging from 4.2 to 34.5 ([Winn et al., 1981a](#); [Blot et al., 1988](#); [Kabat et al., 1994](#)). In one case-control study in the southern USA positive associations were observed among non-smoking women who were snuff dippers, but a significant association was observed for white, but not black women; dry snuff was the predominant form of snuff used by women in that area ([Winn et al., 1981a](#)). Elevated odds ratios persisted with control for poor dentition ([Winn et al., 1981b](#)), use of mouthwashes ([Blot et al., 1983](#)), fruits and vegetables ([Winn et al., 1984](#)), type of respondent (self versus proxy), and alcohol consumption ([Winn, 1986](#)).

(iii) Africa, Middle East, and Asia

In Sudan the majority of a consecutively accrued series of oral cancer cases used *saffa*, an oral snuff, a moistened, powdered tobacco treated with sodium sesquicarbonate ([Elbeshir et al., 1989](#)). Also, in Sudan *toombak* use was higher in oral cancer cases with squamous cell-carcinomas in sites with direct contact with the quid (e.g. floor of mouth) than cases with less or no contact (e.g. palate) ([Idris et al., 1995b](#)). The odds ratio for *toombak* use was 7.3 (4.3–12.4) comparing hospital-based cases with oral cancers in direct contact with the quid versus hospital controls, and 1.4 (0.8–2.5) for cases with oral cancers not usually in direct contact with the quid ([Idris et al., 1995a](#)), adjusting for age, sex, tribe and residence. Ten to twelve percent of the cases and hospital controls smoked. Twenty-one percent of population controls smoked, although most had smoked for less than one year.

Case series from Saudi Arabia have noted a high frequency of use of *shammah* or *al-shammah* in series of oral, pharyngeal, and laryngeal cancer cases ([Amer et al., 1985](#); [Ibrahim et al., 1986](#); [al-Idrissi, 1990](#); [Allard et al., 1999](#)).

In Pakistan, ever using *naswar* was associated with an odds ratio of 9.5 (95%CI: 1.7–52.5; adjusted for cigarette smoking and alcohol consumption) ([Merchant et al., 2000](#)). Reports based on small series of users in which potential confounding by tobacco smoking could not be ruled out also noted higher frequencies of *naswar* use in oral cancer cases than controls or oral cancers among *naswar* users ([Aleksandrova, 1970](#); [Nugmanov & Baimakanov, 1970](#)).

In India, a case-control study of buccal mucosa cancer observed an odds ratio of [2.7] for men and [2.5] for women associated with tobacco chewing among non-smokers ([Chandra, 1962](#)). In a cross-sectional survey, the period prevalence of oral and oropharyngeal cancer among persons who used *pattiwala*, sun-cured tobacco leaf only, was 1.17 per 100 persons compared to 0.36 among non-chewers of tobacco ([Wahi, 1968](#)) [tobacco smoking was not accounted for]. A case-control study of oropharyngeal cancer, using a smokeless tobacco product for teeth cleaning was associated with an odds ratio of 5.2 (95%CI: 2.5–11.8), adjusted for smoking ([Wasnik et al., 1998](#)). In another case-control study in India, snuffing tobacco nasally or orally, generally using *naswar*, was associated with elevated odds ratios for hypopharyngeal cancer in never-smokers and in analyses adjusted for tobacco smoking and alcohol consumption ([Sapkota et al., 2007](#)). [The Working Group noted that in the [Sapkota et al. \(2007\)](#) study, snuff use was nasal as well as oral so the role of oral use could not be separately determined.] In the same study, odds ratios for hypopharyngeal cancer among never-smokers were significantly elevated for *zarda* and non-significantly elevated for *khaini*, after adjusting for centre, age, sex, socioeconomic status, alcohol consumption and tobacco snuffing.

(d) Interactions

In one study in the USA that provided odds ratios for smokers only, smokeless tobacco users only, and smokers who also used smokeless tobacco, each compared to non-users of either, there was no evidence of an interaction between smokeless tobacco use and smoking ([Winn et al., 1981a](#)), nor was there any evidence of an interaction between smokeless tobacco use and alcohol consumption in a similar analysis of that study population ([Winn, 1986](#)).

*2.1.2 Precancerous lesions of the oral cavity**(a) Overview of studies*

Studies on the natural history of oral cancer suggest that several types of potentially malignant lesions and conditions precede the development of cancer of the oral cavity. Oral precancerous lesions of relevance are leukoplakia and erythroplakia. The term leukoplakia will be used below to describe white lesions and erythroplakia to describe red lesions. Several classification systems for the lesions have been used ([Axéll et al., 1976](#); [Pindborg, 1980](#); [Greer & Poulson, 1983](#); [Pindborg et al., 1996](#)), all involving visual inspection of the oral cavity and a diagnosis based on clinical appearance of the lesions to identify the causes of the white and red oral lesions. Smokeless tobacco use has previously been identified as a risk factor for oral premalignant lesions ([IARC, 2007a](#)). Histological and clinical changes occur in the mucosa of snuff users in as few as 2–7 days after initiation of use ([Payne et al., 1998](#)). Furthermore, the location of the lesion in the mouth has been shown to correspond to where the smokeless tobacco is typically placed ([Salem et al., 1984](#); [Zaridze et al., 1986](#); [Ernster et al., 1990](#); [Tomar et al., 1997](#); [Martin et al., 1999](#); [Ayo-Yusuf et al., 2000](#)).

Since [IARC \(2007a\)](#) one cross-sectional study has been published in the USA ([Fisher et al., 2005](#)), one from Sweden ([Roosaar et al., 2008](#)),

and one from Yemen ([Scheifele et al., 2007](#)). Cross-sectional studies and case series from many parts of the world have reported that leukoplakia occurs more commonly among smokeless tobacco users and that persons with lesions are more frequently smokeless tobacco users. Many cross-sectional studies were conducted in the USA ([Greer & Poulson, 1983](#); [Poulson et al., 1984](#); [Offenbacher & Weathers, 1985](#); [Wolfe & Carlos, 1987](#); [Creath et al., 1988](#); [Cummings et al., 1989](#); [Stewart et al., 1989](#); [Ernster et al., 1990](#); [Grady et al., 1990](#); [Creath et al., 1991](#); [Daniels et al., 1992](#); [Sinusas et al., 1992](#); [Grasser & Childers, 1997](#); [Tomar et al., 1997](#); [Martin et al., 1999](#); [Lee et al., 2000](#); [Shulman et al., 2004](#); [Fisher et al., 2005](#); [Sinusas & Coroso, 2006](#)). The types of smokeless tobacco implicated are snus in Sweden ([Salonen et al., 1990](#); [Rolandsson et al., 2005](#)), Finland ([Jungell & Malmström, 1985](#)), and Denmark ([Roed-Petersen et al., 1972](#); [Roed-Petersen & Pindborg, 1973](#); [Rolandsson et al., 2005](#)), chewing tobacco in the United Kingdom ([Tyldesley, 1971](#)) and India ([Jacob et al., 2004](#)), *nass* (*naswar*) in Uzbekistan ([Zaridze et al., 1985, 1986](#); [Evstifeeva & Zaridze, 1992](#)), *toombak* in Sudan ([Idris et al., 1996](#); [Ahmed et al., 2003](#); [Ahmed & Mahgoob, 2007](#)), snuff (finely ground fermented tobacco leaf with the wet ash of an *Amaranthus* species plant) in South Africa ([Ayo-Yusuf et al., 2000](#)), *shammah* in Yemen ([Scheifele et al., 2007](#)) and Saudi Arabia ([Salem et al., 1984](#); [Mani, 1985](#)).

Table 2.5 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.5.pdf>) includes cross-sectional and case-control studies of smokeless tobacco and leukoplakia, listed by country. Eight reports from the USA adjusted for tobacco smoking, either through statistical adjustment or restriction to non-smokers, one in schoolchildren ([Tomar et al., 1997](#)) and the others in adults ([Shulman et al., 2004](#); [Ernster et al., 1990](#); [Grady et al., 1990](#); [Daniels et al., 1992](#); [Greene et al., 1992](#); [Martin et al., 1999](#); [Fisher et al., 2005](#)). The prevalence rate ratio or odds ratio for oral leukoplakia in

current smokeless tobacco users exceeded those of non-users for smokeless tobacco overall in four studies from the USA ([Ernster et al., 1990](#); [Tomar et al., 1997](#); [Martin et al., 1999](#); [Fisher et al., 2005](#)) for snuff in four studies ([Ernster et al., 1990](#); [Tomar et al., 1997](#); [Martin et al., 1999](#); [Fisher et al., 2005](#)) and for chewing tobacco in two ([Ernster et al., 1990](#); [Tomar et al., 1997](#)) but not in a third ([Fisher et al., 2005](#)).

In Uzbekistan *nass* (*naswar*) use was positively associated with oral leukoplakia in non-smokers ([Zaridze et al., 1986](#)) and after adjusting for smoking, alcoholic beverage consumption, and age ([Evstifeeva & Zaridze, 1992](#)). In India, oral precancerous lesions (oral leukoplakia, submucous fibrosis, erythroplakia, and multiple lesions) were associated with tobacco chewing after adjusting for age, sex, BMI, pack-years of smoking, and years of drinking alcohol ([Thomas et al., 2003](#); [Jacob et al., 2004](#)).

(b) Dose-response evidence

(i) Duration and intensity

Strong dose-response relationships have been observed in studies in the USA with intensity and duration of use of smokeless tobacco, snuff or chewing tobacco. The prevalence odds ratio for mucosal lesions increased with increasing intensity (amounts used per day or week) and duration (months, years, minutes or hours per day with tobacco in the mouth; shorter time since last used) of use of smokeless tobacco (chewing tobacco and snuff) ([Ernster et al., 1990](#); [Tomar et al., 1997](#); [Martin et al., 1999](#); [Fisher et al., 2005](#)). Baseball players who used smokeless tobacco only during the playing season had a lower prevalence rate of oral lesions than year-long users, but higher than non-users ([Greene et al., 1992](#)).

In Uzbekistan there was a trend of greater odds ratios for pre-leukoplakia and leukoplakia with the number of times *nass* was used per day, earlier age at initiation of the habit, years used, and lifetime intake ([Evstifeeva & Zaridze, 1992](#)).

In Yemen, there was a dose-response relationship with number of minutes *shammah* was kept in the mouth and the risk was reduced if the mouth was rinsed after using the product ([Scheifele et al., 2007](#)).

(ii) Cessation

The prevalence or prevalence odds ratio for oral lesions were higher in current than in former users in studies in the USA ([Ernster et al., 1990](#); [Tomar et al., 1997](#); [Shulman et al., 2004](#); [Fisher et al., 2005](#)). Former users generally had higher prevalence or prevalence odds ratio (although not always statistically significantly elevated) than never users ([Ernster et al., 1990](#); [Tomar et al., 1997](#); [Fisher et al., 2005](#)). In Uzbekistan, both former (OR, 3.00; 95%CI: 1.08–8.32) and current users (OR, 3.86; 95%CI: 2.60–5.72) had statistically significantly elevated odds ratios associated with *nass* use ([Evstifeeva & Zaridze, 1992](#)).

(c) Severity of lesions

The percentage of more severe leukoplakia lesions (degree 3 and 4) was higher with increasing amount of use, longer duration of use, shorter time since last use of snuff, and exposure time in the mouth in studies in the USA ([Ernster et al., 1990](#); [Grady et al., 1990](#); [Daniels et al., 1992](#); [Greene et al., 1992](#); [Tomar et al., 1997](#); [Martin et al., 1999](#)). Basal-cell hyperplasia was observed in 4% of 132 lesion biopsies from snuff users, while no hyperplasia was found in the 6 biopsies from chewing tobacco users ([Daniels et al., 1992](#)). Severe epithelial atypia was observed in *toombak* users (38%) in a case series in Sudan ([Ahmed et al., 2003](#)). Also in Sudan greater duration of *toombak* use was associated with greater severity of the lesions ([Idris et al., 1996](#)). In a South African study, lesions were more severe among those with more minutes per day of use and the users of the commercial brand compared to home-made snuff ([Ayo-Yusuf et al., 2000](#)).

(d) Types

The prevalence of lesions was higher among snuff users compared with tobacco chewers in several studies ([Ernster et al., 1990](#); [Greene et al., 1992](#); [Tomar et al., 1997](#); [Martin et al., 1999](#)). Among snuff users, the prevalence of lesions and the relative risk varied depending on the brand used ([Grady et al., 1990](#); [Greene et al., 1992](#); [Martin et al., 1999](#)). In Yemen ([Scheifele et al., 2007](#)) the prevalence odds ratio was higher for using black *shammah* compared to white *shammah*. Greater frequency of more severe lesions has been found in users of loose snus compared to men using portion-bag snus ([Andersson & Axéll, 1989](#); [Andersson et al., 1994](#); [Rolandsson et al., 2005](#)).

(e) Reversal or progression of lesions

Table 2.6 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.6.pdf>) provides information from studies that examined reversal or progression of lesions. In men with leukoplakia that were re-examined 1–21 days after the first examination, 15% of the lesions resolved and 18% improved by one degree ([Grady et al., 1991](#)). Smaller lesions were most likely to have resolved in men who decreased or stopped smokeless tobacco use, among users of chewing tobacco compared with those of snuff, among light users, and among seasonal users only. Disappearance or regression of lesions was not associated with duration of smokeless tobacco use or the number of days between the initial examination and follow-up. In a study of military recruits, 97% of the oral lesions observed at the initial examination had completely resolved six weeks after they ceased using tobacco ([Martin et al., 1999](#)). In a study in Denmark, there was a lower percentage of snuff users whose lesions transformed to dysplasia or malignancy compared to patients with leukoplakia who did not use snuff ([Roed-Petersen & Pindborg, 1973](#)).

Men in Sweden with snus-induced lesions followed over 27–29 years did not have a higher risk of oral cancer (not smoking adjusted) compared to the entire Swedish population ([Roosaar et al., 2006](#)). A subset of men had a repeat oral examination 19–22 years after the baseline. Among those who stopped snus entirely or used it less than once per day, 6.1% had a lesion at the follow-up exam. Lesions were still present with the same or lesser severity in 91% of the men who continued use of loose snuff or changed to portion-bag snuff and 8.7% had a worse lesion. Of those who used snus for more hours per day at the follow-up than at baseline, 12.1% had a worse lesion. In an earlier study, after 3–6 months, snus users with oral lesions who used portion-bag snus were more likely to have less severe lesions and users who stopped using snus or who changed to portion bags and changed the placement of the snus in the mouth had no lesions at the original site ([Larsson et al., 1991](#)). Snus users who changed to snus with a lower pH and lower nicotine concentrations had less severe lesions after 24 weeks ([Andersson & Warfvinge, 2003](#)).

In a 10 year follow up study in India, [Gupta et al. \(1980\)](#) reported significantly higher malignant transformation in a group of smokeless tobacco users with precancer.

*2.1.3 Cancer of the oesophagus**(a) Overview of studies*

Studies of smokeless tobacco and oesophageal cancer have been conducted in North America, Europe and Asia. All of the studies reported here examined oesophageal cancer risks associated with use of unsmoked tobacco that was not part of a betel quid. Evidence regarding betel quid is presented in the *Monograph on Betel Quid* in this volume. These studies generally focused on the predominant smokeless tobacco products and behaviours in the countries in which the studies were conducted.

Two studies ([Zendehdel et al., 2008](#); [Nasrollahzadeh et al., 2008](#)) have been published since the previous *Monograph* ([IARC, 2007a](#)).

Major risk factors for oesophageal cancers are tobacco smoking, betel quid chewing, heavy alcohol consumption (only for squamous cell carcinomas of the oesophagus) ([IARC, 2004](#), [IARC, 2010](#)) and BMI (for adenocarcinoma of the oesophagus) ([Kubo & Corley, 2006](#)), making these factors potential confounders in studies of smokeless tobacco. [The Working Group notes that betel quid chewing and smokeless tobacco use are nearly always mutually exclusive in certain geographic regions.]

In two cohort studies ([Boffetta et al., 2005](#); [Zendehdel et al., 2008](#)) smokeless tobacco use and oesophageal cancer has been examined (Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.7.pdf>); both addressed potential confounding by smoking and included incident cases occurring in the first few years of follow-up.

One of the cohort studies was conducted in Norway and study participants were followed for 35 years for cancer incidence ([Boffetta et al., 2005](#)). The relative risk for oesophageal cancer was 1.4 (95%CI: 0.6–3.2) for ever use of snuff compared to never use, adjusted for age and smoking. In a Swedish cohort study ([Zendehdel et al., 2008](#)) the relative risk for squamous cell carcinoma of the oesophagus among non-smoking men who used only snuff compared to never users of tobacco was 3.5 (95%CI: 1.6–7.6) adjusting for age and BMI.

Several case-control studies in the USA have been conducted that did not include odds ratio among non-smokers or did not adjust statistically for smoking behaviours ([Wynder et al., 1957](#); [Wynder & Bross, 1961](#); [Wynder & Stellman, 1977](#); [Pottern et al., 1981](#)). Of the seven case-control studies of smokeless tobacco and oesophageal cancer that did so (Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.8.pdf>),

two were conducted in Sweden ([Lewin et al., 1998](#); [Lagergren et al., 2000](#)), three in the USA ([Martinez, 1969](#); [Williams & Horm, 1977](#); [Williams et al., 1977](#); [Brown et al., 1988](#)), one in India ([Phukan et al., 2001](#)) and one in the Islamic Republic of Iran ([Nasrollahzadeh et al., 2008](#)). Because the survival rate for oesophageal cancer is poor ([Crew & Neugut, 2004](#)), case-control studies may be susceptible to selection bias from not interviewing study cases who died before the time of interview or measurement error due to obtaining information from proxy interviews ([Winn, 1986](#)).

Three case-control studies from the USA (one from Puerto Rico) showed no association between use of smokeless tobacco and oesophageal cancer ([Martinez, 1969](#); [Williams & Horm, 1977](#); [Williams et al., 1977](#); [Brown et al., 1988](#)) after adjusting for smoking or restricting the analysis to non-smokers. The proportion of proxy interviews needed to ascertain smokeless tobacco use in these studies was 45% ([Williams & Horm, 1977](#); [Williams et al., 1977](#)), at least 69% ([Brown et al., 1988](#)), and 12% ([Martinez, 1969](#)).

Both of the Swedish case-control studies were population-based and adjusted the analyses for smoking and alcohol intake ([Lewin et al., 1998](#); [Lagergren et al., 2000](#)). In one of them that involved both squamous cell and adenocarcinoma, no proxy interviews were permitted ([Lagergren et al., 2000](#)). The odds ratio for users of smokeless tobacco only compared to non-users of tobacco was 1.4 (95%CI: 0.9–2.3) for squamous cell carcinoma of the oesophagus and 1.2 (95%CI: 0.7–2.0) for adenocarcinoma of the oesophagus adjusting for age, tobacco smoking, alcohol drinking and other factors. In the other Swedish study ([Lewin et al., 1998](#)) on squamous cell carcinoma, most were interviewed about a month after the case's diagnosis date. The odds ratio for ever use of snuff was 1.2 (95%CI: 0.7–2.2), adjusting for age, region, tobacco smoking and alcoholic beverages.

In a hospital-based case-control study from India an association between smokeless tobacco and oesophageal cancer was found ([Phukan et al., 2001](#)). Relative to persons who neither used smokeless tobacco nor smoked, the odds ratio for persons who used only *chadha* (a type of smokeless tobacco) but did not chew betel quid nor smoke was 3.2 (95%CI: 1.6–9.5) for men and 6.2 (95%CI: 2.4–12.1) for women, adjusting for alcohol. In a study in the Islamic Republic of Iran cases were interviewed at the time of diagnosis (there were no proxy interviews), and only histologically confirmed squamous cell carcinoma were included ([Nasrollahzadeh et al., 2008](#)); when use of different tobacco products was examined in a multivariate model, there was a significant positive association with *nass* use only compared to never users of any tobacco product, after adjustment for education, ethnicity, and total intake of fruit and vegetables.

In a meta-analysis of studies published through 2007 ([Boffetta et al., 2008](#); Table 2.9, available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.9.pdf>), only studies from Europe and the USA that provided information about non-smokers and studies that included smokers but adjusted for tobacco smoking were included. The overall estimate of effect for the five studies of oesophageal cancer was 1.6 (95%CI: 1.1–2.3). In a second meta-analysis [Lee & Hamling \(2009\)](#) included studies from Europe and the USA of smokeless tobacco and oesophageal cancer through May 2008, including and two studies that did not adjust for smoking ([Wynder & Bross, 1961](#); [Wynder & Stellman, 1977](#); Table 2.10, available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.10.pdf>). The overall relative risk among never-smokers was 1.91 (95%CI: 1.15–3.17) and the smoking-adjusted relative risk 1.13 (95%CI: 0.95–1.36). For Scandinavian studies, the summary relative risk in never-smokers was 1.92 (95%CI: 1.00–3.68; one study) and 1.10 (95%CI: 0.92–1.33) when smoking

adjusted. For studies from the USA, the relative risks restricted to never-smokers or adjusted for smoking were identical, 1.89 (95%CI: 0.84–4.25).

(b) Dose-response evidence

(i) Duration and intensity

In one case-control study ([Lagergren et al., 2000](#)), there were no significant increases in risk for years of use up to 25 years, adjusted for smoking, alcohol, and other factors. For more than 25 years of use, the odds ratio for snuff use controlling for smoking, alcohol intake and other factors was 2.0 (95%CI: 0.9–4.1) for squamous cell carcinoma of the oesophagus and 1.9 (95%CI: 0.9–4.0) for adenocarcinoma of the oesophagus. The odds ratio for use of 15–35 quids per week for squamous cell carcinoma was 2.1 (95%CI: 1.0–4.4) and for adenocarcinoma, 2.0 (95%CI: 1.0–4.3). Corresponding estimates for using more than 35 quids per week were 1.0 (95%CI: 0.4–2.4) and 0.8 (95%CI: 0.3–2.0), respectively. In another case-control study ([Lewin et al., 1998](#)), the odds ratio for smokeless tobacco users of more than 50 g per week was 1.9 (95%CI: 0.8–3.9) adjusting for smoking and alcohol intake among other factors. In the Islamic Republic of Iran study ([Nasrollahzadeh et al., 2008](#)), there were significant positive exposure-response relationships for frequency of use per day of *nass*, cumulative use (frequency times duration), and duration of *nass* use. However, these findings were not controlled for tobacco smoking.

(ii) Cessation

In one case-control study of oesophageal cancer ([Lewin et al., 1998](#)), there was no association with snuff use for former or current smokeless tobacco users compared to never smokeless tobacco users.

(c) Types

In northern Europe, the predominant form of smokeless tobacco is snus. Of the four studies from that geographic region – two cohort

([Boffetta et al., 2005](#); [Zendehdel et al., 2008](#)) and two case-control ([Lewin et al., 1998](#); [Lagergren et al., 2000](#)) – all of the odds ratios were greater than 1.0, but statistically significantly elevated only in one study ([Zendehdel et al., 2008](#)). The odds ratios in the three studies from the USA where snuff and chewing tobacco are used, were not statistically significantly elevated ([Martinez, 1969](#); [Williams & Horm, 1977](#); [Brown et al., 1988](#)).

In India, among non-smokers, statistically significantly elevated odds ratios associated with chewing *chadha* were reported for both men and women adjusting for alcohol consumption ([Phukan et al., 2001](#)). In a study in the Islamic Republic of Iran, *nass* users had a significantly increased risk of oesophageal cancer ([Nasrollahzadeh et al., 2008](#)).

It was noted in a report on a case series in Sudan that use of tobacco in the form of *toombak* under the tongue or in the labiodental groove was common in an area where oesophageal cancer incidence rates were high ([Babekir et al., 1989](#)).

(d) Histology

Two studies analysed squamous cell cancer and adenocarcinoma separately ([Lagergren et al., 2000](#); [Zendehdel et al., 2008](#)); in the other studies ([Brown et al., 1988](#); [Phukan et al., 2001](#); [Nasrollahzadeh et al., 2008](#)), most (if not all) of the cases had squamous cell carcinomas. Statistically significantly elevated odds ratios were found for ever use of smokeless tobacco and squamous cell carcinomas in one study ([Zendehdel et al., 2008](#)), in another study ([Lagergren et al., 2000](#)) for users of 15–35 quids per week, and in a third study of predominantly squamous cell carcinomas ([Phukan et al., 2001](#)). In a fourth study from the Islamic Republic of Iran that assessed squamous cell carcinomas, *nass* use was found to have a significant positive association with oesophageal cancer ([Nasrollahzadeh et al., 2008](#)).

Two studies provided odds ratios for use of smokeless tobacco and adenocarcinoma of the oesophagus; in one the odds ratio was

statistically significantly elevated for ever users ([Zendehdel et al., 2008](#)) and in the other ([Lagergren et al., 2000](#)) users of 15–35 quids per week had an increased risk for adenocarcinoma of the oesophagus.

(e) Population characteristics

In the study in India ([Phukan et al., 2001](#)), significantly elevated odds ratios were observed in both men and women.

(f) Subsites of cancers of the upper aerodigestive tract

In some studies smokeless tobacco-associated risks were examined only for oral cancer or provided oral cavity cancer-specific findings. Of these studies, statistically significantly elevated odds ratios for ever use of smokeless tobacco were noted in seven ([Chandra, 1962](#); [Williams & Horm, 1977](#); [Blot et al., 1988](#); [Idris et al., 1995a](#); [Merchant et al., 2000](#)) but no association in two ([Schildt et al., 1998](#); [Accortt et al., 2002](#), 2005; [Luo et al., 2007](#)). Some other studies provided estimates for the oral cavity plus one or more of the pharynx, lip, salivary gland, oesophagus, and larynx. Of these four had positive findings ([Kabat et al., 1994](#); [Lewin et al., 1998](#); [Wasnik et al., 1998](#); [Roosaar et al., 2008](#)) and four had relative risks below one or close to approximately equal to one ([Mashberg et al., 1993](#); [Boffetta et al., 2005](#); [Henley et al., 2005](#); [Rosenquist, 2005](#)). In studies providing information separately for the pharynx, estimates were positive for women with 20 or more years of snuff use in the USA ([Winn et al., 1981a](#)); for hypopharyngeal cancer, estimates were positive in one study in India ([Sapkota et al., 2007](#)) and below one in two other studies ([Williams & Horm, 1977](#); [Lewin et al., 1998](#)).

2.1.4 Cancer of the pancreas

Three cohort studies ([Zheng *et al.*, 1993](#); [Boffetta *et al.*, 2005](#); [Luo *et al.*, 2007](#)), three population-based case-control studies ([Williams & Horm 1977](#); [Farrow & Davis, 1990](#); [Alguacil & Silverman, 2004](#)) and two hospital based case-control studies ([Muscat *et al.*, 1997](#); [Hassan *et al.*, 2007](#)) in North America and in Europe investigated the association between the use of smokeless tobacco and pancreatic cancer.

(a) North America

(i) Cohort study

In the Lutheran Brotherhood Insurance Society cohort with 20 years follow-up, a relative risk of 1.7 (95%CI: 0.9–3.1, based on 16 deaths) adjusted for age, alcoholic beverages and smoking was found for male ever users of smokeless tobacco ([Zheng *et al.*, 1993](#)).

(ii) Case-control studies

No association was found with smokeless tobacco in two population-based case-control studies ([Williams & Horm 1977](#); [Farrow & Davis, 1990](#)). In a population-based case-control study that restricted analyses to lifelong non-smokers of cigarettes, a non-significantly 40% increase in risk for pancreatic cancer (95%CI: 0.5–3.6) was found in those who used smokeless tobacco regularly compared to non-users of tobacco ([Alguacil & Silverman, 2004](#)). Among tobacco chewers who were not current cigarette smokers, an elevated risk of 3.6 (CI: 1.0–12.8) was seen when compared to never-smokers and long-term quitters (≥ 20 years) in one hospital-based case-control study ([Muscat *et al.*, 1997](#)) and no association with chewing tobacco or using snuff was noted in an another hospital-based case-control study ([Hassan *et al.*, 2007](#)). None of the studies adjusted for BMI or alcohol, which are potentially important risk factors for pancreatic cancer (Table 2.11, available at

<http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.11.pdf>).

In a meta-analysis of four studies from the USA, the summary relative risk for pancreatic cancer among users of smokeless tobacco was 1.4 (95%CI: 0.7–2.7) ([Boffetta *et al.*, 2008](#)).

(iii) Duration and intensity

Only a few studies assessed risk in relation to duration and intensity of use, assessing oz per week or grams per day and duration of use. In one study ([Alguacil & Silverman, 2004](#)), the odds ratio for those who used > 2.5 oz of smokeless tobacco a week compared to non-users of tobacco was 3.5 (95%CI: 1.1–10.6) and for those who used smokeless tobacco for more than 20 years was 1.5 (95%CI: 0.6–4.0), adjusted for age, sex, race, cigar smoking and study area.

(b) Europe

In the Norwegian Cohort Study followed up for 35 years the relative risk for pancreatic cancer for ever use of snuff (snus) was 1.67 (95%CI: 1.12–2.50; 45 cases), adjusted for smoking and age ([Boffetta *et al.*, 2005](#)). Among ever users of snuff, the relative risk was 0.85 (95%CI: 0.24–3.07, based on three cases) in never-smokers. In the Swedish construction worker cohort study, analyses were restricted to never smoking men at the time of entry into the study ([Luo *et al.*, 2007](#)). Average follow-up was 20 years and 83 pancreatic cancers were recorded. Compared to never users of any tobacco product, and after adjustment for age and BMI, the relative risk for never smoking current users of snus was 2.1 (95%CI: 1.2–3.6; 18 cases) and in never-smokers who used ≥ 10 g/day snus was 2.1 (95%CI: 1.1–3.8) (Table 2.12, available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.12.pdf>).

A meta-analysis showed a summary relative risk for pancreatic cancer among users of smokeless tobacco based on the two above cohort studies of 1.8 (95%CI: 1.3–2.5) ([Boffetta *et al.*, 2008](#)).

2.1.5 Other cancers

(a) Cancer of the stomach

Four cohort studies ([Kneller et al., 1991](#); [Chao et al., 2002](#); [Boffetta et al., 2005](#); [Zendehdel et al., 2008](#)) and 4 case-control studies ([Williams & Horm, 1977](#); [Hansson et al., 1994](#); [Ye et al., 1999](#); [Phukan et al., 2005](#)) investigated the association between stomach cancer and use of smokeless tobacco. [Phukan et al. \(2005\)](#) also reported exposure to *tuibur* ([Table 1.1](#)).

(i) Cohort studies

In the USA, non-significantly elevated risks associated with smokeless tobacco use were observed among never-smokers compared to men who never used tobacco in the Lutheran Brotherhood cohort study with 20 years follow-up ([Kneller et al., 1991](#)) and in the CPS-II cohort study with 18 years follow-up ([Chao et al., 2002](#)). In the cohort study from Norway (35 years follow-up), a non-significantly elevated risk for snuff use was found ([Boffetta et al., 2005](#)). A total of 343 822 men were analysed in the construction worker cohort study from Sweden (33 years follow-up) and a significant positive relative risk was seen among non-smoking snus users aged 70 and over for cancer in the non-cardia region of the stomach when compared to never users of any tobacco product ([Zendehdel et al., 2008](#); [Table 2.13](#), available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.13.pdf>).

(ii) Case-control studies

[Williams & Horm \(1977\)](#), [Hansson et al. \(1994\)](#) and [Ye et al. \(1999\)](#) found no significant associations with the use of smokeless tobacco products or snuff. The study by [Phukan et al. \(2005\)](#) showed a significantly elevated risk for chewing tobacco alone among non-betel quid users (adjusted for tobacco smoking, alcohol drinking, *tuibur*, education, occupation, income) and for *tuibur* use (adjusted for tobacco smoking,

alcohol drinking, education, occupation, income) ([Table 2.14](#), available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.14.pdf>).

(iii) Dose-response evidence

In one study, risk increased with cumulative dose of tobacco chewing and for *tuibur* use (p for trend < 0.001), each adjusted for other confounding factors ([Phukan et al., 2005](#)).

(iv) Cessation

[Phukan et al. \(2005\)](#) found that risk decreased with years of cessation of *tuibur* use, although the test for trend was not significant.

(b) Cancer of the colon and rectum

In the US Veterans' cohort study with 26 years follow-up ([Heineman et al., 1995](#)), smokeless tobacco users had a relative risk of 1.2 (95%CI: 0.9–1.7; based on 39 deaths) for cancer of the colon and 1.9 (95%CI: 1.2–3.1; based on 17 deaths) for cancer of the rectum compared to those who had never used tobacco. No new data have been published since the previous IARC Monograph ([IARC, 2007a](#)).

(c) Cancer of the extra-hepatic bile duct

In a population-based case-control study in Los Angeles County, USA ([Chow et al., 1994](#)) an odds ratio of 18 (95%CI: 1.4–227.7; based on 3 cases) was found for chewing tobacco and cancer of the ampulla of Vater. [All cases of cancer of the ampulla of Vater who chewed tobacco also smoked.] There have been no new studies published since the previous IARC Monograph ([IARC, 2007a](#)).

(d) Cancers of the digestive system combined

A reduced risk with use of smokeless tobacco was seen in the case-control study by [Sterling et al. \(1992\)](#) and in the National Health and Nutrition Examination Survey (NHANES I) follow-up study that analysed 6805 men and women aged

45–75 years at baseline (1971–75) ([Accortt et al., 2002](#)). The entire NHANES I cohort was reassessed between 1982 and 1984 and analysed 7787 subjects aged 45 and over at baseline. The results showed non-significantly elevated risks for those aged 65 years and over in men and aged 45–64 years in women ([Accortt et al., 2005](#)). [The analysis was limited to incident diseases that required an overnight stay in health care facility. Hence, there is a possibility of underrepresentation of the actual number of cancer cases that occurred in the cohort. Analysis was based on a small sample size, 414 exclusive smokeless tobacco users, and chewing tobacco and snuff use were not analysed separately. Pipe and cigar use was not controlled for in the analysis.]

The hazard ratio for men who reported current use of smokeless tobacco and never used other tobacco products was significantly elevated after adjustment for age, race, educational level, BMI, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake and aspirin use in the CPS I cohort but not in the CPS II cohort (additionally adjusted for status and type of employment) ([Henley et al., 2005](#)).

(e) *Cancer of the gall bladder*

One case–control study in India found positive associations with chewing *khaini* [raw tobacco with lime] and cancer of the gall bladder (OR, 1.65; 95%CI: 0.78–3.49) or chewing tobacco alone (OR, 2.71, 95%CI: 1.22–6.02), unadjusted for other potential confounding factors ([Shukla et al., 2008](#)).

(f) *Cancers of the respiratory tract*

(i) *Nasal cavities*

[Brinton et al. \(1984\)](#) in a case–control study found non-significant sex-adjusted odds ratios for tobacco chewers or snuff users while [Stockwell & Lyman \(1986\)](#) found an odds ratio for smokeless tobacco of 3.3 (95%CI, 0.4–25.9), adjusted for age, race, sex and tobacco use. [The

Working Group noted that information about tobacco use was obtained from medical records and ascertainment bias cannot be ruled out.] No new studies were identified since the previous *IARC Monograph* ([IARC, 2007a](#)).

(ii) *Larynx*

In a case–control study in Florida, USA, a significantly elevated odds ratio for smokeless tobacco use, adjusted for age, race, sex and tobacco smoking was found ([Stockwell & Lyman, 1986](#)). [The Working Group noted that information about tobacco use was obtained from medical records and ascertainment bias cannot be ruled out.] From a case–control study in Sweden [Lewin et al. \(1998\)](#) reported no significant association for current and former use of snuff, adjusted for age, smoking and alcoholic beverages. No new studies were identified since the previous *IARC Monograph* ([IARC, 2007a](#)).

(iii) *Lung*

The NHANES follow-up study ascertained incident cases ([Accortt et al., 2005](#)) and deaths from lung cancer ([Accortt et al., 2002](#)). Never-smoking women who ever used smokeless tobacco had significantly higher mortality compared to never tobacco users. In men, no deaths from lung cancer occurred among those who were never-smokers and used smokeless tobacco. Estimates of the relative risk were adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, recreational physical exercise and fruit/vegetable intake. The results for cancer incidence ([Accortt et al., 2005](#)) showed significantly elevated risks in women aged 65 years and over, based on small numbers of cases among exclusive smokeless tobacco users ($n < 4$ cases). No incident cases of lung cancer occurred in men who used smokeless tobacco. Risk was adjusted for age, race and poverty index ratio. [The Working Group noted limitations to this study. See section on cancers of the digestive system (d).]

In the Cancer Prevention Study I (CPS-I) in the USA, the hazard ratio for lung cancer for current smokeless tobacco users who never used other tobacco products was non-significantly elevated and the corresponding hazard ratio in the CPS-II cohort was significantly elevated, after adjusting for age, race, level of education, BMI, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake, aspirin use and status and type of employment (for CPS-II only) ([Henley et al., 2005](#)). The magnitude of effect was similar for those who chewed tobacco but never used snuff and for those who used snuff but never chewed tobacco. In the Norwegian cohort study the relative risk adjusted for age and smoking was non-significantly reduced for ever users of snus compared to never users ([Boffetta et al., 2005](#)). In the Swedish construction worker cohort study with 279 897 men followed for an average of 20 years there was no significant association for snus use among never-smokers ([Luo et al., 2007](#)).

[Henley et al. \(2007\)](#) used CPS II data to compare mortality among former cigarette smokers who switched to smokeless tobacco (switchers) with those who quit using tobacco entirely (quitters), based on tobacco use ascertained at baseline and followed-up for 20 years. In a subset of the cohort that examined uptake of tobacco after baseline, the proportions of persons taking up cigarette smoking was very low. Compared with quitters, the relative risk of lung cancer was 1.5 (95%CI: 1.2–1.7) for all switchers, 1.3 (95%CI: 1.1–1.6) for switchers to tobacco chewing only, 1.8 (95%CI: 1.2–2.5) for snuff only, and 1.9 (95%CI: 1.2–2.9) for tobacco chewing and snuff combined. Compared with men who never used any tobacco product, the relative risk of lung cancer was 3.9 for quitters and 5.6 for switchers (statistically significant but 95% confidence intervals were not provided). Risk estimates were adjusted for age, number of cigarettes formerly smoked per day, number of years smoking cigarettes, age at which they quit smoking cigarettes, race, educational level, BMI,

exercise level, alcohol consumption, employment type, employment status, fat consumption, fruit and vegetable intake and aspirin use. The analysis was restricted to men because women were not asked whether or not they used smokeless tobacco.

The case-control study of lung cancer by [Williams & Horm \(1977\)](#) reported non-significant risk for smokeless tobacco use in men, adjusted for age, race, and smoking.

(g) *Sarcoma*

In the US Veterans' cohort, the relative risk for soft-tissue sarcomas associated with smokeless tobacco use compared to persons who never used tobacco products was 1.5 (95%CI: 0.8–2.7) ([Zahm et al., 1992](#)). In a population-based case-control study conducted in the USA, the unadjusted odds ratio for ever use of smokeless tobacco was 1.8 (95%CI: 1.1–2.9); the risk was highest for those diagnosed at age 80 years or above (3.2; 95%CI: 1.0–10.1). Risks were elevated but not significantly so when analysed by anatomical site of the soft-tissue sarcoma (upper gastrointestinal; lung, pleura and thorax; head, neck and face) or by cell type (fibromatous; adipose, myomatous) ([Zahm et al., 1989](#)). No new studies were identified since the previous *IARC Monograph* ([IARC, 2007a](#)).

(h) *Cancer of the breast*

[Spangler et al. \(2001, 2002\)](#) conducted a case-control study in Cherokee Native American women and reported a non-significant elevated risk of breast cancer for use of smokeless tobacco. [There was no medical verification of breast cancer and the time relationship between use of smokeless tobacco and breast cancer diagnosis was not reported.] A prospective cohort study of the US population (NHANES I) showed a positive but non-significant association with smokeless tobacco (snuff or chewing tobacco) in women aged 45 years and over based on five breast cancer cases, however the hazard ratios

were below one when stratified by age ([Accortt et al., 2005](#)). [The Working Group noted limitations to this study. See Section on cancer of the digestive system, 2.1.5 (d).]

(i) *Cancer of the uterine cervix*

In a population-based case-control study elevated risks for cervical cancer, adjusted for smoking, age and race, for use of chewing tobacco or snuff were reported ([Williams & Horm, 1977](#)). No new studies were identified since the previous IARC Monograph ([IARC, 2007a](#)).

(j) *Cancer of the prostate*

In two cohort studies significantly elevated risks were found among users of smokeless tobacco compared to never users of tobacco ([Hsing et al., 1990, 1991](#)). [Putnam et al. \(2000\)](#) reported no association with use of snuff and chewing tobacco. [The Working Group noted that data were not presented to support this.] In one case-control study ([Hayes et al., 1994](#)) and one cohort study ([Accortt et al., 2005](#)) non-significantly elevated risks of prostate cancer associated with chewing tobacco were found.

(k) *Cancer of the penis*

In a case-control study of cancer and the penis in India, the relative risk for snuff users was 4.2 (95%CI: 1.6–11.3), adjusted for smoking, tobacco chewing and phimosis ([Harish & Ravi, 1995](#)). [It was not clear whether snuff was used orally or nasally.] No new studies were identified since the previous IARC Monograph ([IARC, 2007a](#)).

(l) *Cancer of the urinary bladder*

Population-based case-control studies conducted in three provinces of Canada ([Howe et al., 1980](#)), in the USA ([Hartge et al., 1985](#); [Slattery et al., 1988](#)) and in Alberta and Ontario provinces of Canada ([Burch et al., 1989](#)) did not show a significant association between chewing

tobacco and bladder cancer. No association with snuff use was seen in the Norwegian cohort ([Boffetta et al., 2005](#)).

(m) *Cancer of the kidney*

Four case-control studies ([Goodman et al., 1986](#); [McLaughlin et al., 1995](#); [Muscat et al., 1995](#); [Asal et al., 1988](#)) and one cohort study ([Boffetta et al., 2005](#)) evaluated the risk associated with smokeless tobacco use. The adjusted risk for chewing tobacco in non-smokers was not significantly elevated in two case-control studies ([Goodman et al., 1986](#); [McLaughlin et al., 1995](#)) and in one cohort study in Norway ([Boffetta et al., 2005](#)). In two studies, a significant association was reported for ever use of smokeless tobacco ([Asal et al., 1988](#); [Muscat et al., 1995](#)) but there was no adjustment for potential confounders in either study. A dose-response relationship was observed: odds ratio 2.5 (95%CI: 1.0–6.1) for chewing 10 times or fewer per week and 6.0 (95%CI: 1.9–18.7) for chewing 11 or more times per week ([Muscat et al., 1995](#)), although there was no adjustment for smoking and other potentially confounding factors.

(n) *Cancer of the brain*

From a population-based case-control study in the USA ([Zheng et al., 2001](#)), no significantly increased risk of brain cancer was reported for either men or women with the use of snuff or chewing tobacco. [Data to support this were not presented.] No new studies were identified since the previous IARC Monograph ([IARC, 2007a](#)).

(o) *Non-Hodgkin lymphoma*

Two population-based case-control studies of non-Hodgkin lymphoma in men were conducted in the USA ([Brown et al., 1992a](#); [Schroeder et al., 2002](#)). [Schroeder et al. \(2002\)](#) found an increased risk for t(14;18)-positive non-Hodgkin lymphoma cases who started chewing tobacco ≤ 18 years of age, after adjusting for age and state (OR, 2.5;

95%CI: 1.0–6.0). No significant associations were observed in the study by [Brown et al., \(1992a\)](#) for any non-Hodgkin lymphoma subtype or overall.

[Bracci & Holly \(2005\)](#) from a population-based case-control study of non-Hodgkin lymphoma conducted in the USA reported significantly elevated risks for non-Hodgkin lymphoma and for follicular and diffuse large cell types in those who used smokeless tobacco. Risk estimates were adjusted for age, level of education and level of average weekly alcohol consumption. [The results are based on only seven cases and six controls.]

(p) *Leukaemia*

[Brown et al. \(1992b\)](#) conducted a population-based case-control study in the USA of chewing tobacco/snuff only and risk for leukaemia. Non-significant elevated risks were seen for all leukaemias, chronic myelogenous leukaemia, chronic lymphocytic leukaemia and myelodysplasia. In the Swedish construction worker cohort study (average follow-up 22.2 years), non-significantly elevated risks for acute lymphocytic and chronic myelogenous leukaemias and no association in men for snuff dipping and acute myelogenous leukaemia and multiple myeloma were found ([Fernberg et al., 2007](#)).

(q) *Myeloma*

In a population-based case-control study in the USA, [Brown et al. \(1992a\)](#) compared users of smokeless tobacco only with never users of tobacco and found an odds ratio of 1.9 (95%CI: 0.5–6.6; based on 5 cases). A Swedish construction worker cohort study showed no association for myeloma in men with snuff dipping ([Fernberg et al., 2007](#)).

(r) *Cutaneous squamous cell carcinoma*

[Odenbro et al. \(2005\)](#) analysed the Swedish cohort study and found a relative risk of 0.64 (95%CI: 0.44–0.95) for the association between

snuff dipping and the incidence of cutaneous squamous cell carcinoma.

2.2 Nasal use

There are no cohort or case-control studies that examined the association between nasal snuff use and nasal cancer.

2.2.1 *Cancers of the oral cavity and pharynx*

(a) *Overview of studies*

Three case-control studies from India investigated the association between nasal snuff use and cancer of oral and pharyngeal subsites (Table 2.15, available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.15.pdf>).

[Sankaranarayanan et al. \(1989a\)](#) focused on cancer of the anterior two-thirds of tongue and floor of the mouth; the age-adjusted odds ratio was 4.27 (95%CI: 1.24–14.67; men only) for occasional nasal snuff users and 3.02 (95%CI: 0.94–9.60) for daily snuff users. For cancer of the gingiva the odds ratio for regular snuff use was 3.04 (95%CI: 0.67–12.65) after adjustment for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use ([Sankaranarayanan et al., 1989b](#)). For cancer of the buccal and labial mucosa, the age-adjusted odds ratio was 3.98 (95%CI: 1.53–10.34) for regular nasal snuff users and 2.28 (95%CI: 0.74–7.03) for occasional nasal snuff users ([Sankaranarayanan et al., 1990a](#)). After adjusting for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use, the odds ratio associated with ever snuff use was 2.93 (95%CI: 0.98–8.77).

In a multicentre case-control study of cancer of the hypopharynx in India, [Sapkota et al. \(2007\)](#) found an odds ratio of 2.85 (95%CI: 1.15–7.08) for tobacco snuffing among never-smokers who did not chew tobacco or a non-tobacco product, adjusting for alcohol use, and other factors [The Working Group noted that snuff use was oral as

well as nasal so the role of nasal use could not be determined separately.]

(b) *Dose–response evidence*

In the study of cancer of the gingiva ([Sankaranarayanan et al., 1989b](#)), the age-adjusted odds ratio for daily nasal snuff use was 3.90 (95%CI: 1.19–12.70) and that for occasional use was 3.78 (95%CI: 1.05–13.54). When categories of high versus low defective nasal snuff use were compared, the odds ratios were significantly elevated for the category of lower intensity for cancers of the tongue ([Sankaranarayanan et al., 1989a](#)) and of the buccal and labial mucosa ([Sankaranarayanan et al., 1990a](#)).

2.2.2 Other cancers

No new studies were identified since the previous *IARC Monograph* ([IARC, 2007a](#)) for the sites listed except for cancer of the nostril.

(a) *Cancer of the oesophagus*

A case–control study of oesophageal cancer from India showed an age-adjusted odds ratio for daily snuff use of 2.39 (95%CI: 0.81–7.04) and that for occasional use of 3.59 (95%CI: 1.20–10.67) ([Sankaranarayanan et al., 1991](#)). [Estimates were not adjusted for smoking or betel quid chewing.]

(b) *Cancer of the paranasal sinuses*

[Shapiro et al. \(1955\)](#) studied Bantu cases of paranasal sinus cancer from radiation therapy department records from 1949–51 of a group of hospitals in South Africa. The authors noted that a high proportion (80%) of the antral cancer cases reported ‘prolonged and heavy’ use of snuff in contrast to 34% of Bantu men with cancer at other sites. The product snuffed by Bantus typically contained powdered tobacco leaves and an ash from aloe plants or other species, with the occasional addition of oil, lemon juice and herbs; typical use was ‘one teaspoonful’ per day ([Keen et al., 1955](#)). [The Working Group noted that the

source and nature of the control group was not described.]

(c) *Cancer of the larynx*

A case–control study from India ([Sankaranarayanan et al., 1990b](#)) of laryngeal cancer showed a non-significant risk for snuff use.

(d) *Cancer of the lung*

[Hsairi et al. \(1993\)](#) conducted a case–control study of bronchial cancer in Tunisia. The odds ratio for ever use of inhaled snuff (‘tabac à priser’), adjusted for age, sex, cigarette use, water pipe and cannabis use was 2.2 (95%CI: 0.9–5.6).

(e) *Carcinoma of the nostril*

[Sreedharan et al. \(2007\)](#) reported a case of squamous cell carcinoma in the right nostril in a 69-year-old woman in Karnataka, south India, with a history of daily snuff usage of more than 2 g for a duration of 30 years.

2.3 Synthesis

2.3.1 Oral use

(a) *Oral cavity and pharynx*

Smokeless tobacco was positively associated with cancers of the oral cavity in a cohort study in northern Europe and several case–control studies, some of which that adjusted for smoking and others that adjusted both for smoking and alcohol. There were elevated risks for every type of smokeless tobacco studied: snuff and chewing tobacco in the USA, snus in northern Europe, *toombak* in Sudan, smokeless tobacco used as a dentifrice in India and *naswar* in Pakistan. Case series implicate *shammah* used in Saudi Arabia as a risk factor for oral cancer. Not all reports were positive, namely some studies in Scandinavia and the USA, including two cohorts with small sample sizes. The evidence is strongest for the

oral cavity, with some indication of increased risks for the hypopharynx, or oropharynx and hypopharynx combined. Dose-response relationships with intensity of use were noted in one study and with duration in another. It is unclear whether risks are elevated in former smokeless tobacco users. Three meta-analyses of studies from northern Europe and the USA were generally consistent. In one meta-analysis an overall relative risk of 1.8 (95%CI: 1.1–2.9) was computed for studies that adjusted for smoking or among non-smokers; in another the relative risk was 1.72 (95%CI: 1.01–2.94) among never-smokers and 1.87 (95%CI: 0.82–4.27) when further adjusted for alcohol among never-smokers. In conclusion, there is strong evidence in humans that smokeless tobacco causes cancer of the oral cavity.

(b) *Precancerous lesions*

Studies in many countries have observed that oral lesions are more common in smokeless tobacco users than non-users, regardless of the type of smokeless tobacco used. The types include snus, snuff, chewing tobacco, smokeless tobacco used as a dentifrice, *naswar*, *toombak*, and *shammah*. In many studies the oral lesions were observed to be in the place in the mouth where users in that geographic region typically place the smokeless tobacco. The prevalence of the lesions increased with various exposure metrics of increasing intensity and duration of use, such as amounts used per day, time kept in mouth, duration of use in months or years. Although some lesions in young persons resolve, the prevalence of lesions in older adult users of these products remains elevated even in former users. There is some evidence from three studies that a small proportion of the lesions among smokeless tobacco users can progress to oral cancer over a period of years, although the rates vary, are not adjusted for any medical intervention to remove the lesions, smoking has not been taken into account, and the follow-up periods are highly variable. Use of smokeless tobacco causes

leukoplakia and erythroplakia, both considered precancerous, with a much higher risk of progressing to cancer than normal mucosa.

(c) *Oesophagus*

Nine studies evaluated the association between smokeless tobacco use and oesophageal cancer. The risks for ever use of smokeless tobacco compared to never use were statistically significantly elevated in one cohort study from Sweden and case-control studies from the Islamic Republic of Iran and India. In a Swedish case-control study, increased risks were observed with 15–35 quids used per week. Smoking could be ruled out as a potential confounder in all of the studies, as well as alcohol intake in two. No increased risk was observed in the three studies from the USA, which included a significant proportion of proxy respondents. Two meta-analyses found that, overall and for the Nordic countries, the estimates of effect for smokeless tobacco use were significantly elevated. The two studies published since the previous *Monograph on Smokeless Tobacco* showed a positive significant association with oesophageal cancer and were adjusted for major confounders. Four of five studies of squamous cell carcinomas and both studies of adenocarcinoma showed significantly positive results.

(d) *Pancreas*

In North America, 3 case-control studies showed no association, one cohort study and two case-control studies showed a non-significant increased risk and one case-control study showed a borderline significant increase in risk. While these studies accounted for smoking, none adjusted for BMI or alcohol, potentially important risk factors for pancreatic cancer. In Europe, two cohort studies showed a significant increase in risk of pancreatic cancer associated with snuff use. Both studies controlled for smoking; one study adjusted for BMI and also showed that the highest risks were seen in the highest exposure

Table 3.1 Carcinogenicity studies of application of smokeless tobacco to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mouse, CAF1 and Swiss (sex NR) Wynder & Wright (1957)	40, 30 controls Skin application 3 × /wk of unburnt cigarette tobacco 50% methanol extract, (dose NR), controls received whole tar extract; 24 mo	Skin (papillomas): CAF1–11/40 (27%), 16/30 (53%) in controls (8 converted to carcinoma)	NR	No adequate control groups
		Swiss–3/40 (7%) (1 converted to carcinoma), 16/30 (53%) in controls (3 converted to carcinoma)	NR	

mo, month or months; NR, not reported

category. There is good evidence to support a causal association between smokeless tobacco use and pancreatic cancer.

(e) Stomach

One cohort study in Sweden showed a significantly higher risk among non-smoking snus users aged 70 years and over for cancer in the non-cardia region of the stomach, not adjusted for alcohol use. One case–control study in India showed significantly higher risks for chewing tobacco alone and for *tuibur* users, with dose-dependent increases in risk. Risk decreased with cessation of *tuibur* use. The risk was not statistically significant in the other studies. Despite some positive findings for chewing tobacco in two different countries and for tobacco smoke-infused water, it was not considered strong enough to conclude for a causal association.

(f) Lung

In summary, in two cohort studies significant positive associations between smokeless tobacco use and lung cancer were found while in three cohort studies and one case–control study there was no association. In one of the positive cohort studies switching from cigarette smoking to smokeless tobacco significantly increased the risk for lung cancer compared to never-tobacco

users, and the risk was of greater magnitude than for quitting all together (RR, 3.9 versus 5.6).

2.3.2 Nasal use

Strong positive associations for cancers of the tongue and floor of mouth, gingiva and buccal and labial mucosa were observed in one study in India. In one positive study snuff use was oral as well as nasal so the role of nasal use could not be determined separately.

3. Cancer in Experimental Animals

Since the previous *IARC Monograph* on Smokeless Tobacco ([IARC, 2007a](#)), only one new study has been published. The collective evidence for the carcinogenicity of smokeless tobacco in experimental animals is summarized below.

3.1 Chewing tobacco, unburned cigarette tobacco, *mishri* and *naswar*

3.1.1 Mouse

Topical application of unburned cigarette tobacco induced skin papillomas in mice ([Wynder & Wright, 1957](#); [Table 3.1](#)). Similar treatment with

Table 3.2 Carcinogenicity studies on administration of smokeless tobacco with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse, Paris albino XVII x 57 black (sex NR) Ranadive et al. (1963)	11–36 animals/ group Totally alkaloid free extract, twice/wk for 95 wk + croton oil/dose and duration not specified, controls received acetone	Papillomas: 22/35 (63%) Controls–3/19 (16%) Carcinomas: 10/35 (27%) Controls–0/19	$P > 0.001$ $P = 0.0097$
Mouse, ICR Swiss (F) Bock et al. (1964, 1965)	30 animals/group A single DMBA application of 125 µg DMBA in 0.25 mL acetone + 0.25 mL acetone extract of unburnt tobacco 2.5 from cigarettes/d, 5 × / wk; controls received a single application of DMBA 125 µg 36 wk	16 papillomas in 7/30 (23%) mice Controls–0/30	$P > 0.01$
Mouse, ICR Swiss (F) Van Duuren et al. (1966)	20 animals/group 150 µg DMBA in 0.1 ml acetone once + (after 2–3 wk) reconstituted extract of flue-cured cigarette tobacco leaf, 25 mg in 0.1 ml solvent, tobacco extract, 3 × /wk; 52 wk	Papillomas: 5/14 (36%) Controls–0/12	$P = 0.04$

d, day or days; F, female; NR, not reported; wk, week or weeks

chewing tobacco extract for 95 weeks followed by croton oil increased the incidence of skin papillomas and carcinomas in mice ([Ranadive et al., 1963](#); [Table 3.2](#)). Application of chewing tobacco extract to benzo[a]pyrene-initiated mouse skin promoted development of a few skin papillomas and carcinomas in mice ([Ranadive et al., 1963](#)). In mice initiated with 7,12-dimethylbenz[a]anthracene (DMBA) applied topically, application of a barium hydroxide extract of unburned tobacco promoted skin papilloma development ([Bock et al., 1964](#); [Table 3.2](#)). Skin-tumour-promoting activity of unburned tobacco was reported in some DMBA-initiated mice in two additional studies ([Bock et al., 1965](#); [Van Duuren et al., 1966](#); [Table 3.2](#)). Application of brown or black *mishri* extracts to DMBA-initiated skin increased significantly the total incidence of papilloma and carcinoma in Swiss mice ([Kulkarni et al., 1989](#); [Table 3.3](#)). Administration of chewing tobacco extracts to the oral mucosa ([Mody & Ranadive,](#)

[1959](#)), skin painting with chewing tobacco extracts ([Mody & Ranadive, 1959](#); [Ranadive et al., 1976](#)), or intravesicular or intravaginal application of *jarda* ([Randeria, 1972](#)) did not induce tumours in mice.

Inhalation of powdered tobacco leaves led to a significant increase in the incidence of tumours of the lung and liver in strain A mice ([Hamazaki & Murao, 1969](#); [Table 3.4](#)). Mice given chewing tobacco extract by oral intubation developed lung adenocarcinoma and hepatocellular carcinoma in one study [with incomplete reporting of the distribution of different neoplasms] ([Bhide et al., 1984](#)). Adding black or brown *mishri* in the diet increased significantly the incidence of forestomach papilloma in Swiss mice ([Kulkarni et al., 1988](#); [Table 3.5](#)).

Table 3.3 Carcinogenicity studies of *mishri* alone or with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse Swiss (M) Kulkarni et al., (1989)	30 animals Topical/a single application of 200 nmol DMBA; 24 mo	No tumours	
	29 animals 200 nmol DMBA + 2.5 mg per application of black <i>mishri</i> extract, 5 d/wk for 20 wk; 24 mo	Skin papillomas: 4/29 (14%)	$P < 0.05$
	30 animals Topical application of black <i>mishri</i> extract, 2.5 mg per application, 5 d/wk for 20 wk; 24 mo	No skin tumours	
	30 animals 200 nmol DMBA + 2.5 mg per application of brown <i>mishri</i> extract, 5 d/wk for 20 wk; 24 mo	Skin papillomas: 4/30 (13%)	$P < 0.05$

d, day or days; M, male; mo, month or months; wk, week or weeks

3.1.2 Rat

Administration of chewing tobacco extract by gavage to vitamin-A-sufficient rats induced benign tumours in the lung and forestomach while similarly treated vitamin-A-deficient rats developed benign tumours in the stomach and pituitary gland and “lymphoma” in the lung [extremely rare tumour in rats] ([Bhide et al., 1991](#); [Table 3.6](#)).

Administration of *mishri* by gavage to vitamin-A-sufficient or vitamin-A-deficient rats increased significantly the proportion of tumour-bearing rats in both groups. Lung adenomas and forestomach papillomas developed in vitamin-A-sufficient animals while multiple neoplasms including lung lymphoma [an extremely rare tumour in rats] pituitary adenoma and forestomach papilloma occurred in vitamin-A-deficient animals. Control animals did not develop tumours ([Ammigan et al., 1991](#); [Table 3.5](#)). No tumours appeared when chewing tobacco extract was applied to the oral mucosa ([Gothoskar et al.,](#)

[1975](#)). Adding black or brown *mishri* in the diet increased significantly the incidence of forestomach papillomas in male and female Sprague-Dawley rats ([Kulkarni et al., 1988](#); [Table 3.5](#)).

3.1.3 Hamster

Application of a chewing tobacco extract to the cheek pouch of Syrian golden hamsters produced squamous cell papillomas and/or carcinomas in a small number of animals ([Rao, 1984](#); [Table 3.7](#)). Adding black or brown *mishri* in the diet significantly increased the incidence of forestomach papillomas ([Kulkarni et al., 1988](#); [Table 3.5](#)). Implantation of chewing tobacco in the cheek pouch ([Peacock & Brawley, 1959](#); [Peacock et al., 1960](#); [Dunham & Herrold, 1962](#); [Summerlin et al., 1992](#)), or application of chewing tobacco extract ([Suri et al., 1971](#); [Ranadive et al., 1976](#)) or *jarda* ([Kandarkar et al., 1981](#)) to the cheek pouch did not induce tumours.

Application of *naswar* to the cheek pouch for life increased incidence of tumours in treated

Table 3.4 Carcinogenicity studies of inhalation of smokeless tobacco in experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mouse, Strain A (M) Hamazaki & Murao (1969)	80 animals/group Inhalation of powdered tobacco leaf, dose (NR), alternate days, controls were untreated; 30 mo	Treated– Lung tumours 12/75 (16%; alveogenic carcinomas 6, squamous cell carcinomas 3, malignant adenomas 3) Leukaemia 11/80 (15%) Hepatocellular carcinomas 3/75 (4%) Controls– Malignant lung adenomas 1/80 Leukaemia 2/80 Hepatocellular carcinomas 0/80 Controls– Malignant lung adenomas 1/80 Leukaemia 2/80 Hepatocellular carcinomas 0/80	Lung tumours: $P < 0.001$ Leukaemias: $P < 0.01$ $P < 0.01$	The incidence of lung tumours and leukaemia was significantly increased in treated animals, the incidence of lung and liver tumours in the untreated controls was unusually low

M, male; mo, month or months, NR, not reported

Table 3.5 Carcinogenicity studies of oral administration of *mishri* alone or with modifiers to experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse, Swiss (M, F) Kulkarni et al. (1988)	26 animals/sex/group Black <i>mishri</i> 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–11/24 (46%) F–11/26 (42%)	$P < 0.01$ vs controls
	26 animals/sex/group Brown <i>mishri</i> 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–14/26 (54%) F–11/26 (42%)	$P < 0.01$ vs controls
	27 M, 31 F (controls) No <i>mishri</i> tobacco, standard diet only; 25 mo	Forestomach (papillomas): M–3/27 (11%) F–1/31 (3%)	$P < 0.01$ vs controls
	27 M, 24 F Brown <i>mishri</i> 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–10/27 (37%) F–9/24 (37%)	$P < 0.01$ vs controls
Hamster Syrian Golden (M, F) Kulkarni et al. (1988)	25 M, 30 F No <i>mishri</i> tobacco, standard diet only; 25 mo	Forestomach (papillomas): M, F–0%	$P < 0.01$ vs controls
	23 M, 26 F Black <i>mishri</i> 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–10/23 (43%) F–7/26 (27%)	$P < 0.01$ vs controls $P < 0.02$ vs controls
	28M, 20F Brown <i>mishri</i> 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–12/28 (43%) F–5/20 (25%)	$P < 0.01$ vs controls $P < 0.01$ vs controls
	23 animals/sex No <i>mishri</i> tobacco, standard diet only; 25 mo	Forestomach (papillomas): M–2/23 (9%) F–1/23 (4%)	
	30 or 31 animals/group VitA sufficient diet + 3 mg <i>mishri</i> extract per application by gavage 5 × /wk; 21 mo	Lung (adenomas and stomach papillomas): 8/30 (27%) Controls–0/31	Total tumour incidence treated vs controls $P < 0.001$
	Controls received VitA sufficient diet + 0.05 ml per application DMSO by gavage 5 × /wk; 21 mo		
Rat Sprague Dawley (M) Ammigan et al. (1991)	30 animals/group Vit A deficient diet + 3 mg <i>mishri</i> extract per application by gavage 5 × /wk; 21 mo	28/30 (93%) Controls–0/30	Total tumour incidence Vit deficient vs controls $P < 0.001$
	Controls received Vit A deficient diet + 0.05 ml per application DMSO by gavage 5 × /wk; 21 mo		

F, female; M, male; mo, month or months; vs, versus; wk, week or weeks

Table 3.6 Carcinogenicity studies of oral administration of chewing tobacco in experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rat Sprague Dawley (M) Bhide et al. (1991)	29, 31 controls Diet containing shark liver oil + tobacco by gavage, 3mg tobacco extract (vacuum dried powder of 100 g tobacco extracted with 1L dichloromethane) in 0.05 ml DMSO, 5 × /wk; controls received diet containing shark liver oil + 0.05 ml DMSO 5 d/wk; 21 mo	Lung (adenomas):3/29 (10%) Forestomach (papillomas): 3/29 (10%) Controls–0/31	$P < 0.05 \chi^2$ test	
	31, 30 controls Diet containing shark liver oil + tobacco by gavage, diet without shark liver oil + tobacco by gavage; controls received diet without shark liver oil + 0.05 ml DMSO, 5 × /wk; 21 mo	Lung (lymphomas): 22/31 (71%) Pituitary (adenomas): 19/31 (61%) Stomach (papillomas): 24/31 (77%) Controls–0/30	$P < 0.001 \chi^2$ test	Primary lymphoma of the lung is extremely rare in rats

d, day or days; mo, month or months; wk, week or weeks

Table 3.7 Carcinogenicity studies of application of smokeless tobacco to the oral mucosa or cheek pouch of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Hamster Syrian golden (M) Suri et al. (1971)	11–12 animals/group Banarasi Tobacco-DMSO extract/not specified; application to the cheek pouch 3 × /wk for 21 wk; controls received DMSO; 21 wk	No tumours found in treated and control animals Leukoplakia: 8/12 (67%)		Short duration of exposure, tobacco/DMSO dose not specified
Hamster Syrian golden (F) Rao (1984)	20, 10 controls Topical application to the cheek pouch of lyophilised aqueous tobacco extract, 1 mg in 0.05 mL water twice/d for 6 mo; controls received topical application of 0.05 mL water; 12 mo	Squamous cell papillomas and carcinomas: 3/17 (18%) Controls–no tumours	NR	Statistics not provided

D, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.8 Carcinogenicity studies of administration of naswar with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	SSignificance	Comments
Hamster Syrian golden (M, F) Kiseleva et al. (1976)	33 M, 28 F <i>Naswar</i> introduced as dry powder in the left buccal pouch (mixture of tobacco 45%, lime 8%, ash 30%, plant oil 12% and water 5%, dose (NR); life time	13 animals with tumours: Liver-6 Mixed-1 Adrenal gland-3 Forestomach-1 Uterus/ovary-1 Skin (melanoma)-1 Large intestine-1	Tumour frequency higher than in controls $P < 0.05$	Dose of <i>naswar</i> not specified Tumour type not specified genderwise
	24 M, 13 F <i>Nas</i> introduced as sunflower oil suspension in the left buccal pouch	Liver: 1 Uterus/ovary: 2 Skin (Papilloma): 1	Tumour frequency higher than in controls, $P < 0.05$	
	46 M, 40 F <i>Nas</i> introduced as sunflower oil suspension in the left buccal pouch	13 animals with tumours: Liver-4 Mixed-1 Adrenal gland-3 Forestomach (papillomas)-4 Uterus/ovary-1 Skin (papilloma)-1 Pancreas-1 No tumours	Tumour frequency higher than in controls $P < 0.05$	
	41 M, 9 F <i>Nas</i> suspension in sunflower oil introduced in oesophagus	3 animals with tumours: Liver-1 Adrenal gland-1 Forestomach (papilloma)-1		
	31 M, 19 F <i>Nas</i> suspension in sunflower oil applied to dorsal skin	2 animals with tumours: Stomach-1 Adrenal gland-1		
	41 M, 69 F Untreated controls			

Table 3.8 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	SSignificance	Comments
Hamster Syrian golden (M, F) Milievskaja & Kiseleva (1976)	184 animals <i>Naswar</i> introduced in the buccal pouch as dry powder or 50% suspension in sunflower oil; life time	Buccal pouch: 0 Forestomach: 5 Liver: 13 Adrenal gland: 6 Others: 9	NR	The number of animals that survived at the time of first tumour appearance was small High mortality was seen even in control animals
	30 animals DMBA only introduced in the buccal pouch once	Buccal pouch: 1 Stomach: 2		
	30 animals 0.1 g DMBA only + <i>naswar</i> introduced in the buccal pouch as dry powder or 50% suspension in sunflower oil; life time	Buccal pouch: 0 Stomach: 5 Others: 1		
	110 untreated controls	Stomach: 1 Adrenal gland: 1		

F, female; M, male; NR, not reported

Table 3.9 Carcinogenicity studies of oral administration of snuff to experimental animals

Reference Species, strain (sex)	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Stenström et al. (2007)	5.9% snuff diet (snus mixed with powdered standard mouse show); 6 mo	Gastric carcinoma in situ		
Mouse, wild type, FVB (M)	8, 11 controls	0/8 Controls: 0/11	NR	
Wild type, FVB <i>Helicobacter pylori</i> infected (M)	20, 8 controls	9/17 Controls: 0/11	NR	Gastric carcinoma in situ invading the mucosa and submucosa
INS-GAS (M)	8 animals/group	4/8 Controls: 2/8	NR	
INS-GAS (M) <i>Helicobacter pylori</i> - infected (M)	22, 8 controls	12/12 Controls: 2/8	NR	Gastric carcinoma in situ invading the mucosa

M, male; mo, month or months; NR, not reported

Table 3.10 Carcinogenicity studies of snuff to the oral mucosa or cheek pouch of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rat, Sprague Dawley (M) Johansson et al., (1989)	30 animals/group Snuff insertion in lip canal, 100 mg per application twice/d, 5 d/wk, controls received cotton pellet dipped in saline; 108 wk	Squamous cell carcinomas: 5 (lip–1, hard palate–2, nasal cavity–1, forestomach–1) Squamous cell carcinomas in situ: hard palate–1 Squamous cell papillomas: 3 (lip–1, hard palate–1, nasal cavity–1) Undifferentiated lip sarcomas: 2 Controls: no tumours	All squamous cell tumours $P < 0.01$ Malignant squamous cell tumours $P < 0.05$
Rat, Sprague-Dawley (M) Johansson et al., (1991)	38, 30 controls Snuff inserted in surgically created lip canal, moist snuff, 150–200 mg/ application twice/d, 5 d/wk for 104 wk, controls received a cotton pellet dipped in saline once/d 5 d/wk for 100 wk	Sarcoma of the lip: 10/38 (26%) Squamous cell carcinomas and papillomas of the oral cavity: 3/38 (8%) (lip palate and buccal mucosa), Controls–1/30 (3%) sarcoma of the lip	Comparison of sarcoma $P < 0.01$ Comparison of all tumours $P < 0.01$

d, day or days; M, male; wk, week or weeks

hamsters compared to controls ([Kiseleva et al., 1976](#); [Milievskaia & Kiseleva, 1976](#); [Table 3.8](#)).

3.2 Snuff

3.2.1 Mouse

Addition of snuff (snus) to the diet induced stomach tumours in gastrin transgenic mice but not in wild-type mice unless they were infected with *Helicobacter pylori* (*H. pylori*). Feeding snuff to *H. pylori*-infected transgenic mice increased gastric carcinoma incidence 2-fold versus control transgenic mice ([Stenström et al., 2007](#); [Table 3.9](#)).

3.2.2 Rat

Application of snuff to the oral mucosa ([Chen, 1989](#)) or swabbing of lips and oral cavity with a snuff extract ([Hecht et al., 1986](#)) did not induce tumours.

In one study, the administration of snuff in a surgically created lip canal did not induce

tumours in the oral cavity ([Hirsch et al., 1984](#)) while a squamous cell carcinoma of the oral mucosa developed in one rat in another study ([Hirsch & Johansson, 1983](#)). Insertion of snuff in a surgically prepared lip canal induced a squamous cell carcinoma in the lip canal, a papilloma in the oral cavity and an olfactory tumour ([Hecht et al., 1986](#)).

Insertion of snuff in a surgically prepared lip canal induced squamous cell carcinoma in the lip, hard palate, nasal cavity and forestomach and a carcinoma in situ in the hard palate. In addition, the treated animals developed squamous cell papillomas in the lip, hard palate and nasal cavity and two undifferentiated lip sarcomas. The incidence of all squamous cell tumours, squamous cell carcinomas and the total number of tumours in the treated group were significantly greater than in controls ([Johansson et al., 1989](#); [Table 3.10](#)).

In another independent study, the insertion of snuff in the surgically prepared lip canal induced two squamous cell papillomas in the lip,

Table 3.11 Carcinogenicity studies of snuff with known carcinogens or modifiers to experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rat, Sprague-Dawley (M) Johansson et al. (1991)	40 animals/group with surgically created lip canal	Sarcomas of the lip: 9/40 (22%)	Significant increase in lip sarcoma over Group 1
	Group 1: DMBA in mineral oil – 70 mg solution + a cotton pellet containing saline 1 × /d, 5 d/wk + snuff 150–200 mg/application.	Squamous cell carcinomas and papillomas of the oral cavity (lip, palate, and buccal mucosa): 3/40 (7%) Controls: 0/40	
	Group 2: DMBA initiation as for control group + snuff in the lip canal twice/d, 5 d/wk.		
	Group 3: Controls initiated with cotton pellets containing 0.1% DMBA in mineral oil in lip canal 3 × /wk for 4 wk only, 104 wk		
	38, 40 controls		
Hamster Syrian golden (M) Park et al. (1986)	Group 4: Initiation with 4 NQO as for control group + snuff in the lip canal twice/d, 5 d/wk, 70 mg 4NQO sol + cotton pellet containing saline 1 × /d, 5 d/wk + snuff 150 – 200 mg/application.	Sarcoma of the lip: 25/38 (66%) Controls–1/40 (2%)	Significant increase in lip sarcoma over control
	Group 5: Controls initiated with 4 NQO (0.5% in propylene glycol) in cotton pellet placed in lip canal 3 × /wk for 4 wk only, 70 mg 4NQO sol + cotton dipped in saline inserted in the lip canal once/d, 5d/wk; 100 wk	Squamous cell carcinomas and papillomas of the oral cavity (lip, palate, and buccal mucosa): 8/38 (21%) Controls–9/40 (22%)	
	15–20 animals/group	No tumours 0/19 (HSV1) No tumours 0/16 (HSV2)	
	Cheek pouches inoculated with HSV1 or HSV2 (groups 1 and 1'), once/mo for 6 mo (no snuff); 6 mo	Invasive squamous cell buccal pouch carcinomas: 10/20 (50%)	
	Cheek pouches inoculated with HSV1 once/mo + snuff 150 mg/pouch, in both pouches twice/d, 5 d/wk for 6 mo; 6 mo (Group 2)	Invasive squamous cell buccal pouch carcinoma: 11/20 (55%)	
	Cheek pouches inoculated with HSV2 once a mo + Snuff 150 mg/pouch in both pouches twice/d, 5 d/wk for 6 mo; 6 mo (Group 3)		Increase in carcinoma $P < 0.05$ Group 2 vs Group 1 Increase in carcinoma $P < 0.05$ Group 3 vs Group 1'

Table 3.11 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Hamster Syrial golden (M) Gijare et al. (1990)	15 or 20 animals/group Application of 0.125 mg DMBA in 50 µl oil, twice/wk for 1 mo to both cheek pouches 0.25% in liquid paraffin; 6 mo	Cheek pouch tumours: 10/15 (66%) Forestomach tumours: 15/15 (100%)	NR
	Application of 0.125 mg DMBA in 50 ml oil, twice/wk for 1 mo + 50 µl snuff in liquid paraffin 20 mg per cheek pouch twice/wk to both cheek pouches 0.25% in liquid paraffin + Manglorian snuff; 6 mo	Cheek pouch tumours: 3/20 (15%) Forestomach tumours: 20/20 (100%)	NR
	Application of 50 µl snuff in liquid paraffin, 20 mg per cheek pouch twice/wk to both cheek pouches; 6 mo	Cheek pouch tumours: 0/20 Forestomach tumours: 17/20 (85%)	NR
	Application of 0.125 mg DMBA in 50 ml oil, twice/wk for 1 mo + 50 µl scented snuff in liquid paraffin 20 mg per cheek pouch twice/wk to both cheek pouches 0.25% in liquid paraffin + Scented snuff; 6 mo	Cheek pouch tumours: 2/20 (10%) Forestomach tumours: 19/20 (95%)	NR
	Untreated controls	No tumours	

d, day or days; M, male; mo, month or months; NR, not reported; vs, versus; wk, week or weeks

10 lip sarcomas and three squamous cell carcinomas in the hard palate. In the control group, a lip sarcoma occurred in one rat. The total incidence of epithelial and mesenchymal tumours of the lip and oral cavity and the incidence of lip sarcoma was significantly greater in snuff-treated rats than in controls ([Johansson et al., 1991](#); [Table 3.10](#)).

In one study, animals were repeatedly administered snuff extracts by the subcutaneous route. No local tumours developed in either treated or control groups ([Schmähl, 1965](#)).

Application of snuff to the surgically created lip canal of rats infected with HSV 1 resulted in the development of squamous cell carcinoma of the oral cavity in 2/7 (28%) rats and a retroperitoneal sarcoma developed in one rat. In the group exposed to snuff alone, one rat each developed a squamous cell carcinoma of the anus and a retroperitoneal sarcoma ([Hirsch et al., 1984](#)).

In animals whose hard palate was treated with 4-Nitroquinoline 1-oxide (4NQO), repeated application of snuff did not enhance the incidence of benign and malignant oral cavity tumours over that in animals treated with 4NQO alone ([Johansson et al., 1989](#)). However, in another study, application of snuff to a 4NQO-treated surgically created lip canal increased the incidence of lip sarcoma ([Johansson et al., 1991](#); [Table 3.10](#)).

3.2.3 Hamster

In hamsters infected with HSV1 or HSV2, insertion of snuff in the cheek pouch increased significantly the incidence of squamous cell carcinoma over that in animals infected with HSV1 or HSV2 and not administered snuff ([Park et al., 1986](#); [Table 3.11](#)). Application of a snuff suspension alone to the cheek pouch resulted in the development of stomach papillomas but did not increase the forestomach papilloma incidence in animals initiated with DMBA ([Gijare et al., 1990](#)). In one study, chronic feeding of

snuff and calcium hydroxide induced a pancreatic carcinoid in one animal only ([Dunham et al., 1975](#)) but did not induce any tumours in another study ([Homburger et al., 1976](#)). Snuff instillation in the cheek pouch did not induce tumours in six studies ([Peacock & Brawley, 1959](#); [Peacock et al., 1960](#), [Dunham & Herrold, 1962](#); [Dunham et al., 1975](#); [Homburger et al., 1976](#); [Park et al., 1986](#)).

3.3 Synthesis

In animals administered various smokeless tobacco preparations, consistent increases were observed for forestomach, lung, oral cavity and nasal tumours in rats; lung, skin, forestomach and liver tumours in mice; and oral cavity (cheek pouch) and forestomach tumours in hamsters.

4. Other Relevant Data

See Section 4 of the *Monograph on Tobacco Smoking* in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of smokeless tobacco. Smokeless tobacco causes cancers of the oral cavity, oesophagus and pancreas.

There is *sufficient evidence* in experimental animals for the carcinogenicity of smokeless tobacco.

Smokeless tobacco is *carcinogenic to humans* (Group 1).

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* Exceptionally, the most recent updates of well-established ongoing surveys and reports, published after the meeting, were included in this Monograph. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.

N'-NITROSONORNICOTINE AND 4-(METHYLNITROSAMINO)-1-(3-PYRIDYL)-1-BUTANONE

N'-Nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were considered by previous IARC Working Groups in 1984 and 2004 ([IARC, 1985](#), [2007](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1. Chemical and physical data

1.1.1 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone

(a) Synonyms and trade names

Chem. Abstr. Services Reg. No.: 64091-91-4

Chem. Abstr. Name: 1-Butanone,

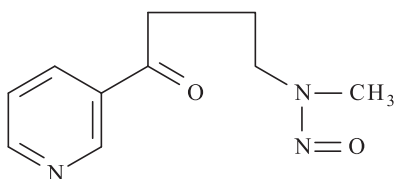
4-(methylnitrosoamino)-1-(3-pyridinyl)-

IUPAC Systematic Name:

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone

Synonym: 4-(N-Methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone

(b) Structural and molecular formulae and relative molecular mass



Relative molecular mass: 207.2

(c) Chemical and physical properties of the pure substance

From [IARC \(2007\)](#)

Description: Light-yellow crystalline solid

Melting-point: 61–63 °C

Spectroscopy data: Infrared, nuclear magnetic resonance and mass spectra have been reported.

Solubility: Soluble in dichloromethane, dimethyl sulfoxide (DMSO), dimethylformamide, ethyl acetate and methanol

Stability: Sensitive to light

1.1.2 N'-Nitrosonornicotine

(a) Synonyms and trade names

Chem. Abstr. Services Reg. Nos: 80508-23-2; 16543-55-8; 84237-38-7

Chem. Abstr. Names: Pyridine, 3-(1-nitroso-2-pyrrolidinyl)-; pyridine,

3-(1-nitroso-2-pyrrolidiny)-, (S)-; pyridine,
3-(1-nitroso-2-pyrrolidiny)-, (+,-)-

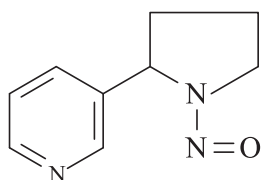
IUPAC Systematic Name:

1'-Demethyl-1'-nitrosonicotine

Synonyms: 1'-Demethyl-1'-nitrosonicotine;
1'-desmethyl-1'-nitrosonicotine; 1'-nitroso-
1'-demethylnicotine; nitrosonornicotine;
N-nitrosonornicotine; 1'-nitrosonornico-
tine; 1-nitroso-2-(3-pyridyl)pyrrolidine;
3-(1-nitroso-2-pyrrolidiny)pyridine

Note: the chemical abstracts services registry number 16543-55-8 and name refer to the (S) stereoisomer; the chemical abstracts services registry number 84237-38-7 and name refer to the racemic mixture that was synthesized and used in the biological studies reported in this *Monograph*.

(b) *Structural and molecular formulae and relative molecular mass*



$C_9H_{11}N_3O$

Relative molecular mass: 177.2

(c) *Chemical and physical properties of the pure substance*

From [IARC \(2007\)](#)

Description: Light-yellow oil

Boiling-point: 154 °C at 0.2 mm

Melting-point: 47 °C; 42–45 °C

Spectroscopy data: Mass, ultraviolet, infrared and nuclear magnetic resonance spectra have been reported.

Solubility: Soluble in acetone and chloroform

Stability: Hygroscopic

1.2 Occurrence in tobacco products

Virtually all commercial tobacco products contain NNN and NNK, and they always occur together. They are mainly formed during the curing of tobacco. There is a great variation in levels of these compounds in mainstream smoke and sidestream smoke of cigarettes and in smokeless tobacco products. This is mainly due to differences in tobacco types used for the various products, in agricultural practices, curing methods, and in manufacturing processes. Factors that lead to relatively high levels of NNN and NNK in cured tobacco include the use of Burley tobacco, the use of midribs from air-cured tobacco or lamina from flue-cured tobacco, storage of tobacco leaves under humid conditions or in bales, processes that encourage bacterial growth thus leading to increased nitrite, and heating with propane during curing ([IARC, 2007](#)).

Since the first reports of NNN and NNK in tobacco ([Hoffmann et al., 1974](#); [Hecht et al., 1978](#)), many studies have quantified their levels in various tobacco products. Extensive compilations of data may be found in previous *IARC Monographs* ([IARC, 2004, 2007](#)). Levels of NNN ranged from 20 to 58000 ng per cigarette and NNK from 19 to 10745 ng per cigarette in tobacco from commercial cigarettes sold in different parts of the world; and from 4 to 2830 ng per cigarette (NNN) and 3 to 1749 ng per cigarette (NNK) in mainstream smoke of internationally available commercial cigarettes. Levels of NNN ranged from 19 to 3080000 ng per gram tobacco and NNK from 10 to 7870000 ng per gram tobacco in smokeless tobacco products worldwide.

Several recent studies have examined levels of NNN and NNK in cigarette tobacco and mainstream smoke, and in smokeless tobacco. [Hammond & O'Connor \(2008\)](#) reported data for 247 brands sold in Canada, and tested in 2004. Mean (\pm standard deviation (SD)). levels of NNN were

significantly higher in the tobacco of imported (1776.2 \pm 817.2 ng/cigarette) than domestic Canadian brands (286.9 \pm 118.3 ng/cigarette) while those of NNK were similar (437.2 \pm 376.1 ng/cigarette imported and 448.5 \pm 237.4 ng/cigarette domestic). Using the Canadian Intense smoking conditions, levels of NNN (353.3 \pm 91.3 ng/cigarette) were significantly higher in mainstream smoke of imported cigarettes than if Canadian brands (53.1 \pm 12.6 ng/cigarette), as were levels of NNK (212.1 \pm 90.8 ng/cigarette imported; 110.3 \pm 33.2 domestic Canadian). These differences are caused by the exclusive use of Virginia flue-cured tobacco in Canadian brands while imported brands – mainly from the USA – use a blend of tobacco types.

The impact of curing using indirect-fired barns instead of direct-fired methods on levels of NNK and NNN in cigarette tobacco and mainstream smoke was examined in a study of Canadian brands. Reductions of 65–78% in tobacco NNN levels and 60–85% in NNK levels were observed while the corresponding reductions in mainstream smoke levels (under ISO conditions) were 57–69% for NNN and 59–72% for NNK ([Rickert et al., 2008](#)).

Levels of NNN and NNK were quantified in the smoke of research cigarettes made from different tobacco varieties, using the ISO method ([Ding et al., 2008](#)). Levels of NNN and NNK were greatest in Burley tobacco smoke, with substantially lower amounts in the smoke of Oriental and Bright cigarettes. Nitrate content of the tobacco was significantly related to levels of smoke NNK (but not NNN), and was inversely proportional to PAH levels. These results are completely consistent with earlier studies ([IARC, 1986](#); [IARC, 2004](#)).

Based on currently available data, NNN and NNK in smokeless tobacco products, expressed per g dry weight, can be divided arbitrarily into three levels:

Level I: less than 2 μ g per g NNN plus NNK;

Level II: 2–10 μ g per g NNN plus NNK;

Level III: greater than 10 μ g per g NNN plus NNK.

The “new” products Taboka, Marlboro Snus, and Camel Snus were introduced in test markets in the USA and probably use pasteurization-like processing parameters designed to reduce levels of NNN and NNK, similar to those used by Swedish Match for products sold in Sweden. The NNN plus NNK levels in these products mostly fall into Level I, while “traditional” smokeless tobacco products manufactured in the USA fall into Level II ([Stepanov et al., 2008a](#)).

Another study reported tobacco-specific nitrosamine levels in 40 top selling brands of USA moist snuff manufactured by four different companies, which collectively held over 97% of the US market in the year in which they were purchased ([Richter et al., 2008](#)). The results for NNN plus NNK demonstrate that 12 brands were in Level II while 27 were in Level III. None were in Level I. In this study, amounts of NNN ranged from 2.2–42.5 μ g/g wet weight while those of NNK ranged from 0.38–9.9 μ g/g wet weight. The amounts in the brand with the highest levels of NNN and NNK are reminiscent of tobacco-specific nitrosamine levels in smokeless tobacco products of the 1970s.

While NNN and NNK have not been detected in oral gum nicotine-replacement therapy products, two recent studies demonstrate that NNN can be formed endogenously in trace amounts in some users of these products ([Stepanov et al., 2009a, b](#)).

2. Cancer in Humans

Two molecular epidemiology studies investigated the relationship of NNK to lung cancer in smokers using nested case–control designs. In one, urinary levels of NNAL plus its glucuronides (total NNAL), metabolites of NNK, were

significantly associated with risk for lung cancer in a dose-dependent manner ([Yuan et al., 2009](#)). Relative to the lowest tertile, risks associated with the second and third tertiles of total NNAL were 1.4 (95%CI: 0.9–2.4) and 2.1 (95%CI: 1.2–3.5), respectively (P for trend = 0.005) after adjustment for smoking history and total cotinine. In a second study, after adjustment for sex, age at randomization, family history of lung cancer, cotinine, *r*-1,*t*-2,3,*c*-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT), and years of cigarette smoking, total NNAL was significantly associated with risk for lung cancer (odds ratio (OR), 1.6 per unit SD increase; 95%CI: 1.1–2.3) ([Church et al., 2009](#)). A similar statistically significant result was obtained for adenocarcinoma risk, but not for nonadenocarcinoma. Although these results demonstrate an association of NNK metabolites with lung cancer in smokers, it is impossible to exclude the potential confounding effect of other carcinogens present in tobacco smoke.

3. Cancer in Experimental Animals

NNK and NNN have been tested for carcinogenicity by various routes of administration in adult mice, rats, and Syrian hamsters, and in limited experiments in mink and ferrets. NNK has also been tested for carcinogenicity in neonatal and infant mice and transplacentally in hamsters. NNK and NNN in combination have been tested in rats and minks. Of all the numerous studies on tumour development in animal models, a selection is presented in this *Monograph*. [Table 3.1](#) includes the studies considered the most representative of the carcinogenicity of NNK and NNN.

3.1 Administration of NNN and NNK

3.1.1 Oral administration

(a) Mouse

Mice given NNK or NNN orally developed both lung and forestomach tumours and a few liver tumours in one study ([Padma et al., 1989](#)).

(b) Rat

Oral administration of NNK in drinking-water caused tumours of the lung, nasal cavity, and liver ([Rivenson et al., 1988](#); [Prokopczyk et al., 1991](#)). In two studies, tumours of the exocrine pancreas were observed following administration of NNK in drinking-water ([Rivenson et al., 1988](#); [Hoffmann et al., 1993](#)). Rats given NNN orally developed tumours of the oesophagus and of the nasal cavity ([Hoffmann et al., 1975](#); [Hecht et al., 1983](#)).

3.1.2 Subcutaneous administration

(a) Rat

NNK given to rats subcutaneously caused tumours of the lung, nasal cavity, and liver ([Hoffmann et al., 1984](#); [Hecht et al., 1986a](#); [Belinsky et al., 1990](#)). Rats given NNN subcutaneously developed tumours of the oesophagus and of the nasal cavity ([Castonguay et al., 1984](#); [Hoffmann et al., 1984](#)).

(b) Hamster

NNK given subcutaneously to Syrian hamsters caused lung tumours ([Hoffmann et al., 1981](#); [Schüller et al., 1990](#)). NNN given subcutaneously to hamsters caused tumours of the trachea ([Hilfrich et al., 1977](#)).

(c) Mink

In one study, NNK caused malignant tumours of the nasal cavity after subcutaneous injection ([Koppang et al., 1997](#)). Subcutaneously injected NNN caused malignant tumours of the nasal cavity in mink ([Koppang et al., 1992, 1997](#)).

Table 3.1 Selected carcinogenicity studies of subcutaneous (sc) or oral exposure to NNK, NNN, and NNK + NNN in rats

Species, strain (sex) Reference	No/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
NNN				
Rat, F344 (M)	80, 80, 80, 30	<i>Nasal cavity</i> 0, 1, 2, 5 ^a	^a P < 0.01	Purity > 99% Lung carcinomas included
Rivinson et al. (1988)	0, 0.5, 1.0, 5.0 ppm in drinking- water, daily 108–128 wk	<i>Lung</i> adenomas: 3, 5, 16 ^a , 2 carcinomas: 3, 4, 4, 25 ^a total: 6, 9, 20 ^a , 27 ^a	^a P < 0.01	adenocarcinomas, adenosquamous carcinomas, and squamous cell carcinomas. Pancreatic tumours were acinar adenomas and acinar or ductal carcinomas
		<i>Liver</i> adenomas: 6, 2, 9, 10 ^a carcinomas: 0, 1, 2, 2 total: 6, 3, 11, 12 ^a	^a P < 0.01	
		<i>Exocrine pancreas</i> adenomas: 1, 5, 8 ^b , 1 carcinomas: 0, 0, 1, 1 total: 1, 5, 9 ^a , 2	^a P < 0.01 ^b P < 0.05	
Rat, F344 (M)	30 animals/group 0, 15 mmolar aqueous solution; 0.3 mL by oral swabbing, 3 ×/wk (wk 1), daily (wk 2–4), and twice/d (wk 5–61) Up to 61 wk	<i>Nasal cavity</i> adenomas or papillomas: 0/30, 13/29 (45%) carcinomas: 0/30, 2/29 (7%)	NR	Purity > 99% Lung carcinomas were adenocarcinomas and adenosquamous carcinomas.
Prokopczyk et al. (1991)		<i>Lung</i> adenomas: 0/30, 5/29 (17%) carcinomas: 0/30, 23/29 (79%)	NR	
		<i>Liver</i> adenomas: 0/30, 9/29 (31%) carcinomas: 0/30, 3/29 (10%)		
		<i>Oral cavity</i> papilloma: 0/20, 1/29 (3%)		

Table 3.1 (continued)

[illegible]

Table 3.1 (continued)

[illegible]

Species, strain (sex) No/g

d, day or days; F, female; M, male; mo, month or months; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosornicotine; NR, not reported; NS, not significant; SC, subcutaneous; wk, week or weeks

3.1.3 Intraperitoneal administration

(a) Mouse

NNK or NNN given to mice intraperitoneally increased the incidence of lung adenomas and carcinomas after less than one year ([Hecht et al., 1978, 1988, 1989](#); [Rivenson et al., 1989](#); [Belinsky et al., 1992](#); [Amin et al., 1996](#); [Castonguay et al., 1983](#)).

(b) Hamster

NNN given intraperitoneally to hamsters caused tumours of the trachea and nasal cavity ([McCoy et al., 1981](#)).

3.1.4 Skin application

When applied topically to SENCAR mice, NNK was weakly active as a skin tumour initiator, but lung tumours were observed, while NNN was inactive ([LaVoie et al., 1987](#)). A few skin tumours developed in mice given NNN by skin application for 104 weeks ([Deutsch-Wenzel et al., 1985](#)).

3.1.5 Perinatal administration

NNK increased both lung and liver tumours when given intraperitoneally to neonatal and infant mice ([Anderson et al., 1991](#)) but was not a transplacental carcinogen when given intraperitoneally to pregnant females ([Beebe et al., 1993](#)). NNK injected subcutaneously to pregnant Syrian hamsters caused tumours of the nasal cavity, larynx, and trachea in offspring in one experiment ([Correa et al., 1990](#)).

3.1.6 Administration with known carcinogens

In one study, NNK and NNN in combination caused oral cavity papillomas and lung carcinomas when administered to rats by swabbing the lips and oral cavity with an aqueous solution of the nitrosamines ([Hecht et al., 1986b](#)); oral cavity tumours were rarely observed in rats given NNK alone. In one study, NNK and NNN

in combination caused nasal cavity tumours in mink of both sexes ([Koppang et al., 1997](#)). Offspring of Syrian hamsters given ethanol in drinking-water during pregnancy and NNK by intratracheal instillation on day 15 of pregnancy developed tumours of the nasal cavity, exocrine pancreas, and adrenal medulla ([Schüller et al., 1994, 2002](#)). In a single study of limited duration, NNK given by injection concurrently with cigarette smoke by inhalation caused lung tumours in 6 of 12 ferrets within six months ([Kim et al., 2006](#)).

3.2 NNK and NNN metabolites

NNN-1-*N*-oxide given in drinking-water caused tumours of the oesophagus and nasal cavity in rats but not in hamsters ([Hecht et al., 1983](#)). In a short-term study, NNK-1-*N*-oxide and 4-(methylnitrosamino)-1-(3-pyridyl) butan-1-ol (NNAL) given intraperitoneally caused lung tumours in mice and was as effective as NNK. Similarly, in a lifetime study in rats, NNAL was equally as effective as NNK in inducing lung tumours ([Rivenson et al., 1988](#)). 4'-Hydroxy-NNN given intraperitoneally slightly increased the incidence and multiplicity of lung tumours, while 3'-hydroxy-NNN and NNN-1-*N*-oxide had no significant carcinogenic effect ([Castonguay et al., 1983](#)).

3.3 Synthesis

NNK by various routes of administration consistently caused tumours of the lung in mice, hamsters and rats, and tumours of the nasal cavity in rats and mink. NNN given by various routes and particularly in drinking-water consistently caused tumours of the oesophagus in rats, and in many studies caused tumours of the nasal cavity in multiple species. NNN and NNK administered in combination caused tumours of the oral cavity in rats and nasal cavity in mink. [Table 3.2](#) summarizes the reports of tumours induced in

Table 3.2 Summary of reports of tumours induced in experimental animals by NNK and NNN

Compound/ species	Lung	Nasal cavity	Oral cavity	Trachea	Oesophagus	Fore- stomach	Pancreas (exocrine)	Liver	Adrenal gland	Skin
NNK										
Mouse	x					x		x		x ^a
infants	x							x		
Rat	x	x					x	x		
Hamster progeny	x	x		x			x ^c		x	
Mink		x								
Ferret	x ^b									
NNN										
Mouse	x					x				x
Rat		x			x					
Hamster		x		x						
Mink		x								
NNK + NNN										
Rat	x		x							
Mink		x								

^a Initiator only (SENCAR mouse skin)

^b Co-exposure to NNK and cigarette smoke

^c Transplacental co-exposure to NNK and ethanol

NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N'*-nitrosonornicotine

From [IARC \(2007\)](#)

experimental animals after exposure to NNK and/or NNN.

4. Other Relevant Data

See Section 4 of the *Monograph* on Tobacco Smoking in this volume.

5. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *N'*-nitrosonornicotine (NNK) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNN).

There is *sufficient evidence* in experimental animals for the carcinogenicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

There is *sufficient evidence* in experimental animals for the carcinogenicity of *N'*-nitrosonornicotine.

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone and *N'*-nitrosonornicotine are *carcinogenic to humans (Group 1)*.

In making the overall evaluation, the Working Group took into consideration the following mechanistic evidence, detailed in Section 4 of the *Monograph* on Tobacco Smoking in this volume.

NNK and NNN are the most abundant strong carcinogens in smokeless tobacco; their uptake and metabolic activation has been clearly documented in smokeless tobacco users. Combined application of NNN and NNK to the oral mucosa of rats induced oral tumours, consistent with their induction by smokeless tobacco. One of the mechanisms of carcinogenicity is cytochrome-P450-mediated α -hydroxylation, which leads to the formation of DNA and haemoglobin adducts that have been detected in users of tobacco.

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BETEL QUID AND ARECA NUT

Betel quid and areca nut were considered by previous IARC Working Groups in 1984, 1987 and 2003 ([IARC, 1985, 1987, 2004](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Constituents of betel quid

1.1.1 Definitions

Betel quid chewing is an ancient practice in the Indian subcontinent and many parts of Asia, and is still prevalent today. In modern times the term “betel quid” for most people is synonymous with “*pan*,” a chewing item used in India and neighbouring countries.

The term “quid” denotes a substance or a mixture of substances that is placed and retained in the mouth, and often swallowed. Apart from areca nut it may contain a variety of ingredients, including betel leaf and tobacco ([Zain et al., 1999](#); [IARC, 2004](#)).

In India and neighbouring countries, dry areca nut pieces or tobacco may be chewed alone, as a mixture of areca nut, tobacco and slaked lime, or tobacco and slaked lime. Dry powdered ready-to-chew mixtures containing areca nut, catechu, lime, unspecified spices without betel leaf and with or without tobacco are sold commercially in India ([Ramchandani et al., 1998](#)). The product that does not contain tobacco is called *pan masala*

while the term *gutka* is used for the product that contains tobacco in addition to the ingredients of *pan masala* ([Nair et al., 2004](#)). In the south-eastern part of China, unprocessed fresh areca nut is treated with maltose and lime. It is cut into pieces and chewed with a few drops of cassia oil ([Tang et al., 1997](#)).

A *pan* comprises mainly betel leaf (*Piper betel*), areca nut (*areca catechu*), catechu and slaked lime. The basic ingredients may be supplemented with condiments, sweetening agents and tobacco as per individual preference ([IARC, 1985](#)). The ingredients are placed on the betel leaf and the leaf is folded into a triangular-shaped object to obtain a betel quid with or without tobacco. Like slaked lime, thick paste of catechu may be smeared on the betel leaf or small bits of dry catechu may be placed on the betel leaf before it is folded to form a *pan*. Three types of betel quid are consumed in Taiwan, China. These are *lao-hwa* quid, betel quid and stem quid ([Yang et al., 2001](#)). *Lao-hwa* quid is prepared by inserting a piece of inflorescence of *Piper betel* L. and red lime into an unripe areca nut. Another variety of Taiwanese betel quid is prepared by wrapping two halves of an unripe areca nut and white slaked lime in a betel leaf. The third variety is similar to the *lao-hwa* quid except that stems

Table 1.1 Composition of the different types of areca-containing chewing substances

	Areca nut ^a	Betel ^b		Catechu ^d	Tobacco ^e	Slaked lime
		Leaf	Inflorescence	Stem ^c		
Areca nut	X					
Betel quid without tobacco	X	X			(X) ^f	X
Betel quid with tobacco	X	X			(X) ^f	X
Gutka	X				X	X
<i>Pan masala</i> ^g	X				X	X
Mawa	X				X	X
<i>Mainpuri</i> tobacco	X				X	X
<i>Lao-hwa</i> (Taiwan, China)	X ^g		X			X
Betel quid (Taiwan, China)	X ^g	X				X
Stem quid (Taiwan, China)	X ^g			X		X

^a May be used unripe, raw or processed by baking, roasting or baking with sweetening, flavouring and decorative agents (see [Table 1.2](#))

^b In place of the leaf, the inflorescence or its stem may also be used (see [Table 1.2](#))

^c Stem of inflorescence

^d In powdered or paste form (see [Table 1.2](#))

^e In flaked, powdered or paste form, with or without processing, with or without sweetening (see [Table 1.2](#))

^f (X) means optional

^g Used in unripe form

Adapted from [IARC \(2004\)](#)

of *Piper betel* L. are used in place of the inflorescence ([IARC, 2004](#)). While flavouring agents may be added to the Taiwanese betel quid, it does not contain tobacco. Different types of areca nut-containing chewing products and their ingredients are listed in [Table 1.1](#).

1.1.2 Main ingredients of a quid

Areca nut, the major constituent of a betel quid, is the fruit of the *Areca catechu* L., a palm tree that grows in South and South-East Asia and the Pacific islands.

The chemical composition of areca nut has been reported in many studies ([Raghavan & Baruah, 1958](#); [Shivashankar et al., 1969](#); [Arjungi, 1976](#); [Jayalakshmi & Mathew, 1982](#)). The major constituents are carbohydrates, fats, proteins, crude fibre, polyphenols, alkaloids and minerals. The concentrations of various constituents vary between raw and ripe areca nuts ([Jayalakshmi & Mathew, 1982](#)). Arecaidine, arecoline, guvacine and guvacoline are the four alkaloids conclusively identified in areca nut ([Raghavan & Baruah,](#)

[1958](#); [Huang & McLeish, 1989](#); [Lord et al., 2002](#)). Areca nut also contains sodium, magnesium, calcium, vanadium, manganese and copper ([Wei & Chung, 1997](#); [Ridge et al., 2001](#)).

Betel leaf (*Piper betel* L.) is a vine cultivated in many South-Asian countries including India. It contains betel oil, which includes phenolic compounds such as hydroxychevicol, eugenol phenol, and chevicol. Trace elements, vitamin C and carotenes are also present in betel leaf ([Wang & Wu, 1996](#); [Zaidi et al., 2002](#)).

Slaked lime is prepared from seashells or quarried from limestone in regions that are far from the sea. Seashells are roasted, finely powdered and water is added to make slaked lime paste. The pH of slaked lime obtained from seashells or limestone is similar ([Bhonsle et al., 1992](#)).

Catechu is a common ingredient of betel quid. It is a reddish brown substance derived from the heartwood of the *Acacia Catechu* tree, which is indigenous to India and Myanmar. It is obtained from the resins extracted from the matrix of *Acacia catechu* or *Acacia suma* ([Muir](#)

Table 1.2 Forms of different betel quids that contain areca nut and regions where they are used

Some common names and spellings	Major ingredients	Country where used
Betel quid	Areca nut (fresh, unripe) alone or with lime Areca nut (dried, unripe) alone or with lime Areca nut (cured, ripe) alone or with lime Areca nut (fresh, unripe) with lime and betel leaves	Southern China, Pacific Islands Hunan Province in China South Asia Taiwan, China, Hainan Island, Papua New Guinea and Pacific Islands
<i>Lao-hwa</i> quid	Areca nut (fresh, unripe) with lime and betel inflorescence	Taiwan, China (<i>lao-hwa</i> quid), Papua New Guinea
Stem quid	Areca nut (fresh, unripe) with lime and betel stem Areca nut (fresh, unripe) with betel leaves Areca nut (cured, ripe) with lime and betel leaves	Taiwan, China Guam South Asia
<i>Pan</i> or <i>paan</i>	Areca nut (cured, ripe) with lime, an additional source of catechins, flavourings and betel leaves	South Asia
<i>Pan</i> or <i>paan</i> with tobacco, (the most common form)	Areca nut (cured, ripe) with lime, an additional source of catechins, flavourings, tobacco and betel leaves	South Asia, parts of South-eastern Asia
<i>Pan masala</i> or <i>chaalia</i>	Areca nut (cured, ripe) with lime, catechu, flavourings and other chemicals	India (<i>paan masala</i>), Pakistan (<i>chaalia</i>)
<i>Mawa</i> , <i>kharra</i>	Areca nut (cured, ripe) with lime, catechu, flavourings and other chemicals and tobacco – a variant of <i>pan masala</i> – usually called <i>gutka</i> ; similar products with different proportions and shavings of areca nut	India

& Kirk, 1960). The main constituents of catechu are catechin, catechu tannic acid, quercetin and catechu red (IARC, 2004). Catechu contains a variety of trace elements as well (Zaidi *et al.*, 2002).

The chewing tobacco added to a betel quid is prepared from sun-dried and partly fermented coarse leaves of *Nicotiana tabacum* and *Nicotiana rustica* (IARC 2004).

A list of different forms in which areca nut is used is given in Table 1.2 (Gupta & Warnakulasuriya, 2002; IARC, 2004).

1.2 Prevalence of use

1.2.1 Distribution of betel quid chewing worldwide

It has been estimated that betel quid is used by about 10–20% of the world's population and that globally up to 600 million users chew areca

nut (Gupta & Warnakulasuriya, 2002). Users are distributed around the world, but concentrated in South and South-eastern Asia, including South-eastern China, Hainan Island and Taiwan, China, and the Pacific Islands, as well as in areas of immigration of peoples from South Asia, e.g. in the Malay peninsula, eastern and southern Africa, Europe and North America. Concern among health professionals over increasing use of areca nut among South Asians and in Taiwan, China, have led to increasing numbers of prevalence surveys in the past several years.

In South Asia, South-eastern Asia, and parts of the Pacific Islands, the most common way of chewing betel quid is by inserting smokeless tobacco in the quid. Betel quid is chewed exclusively without tobacco in Southern China, Taiwan, China and Papua New Guinea, but in these areas, most chewers are also cigarette smokers. Emigrants from these areas have

carried their betel quid practices to the countries of immigration.

In South Asia, dry mixtures of areca nut and betel quid related ingredients (minus the betel leaf) are prepared industrially and sold in sachets. The most popular form contains tobacco and is usually called *gutka*, a variant of *pan masala*. These forms are now being exported from India to over 50 countries. Surveys on the prevalence of areca nut use across the world are summarized in Table 1.3 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table1.3.pdf>) and Table 1.4 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table1.4.pdf>).

1.2.2 Prevalence by country or region

(a) Adults

Information from several countries, especially in South-eastern Asia, has indicated that areca nut usage may be dying out in Cambodia, Indonesia, Thailand, and Viet Nam as it has declined considerably and become confined to the older middle aged and elderly groups. In contrast, rapidly increasing prevalence of areca nut usage has been registered in India and Taiwan, China (IARC, 2004). This corresponds, in India, to the introduction of industrially manufactured areca nut products, especially *pan masala*, *gutka* and *mawa*, while betel quid use has declined; and in Taiwan, China, to changes in marketing of betel quid, where young women sell betel quid and cigarettes on roadsides.

Surveys on prevalence of areca nut use have been conducted in India, Pakistan, Taiwan, China, the People's Republic of China, Thailand, the United Kingdom and the United States.

(i) India

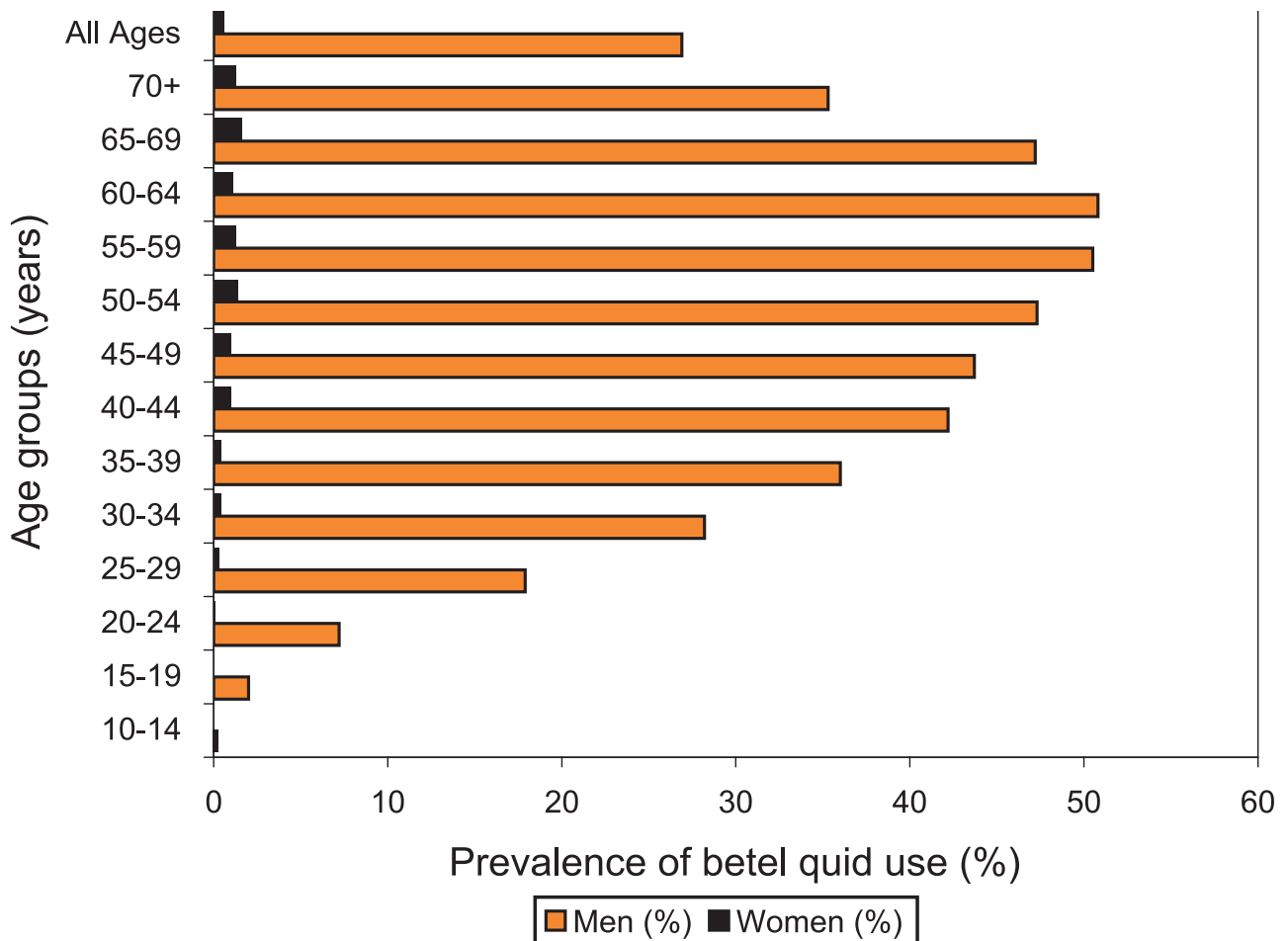
In India, prevalence of areca nut chewing nationwide can be estimated at around 30% of men and 7% of women, since the National Family Health Survey found 36.5% of men and 8.4% of

women aged 15–49 years chewing some form of tobacco, “including *pan masala*, *gutka*, and other tobacco” (IIPS, 2007). [The Working Group noted that *pan masala* does not contain tobacco.] Since in many states of India tobacco is mainly chewed in the form of betel quid, and betel quid is mainly chewed with tobacco, the prevalence of “tobacco chewing” is only slightly higher than that of areca nut use. Local surveys have found betel quid use to be as high as 80% among both male and female adult school personnel in Mizoram; *gutka* was used by 44.8% of male school personnel in Sikkim (Sinha *et al.*, 2003). Reasons for use of tobacco products, including those containing areca nut (*gutka*, *mawa*, and *pan*, i.e. betel quid), among non teaching university personnel in Mumbai included peer pressure, the media (TV, advertisements, films, sports) as well as family influence (Bansode, 2002). In Chitrakoot, Madhya Pradesh, on the border with Uttar Pradesh, 46% of dental outpatients were current *gutka* users (Anwar *et al.*, 2005). In two districts of Uttar Pradesh in 2001, the prevalence of betel quid with tobacco use was only 2.0% (2.3% men, 1.4% women) (Chaudhry *et al.*, 2001). Fig. 1.1 and 1.2 present the age and sex distribution of use of betel quid with tobacco in Karnataka and Uttar Pradesh, respectively (Chaudhry *et al.*, 2001).

A statewide survey in 63 districts of Uttar Pradesh found that among 1209 *pan* [betel quid] and *pan masala* users, 94.4% (1141) used *pan* while 59.1% ($n = 714$) used both *pan* and *pan masala*, mostly by incorporating *pan masala* into *pan*. Additionally, 5.6% ($n = 68$) were exclusive *pan masala* users (Tripathi *et al.*, 2006).

(ii) Pakistan

A few recent studies in low-income urban areas of Karachi, Pakistan, have found 30–40% use of areca nut use among adults, as betel quid, areca nut by itself (*chaalia*), *gutka* and packaged *chaalia*, the equivalent of Indian *pan masala* (Mazahir *et al.*, 2006; Nisar *et al.*, 2007; Tanwir *et al.*, 2008). Among the ethnic groups in Karachi,

Fig. 1.1 Current use of betel quid with tobacco by age and sex in Karnataka

From [Chaudhry et al. \(2001\)](#)

the Mohajir appear to have a higher prevalence of use of areca nut products ([Mazahir et al., 2006](#)). Adolescents prefer *chaalia* ([Mazahir et al., 2006](#)), while adults over 30 years prefer betel quid ([Tanwir et al., 2008](#)).

(iii) Bangladesh

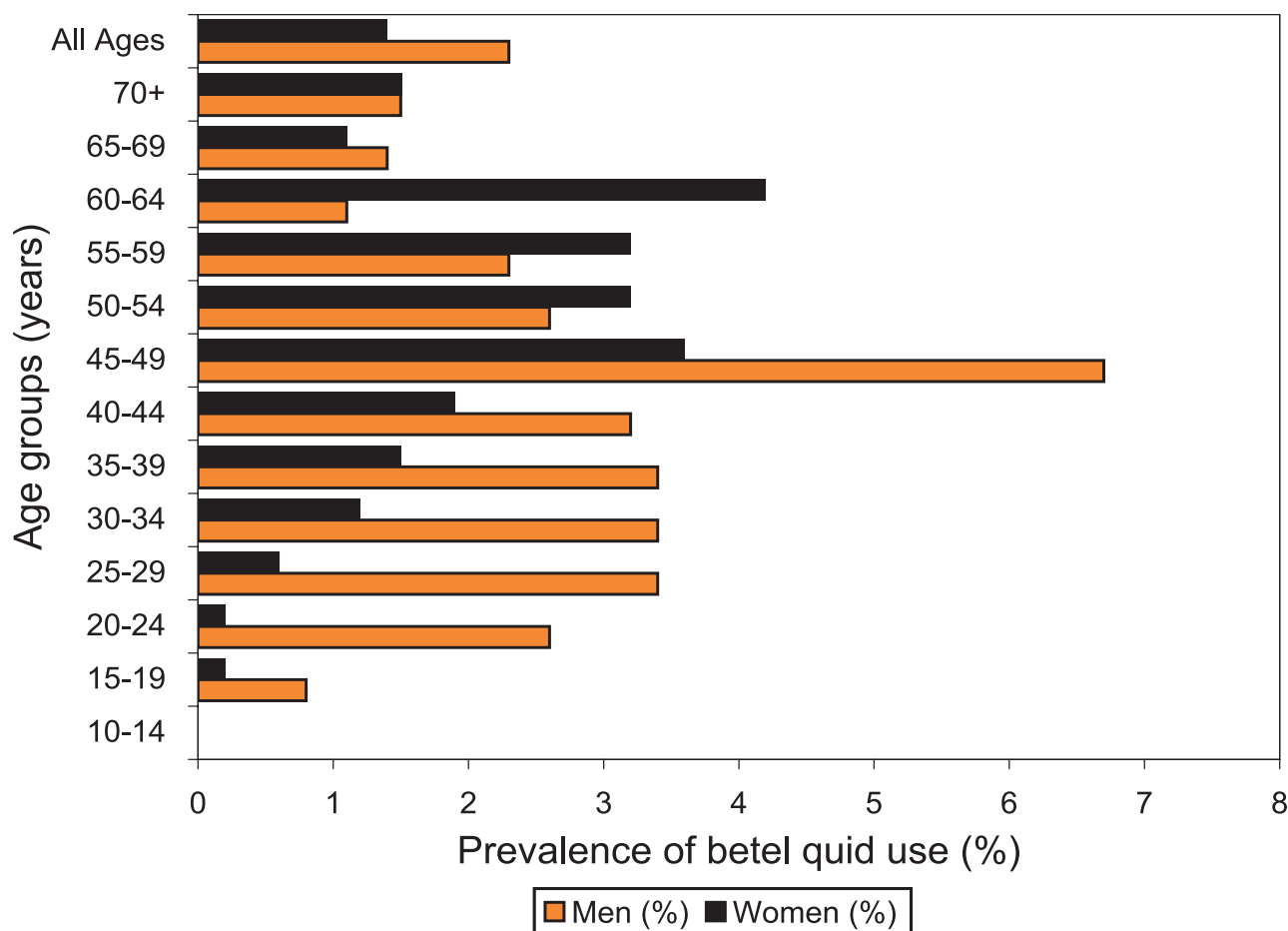
A rural oral screening study in Bangladesh found that 40% of adult villagers of Kishore Ganj used areca nut with slaked lime and tobacco in various combinations ([Eswar, 2002](#)).

(iv) Thailand

In a survey of 4955 rural adults aged 30–89 years in Thailand, 17% reported using betel quid ([Chatrchaiwiwatana, 2007](#)). Betel quid chewing has been reported to be on the decline in Thailand as early as 1955 as a result of educational campaigns, and to be more common in the older population ([Reichert, 1995](#)).

(v) China

National surveys in Taiwan, China, indicate that 20.9% of men and 1.2% of women chew betel quid. Prevalence was highest in the

Fig. 1.2 Current use of betel quid with tobacco by age and sex in Uttar Pradesh

The age-wise *pan*-tobacco usage pattern of men and women differs significantly, but prevalence may be too low to be interesting.
 From [Chaudhry et al. \(2001\)](#)

aboriginal population: 54.3% of men and 33.8% of women ([Yap et al., 2008](#)). Betel quid chewing is more common among those who consume alcohol or who smoke. In another study, betel quid was chewed by 34.7% of aboriginal pregnant women ([Chou et al., 2009](#)). Almost all betel quid chewers started chewing after they started smoking, particularly so among people over 25 years ([Wen et al., 2005a](#)). Two thirds of the increase in betel quid chewing in the past decade has been attributed to the opening of the market to foreign cigarette brands in 1987, after which these cigarettes began to be placed in betel quid

stalls. Betel quid sales increased dramatically as smokers turned to betel quid stalls to purchase cigarettes. Notably, 34% of betel quid chewers smoke, while 3% of non-smokers chew. Per capita consumption of betel quid increased 5 fold from 1981 to 1996 ([Wen et al., 2005b](#)).

In the People's Republic of China, betel quid chewing is most common in, but not confined to, Yunnan and Hunan provinces and Hainan Island, all located in the south-eastern part of China. In Hunan, a land locked province where areca nut is not grown, the nuts are cut in half with the husk and dried, flavoured and industrially

packaged. Reports on prevalence of betel quid chewing from China are limited; a review of the Chinese literature from the late 1980s and early 1990s showed that prevalence in Hunan at that time was between 64.5% and 82.7% ([Zhang & Reichart, 2007](#)).

(vi) Pacific Islands

In the Pacific islands, betel quid chewing is high among adults: 72% of men and 80% of women in Palau ([Ysaol et al., 1996](#)); and 76.8% of adults (83.0% men, 68.4% women) in the Solomon Islands ([Tovosia et al., 2007](#)) use betel quid.

(vii) Immigrants

In areas of immigration of South Asians, such as the United Kingdom, people of Bangladeshi origin appear to have the highest prevalence of betel quid use (mostly with tobacco) from around 30% to over 90% in both men and women ([IARC, 2004](#)). In a recent study of Bangladeshi women in the United Kingdom aged 18–39 years, prevalence of betel quid chewing was 25–35% ([Núñez-de la Mora et al., 2007](#)).

[Changrani et al. \(2006\)](#) from the United States found 25% current use of betel quid and 6% *gutka* use among people of Bangladeshi origin, but a reverse pattern among people of Indian-Gujarati origin, with 2% current betel quid use and 24% *gutka* use. Areca nut and betel quid chewing without tobacco have been reported from South Africa for many years among the population of Indian origin, but no recent studies are available.

(b) Children and youth

In India *pan masala* use and *gutka* use have increased among children, also in rural areas, as a mouth freshener and a status symbol. Even after an educational intervention and a local ban on *gutka* sales near schools, 46% of 986 rural school-children aged 10–15 years in Madhya Pradesh were using *gutka* regularly ([Chaturvedi et al., 2002](#)). In a state-wide survey in Uttar Pradesh in 2002, 9.9% of students in 8th through 10th grades

(mostly 13–15 years) were currently using *gutka* (at least once in 30 days) ([Sinha & Gupta, 2005](#)). In a survey of 385 rural adolescents (15–19 years) in villages of Wardha, Maharashtra in 2008, 17.1% were using *gutka* (31.7% boys, 4.0% girls) and 26.2% (54.1% boys, 1.0% girls) were using *kharra* [*mawa*] ([Dongre et al., 2008](#)). In a very small unpublished survey in a small town in Gujarat in 1999, 16% of boys in 8th and 9th grades were using *gutka* ([Gupta & Ray, 2002](#)). In a survey in Delhi, 10.2% of 2387 urban students aged 10–18 years were using betel quid with tobacco ([Kapil et al., 2005a](#)).

Male college students (16–23 years) in Karnataka in 1998 who smoked cigarettes said they sometimes substituted *gutka* for a cigarette when and where it was inappropriate to smoke. Though believed it to be very harmful and addictive, some students used *gutka* to help themselves quit smoking and then switched to *pan masala* to wean themselves off *gutka*. Those who believed that *gutka* was more addictive than cigarettes thought this strategy was unwise ([Nichter et al., 2004](#)).

Use of areca nut products is prevalent among youth in other South Asian countries. In a deprived area of Karachi, Pakistan, 47.2% of school boys aged 10–16 years were using areca nut by itself; [12.6%] used betel quid without tobacco and 16.1% used *gutka* or other smokeless tobacco products ([Rozi & Akhtar, 2007](#)). In Pokhara City, Nepal, ever use of *pan masala* and *gutka* by adolescents aged 13–15 years was found to be 51.4% in boys and 30.3% in girls ([Paudel, 2003](#)).

Among adolescent students in Taiwan, China, overall use of betel quid was 3.9% (6.6% boys, 1.5% girls), and ranged from 0.8% in cities to 4.3% in towns and 7.6% in villages ([Wang et al., 2003a](#)). The most variance in prevalence of betel quid use is found by type of school, ranging from 10.3% boys and 1.4% girls in general schools to 20.6% in boys and 4.7% in girls in agricultural schools ([Wang et al., 2004](#)). It was found that 26.9% of

ex-chewers and 22.3% of current chewers tried betel quid for the first time in elementary school. Peer pressure was the most important influence, followed by fathers giving the nuts to their child ([Wang et al., 2003a](#)). A survey of fourth grade elementary students in northern Taiwan, China, found ever chewers to be 10.8% in city schools and 56.6% in mountain schools, reflecting a higher prevalence in aboriginal population in mountainous areas ([Huang et al., 2009](#)).

Areca nut and tobacco practices and products from India are also becoming popular among children in countries of immigration, especially but not exclusively among children of Asian origin. A study from United Republic of Tanzania found that *gutka* and other packaged oral products imported from India were beginning to be used by adolescent students there, including those not of Indian origin ([Kaduri et al., 2008](#)). In the United Kingdom, betel quid chewing is known to be taken up by students of South Asian origin, and *gutka* is available and has been reportedly used among them ([Warnakulasuriya, 2002](#)). In East London, three quarters of the students of Bangladeshi origin in ninth grade had ever tried betel quid [apparently no question was asked about *gutka*] ([Jayakody et al., 2006](#)).

2. Cancer in Humans

2.1 Cancer of the oral cavity

Studies on betel quid and oral cavity cancers have been conducted in India, Pakistan, Sri Lanka, Thailand, Taiwan, China, South Africa, and Papua New Guinea. These populations differ in their patterns of betel quid use and the products and ingredients added to the quid ([Yang et al., 2001](#); [Gupta & Warnakulasuriya, 2002](#)). Betel quid is defined as any chewing substance that contains areca nut. In evaluating betel quid exposure, the main distinction is whether or not tobacco is added to the betel quid. When this was

not explicitly stated, tobacco was considered to be absent from the betel quid only if the study was conducted in a region/ethnicity where it is uncommon/unlikely for tobacco to be added to the betel quid (i.e. Taiwan, China). However if there was good background information that the habit of betel quid chewing was very prevalent in a region/ethnicity (i.e. India, Sri Lanka, persons of Indian descent), studies that assessed “tobacco chewing” and mentioned betel quid chewing in the exposure assessment were considered as exposure to betel quid with added tobacco. If this background information was not available, studies that assessed tobacco chewing without mention of betel quid chewing were excluded from both this *Monograph* and the *Monograph on Smokeless Tobacco* in this volume. Studies that evaluated genetic polymorphisms as a main effect and their interaction with betel quid chewing were also excluded even if a crude relative risk for betel quid chewing could be calculated.

2.1.1 Overview of studies

When the carcinogenicity of betel quid was first evaluated in 1984 ([IARC, 1985](#)), the relationship between betel quid chewing and cancer of the oral cavity had been investigated in four cohort studies ([Wahi, 1968](#); [Mehta et al., 1972](#); [Bhargava et al., 1975](#); [Gupta et al., 1980](#)) and many case-control studies ([Orr, 1933](#); [Sanghvi et al., 1955](#); [Sarma, 1958](#); [Khanolkar, 1959](#); [Shanta & Krishnamurthi, 1959, 1963](#); [Chandra, 1962](#); [Wahi et al., 1965](#); [Hirayama, 1966](#); [Jussawalla & Deshpande, 1971](#); [Khanna et al., 1975](#); [Kwan, 1976](#); [Notani & Sanghvi, 1976](#); [Simarak et al., 1977](#); [Jafarey et al., 1977](#)). The effect of betel quid without added tobacco was investigated in only a few studies.

When the available evidence was evaluated in 2003 ([IARC, 2004](#)), 15 additional case-control studies had been published ([Sankaranarayanan et al., 1989a, b, 1990a](#); [Nandakumar et al., 1990](#); [van Wyk et al., 1993](#); [Rao et al., 1994](#); [Ko et al.,](#)

1995; [Lu et al., 1996](#); [Rao & Desai, 1998](#); [Wasnik et al., 1998](#); [Dikshit & Kanhere, 2000](#); [Merchant et al., 2000](#); [Balaram et al., 2002](#); [Chen et al., 2002](#); [Znaor et al., 2003](#)).

The case-control studies of cancer of the oral cavity that clearly distinguish betel quid without and with added tobacco are summarized in Table 2.1 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.1.pdf>) and Table 2.2 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.2.pdf>) respectively. The derived relative risk estimates ranged from 1.5 to 58.4 for use of betel quid without tobacco and from 0.7 to 45.9 for betel quid with tobacco. Most of these studies adjusted for potential confounders such as tobacco smoking, use of smokeless tobacco, alcohol use, and HPV infection.

Since then there have been several publications assessing the association between betel quid chewing and cancer of the oral cavity ([Wen et al., 2005a](#); [Yang et al., 2005a](#); [Subapriya et al., 2007](#); [Thomas et al., 2007](#); [Muwonge et al., 2008](#); [Yen et al., 2008b](#); [Jayalekshmi et al., 2009](#)). The relative risk estimates from the three case-control studies ranged from 2.03 to 5.4 for use of betel quid without tobacco and from 3.19 to 11.8 for betel quid with tobacco.

2.1.2 Risk by type of agent

(a) Betel quid without added tobacco

An increased risk of statistical (or borderline) significance associated with betel quid chewing without tobacco was reported from all case-control studies of cancer of the oral cavity that considered this after adjusting for smoking and/or alcohol intake ([Nandakumar et al., 1990](#); [Ko et al., 1995](#); [Lu et al., 1996](#); [Wasnik et al., 1998](#); [Dikshit & Kanhere, 2000](#); [Merchant et al., 2000](#); [Balaram et al., 2002](#); [Chen et al., 2002](#); [Znaor et al., 2003](#); [Subapriya et al., 2007](#); [Thomas et al., 2007](#); [Muwonge et al., 2008](#); Table 2.1 online). [Znaor et](#)

[al. \(2003\)](#) reported an increased risk for cancer of the oral cavity associated with the use of betel quid without added tobacco in non-smoking and non-drinking men that had no other known risk factors (OR, 3.39; 95%CI: 2.04–5.66) after adjustment for age, centre and education level. In a study in Pakistan ([Merchant et al., 2000](#)) an increased risk for oral cancer was associated with the use of betel quid without added tobacco, after adjusting for smoking and alcohol. Data from Taiwan, China and Papua New Guinea, where betel quid is generally used without tobacco, also support this association.

In three cohort studies ([Bhargava et al., 1975](#); [Yang et al., 2005a](#); [Yen et al., 2008b](#)) increased risks of cancer of the oral cavity among betel quid chewers were found ([IARC, 2004](#); Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.3.pdf>); in two of these studies ([Bhargava et al., 1975](#); [Yang et al., 2005a](#)), incident cancers only occurred among betel quid chewers. [Yen et al. \(2008b\)](#) reported that the use of betel quid was significantly associated with cancer of the oral cavity in subjects who were neither smokers nor drinkers (OR, 10.97; 95%CI: 3.22–37.34). In a nested case-control study conducted in India, betel quid use without added tobacco was associated with cancer of the oral cavity overall ([Muwonge et al., 2008](#)). Among women [with a low prevalence of smoking in this population], the risk was highly significant after adjusting for smoking and drinking.

In a meta-analysis [Thomas et al. \(2007\)](#) included 11 independent studies that examined risk of cancer of the oral cavity associated with chewing betel quid without added tobacco ([Chandra, 1962](#); [Hirayama, 1966](#); [Jafarey et al., 1977](#); [Ko et al., 1995](#); [Lu et al., 1996](#); [Dikshit & Kanhere, 2000](#); [Merchant et al., 2000](#); [Balaram et al., 2002](#); [Chen et al., 2002](#); [Znaor et al., 2003](#); [Thomas et al., 2007](#)). These studies either excluded smokers or controlled for smoking. The overall odds ratio estimated for betel quid

without tobacco was 2.14 (95%CI: 1.06–4.32) among non-smokers and 3.50 (95%CI: 2.16–5.65) in studies that adjusted for smoking.

(b) *Betel quid with added tobacco*

Significantly increased risks for cancer of the oral cavity associated with chewing betel quid with added tobacco were observed in all of the case-control studies that considered this (Orr, 1933; Sanghvi *et al.*, 1955; Sarma, 1958; Khanolkar, 1959; Shanta & Krishnamurthi, 1959, 1963; Chandra, 1962; Hirayama, 1966; Wahi *et al.*, 1965; Wahi, 1968; Jussawalla & Deshpande, 1971; IARC, 1985; Sankaranarayanan *et al.*, 1989a, b, 1990a; Nandakumar *et al.*, 1990; van Wyk *et al.*, 1993; Rao *et al.*, 1994; Rao & Desai, 1998; Wasnik *et al.*, 1998; Dikshit & Kanhere, 2000; Merchant *et al.*, 2000; Balaram *et al.*, 2002; Znaor *et al.*, 2003; Subapriya *et al.*, 2007; Muwonge *et al.*, 2008; Table 2.2 online) and in two cohort studies (Wahi, 1968; Gupta *et al.*, 1980). All of the case-control studies adjusted for smoking and some studies additionally adjusted for alcohol use.

(c) *Areca nut and betel inflorescence*

The risk of chewing areca nut alone without other ingredients (particularly tobacco) was examined in one Indian study (Wasnik *et al.*, 1998), a suggestive increased risk of cancer of the oropharynx was reported (OR, 2.6; 95%CI: 0.9–7.7).

In a study in Taiwan, China, the risk for cancer of the oral cavity was highest among those who chewed only unripe areca nut (OR, 11.6; 95%CI: 3.7–36.9; 41 exposed cases) compared with those who chewed betel leaf alone (OR, 0.1; 95%CI: 0.0–6.3; 1 exposed case) or a mixture of the two (OR, 8.5; 95%CI: 2.7–26.3; 34 exposed cases) after adjustment for education, occupation, smoking and drinking (Ko *et al.*, 1995).

2.1.3 Exposure–response relationship

(a) *Intensity and duration*

An exposure–response relationship (by various metrics of exposure such as intensity, duration, age at starting or betel quid-years) between betel quid chewing and oral cancer was demonstrated in several studies (Orr, 1933; Sankaranarayanan *et al.*, 1989a, b, 1990a; Nandakumar *et al.*, 1990; Rao *et al.*, 1994; Lu *et al.*, 1996; Rao & Desai, 1998; Wasnik *et al.*, 1998; Dikshit & Kanhere, 2000; Merchant *et al.*, 2000; Balaram *et al.*, 2002; Znaor *et al.*, 2003; Thomas *et al.*, 2007; Muwonge *et al.*, 2008; Jayalekshmi *et al.*, 2009; IARC, 1985; Table 2.4 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.4.pdf>). Not all reports distinguished whether or not tobacco was added to the betel quid, though many controlled for smoking, consumption of alcoholic beverages, or both. [Merchant *et al.* (2000) did not present odds ratios and corresponding 95% confidence intervals were not present for the tertiles of paan-years (P for trend = 0.004 for paan-years with tobacco and P for trend = 0.0008 for paan-years without tobacco.)]

(b) *Cessation*

The effect of cessation has not been examined extensively. In one study, having quit chewing betel quid with added tobacco 10 years earlier or within 10 years did not demonstrate a beneficial effect in either sex (Balaram *et al.*, 2002). Znaor *et al.* (2003), however, were able to demonstrate a decrease of risk for cancer of the oral cavity after 10 years or more of quitting. [Znaor *et al.* (2003) did not distinguish whether or not tobacco was added to the quid for this analysis.]

2.1.4 Anatomical subsites of cancer

Some authors reported site-specific (gingiva, tongue, mouth) differences in relative risk (Sanghvi *et al.*, 1955; Khanolkar, 1959; Shanta

& Krishnamurthi, 1959, 1963; Chandra, 1962; Hirayama, 1966; Wahi, 1968; Jussawalla & Deshpande, 1971; Kwan, 1976; Sankaranarayanan *et al.*, 1989b; Rao & Desai, 1998; Znaor *et al.*, 2003). In non-smokers and non-drinkers, Wahi (1968) reported the highest risks for the buccal mucosa, gingiva and lip combined associated with chewing betel quid with tobacco. After adjusting for smoking and alcohol, Znaor *et al.* (2003) reported higher risks for the mouth compared to the tongue, for betel quid use both with or without tobacco.

2.1.5 Population characteristics

In most studies, markedly higher estimates of risk for cancer of the oral cavity were found in women than in men for betel quid chewing, with or without tobacco (Sanghvi *et al.*, 1955; Chandra, 1962; Shanta & Krishnamurthi, 1963; Hirayama, 1966; Wahi, 1968; Notani & Sanghvi, 1976; Jafarey *et al.*, 1977; Simarak *et al.*, 1977; Sankaranarayanan *et al.*, 1989a, b, 1990a; Nandakumar *et al.*, 1990; van Wyk *et al.*, 1993; Rao *et al.*, 1994; Rao & Desai, 1998; Dikshit & Kanhere, 2000; Balaram *et al.*, 2002; Znaor *et al.*, 2003; Muwonge *et al.*, 2008; Yen *et al.*, 2008b; Jayalekshmi *et al.*, 2009).

2.1.6 Interactions

Among the many studies of cancer of the oral cavity that have examined multiple habits with 2- and 3-way combinations among tobacco smoking, alcohol drinking and betel quid chewing, only a few studies formally tested for interaction. Table 2.5 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.5.pdf>) and Table 2.6 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.6.pdf>) provide data from studies reporting combined odds ratios for combination of habits. Findings are not

consistent across studies. In general interaction is at an additive level only.

In three studies the interaction between betel quid chewing without added tobacco and tobacco smoking was examined (Ko *et al.*, 1995; Znaor *et al.*, 2003; Thomas *et al.*, 2007) and it was found that risk was highest in those who smoked, drank alcohol and chewed betel quid. For subjects consuming betel quid (with or without added tobacco) there was an interaction with smoking among non-alcohol drinkers by Znaor *et al.* (2003) ($P = 0.00$). However, in another study from India, there was no suggestion of an interaction between betel quid chewing with or without added tobacco and tobacco smoking (Muwonge *et al.*, 2008). For those chewing betel quid with tobacco, interactions with tobacco smoking were found in a few other studies (Sankaranarayanan *et al.*, 1989a, b, 1990a; Dikshit & Kanhere, 2000), and were significant in some (Sankaranarayanan *et al.*, 1989a, b, 1990a). In a study that examined 2-way interactions between betel quid chewing and consumption of alcoholic beverages, evidence suggestive of a synergistic effect was observed in men who chewed betel quid with tobacco (Znaor *et al.*, 2003). However, in another study from India, there was no suggestion of an interaction between betel quid chewing with or without added tobacco and consumption of alcoholic beverages (Muwonge *et al.*, 2008).

The 3-way interaction of betel quid chewing, tobacco smoking and consumption of alcoholic beverages was considered in few studies (Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.7.pdf>). While the interactions were found significant in two studies (Sankaranarayanan *et al.*, 1989a; Znaor *et al.*, 2003) and, in 2 other studies from India there was no suggestion of an interaction (Sankaranarayanan *et al.*, 1990a; Muwonge *et al.*, 2008).

2.1.7 Population attributable risk

The population attributable risk fraction of cancer of the oral cavity was observed to be 66% for chewers of betel quid with tobacco in Bhopal, India ([Dikshit & Kanhere, 2000](#)). In a study in Trivandrum, India, the adjusted population attributable risk fraction estimated for women for having ever chewed (81.2%) was nearly double that of men (42.6%) ([Muwonge et al., 2008](#)).

2.2 Precancerous lesions of the oral cavity

Precancerous lesions or potentially malignant disorders of the oral cavity precede cancer development and largely contribute to the burden of cancer of the oral cavity in South Asia. In the restricted geographic locations where people consume betel quid, the disorders of concern are leukoplakia, erythroplakia, erythroleukoplakia, and oral submucous fibrosis ([Warnakulasuriya et al., 2007](#)).

In India, betel quid or areca nut use either alone or in combination with tobacco account for most of the leukoplakia cases ([Smith et al., 1975](#); [Gupta et al., 1980](#)). The studies examining the association between betel quid chewing and oral precancerous lesions undertaken before 2004 were reviewed in previous *IARC Monographs* ([IARC, 1985, 2004](#)). The relative risk estimates for oral leukoplakia ([Hashibe et al., 2000a](#); [Shiu et al., 2000](#); [Yang et al., 2001](#); [Lee et al., 2003](#)), erythroplakia ([Hashibe et al., 2000b](#)), oral submucous fibrosis ([Sinor et al., 1990](#); [Maher et al., 1994](#); [Gupta et al., 1998](#); [Hazare et al., 1998](#); [Shah & Sharma, 1998](#); [Hashibe et al., 2002](#)) ranged from 7 to around 30. Other studies of oral submucous fibrosis reported high risks associated with betel quid use: RR 32 (95%CI: 6–177) for betel quid without tobacco and RR 154 (95%CI: 34–693) for areca nut alone ([Maher et al., 1994](#)); RR 75.6 among users of mawa (a mixture of areca nut, tobacco and slaked lime) ([Gupta et al., 1998](#))

and RR 49.2 (95%CI: 24.3–99.6) among betel quid chewers (with and without added tobacco) ([Hashibe et al., 2002](#)).

Since then new evidence has accumulated on the association between betel quid and areca nut use and oral pre-cancer. Some of these studies evaluated the risks for combinations of oral mucosal disorders grouped together (oral precancer; oral potentially malignant disorders) or separately for leukoplakia, erythroplakia or oral submucous fibrosis. Data from these new studies are summarized in Table 2.8 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.8.pdf>). In two cross-sectional studies from Sri Lanka and Taiwan, China, where betel quid is used without added tobacco, significant associations for areca quid/betel quid chewing with oral precancerous lesions were found. The risks were 8.40 (95%CI: 5.13–13.75) in Taiwan, China ([Chung et al., 2005](#)) and 3.01 (95%CI: 2.25–4.0) in Sri Lanka (betel quid with or without added tobacco) ([Ariyawardana et al., 2007](#)). Both studies were adjusted for tobacco smoking and alcohol drinking. In several case-control studies (in India, Sri Lanka, Taiwan, China and Papua New Guinea), use of betel quid without added tobacco in non tobacco smokers and/or non alcohol drinkers was associated with an increased risk in oral precancerous lesions ([Jacob et al., 2004](#); [Yang et al., 2005b](#); [Thomas et al., 2008](#)). The risks for oral leukoplakia and erythroplakia were significantly elevated in betel quid chewers with tobacco, as well as in those chewing betel quid without tobacco in an Indian population ([Jacob et al., 2004](#)) and among Taiwan, China, Chinese populations, who do not add tobacco to their betel quid ([Shiu et al., 2000](#); [Chen et al., 2006](#); [Yen et al., 2007](#)). In some of these studies significant exposure-response relationships were found ([Jacob et al., 2004](#); [Yang et al., 2005b](#); [Yen et al., 2008a](#)). [Shiu et al. \(2000\)](#) found that betel quid use without added tobacco is a significant factor influencing malignant transformation of oral leukoplakia (OR, 4.59;

95%CI: 1.25–16.86). [Ho et al. \(2009\)](#) however found no positive association with betel quid use without added tobacco and malignant transformation of existing premalignant disorders (OR, 0.98; 95%CI: 0.36–2.97). [Yang et al. \(2005b\)](#) reported a significant positive association for betel quid chewing without tobacco (among non smokers) with oral submucous fibrosis from a case–control study in Taiwan, China (OR, 4.51; 95%CI: 1.20–16.94). In a further study from Sri Lanka, [Ariyawardana et al. \(2006\)](#) found that betel quid chewing with and without tobacco was the only significantly associated risk factor in oral submucous fibrosis (OR, 171.8; 95%CI: 36.35–812.25) and there was no interaction with either tobacco smoking or alcohol use. However, alcohol drinking had a significant effect on the malignant transformation in oral submucous fibrosis, while areca/betel quid chewing showed no association ([Ho et al., 2007](#)). In a study from the People’s Republic of China, duration of betel quid use without added tobacco was associated with a significantly increased risk (OR for longest duration, 10.15; 95%CI: 2.72–37.79) for malignant transformation of oral submucous fibrosis, (P for trend = 0.008) ([Zhou et al., 2008](#)). [The Working Group noted that interpretation of these results may be hampered by the use of oral submucous fibrosis controls]. In a further case–control study ([Ahmad et al., 2006](#)), *gutka* and other areca nut products had a highly significant association with oral submucous fibrosis ($\chi^2 = 188.14$, $P < 0.001$). [The Working Group noted that oral submucous fibrosis is not associated with tobacco use or alcohol drinking.]

Intervention studies demonstrated that reduction in the use of betel quid with added tobacco resulted in lowering the incidence of precancerous lesions ([Gupta et al., 1986, 1992](#)) and cessation resulted in development of no new precancerous lesions ([Gupta et al., 1995](#)).

[Thomas et al. \(2008\)](#) included 6 studies in a meta-analysis that examined risk of oral precancerous disorders associated with betel quid

without tobacco. These studies either excluded smokers or controlled for smoking. Among non-smokers with oral precancerous lesions their overall odds ratio estimated for betel quid without tobacco was 10.13 (95%CI: 4.09–25.08) and in studies that adjusted for smoking the combined odds ratio was 5.17 (95%CI: 2.79–9.57).

2.3 Other cancers of the upper aerodigestive tract

2.3.1 Cancers of the pharynx

(a) Nasopharynx

In a cohort study from Taiwan, China, where tobacco is never added to betel quid ([Wen et al., 2005a](#)), betel quid chewers who smoked had an increased risk of death from cancer of the nasopharynx (RR, 4.2; 95%CI: 1.5–11.4) after adjusting for age, alcohol use and education (Table 2.9 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.9.pdf>). [There has been no publication from Taiwan, China where betel quid chewing was reported separately from smoking, because most betel quid chewers smoke.] Positive associations with 20 or more years of areca nut use were found in a case–control study of cancer of the nasopharynx from Taiwan, China ([Yang et al., 2005](#); Table 2.10 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.10.pdf>). [The models were adjusted for age and sex but it was unclear if they were further adjusted for other factors such as cigarette smoking, Guangdong salted fish consumption during childhood, and cumulative wood dust exposure]. Two case–control studies of cancer of the nasopharynx from India, where tobacco is commonly added to the betel quid, also found positive associations with betel quid chewing ([Jussawalla & Deshpande, 1971](#); [Chelleng et al., 2000](#)).

(b) Oropharynx

Cancer of the oropharynx has been associated with chewing betel quid with added tobacco ([Sanghvi et al., 1955](#); [Khanolkar, 1959](#); [Shanta & Krishnamurthi, 1963](#); [Hirayama, 1966](#); [Jussawalla & Deshpande, 1971](#); [Wasnik et al., 1998](#); [Dikshit & Kanhere, 2000](#); [Znaor et al., 2003](#)) and without added tobacco ([Shanta & Krishnamurthi, 1963](#); [Hirayama, 1966](#); [Jussawalla & Deshpande, 1971](#); [Wasnik et al., 1998](#); [Znaor et al., 2003](#)) in all of the studies in which it was assessed ([IARC \(2004\)](#) and Table 2.10 online. [The Working Group noted that the title of the study by [Dikshit & Kanhere \(2000\)](#) mentioned ‘oropharyngeal’ but the authors made occasional references to ‘oral cavity’ in the article]. None of the studies controlled for HPV, an important risk factor for cancer of the oropharynx. All of the studies were conducted in India, and [Hirayama \(1966\)](#) additionally enrolled subjects from Sri Lanka.

(c) Hypopharynx

Several positive associations between cancer of the hypopharynx and chewing betel quid (with or without added tobacco or unspecified) have been reported ([Sanghvi et al., 1955](#); [Shanta & Krishnamurthi, 1963](#); [Jussawalla & Deshpande, 1971](#); [Simarak et al., 1977](#); [Znaor et al., 2003](#); [Sapkota et al., 2007](#); [IARC \(2004\)](#) and Table 2.10 online. Most analyses accounted for tobacco use and two additionally adjusted for alcohol drinking ([Znaor et al., 2003](#); [Sapkota et al., 2007](#)). For users of products containing both tobacco and areca nut (*mawa*, *pan* with tobacco and *gutka*), statistically significant results were seen for each of those behaviours (separately evaluated) for never smokers only, with adjustment for snuff use (nasal or oral), alcohol, drinking and smoking ([Sapkota et al., 2007](#)).

(d) Pharynx

In several case-control studies a positive association between chewing betel quid with added tobacco and cancer of the pharynx has been found after controlling for tobacco smoking ([Sanghvi et al., 1955](#); [Shanta & Krishnamurthi, 1963](#); [Jussawalla & Deshpande, 1971](#); [Simarak et al., 1977](#); [Wasnik et al., 1998](#); [Dikshit & Kanhere, 2000](#); [Znaor et al., 2003](#); [Sapkota et al., 2007](#); [IARC, 2004](#); Table 2.10 online). [Znaor et al. \(2003\)](#) and [Sapkota et al. \(2007\)](#) additionally adjusted for alcohol drinking. [Znaor et al. \(2003\)](#) also found dose-dependent increases in risk of combined oro-, hypo- and unspecified pharyngeal cancers by amount used, duration of use and cumulative use of unspecified betel quid (considered to be mostly with added tobacco).

In two studies chewing of betel quid without added tobacco was found to be positively associated with cancer of the pharynx ([Znaor et al., 2003](#); [Lee et al., 2005a](#)), after adjusting for tobacco smoking and alcohol drinking. [Lee et al. \(2005a\)](#) showed dose-dependent increases in risk of combined hypo- and oro-pharyngeal cancers by age of chewing initiation and amount chewed. The highest odds ratios were for people who used betel inflorescence and for those who swallowed the juice of the quid ([Lee et al., 2005a](#)).

2.3.2 Cancer of the oesophagus

The risk of cancer of the oesophagus associated with chewing betel quid with added tobacco has been assessed in several studies ([IARC, 2004](#); Table 2.10 online). These included studies carried out in India that specifically assessed betel quid with added tobacco ([Shanta & Krishnamurthi, 1963](#); [Jussawalla & Deshpande, 1971](#); [Jayant et al., 1977](#); [Sankaranarayanan et al., 1991](#); [Znaor et al., 2003](#)); others carried out in India that did not specify as to whether tobacco was added to the betel quid ([Sanghvi et al., 1955](#); [Nandakumar et al., 1996](#); [Chitra et al., 2004](#)); and studies in Thailand ([Phukan et al., 2001](#); [Boonyaphiphat](#)

[et al., 2002](#)) where tobacco is typically added to the quid. The majority of studies reported positive associations but only three ([Nandakumar et al., 1996](#); [Boonyaphiphat et al., 2002](#); [Znaor et al., 2003](#)) controlled for both smoking and alcohol use. In a case-control study in Kerala, India no association of cancer of the oesophagus with chewing betel quid with added tobacco was found but there was no control for smoking ([Sankaranarayanan et al., 1991](#)). In the case-control study in Thailand odds ratios increased with increasing number of quids chewed from 1.47 (95%CI: 0.9–2.3) with chewing less than 10 quids per day to 5.6 (95%CI: 2.7–11.8) for chewing more than 10 quids per day ([Boonyaphiphat et al., 2002](#)).

The association between betel quid without added tobacco and cancer of the oesophagus has been evaluated in eight studies ([Shanta & Krishnamurthi, 1963](#); [Jussawalla & Deshpande, 1971](#); [Wu et al., 2001, 2004a, 2006](#); [Znaor et al., 2003](#); [Lee et al., 2005b, 2007](#)); five analyses controlled for tobacco smoking and alcohol drinking ([Znaor et al., 2003](#); [Wu et al., 2004a, 2006](#); [Lee et al., 2005b, 2007](#)). Positive associations were found in all studies, of which six ([Jussawalla & Deshpande, 1971](#); [Wu et al., 2001, 2004a](#); [Znaor et al., 2003](#); [Lee et al., 2005b, 2007](#)) were statistically significant. Significant dose-response relationships after controlling for smoking and alcohol were observed by [Lee et al. \(2005b, 2007\)](#). In a cohort study based on a national survey and community, [Wen et al. \(2005a\)](#) could not separate the effect of chewing betel quid without added tobacco and tobacco smoking since currently most betel quid chewers smoke in Taiwan, China (Table 2.9 online). The highest relative risks were reported in Taiwan, China among those who chewed betel inflorescence ([Wu et al., 2004a](#), [Lee et al., 2005b, 2007](#); [Wu et al., 2006](#)). [Betel inflorescence contains a high concentration of safrole, a possible human carcinogen (IARC Group 2B)].

In two studies risk was evaluated for cancer at subsites of the oesophagus. The highest

magnitude of effect associated with chewing betel quid were reported for the upper third of the oesophagus in Taiwan, China ([Lee et al., 2007](#)) and for the middle-third of the oesophagus in India ([Nandakumar et al., 1996](#)). Both studies controlled for tobacco smoking and alcohol drinking.

2.3.3 Cancer of the larynx

In India, where tobacco is commonly added to the betel quid, positive associations with chewing betel quid were found in two case-control studies of cancer of the larynx ([Jussawalla & Deshpande, 1971](#); [Kapil et al., 2005b](#)) while in two other case-control studies there was no association ([Sankaranarayanan et al., 1990b](#); [Sapkota et al., 2007](#); [IARC, 2004](#); Table 2.10 online). [[Jussawalla & Deshpande \(1971\)](#), [Sankaranarayanan et al. \(1990b\)](#) and [Kapil et al. \(2005b\)](#) did not adjust for smoking or drinking habits.] In Taiwan, China ([Lee et al., 2005a](#)), chewing betel quid without added tobacco was positively but not significantly associated with the risk of cancer of the larynx, after adjusting for smoking and alcohol (OR, 1.3; 95%CI: 0.7–2.5).

2.3.4 Interactions

Several studies have reported the joint effects of chewing betel quid, adding chewing tobacco, smoking tobacco and/or drinking alcohol. A re-analysis of the data from [Jussawalla & Deshpande \(1971\)](#) found that chewing and smoking practices interacted synergistically for cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus ([Jayant et al., 1977](#)). [Znaor et al. \(2003\)](#) also showed a synergistic relationship between betel quid chewing, tobacco smoking and alcohol consumption for cancer of the pharynx. These findings are similar to those on smoking and betel quid chewing from a cohort study in Taiwan, China with nasopharyngeal and oesophageal cancer as reported outcomes ([Wen](#)

[et al., 2005a](#)). The common occurrence of dual or multiple substance use (chewing betel quid, adding chewing tobacco, smoking tobacco and drinking alcohol) in populations makes these findings important, as the magnitude of effect is highest for those who combine these habits.

2.4 Cancer of the liver

2.4.1 Cohort studies

Three cohort studies conducted in Taiwan, China, investigated the association between betel quid use [without added tobacco] and cancer of the liver ([Sun et al., 2003](#); [Wang et al., 2003b](#); [Wen et al., 2005a](#); Table 2.11 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.11.pdf>). [Sun et al. \(2003\)](#) found a synergistic association between hepatocellular carcinoma and betel quid chewing without added tobacco in those with hepatitis C virus (HCV) infection. [The number of cases was small (2 cases among betel quid chewers with HCV infection; 8 cases among betel quid chewers without HCV infection) and there was no adjustment for tobacco smoking and alcohol consumption.]

[Wang et al. \(2003b\)](#) found high and statistically significant relative risks for hepatocellular carcinoma associated with betel quid chewing without added tobacco. Compared to Hepatitis B surface Antigen (HBsAg) seronegative men who did not chew betel quid, chewing betel quid without added tobacco conferred a relative risk of 3.43 (95%CI: 1.19–9.89), with a dose–response relationship for quantity chewed per day (P trend = 0.007). [The Working Group noted that the authors adjusted for liver function at baseline but did not adjust for tobacco smoking and alcohol consumption.] [Wen et al. \(2005a\)](#) conducted a cohort study in Taiwan, China and found a statistically significant positive association with liver cancer and cirrhosis of the liver, after adjusting for HBsAg, for those who both

smoked cigarettes and chewed betel quid without added tobacco (RR, 1.8; 95%CI: 1.1–2.8). The magnitude of effect observed was much higher than that observed for those who only smoked but did not chew betel quid. [The Working Group noted that there were too few non smoking betel chewers to calculate a relative risk for them in this study].

2.4.2 Case–control studies

Two case–control studies ([Tsai et al., 2001, 2004](#)) and one cross-sectional study ([Wu et al., 2009a](#)) from Taiwan, China, and one case–control study from Thailand ([Srivatanakul et al., 1991](#)) showed significant associations between chewing betel quid without added tobacco and hepatocellular carcinoma (Table 2.12 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-05-Table2.12.pdf>). [It was not specified whether or not tobacco was added to the betel quid in [Srivatanakul et al., 1991](#)]. [Tsai et al. \(2001\)](#) reported an exposure–response relationship and a synergy with viral infection after adjusting for infection with hepatitis virus (HBV and HCV), tobacco smoking, alcohol consumption and socio-demographic variables. [Tsai et al. \(2004\)](#) showed significant associations of hepatocellular carcinoma with betel quid chewing, using two separate control groups (healthy population-based controls and cirrhosis patients). Furthermore, an exposure–response relationship was observed with the duration and quantity of betel quid chewed (P for trend < 0.0001). There was also a positive association between betel quid chewing without tobacco and cirrhosis, a precursor to liver cancer ([La Vecchia et al., 1998](#)).

Betel quid appears to act synergistically with viral infections in causing liver cancer. When comparing hepatocellular carcinoma patients to healthy controls, the odds ratio associated with chewing betel quid without tobacco among persons positive for a hepatitis virus (HBV or HCV) was statistically significantly elevated and

orders of magnitude higher than the odds ratio associated with being hepatitis virus positive and a non-chewer or being a chewer and hepatitis virus negative. [No formal test for interaction was presented and the 95% confidence intervals were wide due to the small sample size. It was not possible to determine whether these models were adjusted for alcohol consumption, tobacco smoking or other confounding factors. There was some overlap in cases between [Tsai et al. \(2001\)](#) and [Tsai et al. \(2004\)](#).]

A population-based study of liver cirrhosis and hepatocellular carcinoma combined was conducted in Keelung, northern Taiwan, China on 60 326 persons aged 30 years and above who were enrolled in a screening programme ([Wu et al., 2009a](#)). [Prevalent and incident cases were combined.] There was a statistically significant positive association with chewing betel quid without added tobacco and significant exposure-response relationships for the number of quids chewed daily, number of years of chewing, cumulative exposure (portion-days), and age at initiation (P for trend < 0.01) after adjusting for sex, HBsAg, anti-HCV antibodies, cumulative exposure to alcohol consumption and cigarette smoking. Betel quid chewers who were seronegative for both HBsAg and anti-HCV had a hazard ratio of 5.09 (95%CI: 2.87–9.03); a synergistic association was observed for betel quid chewing and seropositivity for one or both viral markers (hazard ratios ranged from 25–29). [The Working Group noted that the most popular type of betel quid in Keelung includes unripe nuts, betel inflorescence and red lime paste and is swallowed after chewing. It was mentioned that aflatoxin is commonly present in areca nuts, but this was according to a reference from India, where ripe nuts are used for chewing and may be stored for long periods, making them susceptible to mould. Both prevalent and incident cases were included and hepatocellular carcinoma and liver cirrhosis cases were combined, which limits the

interpretation of the data for the carcinogenicity of betel quid chewing.]

2.5 Other cancers

2.5.1 Cancer of the stomach

In a case-control study on stomach cancer from Taiwan, China [Wu et al. \(2004b\)](#) found a positive association with cumulative chewing of betel quid without added tobacco (betel-years): the odds ratios increased with higher consumption, after adjusting for alcohol consumption, tobacco smoking and *H. pylori* infection (P for trend = 0.03). In a hospital-based case-control study from Chennai, India ([Gajalakshmi & Shanta, 1996](#)), elevated odds ratios (not statistically significant) of similar magnitude (range 1.2–1.4) were observed for chewing areca nut only, betel quid only, and betel quid with added tobacco, although the risk disappeared after adjusting for tobacco smoking, alcohol consumption and diet. From a hospital-based case-control study of stomach cancer in Mizoram, India [Phukan et al. \(2005\)](#) reported elevated odds ratios for chewing betel quid with or without added tobacco, with significant trends for increasing odds ratios with increasing exposure (according to various exposure metrics) after adjusting for alcohol drinking, smoking, use of *tuibur*, level of education, occupation and income group.

2.5.2 Cancer of the cervix

One study described the association between betel quid chewing (with or without added tobacco) and cervical cancer in which nearly all women were non-smokers and in which all cases, but one, were HPV positive ([Rajkumar et al., 2003](#)). There was an association between the use of betel quid without tobacco and cervical cancer; among women who reported using betel quid more than 5 times per day the odds ratio was 4.0

(95%CI: 1.20–13.33) with a significant trend with increasing number of times used per day.

A cross-sectional study derived from a screening programme ([Chakrabarti et al., 1990](#)) showed an association between betel quid chewing with and without tobacco and cervical dysplasia. [Women with cytoepidemiological evidence of infection with HPV, HSV, *Trichomonas vaginalis* and *Chlamydia trachomatis* were excluded from the study.]

2.5.3 Cancers of the lung, colon and gallbladder

Several studies have assessed the association between chewing betel quid with or without added tobacco and cancer of the lung ([Wen et al., 2005a](#)), colon ([Wu et al., 2009b](#)) and gallbladder ([Pandey & Shukla, 2003](#); [Shukla et al., 2008](#)).

2.6 Synthesis

2.6.1 Oral cavity

Chewing betel quid, both with and without added tobacco, causes cancer of the oral cavity ([IARC, 2004](#)). Recent studies, many of which were adjusted for tobacco smoking, consumption of alcoholic beverages, and/or HPV infection, the major risk factors for oral cancer, confirmed this evaluation. Additionally, positive exposure–response relationships were reported in some studies.

2.6.2 Precancerous lesions of the oral cavity

Many cohort, case–control and cross-sectional studies from a wide range of countries have noted a high prevalence of oral precancerous disorders (leukoplakia, erythroplakia, oral submucous fibrosis) among users of betel quid and areca nut compared to non-users. Among betel quid users with added tobacco in Sri Lanka and India, significant associations were reported in four studies after adjusting for or stratifying

by tobacco smoking or consumption of alcoholic beverages. The association between betel quid without added tobacco and precancerous disorders was examined in 6 studies from India, Taiwan, China and Papua New Guinea. A significant positive association was found in all studies and a significant dose–response was observed in 2 of them. Among users of areca nut only, significant associations were reported after adjusting for stratifying by tobacco smoking or consumption of alcoholic beverages. A significant positive association was reported from three studies in Pakistan and India that examined the association between areca nut use and oral submucous fibrosis.

2.6.3 Pharynx

Numerous studies, some of cohort and many of case–control design, have been performed on chewing betel quid, with or without tobacco, and the risk for cancers of the naso-, oro- and hypopharynx, or of the pharynx not otherwise specified. Chewing betel quid with added tobacco is causally associated with cancers of the pharynx and its subsites. Positive exposure–response relationships were noted in some studies, strengthening the credibility of a causal association. In some studies it was possible to demonstrate a synergistic relationship between betel quid chewing, tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the pharynx.

2.6.4 Oesophagus

One cohort and several case–control studies have been performed on chewing betel quid and the risk for cancer of the oesophagus. Chewing betel quid, both with and without added tobacco, causes cancer of the oesophagus. Positive exposure–response relationships were reported in some studies, strengthening the credibility of a causal association. A synergistic relationship

between betel quid chewing, tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the oesophagus was demonstrated in some studies.

2.6.5 Liver

The association between betel quid without added tobacco and cancer of the liver has been evaluated in six studies: 3 cohort studies, 2 case-control and 1 cross-sectional study. Five studies were from Taiwan, China, where betel quid is chewed without added tobacco, and one study was from Thailand, in which the use of betel quid with or without added tobacco was not specified. Significant positive associations were observed in 4 of the 5 Taiwanese studies, although confounding by tobacco smoking, alcohol consumption, hepatitis B or C virus positivity could not be ruled out. Significant positive dose-response relationships with the amount of betel quid chewed were observed in two studies, although confounding could not be ruled out.

2.6.6 Other sites

Several epidemiological studies assessed cancers at other sites but there are not enough data to permit a conclusion.

3. Cancer in Experimental Animals

Several studies investigating the carcinogenicity of betel quid and areca nut in experimental animal have inadequate numbers of animals per group, inadequate frequency and duration of treatment, absence of appropriate controls, ambiguous description of lesions, low survival of animals and inadequate reporting of survival data. Studies that were considered uninformative are not included in the present evaluation.

Representative studies are reported below and are described in [Tables 3.1, 3.2, 3.3](#).

3.1 Mouse

Administration of either areca nut, areca nut and tobacco, arecoline or *pan masala* by skin application did not produce tumours in some studies ([Ranadive et al., 1976](#); [Pai et al., 1981](#); [Ramchandani et al., 1998](#)). Topical application of an extract of areca nut extract and tobacco produced epidermoid carcinomas in a small number (2/23) of C17 mice ([Ranadive et al., 1976](#)).

A group of 21 male Swiss mice was administered 0.1 mL of an aqueous extract of areca nut (containing 1.5 mg arecoline and 1.9 mg polyphenol) by gavage on five days a week for life. Twelve out of 21 treated mice developed tumours (five hepatocellular carcinomas [$P < 0.05$], two liver haemangiomas, two lung adenocarcinomas, one adenocarcinoma, one squamous cell carcinoma of the stomach, and one leukaemia). No tumour was observed in 20 untreated controls ([Bhide et al., 1979](#)).

Administration of 0.1 mL of an aqueous extract of areca nut (containing 1.5 mg arecoline) on five days a week for life by gavage produced lung adenocarcinomas in 47% (9/19, $P < 0.05$) of male Swiss mice. One untreated control mouse of 20 developed a lung adenocarcinoma ([Shirname et al., 1983](#)).

Administration by gavage of arecoline hydrochloride, a component of areca nut, induced three squamous cell carcinomas of the stomach, four lung adenocarcinomas and eight liver haemangiomas [not significant] in 43% (15/35) male Swiss mice. One untreated control mouse of 20 developed an unspecified tumour ([Bhide et al., 1984](#)).

Dietary feeding of unprocessed areca nut or application of a paste of unprocessed areca nut to the oral cavity of male and female Swiss mice induced squamous cell carcinomas and papillomas in the oesophagus of a small number of

Table 3.1 Carcinogenicity studies of administration of areca nut or betel quid in experimental animals

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence and/or multiplicity of tumours	Significance	Comments
Mouse, Swiss (M, F) Lifetime Ranadive et al. (1976)	Subcutaneous injection	Fibrosarcomas:		
	Areca nut (hot aqueous extract), 50 mg/mL, 0.2 mL, once/wk for 6 wk; 20/group	14/20	[P < 0.0001]	
	Areca nut (cold aqueous extract), 50 mg/mL, 0.2 mL, once/wk for 6 wk; 20/group	10/20	[P < 0.001]	
	Distilled water, 0.2 mL, once/wk for 10 wk; 25/group	0/25	-	
Mouse, Swiss (M, F) Lifetime Ranadive et al. (1976)	Topical application	Skin tumours:		
	Areca nut/DMSO extract, 30 g areca nut in 20 mL DMSO, 0.1 mL, 3 × /wk; 10M+8F/group	0/18	NS	
	Tobacco/DMSO extract, 5 g tobacco in 20 mL DMSO, 0.1 mL, 3 × /wk; 10M+6F/group	0/16	NS	
	Areca nut + tobacco/DMSO extract, 30 g areca nut + 5 g tobacco in 20 mL DMSO, 0.1 mL, 3 × /wk; 11M+12F/group	1/23 (papillomas), 2/23 (carcinomas)	NS	
Mouse, Swiss (M) Lifetime Shivapurkar et al. (1980)	DSMO 0.1 mL, 3 × /wk; 9M+12F/group	0/21	-	Age not specified
	Subcutaneous injection			
	Areca nut/polyphenol fraction, 0.1 mL, once/wk for 13 wk (total dose, 24.7 mg polyphenol)	20/20 (fibrosarcoma, 16/20; hepatoma, 1/20; lung adenocarcinoma, 3/20)	[P < 0.0001] (fibrosarcomas)	
	Betel quid aqueous extract, 0.2 mL, once/wk for 13 wk (total dose, 38.4 mg alkaloid + 46.0 mg polyphenol)	7/20 (fibrosarcoma)	[P < 0.01]	
Rat, NIH Black (M, F) 68 wk Kapadia et al. (1978)	Distilled water, 0.1 mL, once/wk for 13 wk 20/group	0/20	-	
	Subcutaneous injection	Fibrosarcomas:		
	Areca nut/tannin rich areca nut extract, 0.5 mL, once/wk for 56 wk	30/30	Significant	
	Saline, 0.5 mL, once/wk for 56 wk 30/group	0/30	-	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence and/or multiplicity of tumours	Significance	Comments
Hamster, Syrian golden 21 wk Suri et al. (1971)	Cheek pouch application	Cheek pouch squamous cell carcinomas:		
	DMSO extract of areca nut, 3 × /wk	8/21	[P < 0.05]	
	DMSO extract of areca nut + tobacco, 3 × /wk	16/21	[P < 0.0001]	
	DMSO-treated control, 3 × /wk	0/11	-	
Hamster, Syrian golden & white mutant (M, F) 21 mo Ranadive et al. (1979)	Cheek pouch application	Forestomach carcinomas– Cheek pouch carcinomas:		Lack of information on sex and strain distribution.
	Areca nut aqueous extract, 3 × /wk	4/21–1/21	[P < 0.05]–[NS]	
	Polyphenol fraction of areca nut, 3 × /wk	4/20–1/20	[P < 0.05]–[NS]	
	Areca nut pieces + aqueous extract of areca nut, 3 × /wk	6/13–0/13	[P < 0.001]–[NS]	
	Betel quid aqueous extract, 3 × /wk	5/20–0/20	[P < 0.01]–[NS]	
	Betel quid aqueous extract + tobacco, 3 × /wk	4/13–0/13	[P < 0.01]–[NS]	
	Untreated control	0/30–0/30	-	
	13–30/group			
Hamster, Syrian golden & white mutant (M, F) 21 mo Ranadive et al. (1979)	Cheek pouch implantation	Forestomach carcinomas– Cheek pouch carcinomas:		Lack of information on sex and strain distribution.
	Areca nut powder, in capsule, 1 × /2wk	6/19–4/19	[NS]–[NS]	
	Capsule control	0/9–0/9	-	
	Betel quid, 0.8–13 mg of material in wax pellet, once/2wk	8/18–4/18	[P < 0.001]– [P < 0.05]	
	Betel quid + tobacco, 0.8–13 mg of test material in wax pellet, once/2wk	6/21–3/21	[P < 0.01]–[NS]	
	Wax pellet control	0/25–0/25	-	
	9–25/group			

DMSO, dimethyl sulfoxide; F, female; M, male; mo, month or months; NS, not significant; wk, week or weeks

Table 3.2 Carcinogenicity studies of administration of *pan masala* in mice

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence and/or multiplicity of tumours	Significance	Comments
Mouse, Swiss S/RV/Cri (M, F) Lifetime Bhisey et al. (1999)	Diet			Positive trend for lung adenocarcinoma ($P < 0.004$)
	Normal diet	0/108		
	<i>Pan masala</i> 2.5% in diet, lifetime	Liver haemangioma, 7/108; lung adenocarcinoma, 3/108; liver adenocarcinoma, 1/108; hepatoma, 1/108; forestomach papilloma, 1/108		
Mouse, Swiss (M, F) 56 wk Nigam et al. (2001)	<i>Pan masala</i> 5% in diet, lifetime	Liver haemangioma, 1/108; lung adenocarcinoma, 5/108; forestomach carcinoma, 1/108; testicular lymphoma, 1/108		
	108/group			
	Diet		NS	
Mouse, ICRC (M, F) 6 mo Ramchandani et al. (1998)	<i>Pan masala</i> 2% in diet, 56 wk	Lung tumour, 2/12; haemangioma, 1/12; haemangioendothelioma, 1/12		
	Normal diet, 56 wk	Lung tumour, 1/12		
	12/group			
Mouse, ICRC (M, F) 6 mo Ramchandani et al. (1998)	Gavage			EPME tested as promoter
	NDEA in drinking-water for 4 d (16 mg/kg bw) followed by EPME by gavage (25 mg/treatment) 5 × /wk for 6 mo	Forestomach papilloma, 17/26; esophageal papilloma, 11/26	$P < 0.001$; $P < 0.01$	
	NDEA in drinking-water for 4 d (16 mg/kg bw) followed by distilled water by gavage 5 × /wk for 6 mo	Forestomach papilloma, 5/27; esophageal papilloma, 3/27	-;-	
	30/group			

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence and/or multiplicity of tumours	Significance	Comments
Mouse, Swiss Bare (F) 40 wk Ramchandani et al. (1998)	Topical application DMBA (20 nmol in 100 µl acetone) followed by EPME (25 mg in 100 µl acetone) 2x/ wk for 40 wk DMBA (20 nmol in 100 µl acetone) followed by 100 µl acetone twice/wk for 40 wk 15/group	Skin papilloma: 6.8/mouse Skin papilloma: 4.2/mouse	$P < 0.05$	EPME tested as promoter

bw, body weight; d, day or days; DMBA, 7,12-dimethylbenz[*a*]anthracene; EPME, Ethanolic *pan masala* extract; F, female; M, male; mo, month or months; NDEA, N-nitrosodiethylamine; NS, not significant; wk, week or weeks

Table 3.3 Carcinogenicity studies of administration of areca nut, betel quid or betel leaf with known carcinogens or modifiers of cancer risk in experimental animals

Species, strain (sex)	Route	Dosing regimen	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Duration		Animals/group at start			
Reference					
Mouse, Swiss (M)	Intragastric instillation				
180 d	BLE (1 mg/d, 5 × /wk) for 2 wk, followed by B[a]P by gavage (1 mg/d, 2 × /wk) for 4 wk, followed by BLE (1 mg/d, twice/wk) for 2 wk		Forestomach papilloma: 0.9/ mouse	$P < 0.005$, tumour multiplicity inhibition	
Padma et al. (1989)					
	B[a]P by gavage (1 mg/d, twice/wk) for 4 wk		Forestomach papilloma: 4.9/ mouse	-	
20/group					
Mouse, Swiss (M)	Drinking-water				
180 d	NNN, application to tongue (22 mg/mouse)		Total: 13/19 (lung, 4/19; stomach, 5/19; Lung + stomach, 3/19; Liver + stomach, 1/19)	-	
Padma et al. (1989)					
	NNN, application to tongue (22 mg/mouse); BLE in drinking-water 5 × /wk (2.5 mg/d)		Total: 3/21 (lung)	[$P < 0.005$], inhibition of stomach tumourigenesis	
	NNK, application to tongue (22 mg/mouse)		Total: 10/13 (lung, 8/13; stomach, 1/13;lung + liver, 1/13)	-	
	NNK, application to tongue (22 mg/mouse); BLE in drinking-water 5 × /wk (2.5 mg/d)		Total: 7/15 (lung, 5/15; stomach, 1/15; lung + LIVER, 1/15)	NS	
	Untreated control		Total: 2/18 (lung)	-	
20/group					
Hamster, Syrian golden (M)	Cheek pouch insertion				
30 wk	DMBA 0.5%, 3 × /wk for 4 wk		Cheek pouch	-	
Wong et al. (1992)			Squamous cell carcinoma: 1/9		
	DMBA 0.5%, 3 × /wk for 4 wk, followed by betel quid twice/wk for 24 wk 10/group		Squamous cell carcinoma: 6/9	$P < 0.05$	
Hamster, Syrian golden (M)	Cheek pouch insertion				
18 wk	DMBA 0.5%, 3 × /wk for 6 wk		Cheek pouch	-	
Wong et al. (1992)			Squamous cell carcinoma: 1/9		
	DMBA 0.5%, 3 × /wk for 6 wk, followed by betel quid twice/wk for 12 wk		Squamous cell carcinoma: 7/7	$P < 0.01$	
	10/group				

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Hamster, Syrian golden (M) 35 wk lin et al. (1996)	Cheek pouch insertion or painting DMBA 0.5%, 3 × /wk for 4 wk DMBA 0.5%, 3 × /wk for 4 wk, followed by areca nut fibre 3 × /wk for 24 wk DMBA 0.5%, 3 × /wk for 4 wk, followed by cold aqueous extract of areca nut 3 × /wk for 24 wk 10/group	Cheek pouch Squamous cell carcinoma: 2/9 Squamous cell carcinoma: 9/10	- $P < 0.01$ $P < 0.05$	

BLE, Betel leaf extract; B[a]P, benzo[a]pyrene; d, day or days; DMBA, 7,12-dimethylbenz[a]anthracene; M, male; NNN, N'-Nitrosomethylamine; 1-(3-pyridyl)-1-butanone; NS, not significant; wk, week or weeks

animals. No oesophageal tumours were observed in control mice ([Rao & Das, 1989](#)).

Subcutaneous injections of hot and cold areca nut extracts to Swiss mice increased the incidence of fibrosarcomas at the injection site ([Ranadive et al., 1976](#)). Subcutaneous injections of a polyphenol fraction of areca nut to Swiss mice produced fibrosarcomas in 80% (16/20) of the animals ([Shivapurkar et al., 1980](#)). In the same study, 35% (7/20) of mice concurrently treated with an aqueous extract of betel quid developed fibrosarcomas.

In a skin tumourigenesis experiment using 7,12-dimethylbenz[*a*]anthracene (DMBA) plus croton oil, feeding of areca nut did not influence the incidence of skin papilloma in Swiss mice ([Singh & Rao, 1995](#)).

Betel leaf extract given to mice treated with benzo[*a*]pyrene (B[*a*]P) by gavage reduced the incidence and multiplicity of B[*a*]P-induced forestomach papillomas ([Padma et al., 1989](#); [Bhide et al., 1991](#)). It also reduced stomach tumour incidence in mice treated with *N'*-nitrosomornicotine or 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone ([Padma et al., 1989](#)).

Lifetime feeding of a diet containing either 2.5% or 5% *pan masala* to Swiss mice induced a variety of benign and malignant tumours in the liver, stomach and lung. No tumours were found in controls. A significant positive trend ($P = 0.004$) with dose was observed in the number of mice with lung adenocarcinoma ([Bhisey et al., 1999](#)).

Administration of *pan masala* in the diet produced liver haemangiomas and papillary adenomas of the lung in Swiss mice [not significant]. A few lung adenomas, liver tumours, and benign tumours at some other sites were also observed in mice receiving *pan masala* and tobacco in the diet ([Nigam et al., 2001](#)).

Topical application of an extract of *pan masala* to the skin of DMBA-initiated Swiss mice increased significantly the tumour multiplicity of skin papillomas. In the same study,

administration of a *pan masala* extract by gavage to ICRC mice given *N*-nitrosodiethylamine (NDEA) in the drinking-water increased the incidence of squamous cell papillomas of the forestomach and oesophagus ([Ramchandani et al., 1998](#)).

3.2 Rat

Subcutaneous injection of a tannin rich-extract of areca nut produced fibrosarcomas at the injection site in 30/30 NIH Black rats. No tumours were observed in 30 saline-treated controls ([Kapadia et al., 1978](#)).

Dietary administration of areca nut to ACI rats fed vitamin A-sufficient or -deficient diets did not increase tumour incidence ([Tanaka et al., 1983](#)).

In ACI rats treated with 4-nitroquinoline-1-oxide in the drinking-water followed by areca nut in the diet, the incidence of squamous cell carcinoma of the tongue was significantly greater (12/17 versus 4/14, $P < 0.0205$) than in animals given 4-nitroquinoline-1-oxide alone ([Tanaka et al., 1986](#)).

Oral administration to Holtzman rats of an aqueous extract of betel leaf inhibited DMBA-induced mammary carcinogenesis (6/26 versus 17/27, $P < 0.05$) when given concurrently with DMBA ([Rao et al., 1985](#)).

3.3 Hamster

A topical application of either DMSO extracts of areca nut or areca nut with tobacco on the cheek-pouch mucosa increased the incidence of squamous cell carcinoma and leukoplakia in Syrian golden hamster ([Suri et al., 1971](#)).

Implantation in the cheek pouch of either (i) areca nut powder or (ii) betel quid with or without tobacco produced cheek-pouch carcinomas and forestomach carcinomas in Syrian golden hamsters and white mutant hamsters. In

the same study, topical application of extracts of betel quid with or without tobacco increased the incidence of forestomach carcinomas. Also, application of either (i) areca nut, (ii) a polyphenol fraction of areca nut, or (iii) areca nut pieces with extract of areca nut increased the incidence of forestomach carcinomas ([Ranadive et al., 1979](#)). [The Working Group noted the lack of information on sex and strain distribution.]

Application of an extract of areca nut to the B[a]P-initiated cheek pouch of Syrian golden hamsters led to a slight increase in the incidence of squamous cell papillomas and carcinomas compared to B[a]P-only-treated animals. In the same study, application of betel leaf extract to B[a]P-initiated hamster cheek pouch reduced significantly the incidence of squamous cell papillomas and carcinomas ([Rao, 1984](#)).

Administration to the hamsters cheek-pouch of either areca nut fibre or areca nut extract by insertion ([Lin et al., 1996](#)) or arecaine by painting ([Lin et al., 1996](#)) increased significantly the incidence of cheek pouch squamous cell carcinomas initiated by application of DMBA.

Concomitant treatment of hamster cheek pouch with DMBA and with an extract of betel quid, by insertion or painting, increased significantly the incidence ([Wong et al., 1992](#)) or multiplicity ([Lin et al., 1997](#)) of cheek pouch squamous cell carcinomas.

3.4 Baboon

Insertion into a surgically created buccal pouch for 42 months of a betel quid preparation with tobacco in seven baboons or without tobacco in five baboons did not lead to tumour formation ([Hamner, 1972](#)).

3.5 Synthesis

In mice, administration by gavage of areca nut extracts containing arecholine increased the incidence of lung adenocarcinoma in one study and of hepatocellular carcinomas in another study. Subcutaneous injections of hot and cold areca nut extracts in one study and of a polyphenol fraction of areca nut in another study increased the incidence of fibrosarcoma. In one study in rats, subcutaneous injection of an areca nut extract also produced fibrosarcomas.

In mice, subcutaneous injection of an extract of betel quid increased the incidence of fibrosarcoma in one study.

In one study in hamsters, topical application of extracts of areca nut or areca nut with tobacco increased the incidence of cheek pouch squamous cell carcinoma. In another similar study, betel quid and betel quid plus tobacco extracts, and areca nut pieces, extracts and polyphenol fractions, increased the incidence of forestomach carcinomas. In a third study, cheek pouch implantation of betel quid increased the incidence of forestomach and cheek pouch carcinomas; implantation of betel quid plus tobacco increased the incidence of forestomach carcinomas. Areca nut or betel quid also promoted DMBA-induced cheek pouch squamous cell carcinomas.

In one study in mice, feeding of a diet containing *pan masala* increased the incidence of lung adenocarcinomas. *Pan masala* also enhanced DMBA-induced skin papillomas and NDEA-induced forestomach and oesophagus papillomas.

Betel leaf extracts reduced the incidence of B[a]P-induced squamous cell tumours of the oral cavity in hamsters, of B[a]P-induced forestomach papillomas and NNN- and NNK-induced stomach tumours in mice, and of DMBA-induced mammary tumours in rats.

4. Other Relevant Data

For the effects of chewing betel quid and areca nut with tobacco, we refer the reader to Section 4 of the *Monograph on Tobacco Smoking* in this volume.

4.1 Distribution and metabolism of the constituents of betel quid

Metabolism, toxicity, genotoxicity, mutation induction in cancer-related genes, immunomodulatory effects and gene–environment interactions have been investigated for arecoline, the major alkaloid in areca nut, and for other betel-quid ingredients, e.g. catechu, betel leaf and slaked lime. In addition, reactive oxygen species and areca nut-derived nitrosamines are produced *in situ* in saliva during betel-quid chewing, and their adverse effects have been studied in the oral cavity of betel-quid chewers and in experimental systems.

Areca nut contains several alkaloids and tannins (polyphenols). Arecoline is the most abundant alkaloid, whereas arecaidine, guvaine and guvacoline occur in smaller quantities (Fig. 4.1). In rodents, arecoline is rapidly metabolized in both liver and kidney. In rats, arecoline is de-esterified in the liver to arecaidine, and both arecoline and arecaidine are excreted as the mercapturic acid ([Boyland & Nery, 1969](#)). The metabolism of arecoline and arecaidine was investigated in the mouse using a metabolomic approach ([Giri et al., 2006](#)). The major metabolite of both alkaloids, *N*-methylnipecotic acid, is a newly discovered metabolite (see Fig. 4.1). A total of 11 metabolites of arecoline were identified. Arecaidine shares six of these with arecoline.

4.1.1 Formation of *N*-nitroso compounds in the oral cavity

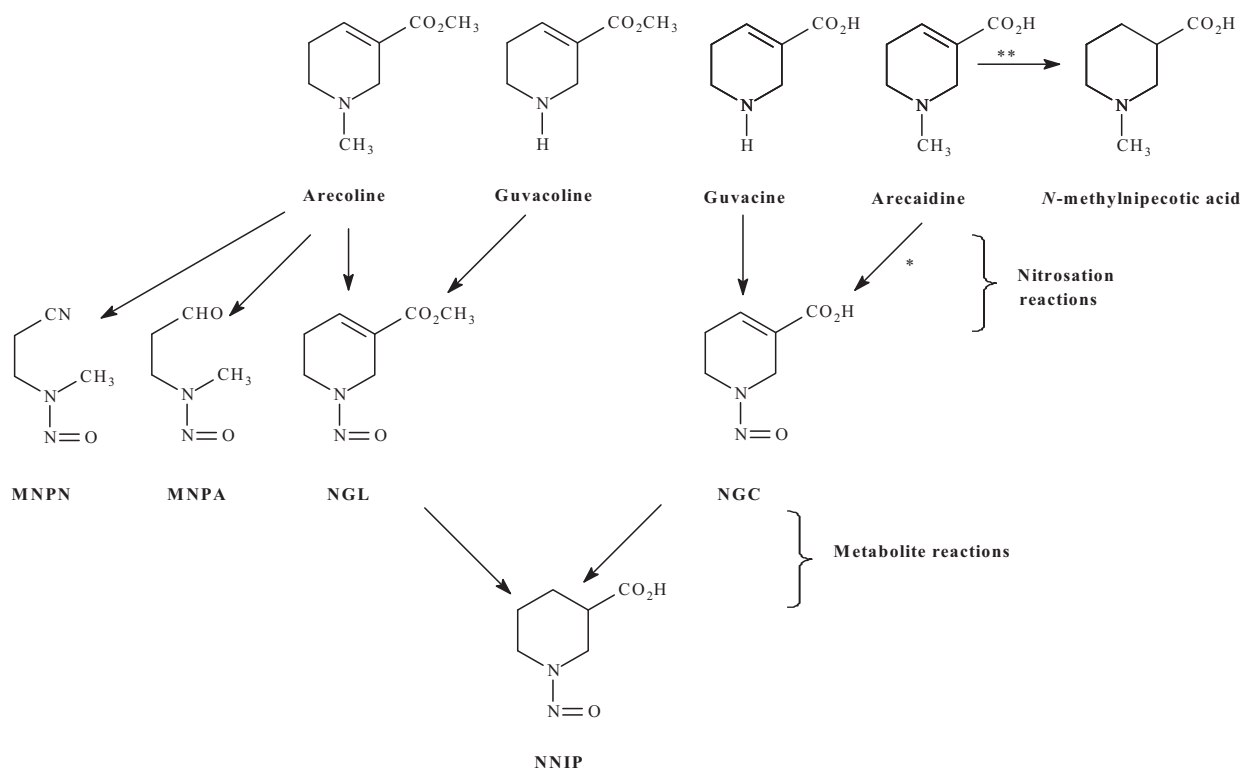
Areca nut contains secondary and tertiary amines that can be nitrosated in saliva during betel-quid chewing by reaction with nitrite in the presence of thiocyanate as a nitrosation catalyst (Fig. 4.1).

Three areca nut-derived nitrosamines, i.e. 3-methylnitrosaminopropionitrile (MNPN; a rodent carcinogen), *N*-nitrosoguvaine (NGC) and *N*-nitrosoguvacoline (NGL) have been detected in the saliva of betel-quid chewers ([Nair et al., 1985](#); [Prokopczyk et al., 1987](#); [IARC, 2004](#)). The formation of these nitrosamines can be mimicked *in vitro* by nitrosation with nitrite, thiocyanate and arecoline, which are all present in saliva. Endogenous nitrosation reactions in the oral cavity have been demonstrated in chewers of betel quid mixed with proline (a probe for ingested secondary amines), by measuring increased levels of *N*-nitrosoproline in saliva and urine ([Nair et al., 1987a](#)). As chewers often swallow the quid – which contains nitrosamine precursors – the intragastric nitrosation reaction of secondary and tertiary amines may occur at higher rates due to the low pH in the stomach ([Nair et al., 1985](#)).

4.1.2 Formation of reactive oxygen species in the oral cavity

Direct evidence that oxidative stress and reactive oxygen species such as the hydroxyl radical (HO•) are generated in the oral cavity during betel-quid chewing was provided by measuring the formation of *ortho*- and *meta*-tyrosines from L-phenylalanine in human saliva ([Nair et al., 1995](#)). Auto-oxidation of polyphenols in areca nut and catechu generates the superoxide anion (O₂^{•−}), especially at the high pH of slaked lime. The superoxide anion is converted to H₂O₂, which reacts in the presence of copper and iron ions (present in µg/gram amounts in

Fig. 4.1 Relationship of areca-nut alkaloids to areca-nut-derived nitrosamines (formed by nitrosation) and a urinary metabolite of *N*-nitrosoguvacoline and *N*-nitrosoguvacine



Adapted from [Wenke & Hoffmann \(1983\)](#), [Nair et al. \(1985\)](#), and [Ohshima et al. \(1989\)](#)

MNPA, 3-methylnitrosaminopropionaldehyde; MNPN, 3-methylnitrosaminopropionitrile; NGC, *N*-nitrosoguvacine; NGL, *N*-nitrosoguvacoline; NNIP, *N*-nitrosonipecotic acid

* It is likely that nitrosation of arecaidine would produce NGC but this has not been demonstrated.

** *N*-methylnipecotic acid is a recently isolated metabolite of arecoline; nitrosation reactions on this metabolite have not been studied ([Giri et al., 2006](#)).

areca nut, catechu and slaked lime) to generate hydroxyl radicals ([Nair et al., 1987b](#)). These can induce oxidation of deoxyguanosine to yield 8-hydroxydeoxyguanosine 8-(OH-dG) and DNA strand-breaks ([IARC, 2004](#)). Areca-nut extract and arecoline treatment led to depletion of glutathione (GSH) and reduction of glutathione-S-transferase (GST) activity in human oral cells and in rodent liver; both processes are known to increase cellular damage and DNA lesions ([Chang et al., 2001a, b](#)).

4.2 Genetic and related effects

The genetic and related effects of areca nut and the various constituents of betel quid without tobacco were reviewed in detail by [IARC \(2004\)](#) and are summarized below.

4.2.1 Humans

Elevated formation of micronuclei has been reported in oral exfoliated cells in chewers of betel quid without tobacco. Micronucleus formation has been observed in precancerous lesions in the oral cavity of chewers of betel quid alone ([Dave et al., 1991](#); [Kayal et al., 1993](#)), and betel

quid with tobacco ([Stich et al., 1989, 1991](#); [Nair et al., 1991](#)).

Elevated sister-chromatid exchange and micronucleus formation have been demonstrated in cultured peripheral lymphocytes collected from chewers of areca nut without tobacco and slaked lime ([Dave et al., 1991, 1992](#); [Desai et al., 1996](#)) and with tobacco ([Adhvaryu et al., 1986](#)).

In subjects chewing betel quid without tobacco accumulation of p53 protein was observed ([Kaur et al., 1994, 1998](#); [Yan et al., 1996](#); [Thongsuksai & Boonyaphiphat, 2001](#); [Chang et al., 2002a](#)). *TP53* mRNA was frequently downregulated in betel quid chewing associated oral cancer ([Tsai et al., 2008](#)).

Arecoline modulates matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), as well as the activity of lysyl oxidase, which leads to the accumulation of collagen in oral mucosal fibroblasts ([Trivedy et al., 1999a, 2001](#); [Chang et al., 2002b](#)). Areca-nut polyphenols inhibit collagenases and increase the cross-linkage of collagen, reducing its degradation ([Scutt et al., 1987](#)). These events may underlie the generation of oral submucous fibrosis in betel-quid chewers ([Chang et al., 2002b](#)), which could be further enhanced by the release of copper ions, present in areca nut, catechu and slaked lime into the oral cavity of the chewers; inorganic copper salts increased the production of collagen by oral fibroblasts ([Trivedy et al., 1999b, 2001](#)).

Cyclooxygenase-2 (COX2) is an inducible enzyme responsible for prostaglandin synthesis in certain inflammatory diseases. Its expression was significantly higher in oral submucous fibrosis specimens than in buccal mucosal fibroblasts ([Tsai et al., 2003](#)).

In an oral epithelial cell line, arecoline was found to elevate the expression of the heat-shock protein HSP70 and haem oxygenase HO-1 mRNA in a dose- and time-dependent manner ([Lee et al., 2008a, b](#)). Expression of HSP70 and HO-1 was significantly higher in specimens of human oral squamous cell carcinoma associated with

areca-quid chewing. Areca-nut extracts increased the expression of inflammatory cytokines, tumour necrosis factor- α , interleukin-1- β , interleukin-6, and interleukin-8, in peripheral blood mononuclear cells ([Chang et al., 2009](#)).

Collagen-related genes (*COLA1* and *COLA2*) and collagenase-1 lysyl oxidase, transforming growth factor β (TGF- β 1) and cystatin C involved in oral submucous fibrosis and DNA-repair genes (X-ray repair cross complementing 1 *XRCC1*) have been investigated in small studies in India, Taiwan, China, in relation to oral and oesophageal cancer and premalignant lesions ([Lee et al., 2001](#); [Chiu et al., 2002](#)). No clear gene-environment interactions could be established because of the concurrent confounding by tobacco chewing and smoking or alcohol consumption ([IARC, 2004](#)).

4.2.2 Experimental systems

(a) Areca nut extracts

Extracts of betel quid and *pan masala* induced sister chromatid exchange and sperm abnormalities in mice. Betel quid extracts were mutagenic in bacteria and induced chromosomal aberrations, sister chromatid exchange and micronucleus formation in Chinese hamster ovary cells.

Aqueous extracts of areca nut produced gene conversion in yeast, DNA strand-breaks, gene mutation, chromosomal aberrations, sister chromatid exchange and micronucleus formation in rodent cells, both *in vitro* and *in vivo*. It also induced cell transformation in mouse C3H10T1/2 cells and DNA strand-breaks, unscheduled DNA synthesis and DNA-protein crosslinks in cultured human buccal and laryngeal epithelial cells.

(b) Areca nut alkaloids

Arecoline and other areca-nut alkaloids gave positive responses in most bacterial mutagenicity assays, and induced chromosomal aberrations,

micronucleus formation and sister chromatid exchange in mammalian cells, both *in vitro* and *in vivo*. Arecoline inhibited *Tp53* mRNA expression and its transactivating function, repressed DNA repair and triggered DNA damage response in human epithelial cells (Tsai *et al.*, 2008).

(a) Areca-nut-derived nitrosamines

Three areca-nut-derived nitrosamines, i.e. *N*-nitrosoguvacoline (NGL), *N*-nitrosoguvacine (NGC) and 3-methylnitrosaminopropionitrile (MNPN), were detected in the saliva of chewers of betel quid without tobacco. Genotoxic effects of these nitrosamines and of 3-methylnitrosaminopropionaldehyde (MNPA) can be summarized as follows: NGL but not NGC was mutagenic to bacteria. MNPN did not induced DNA single-strand breaks in human buccal epithelial cells (Sundqvist *et al.*, 1989). MNPN formed the DNA adducts 7-methylguanine and *O*⁶-methylguanine (a pro-mutagenic DNA adduct) as well as (2-cyanoethyl)guanines in treated rats (Prokopczyk *et al.*, 1987, 1988). MNPA was not mutagenic in the presence of a metabolic activating system but caused single-strand breaks and DNA crosslinks in human buccal epithelial cells (Sundqvist *et al.*, 1989; Sundqvist & Grafström, 1992).

In Taiwan, China, areca nut is often chewed with fresh betel inflorescence). Betel inflorescence contains safrole and hydroxychavicol at relatively high concentrations (10–15 mg/g fresh nut) (IARC, 2004). Safrole is a possible human carcinogen (IARC, 1987). Taiwanese betel quid-chewers had 3-fold higher urinary excretion of hydroxychavicol, a metabolite of safrole, than non-chewers (Chang *et al.*, 2002c). They also had a high frequency of safrole-like DNA adducts (detected by ³²P-postlabelling) in the oral cavity that co-eluted with synthetic safrole-2′deoxyguanosine 3′-monophosphate adducts (Chen *et al.*, 1999). In HBsAg/HCV seronegative hepatocarcinoma, safrole-type DNA adducts were found in hepatic tissues of hepatocarcinoma

patients who had chewed betel quid for > 10 years (Chung *et al.*, 2008).

4.3 Mechanistic considerations

Betel quid and areca-nut ingredients and extracts exert a variety of genetic and related effects (Section 4.2.1). Continuous local irritation of buccal epithelial cells caused by betel quid and its ingredients, particularly areca nut and slaked lime, can generate chronic inflammation, oxidative stress and cytokine production. Reactive oxygen species generated during chewing of betel quid and other genotoxic reactants formed from arecoline and areca nut-derived nitrosamines, can lead to DNA- and genetic damage in exposed oral keratinocytes. Persistent oxidative stress can drive affected cells to uncontrolled proliferation and hyperplastic/dysplastic lesions. Chronic occurrence of these toxic insults in the oral cavity of chewers could drive these pre-neoplastic cells towards full malignancy.

4.4 Synthesis

These mechanistic data support the causal associations for carcinogenicity observed in humans at several target sites (indicated in Section 2 of this *Monograph*) for chewers of betel quid without tobacco, and areca nut.

5 Evaluation

There is *sufficient* evidence in humans for the carcinogenicity of betel quid with added tobacco. Betel quid with added tobacco causes cancers of the oral cavity, pharynx and oesophagus.

There is *sufficient* evidence in humans for the carcinogenicity of betel quid without added tobacco. Betel quid without added tobacco causes cancers of the oral cavity and oesophagus. Also, a positive association has been observed between

exposure to betel quid without added tobacco and cancer of the liver.

There is *sufficient* evidence in experimental animals for the carcinogenicity of betel quid with added tobacco.

There is *sufficient* evidence in experimental animals for the carcinogenicity of betel quid without added tobacco.

There is *sufficient* evidence in experimental animals for the carcinogenicity of areca nut.

There is *limited* evidence in experimental animals for the carcinogenicity of *pan masala*.

There is *evidence suggesting lack of carcinogenicity* of betel leaf in experimental animals.

Betel quid with added tobacco is *carcinogenic to humans* (Group 1).

Betel quid without added tobacco is *carcinogenic to humans* (Group 1).

Areca nut is *carcinogenic to humans* (Group 1).

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CONSUMPTION OF ALCOHOLIC BEVERAGES

Consumption of alcoholic beverages was considered by previous IARC Working Groups in 1987 and 2007 ([IARC, 1988, 2010](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Types and ethanol content of alcoholic beverages

1.1.1 Types of alcoholic beverages

The predominant types of commercially produced alcoholic beverages are beer, wine and spirits. Basic ingredients for beer are malted barley, water, hops and yeast. Wheat may be used. Nearly all wine is produced from grapes, although wine can be also made from other fruits and berries. Spirits are frequently produced from cereals (e.g. corn, wheat), beet or molasses, grapes or other fruits, cane sugar or potatoes. Main beverage types (i.e. beer, wine and spirits) may be consumed in combination with each other to fortify the strength of an alcoholic beverage (e.g. fortified wine, in which spirits are added to wine) ([WHO, 2004](#)).

In addition to commercialized products, in many developing countries different types of home- or locally produced alcoholic beverages such as sorghum beer, palm wine or sugarcane spirits are consumed ([WHO, 2004](#)). Home- or locally produced alcoholic beverages are produced through fermentation of seed, grains,

fruit, vegetables or parts of palm trees, by a fairly simple production process.

1.1.2 Ethanol content of alcoholic beverages

Percentage by volume (% vol) is used to indicate the ethanol content of beverages, which is also called the French or Gay-Lussac system. Alcohol content differs according to the main beverage type and may also vary by country. Commonly, 4–5% vol are contained in beer, about 12% vol in wine and about 40% vol in distilled spirits. However, lower or higher ethanol content in alcoholic beverages is also possible. The ethanol content in beer can range from 2.3% vol to over 10% vol (lower alcohol content in home- or locally produced alcoholic beverages such as sorghum beer), in wine from 8 to 15% vol, and in spirits from 20% vol (aperitifs) to well over 40% vol (e.g. 80% vol in some kinds of absinthe). There is a trend in recent years towards higher (13.5–14.5%) alcohol volume in consumed wines, associated with technology advances and increasing proportion in overall consumption of wines produced outside the traditional wine-growing regions of Europe ([IARC, 2010](#)).

To calculate the amount of ethanol contained in a specific drink, the amount (e.g. ml) of

alcoholic beverage consumed for each type of beverage (e.g. a 330-mL bottle of beer) is multiplied by the percentage of alcohol by volume, i.e. the proportion of the total volume of the beverage that is alcohol (e.g. $(330 \text{ mL}) \times (0.04) = 13.2 \text{ mL}$ of ethanol in a bottle of beer). Conversion factors may be used to convert the volume of alcoholic beverage into grams of ethanol, or volumes of alcohol may be recorded in ‘ounces’. Conversion factors for these different measures ([WHO, 2000](#)) are as follows:

- 1 mL ethanol = 0.79 g
- 1 UK oz = 2.84 cL = 28.4 mL = 22.3 g
- 1 US fluid oz = 2.96 cL = 29.6 mL = 23.2 g

1.2 Chemical composition

The main components of most alcoholic beverages are ethanol and water. Some physical and chemical characteristics of anhydrous ethanol are as follows ([O’Neil, 2001](#)):

Chem. Abstr. Services Reg. No.: 64–17.5

Formula: $\text{C}_2\text{H}_5\text{OH}$

Relative molecular mass: 46.07

Synonyms and trade name: Ethanol, ethyl alcohol, ethyl hydroxide, ethyl hydrate, absolute alcohol, anhydrous alcohol, dehydrated alcohol

Description: Clear, colourless, very mobile, flammable liquid, pleasant odour, burning taste

Melting-point: -114.1°C

Boiling-point: 78.5°C

Density: d_4^{20} 0.789

Refractive index: n_D^{20} 1.361

In addition to ethanol and water, wine, beer and spirits contain volatile and non-volatile compounds. Volatile compounds include aliphatic carbonyl compounds, alcohols, monocarboxylic acids and their esters, nitrogen- and sulfur-containing compounds, hydrocarbons, terpenic compounds, and heterocyclic and aromatic compounds. Non-volatile extracts of alcoholic beverages comprise unfermented

sugars, di- and tribasic carboxylic acids, colouring substances, tannic and polyphenolic substances and inorganic salts ([IARC, 2010](#)).

Occasionally, toxic additives, that are not permitted for use in commercial production have been identified in alcoholic beverages. These include methanol, diethylene glycol (used as sweetener) and chloroacetic acid or its bromine analogue, sodium azide and salicylic acid, which are used as fungicides or bactericides ([Ough, 1987](#)).

Contaminants may also be present in alcoholic beverages. Contaminants are defined as substances that are not intentionally added but are present in alcoholic beverages due to production, manufacture, processing, preparation, treatment, packing, packaging, transport or holding, or as a result of environmental contamination. Contaminants and toxins found in alcoholic beverages are nitrosamines, mycotoxins, ethyl carbamate, pesticides, thermal processing contaminants, benzene, and inorganic contaminants such as lead, cadmium, arsenic, copper, chromium, inorganic anions, and organometals ([IARC, 2010](#)).

In view of the potential carcinogenicity of acetaldehyde and its known toxic properties, recent studies attempted to estimate exposure to acetaldehyde from alcoholic beverages outside ethanol metabolism at known levels of alcohol exposure. The average exposure to acetaldehyde as a result of consumption of alcoholic beverages, including “unrecorded alcohol,” was estimated at 0.112 mg/kg body weight/day ([Lachenmeier et al., 2009a](#)). Levels of acetaldehyde in alcoholic beverages vary from less than 1 g/hL of pure alcohol up to 600 g/hL, and high concentrations of acetaldehyde were documented in alcoholic beverages commonly consumed in many parts of the world, including distilled beverages from Brazil, the People’s Republic of China, Guatemala, Mexico, and the Russian Federation, as well as calvados and fortified wines and fruit and marc spirits from Europe ([Lachenmeier &](#)

[Sohnius, 2008](#); [Linderborg et al., 2008](#); [Kanteres et al., 2009](#); [Lachenmeier et al., 2009b](#)).

1.3 Trends in consumption of alcoholic beverages

Volume, pattern and quality of consumed alcohol are included in the description of differential exposure to alcohol.

In a development of the WHO Global Alcohol Database, WHO has developed the Global Information System on Alcohol and Health ([WHO, 2008](#)). In 2008–09, WHO conducted the Global Survey on Alcohol and Health, collecting data on alcohol consumption, alcohol-related harm and policy responses from its Member States.

Total adult per capita consumption in litres of pure alcohol is defined as the total amount of alcohol consumed per person, taking into account recorded consumption (i.e. alcoholic beverages consumed that are recorded in official statistics of production, trade or sales) and unrecorded consumption (i.e. alcoholic beverages consumed that are not recorded in official statistics and that can come from a variety of sources such as home- or informally produced alcohol, illegal production and sale, smuggling and cross-border shopping), and subtracting consumption by tourists, if possible. Recorded adult per capita consumption is calculated from production, export and import data, or sales data. Unrecorded consumption is computed from representative surveys, specific empirical investigations or expert opinion. The percentage of lifetime and past-year abstainers provide important information about drinking in a population and complement the indicator on total adult (15+ years) per capita consumption.

Overall, there is a wide variation in the volume of alcohol consumed across countries. As presented in [Table 1.1](#) and Table 1.2 (available at <http://monographs.iarc.fr/ENG/Monographs/>

[vol100E/100E-06-Table1.2.pdf](#)), the countries with the highest overall consumption of alcohol per capita among the adult (15+ years) population can be found in the the WHO Regional Office for European Region (12.2 L of pure alcohol per capita), and more specifically in eastern Europe. The next highest alcohol consumption is in the WHO Region of the Americas (8.7 L of pure alcohol per capita). Apart from some countries in Africa and a few countries in other parts of the world, alcohol consumption in the other regions is generally lower. The WHO Eastern Mediterranean Region ranks lowest with 0.7 litres of alcohol consumed per adult. Total adult (15+ years) per capita consumption in litres of pure alcohol by region and country is an indicator of the alcohol consumption level of the adult population, irrespective of the number of abstainers (i.e. people who do not drink alcohol) in the country.

Globally, men consume more alcohol than women. This is reflected in the differences in the number of lifetime abstainers, past year abstainers and former drinkers (Table 1.2 on-line). Lifetime abstainers are defined as the proportion of people (15+ years) in a given population who have not consumed any alcohol during their lifetime, assessed at a given point in time. Past year abstainers are people aged 15+ years who did not consume any alcohol during the past year. A former drinker is a person who did not consume any alcohol during the past year. Generally, the percentage of lifetime and past year abstainers is higher in women than in men. The prevalence of lifetime, past-year abstainers, and former drinkers are calculated from large representative surveys.

Table 1.2 (on-line) provides information about the trend (i.e. robust estimate of five-year change) in per capita consumption (2001–05) of recorded alcohol, that is, indicates if consumption remained stable, increased, decreased, or if no conclusion could be drawn. To estimate five-year change in recorded adult (15+ years) per

Table 1.1 Estimate for total adult (15+ years) per capita consumption, by WHO region, average 2003–05

WHO Region	Adult (15+) per capita consumption*, total (recorded and unrecorded), average 2003–05
African Region (AFRO)	6.2
Region of the Americas (AMRO)	8.7
Eastern Mediterranean Region (EMRO)	0.7
European Region (EURO)	12.2
South-East Asian Region (SEARO)	2.2
Western Pacific Region (WPRO)	6.3

* in litres of pure alcohol

Source: [WHO \(2008\)](#)

AFRO: Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe

AMRO: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States of America, Uruguay, Venezuela (Bolivarian Republic of)

EMRO: Afghanistan, Bahrain, Djibouti, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen

EURO: Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Republic of the Republic of Moldova, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan

SEARO: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste

WPRO: Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, New Zealand, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Singapore, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

capita consumption, three-year moving averages were calculated for per capita consumption of recorded alcohol for each year in the five-year period from 2001 to 2005.

Recent data on trends in consumption of alcoholic beverages indicate that the European Region and the Region of the Americas maintain a steady high consumption of alcoholic beverages, with 20% of all countries showing an increase in consumption. Alcohol consumption remains low in the Eastern Mediterranean Region. In the African Region, out of 50 countries, 20% show a decrease and 20% an increase in consumption. There is a recent and continuing increase in alcohol consumption in several low and middle-income countries in the South-East

Asia and Western Pacific Regions, which probably reflects economic development and increases in consumers' purchasing power as well as increases in the marketing of branded alcoholic beverages ([WHO, 2007](#)).

2. Cancer in Humans

2.1 Description of cohort studies

2.1.1 Studies in the general population

Cohort studies are classified by the country in which the study was conducted (Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.1.pdf>). The majority of

cohort studies have been conducted in the USA, western Europe and Japan. Since the previous IARC Monograph (IARC, 2010), data on the association between alcohol consumption and risk of cancer have been published from several cohorts, including updates of cohorts described previously (Bongaerts *et al.*, 2006, 2008; Li *et al.*, 2006, 2009b; Weinstein *et al.*, 2006; Ericson *et al.*, 2007; Ferrari *et al.*, 2007; Ishihara *et al.*, 2007; Ozasa, 2007; Sutcliffe *et al.*, 2007; Thygesen *et al.*, 2007, 2008a, b; Fan *et al.*, 2008; Ide *et al.*, 2008; Kabat *et al.*, 2008; Nielsen & Grønbaek, 2008; Rohrmann *et al.*, 2008, 2009; Shimazu *et al.*, 2008; Friberg & Wolk, 2009; Ishiguro *et al.*, 2009; Heinen *et al.*, 2009; Klatsky *et al.*, 2009; Rod *et al.*, 2009; Thun *et al.*, 2009; Weikert *et al.*, 2009) and reports from recently established cohorts and some older cohorts from which data on alcohol consumption and risk of cancer were not available (Nakaya *et al.*, 2005; Velicer *et al.*, 2006; Akhter *et al.*, 2007; Chlebowski *et al.*, 2007; Freedman *et al.*, 2007a, b; Friborg *et al.*, 2007; Gwack *et al.*, 2007; Khurana *et al.*, 2007; Lim *et al.*, 2007; Mørch *et al.*, 2007; Sung *et al.*, 2007; Tsong *et al.*, 2007; Visvanathan *et al.*, 2007; Zhang *et al.*, 2007a; Ansems *et al.*, 2008; Brinton *et al.*, 2008, 2009; Chao *et al.*, 2008; Lim & Park, 2008; Muwonge *et al.*, 2008; Ohishi *et al.*, 2008; Toriola *et al.*, 2008, 2009; Allen *et al.*, 2009; Duffy *et al.*, 2009; Engeset *et al.*, 2009; Gibson *et al.*, 2009; Gong *et al.*, 2009; Jiao *et al.*, 2009; Johansen *et al.*, 2009; Lew *et al.*, 2009; Setiawan *et al.*, 2009; Chao *et al.*, 2010).

2.1.2 Studies in special populations

This group of studies is characterized by the assumption that the study subjects have a pattern of consumption of alcoholic beverages that is different from that of the general population, e.g. alcoholics, brewery workers, members of a temperance organization (Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.2.pdf>). Because of the

availability of national registries of populations, inpatients and cancer, these studies were largely performed in Scandinavian countries. The estimation of risk in these individuals is not based upon a comparison of exposed and unexposed subjects within the cohort, but with the expected rates of cancer in the general population. Thygesen *et al.* (2009) is the only report from cohorts of special populations that has been published since IARC (2010).

2.2.Cancers of the upper aerodigestive tract

2.2.1. Cancer of the oral cavity and pharynx

It was concluded in the previous IARC Monograph (IARC, 2010) that consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx, and that the risk increases in a dose-dependent manner.

(a) Overview of cohort and case-control studies

The association of consumption of alcoholic beverages and risk of cancer of the oral cavity and/or pharynx has been assessed in six cohort studies (Freedman *et al.*, 2007a; Friborg *et al.*, 2007; Ide *et al.*, 2008; Muwonge *et al.*, 2008; Allen *et al.*, 2009; Weikert *et al.*, 2009; Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.3.pdf>). Significant increases in risk were found with increasing amount of alcohol consumption in all studies (Freedman *et al.*, 2007a; Friborg *et al.*, 2007; Ide *et al.*, 2008; Allen *et al.*, 2009; Weikert *et al.*, 2009), increasing frequency of consumption (Friborg *et al.*, 2007; Muwonge *et al.*, 2008), and duration of consumption (Muwonge *et al.*, 2008). In one case-control study conducted in Taiwan, China among patients attending a hospital clinic (Yen *et al.*, 2008) no association was found among non-smokers and a positive association among drinkers and smokers (Table 2.4 available at <http://monographs.iarc.fr/ENG/Monographs/>

[vol100E/100E-06-Table2.4.pdf](#)). [No information on the quantity of alcohol or tobacco consumption was available.] In a case-control study in Uruguay ([De Stefani et al., 2009](#)) a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the oral cavity and pharynx was found (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

Undifferentiated nasopharyngeal carcinoma (NPC), which is common in parts of Southern Asia, North Africa and the Arctic, is associated with Epstein-Barr virus and preserved foods (see the *Monograph* on Chinese-style Salted Fish in this volume). [Friborg et al. \(2007\)](#) confirmed earlier results suggesting limited or no association between alcohol and undifferentiated NPC ([Yu et al., 2002](#)). However, in a Western population where differentiated forms of NPC are more common, a significantly increased risk of NPC has been associated with heavy drinking (> 21 drinks per week) ([Vaughan et al., 1996](#)), indicating a difference in etiology between differentiated and undifferentiated types of NPC (Table 2.4 on-line).

[Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the oral cavity and pharynx among Danish alcohol abusers compared with national rates. [This cohort study provided no information on individual exposures or results adjusted for potential confounders.] See Table 2.5 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.5.pdf>.

(b) *Intensity and duration*

Previous studies consistently showed that consumption of alcoholic beverages is associated with an increased risk of cancer of the oral cavity and/or pharynx, although the nature of the dose-response relationship is not fully understood ([IARC, 2010](#)). In most studies an approximate threefold increased risk was found at relatively high levels of intake (i.e. > 60 g/day).

There is increasing evidence from recent cohort studies that risk may already be increased at more moderate intake, particularly in women ([Freedman et al., 2007a](#); [Allen et al., 2009](#); [Weikert et al., 2009](#)).

A pooled analysis of the International Head and Neck Cancer Epidemiology Consortium, which specifically examined the association of alcohol consumption and duration, found that among drinkers of 10 drinks per day or less, the association with total drink-years increased with increasing drinks/day, indicating that more drinks/day for a shorter duration was more deleterious than fewer drinks/day for a longer duration ([Lubin et al., 2009](#)).

(c) *Effect of cessation*

A meta-analysis of 13 case-control studies of cancer of the oral cavity and pharynx combined found that compared with current drinkers, risk did not decrease until 10 years or more after cessation of drinking (odds ratio (OR), 0.67; 95%CI: 0.63–0.73) ([Rehm et al., 2007](#)) (Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.6.pdf>). Consistent with many earlier studies, risks were found to be elevated among recent former drinkers, most likely due to ill health directly related to the cancer or its precursors.

(d) *Types of alcoholic beverage*

Some studies have assessed whether the association of consumption of alcoholic beverages on risk varies by beverage type, and have found broadly similar associations in wine, beer and spirit drinkers ([Freedman et al., 2007a](#); [Allen et al., 2009](#)).

(e) *Population characteristics*

The association of consumption of alcoholic beverages with risk of cancer of the oral cavity and pharynx is increased in both men and women ([Freedman et al., 2007a](#); [Weikert et al., 2009](#)).

Studies have been hampered with low numbers of women at the highest levels of exposure.

(f) *Histological subtype*

Very few studies have examined the association of consumption of alcoholic beverages by histological subtype for cancers of the oral cavity and pharynx. From a large-scale cohort study, [Weikert et al. \(2009\)](#) reported that both baseline and lifetime alcohol intake were associated with an increased risk of squamous cell carcinoma of the oral cavity and the pharynx, with an increased risk of 10% (95%CI: 8–13%) per 10 g per day increase in lifetime alcohol intake.

(g) *Association among non-smokers*

There is evidence from a pooled analysis of 15 case-control studies that increasing consumption of alcoholic beverages increases risk of cancer of the oral cavity and oropharynx/hypopharynx cancer among never smokers, with risk estimates of 1.23 (95%CI: 0.59–2.57) and 5.50 (95%CI: 2.26–13.36), for 5 or more drinks/day versus never drinkers, for the two cancer sites, respectively ([Hashibe et al., 2007](#); Table 2.6 on-line). One study in Taiwan, China found no association with alcohol consumption among non-smoking ever-drinkers for cancer of the oral cavity ([Yen et al., 2008](#)). [No information was provided on the quantity of alcohol consumed.]

(h) *Joint effect of alcoholic beverages and tobacco smoking*

It is well established that there is a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the oral cavity and pharynx, with very high risks observed in individuals who are both heavy drinkers and heavy smokers, corresponding to a greater than a multiplicative interaction ([IARC, 2010](#)). The joint effect of alcohol consumption and tobacco smoking on the risk of cancers of the oral cavity

and pharynx is described in Section 2.20 of the *Monograph* on Tobacco Smoking in this volume.

2.2.2 Cancer of the larynx

It was concluded in the previous *IARC Monograph* ([IARC, 2010](#)) that consumption of alcoholic beverages is causally related to cancer of the larynx, and that the risk increases in a dose-dependent manner.

(a) *Overview of cohort and case-control studies*

Since [IARC \(2010\)](#), the association of consumption of alcoholic beverages and risk of cancer of the larynx has been assessed in three general-population cohort studies ([Freedman et al., 2007a](#); [Allen et al., 2009](#), [Weikert et al., 2009](#); Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.7.pdf>) and one case-control study ([Garavello et al., 2006](#); Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.8.pdf>), all of which found significant increases in risk associated with alcohol consumption. In one further case-control study in Uruguay ([De Stefani et al., 2009](#)) a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the larynx was found (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

[Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the larynx among Danish alcohol abusers compared with national rates (Table 2.5 on-line). This study provided no information on individual exposures or results adjusted for potential confounders

(b) *Intensity and duration*

Previous studies consistently showed that increasing alcohol consumption is associated with an increased risk of cancer of the larynx ([IARC, 2010](#)). [Bagnardi et al. \(2001\)](#) reported risk

estimates of 1.38 (95%CI: 1.32–1.45) for intake of 25 g alcohol per day, 1.94 (95%CI: 1.78–2.11) for 50 g per day, and 3.95 (95%CI: 3.43–4.57) for 100 g per day from a meta-analysis of 20 case–control studies, including over 3500 cases. An increased risk for cancer of the larynx was found for women drinking above one drink/day in a large cohort of United Kingdom women [equivalent to an increased risk of 1.44 (95%CI: 1.10–1.88) per 10 g alcohol per day] ([Allen et al., 2009](#)). This is consistent with the 1.38 (95%CI: 1.10–1.73) estimate per 10 g per day reported among women in the European Prospective Investigation into Cancer and Nutrition ([Weikert et al., 2009](#)). Compatible with this, [Freedman et al. \(2007a\)](#) reported a risk estimate of 2.15 (95%CI: 0.82–5.65) among women associated with 3 or more drinks/day from the NIH-AARP Diet and Health Study. Among men, the dose–response relationship is slightly weaker ([Freedman et al., 2007a](#); [Weikert et al., 2009](#)), although it is difficult to determine whether these differences are due to chance because of the relatively low number of cases in women. In a large case–control study in Italy there was clear evidence of a dose–response relationship for men and women combined ([Garavello et al., 2006](#)).

A pooled analysis of the International Head and Neck Cancer Epidemiology Consortium, which specifically examined the association of quantity and duration of alcohol consumption, found that among drinkers of 10 drinks per day or less, the association with total drink-years increased with increasing drinks/day, indicating that more drinks/day for a shorter duration was more deleterious than fewer drinks/day for a longer duration ([Lubin et al., 2009](#)).

(c) *Effect of cessation*

Few studies have assessed whether the risk for cancer of the larynx declines since stopping drinking. [Altieri et al. \(2002\)](#) reported a risk estimate of 0.53 (95%CI: 0.15–1.94) for stopping drinking for 20 years or more ago compared with

current drinkers; the risk for never-drinkers was 0.56 (95%CI: 0.31–0.99).

(d) *Types of alcoholic beverage*

Evidence suggests that the most frequently consumed beverage in a population tends to be associated with the highest risk of cancer of the larynx. Data published recently largely supports this view ([Garavello et al., 2006](#)). The NIH-AARP Diet and Health Study found a stronger association for spirits than for beer or wine consumption among men ([Freedman et al., 2007a](#)). [The Working Group noted the small number of cases.]

(e) *Risk among non-smokers*

There is evidence from a pooled analysis of 11 case–control studies, based on 121 cases of laryngeal cancer, that increasing alcohol consumption increases the risk for cancer of the larynx among never smokers, with a risk estimate of 2.98 (95%CI: 1.72–5.17) for 5 or more drinks/day versus never drinkers ([Hashibe et al., 2007](#); Table 2.6 on-line).

(f) *Joint effect of alcoholic beverages and tobacco smoking*

Evidence suggests that there exists a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the larynx, with very high risks observed in individuals who are both heavy drinkers and heavy smokers. More recent studies that have examined the joint effect of alcohol consumption and tobacco smoking on the risk of cancer of the larynx are described in Section 2.20 of the *Monograph on Tobacco Smoking* in this volume.

2.2.3 *Cancer of the oesophagus*

It was concluded in the previous *IARC Monograph* ([IARC, 2010](#)) that consumption of alcoholic beverages is causally associated with cancer of the oesophagus. The increased risk is

largely restricted to squamous cell carcinoma, with little or no association for adenocarcinoma of the oesophagus.

(a) Overview of cohort and case-control studies

Since [IARC\(2010\)](#), the association of consumption of alcoholic beverages and risk of cancer of the oesophagus has been assessed in six cohort studies ([Freedman et al., 2007b](#); [Ozasa et al., 2007](#); [Fan et al., 2008](#); [Allen et al., 2009](#); [Ishiguro et al., 2009](#); [Weikert et al., 2009](#); Table 2.9 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.9.pdf>) and four case-control studies ([Lee et al., 2005](#); [Vioque et al., 2008](#); [Benedetti et al., 2009](#); [Pandeya et al., 2009](#); Table 2.10 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.10.pdf>), all of which found significant increases in risk with alcohol consumption. A case-control study in Uruguay ([De Stefani et al., 2009](#)) found a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the oesophagus (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

[Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the oesophagus among Danish alcohol abusers compared with national rates (Table 2.5 on-line). [This study provided no information on individual exposures or results adjusted for potential confounders.]

(b) Intensity and duration

Data reviewed previously ([IARC, 2010](#)) consistently showed that increasing consumption of alcoholic beverages is associated with an increased risk of cancer of the oesophagus. Consistently, a 3–8 fold increased risk with high intakes of alcohol has been reported in more recent studies ([Lee et al., 2005](#); [Freedman et al., 2007b](#); [Ozasa et al., 2007](#); [Fan et al., 2008](#); [Vioque et al., 2008](#); [Ishiguro et al., 2009](#); [Pandeya et al., 2009](#)). Smaller increases in risk at lower amounts

of alcohol intake have been found by analysis of large cohorts in Europe, with a significant increased risk of approximately 20% per 10 g alcohol per day ([Allen et al., 2009](#); [Weikert et al., 2009](#)).

In several studies an increased risk has been found with duration of drinking ([Lee et al., 2005](#); [Ozasa et al., 2007](#); [Fan et al., 2008](#); [Vioque et al., 2008](#)), frequency of drinking ([Ozasa et al., 2007](#)), a lower age at starting drinking ([Ozasa et al., 2007](#); [Fan et al., 2008](#)), or cumulative intake ([Benedetti et al., 2009](#)). Risk is similar when alcohol consumption is based on measures of either baseline or lifetime alcohol consumption ([Fan et al., 2008](#); [Weikert et al., 2009](#)).

(c) Effect of cessation

In several studies the risk for cancer of the oesophagus was reduced with increasing time since cessation of drinking. In a meta-analysis of 5 case-control studies [Rehm et al. \(2007\)](#) reported that compared with current drinkers, risk was not reduced until 5 years or more after cessation of drinking (OR, 0.85; 95%CI: 0.78–0.92) and approached that of nondrinkers after 15 years or more since quitting drinking (Table 2.6 on-line). Similar results were obtained from a cohort study ([Ozasa et al., 2007](#)). Risks are elevated among more former drinkers, who most likely cease drinking due to ill health directly related to the cancer or its precursors ([Rehm et al., 2007](#); [Vioque et al., 2008](#); [Ozasa et al., 2007](#)).

(d) Types of alcoholic beverage

Most previous studies found no material difference in the association of consumption of alcoholic beverages on risk of cancer of the oesophagus according to specific beverage types, with the most commonly consumed beverage tending to be associated with the highest risk. This is supported by data from more recent studies ([Lee et al., 2005](#); [Freedman et al., 2007b](#); [Fan et al., 2008](#); [Vioque et al., 2008](#); [Allen et al., 2009](#); [Pandeya et al., 2009](#)).

(e) Population characteristics

All recent studies have found significant positive associations in both men ([Fan et al., 2008](#); [Benedetti et al., 2009](#); [Ishiguro et al., 2009](#)) and women ([Allen et al., 2009](#)), and in studies that have stratified by sex ([Pandeya et al., 2009](#)).

(f) Risk associated with facial flushing response

One cohort study in Japan examined the association of consumption of alcoholic beverages with cancer of the oesophagus according to whether the cohort members experienced a facial flushing response. Although the risk associated with a high alcohol intake among men with a flushing response was higher than among those with no flushing response, the differences were not significant. Details of the association of alcohol consumption according to genetic variants in alcohol-metabolizing genes related to the flushing response are presented in Section 2.19.

(g) Histological subtypes

In the previous *IARC Monograph* it was concluded that consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus (OSCC), with no or little association with adenocarcinoma of the oesophagus ([IARC, 2010](#)). Data published since a strong association with OSCC or non-adenocarcinoma ([Lee et al., 2005](#); [Freedman et al., 2007b](#); [Fan et al., 2008](#); [Vioque et al., 2008](#); [Allen et al., 2009](#); [Benedetti et al., 2009](#); [Ishiguro et al., 2009](#); [Pandeya et al., 2009](#); [Weikert et al., 2009](#)), and no association with alcohol consumption and adenocarcinoma of the oesophagus ([Freedman et al., 2007b](#); [Allen et al., 2009](#); [Benedetti et al., 2009](#); [Pandeya et al., 2009](#)).

(h) Association among non-smokers

Data on the association of consumption of alcoholic beverages with risk of cancer of the oesophagus among non-smokers are limited. [Pandeya et al. \(2009\)](#) reported higher risks with

increasing alcohol consumption among current smokers compared to never smokers from a case-control study in Australia. [The low numbers of highly exposed cases among never smokers makes it difficult to draw any conclusions.]

(i) Joint effect of alcoholic beverages and tobacco smoking

Evidence suggests a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk for cancer of the oesophagus, with very high risks observed in individuals who were both heavy drinkers and heavy smokers. Recent studies that have examined the joint effect of alcohol consumption and tobacco smoking on the risk of cancer of the oesophagus are described in Section 2.20 of the *Monograph on Tobacco Smoking* in this volume.

*2.2.4. Cancers of the upper aerodigestive tract combined**(a) Overview of cohort and case-control studies*

In the previous *IARC Monograph* ([IARC, 2010](#)) the association between consumption of alcoholic beverages and risk of cancer of the upper aerodigestive tract combined was not evaluated. Since then, three cohort studies ([Thygesen et al., 2007](#); [Allen et al., 2009](#); [Weikert et al., 2009](#); Table 2.11 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.11.pdf>) and one case-control study ([Zaridze et al., 2009](#); Table 2.12 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.12.pdf>) have examined the association of alcoholic beverage consumption and cancers of the upper aerodigestive tract (i.e. oral cavity, pharynx, larynx and oesophagus combined), and one reported on cancers of the oral cavity, pharynx and larynx combined ([Freedman et al., 2007a](#)). All studies reported significant increases in risk with alcoholic beverage consumption, observed in both men and women ([Freedman](#)

[et al., 2007a](#); [Thygesen et al., 2007](#); [Allen et al., 2009](#); [Weikert et al., 2009](#); [Zaridze et al., 2009](#)).

(b) *Intensity and duration*

In one cohort study an increased risk for cancer of the upper aerodigestive tract combined was observed only among those who had a relatively high alcohol intake (i.e. 42 drinks/week or more) ([Thygesen et al., 2007](#)). Other studies have reported increases in risk at more moderate levels of consumption, particularly among women ([Freedman et al., 2007a](#); [Allen et al., 2009](#); [Weikert et al., 2009](#)).

(c) *Types of alcoholic beverage*

The association of consumption of alcoholic beverages on risk of cancer of the upper aerodigestive tract combined does not vary by beverage type, as found in a meta-analysis of 15 case-control studies ([Purdue et al., 2009](#); Table 2.6 on-line) and cohort studies ([Allen et al., 2009](#); [Weikert et al., 2009](#)).

(d) *Association among non-smokers*

Few studies have had sufficient statistical power to assess reliably the association of consumption of alcoholic beverages by smoking status with cancers of the upper aerodigestive tract combined. Most previous studies (as outlined in [IARC, 2010](#)), as well as recent data from the European Prospective Investigation into Cancer and Nutrition have found similar increased risks with increasing alcohol intake among both non-smokers and smokers ([Weikert et al., 2009](#)). In a large cohort study among women in the United Kingdom with a low to moderate alcohol intake, alcohol consumption was not associated with an increased risk of cancers of the upper aerodigestive tract in never smokers or former smokers, but was strongly associated with an increased risk among current smokers ([Allen et al., 2009](#)).

2.3 Cancer of the colorectum

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that consumption of alcoholic beverages is causally related to cancer of the colorectum. This conclusion was largely based on a pooled analysis of eight cohort studies of alcohol intake and cancer of the colorectum conducted in Europe and North America, which found a relative risk (RR) of about 1.4 for cancer of the colorectum with regular consumption of high intakes of alcohol (≥ 45 g/d), compared to non-drinkers, in men and women combined, and which was not related to beverage type ([Cho et al., 2004](#)).

2.3.1 Cohort studies and meta-analyses of cohort studies

Since [IARC \(2010\)](#), 12 cohort studies have evaluated the association between consumption of alcoholic beverages and risk of cancer of the colorectum and/or cancer of the colon and rectum separately (Table 2.13 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.13.pdf>). Of the nine cohort studies that examined the association of consumption of alcoholic beverages and risk of cancer of the colorectum, seven confirmed a significant positive association ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Ishihara et al., 2007](#); [Tsong et al., 2007](#); [Bongaerts et al., 2008](#); [Thygesen et al., 2008b](#); [Toriola et al., 2008](#)). In only two cohort studies was no overall association reported, although both of these likely included very few cases with a high alcohol intake ([Kabat et al., 2008](#); [Lim & Park, 2008](#)). In one further study ([Engeset et al., 2009](#)) no association with a predominantly alcohol-based dietary pattern and cancer of the colorectum was found. [No quantitative assessment of alcohol intake per se was provided and the contribution of other foods to this dietary pattern was not known.] Of the seven studies that evaluated cancer of the colon and rectum

separately ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Ozasa, 2007](#); [Tsong et al., 2007](#); [Thygesen et al., 2008b](#); [Bongaerts et al., 2008](#); [Allen et al., 2009](#)), three reported a significant increased risk with alcohol intake for both sites ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Tsong et al., 2007](#)). This is consistent with findings from one meta-analysis and one pooled analysis (Table 2.14 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.14.pdf>). In a meta-analysis of 21 cohort studies a significant increased risk for cancer of the colorectum, and for colon and rectal cancer separately, for heavy drinkers compared to light or non-drinkers was found ([Huxley et al., 2009](#)). There was also a significant positive association of consumption of alcoholic beverages for men and women with both cancer of the colon and of the rectum in a pooled analysis of five cohort studies in Japan ([Mizoue et al., 2008](#)). [Thygesen et al. \(2008b\)](#) reported an increased risk for colon cancer and not for rectal cancer; in two other studies a significant increased risk for rectal cancer and a weaker, non-significant positive association for colon cancer was found ([Ozasa, 2007](#); [Bongaerts et al., 2008](#)). [Such inconsistency may be due to the small numbers of heavy drinkers in each subsite.] In the largest study to date, with over 4000 cases of colon and over 2000 cases of rectal cancer, no association of alcohol intake was found with colon cancer and a small, but statistically significant, increased risk for rectal cancer ([Allen et al., 2009](#)). [The Working Group noted that the reason for the lack of association with colon cancer in this study of United Kingdom women is not clear, but may, in part, relate to the narrower range of alcohol intake (which was mostly low to moderate), resulting in limited power to detect an association at higher levels of alcohol intake]. Most of the studies in which the association of alcohol intake has been examined by more detailed subsite definitions within the colon are more consistent in showing a positive association with alcohol intake for cancer of

the distal colon, but a weak or null association for cancer of the proximal colon ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Bongaerts et al., 2008](#); [Thygesen et al., 2008b](#)).

2.3.2 Cohort studies in special populations

Since [IARC \(2010\)](#), in one cohort study in the Netherlands a significantly higher rate of rectal cancer among male alcohol abusers compared with national rates, but no association with colon cancer was found (Table 2.15 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.15.pdf>). Among women, rates of both colon and rectal cancer were similar among alcohol abusers and the national population, although there were relatively low numbers for each cancer site ([Thygesen et al., 2009](#)). [This study provided no information on individual exposures or results adjusted for potential confounders.]

2.3.3 Case-control studies

Since [IARC \(2010\)](#), reports on the association of consumption of alcoholic beverages and cancer of the colorectum have come from 10 case-control studies. There was a significant positive association in five, three of which found an increased risk of cancer of the colorectum at relatively high levels of consumption ([Gao et al., 2008](#); [Lightfoot et al., 2008](#); [Benedetti et al., 2009](#)) and for two studies in the Far East an increased risk among drinkers was reported ([Sriamporn et al., 2007](#); [Wei et al., 2009](#)). [Information on quantity of intake was not available for these studies.] (Table 2.16 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.16.pdf>). No association for consumption of alcoholic beverages and cancer of the colorectum was reported for five case-control studies ([Wang et al., 2006a](#); [Murtaugh et al., 2007](#); [Pereira Serafim et al., 2008](#); [Ganesh et al., 2009](#); [Wu et al., 2009](#)). [These studies were conducted in populations with a low

intake of alcoholic beverages ([Wang et al., 2006a](#); [Murtaugh et al., 2007](#); [Ganesh et al., 2009](#)) and/or had a small sample size and limited exposure information ([Pereira Serafim et al., 2008](#); [Ganesh et al., 2009](#); [Wu et al., 2009](#)).]

2.3.4 Dose–response relationship

One pooled analysis of eight cohort studies ([Cho et al., 2004](#)) and several independent studies found an increased risk for cancer of the colorectum for an alcohol intake of 20 g/day or more ([Gao et al., 2008](#)), 30 g/day or more ([Ferrari et al., 2007](#); [Bongaerts et al., 2008](#)) or 45 g/day or more ([Akhter et al., 2007](#)). A pooled analysis of five cohort studies conducted in Japan also found an increased risk for cancer of the colorectum above 23 g/day, evident for both cancer of the colon and of the rectum for both men and women ([Mizoue et al., 2008](#)). Other studies found an increased risk for cancer of the colorectum or rectum only with lower amounts of alcohol (i.e. of the order of 1 drink/d or 10 g/d) ([Tsong et al., 2007](#); [Thygesen et al., 2008b](#); [Allen et al., 2009](#)).

2.3.5 Types of alcoholic beverage

(a) Other metrics of exposure

Few studies have examined the association between cancer of the colorectum and other metrics of exposure (average alcohol intake, over a lifetime or specifically during early adulthood, age at starting, duration). The limited evidence suggests that there is no strong association with duration of drinking in years or age at started drinking ([Ferrari et al., 2007](#); [Ozasa, 2007](#); [Wu et al., 2009](#)). In most earlier studies and some recent studies the risk associated with a baseline measure of intake is similar to a measure of average lifetime intake ([Ferrari et al., 2007](#); [Thygesen et al., 2008b](#)), [Benedetti et al. \(2009\)](#) reported an increased risk with increasing cumulative intake. There is also very limited information on whether the frequency of drinking is an

important determinant of risk. In three studies no association with frequency of alcohol intake (drinks/day) was found ([Ozasa, 2007](#); [Lim & Park, 2008](#); [Benedetti et al., 2009](#)), while in others the frequency of intake was associated with an increased risk among those with a high intake of alcohol (> 15 g/d), but not among those with lower intake of alcohol ([Mizoue et al., 2008](#); [Thygesen et al., 2008b](#)).

The association of consumption of alcoholic beverages and cancer of the colorectum does not appear to differ by beverage type ([Ferrari et al., 2007](#); [Tsong et al., 2007](#); [Bongaerts et al., 2008](#); [Thygesen et al., 2008b](#)).

2.3.6 Population characteristics

The association of consumption of alcoholic beverages and cancer of the colorectum appears to be similar for men and women ([Ferrari et al., 2007](#); [Bongaerts et al., 2008](#)). There is a causal association between cigarette smoking and risk for cancer of the colorectum (see the *Monograph on Tobacco Smoking* in this volume). Most studies of consumption of alcoholic beverages have adjusted for smoking status. In studies that stratified the analysis by smoking status most found an increased risk among both never and current smokers, with the risk estimates slightly higher in current or ever smokers compared to never smokers ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Tsong et al., 2007](#)).

[Ferrari et al. \(2007\)](#) did not find a statistically significant interaction term between alcohol drinking and smoking with regard to cancers of the colorectum. [Tsong et al. \(2007\)](#) reported that the interaction effect between alcohol and smoking was not statistically significant on risk of cancer of the colorectum overall and rectal cancer alone (both $P > 0.19$), while the interaction effect on colon cancer risk was of marginal statistical significance ($P = 0.051$).

Few studies have examined whether the association of alcohol with cancer of the colorectum

varies by folate status; the European Prospective Investigation into Cancer and Nutrition found some evidence that the risk for colorectal cancer associated with alcohol intake was stronger in individuals with a low folate intake, but the interaction term was of marginal statistical significance ([Ferrari et al., 2007](#)), and two other studies found no evidence that the association of alcohol intake with risk differed according to intake of folate, or intake of related nutrients such as vitamin B6, vitamin B12 or methionine ([Ishihara et al., 2007](#); [Kabat et al., 2008](#)).

2.4 Cancer of the liver and hepatobiliary tract

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that consumption of alcoholic beverages is causally related to risk of cancer of the liver. This conclusion was based on a considerable number of cohort and case-control studies.

Chronic infection with hepatitis viruses B and C are the major causes of cancer of the liver. The increased risk associated with consumption of alcoholic beverages has been found consistently among individuals infected with hepatitis viruses as well as among uninfected individuals. Quantification of the effect of consumption of alcoholic beverages on the risk of cancer of the liver cannot be determined reliably since cirrhosis and other liver disorders that often predate cancer of the liver tend to lead to a decrease in or the cessation of consumption of alcoholic beverages many years before the occurrence of cancer of the liver.

The previous *IARC Monograph* did not separately evaluate the effect of consumption of alcoholic beverages on the risk of cholangiocarcinoma.

2.4.1 Hepatocellular carcinoma

Three cohort studies ([Gwack et al., 2007](#); [Ohishi et al., 2008](#); [Allen et al., 2009](#); Table 2.17 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.17.pdf>) and three case-control studies ([Hassan et al., 2008](#); [Benedetti et al., 2009](#); [Zaridze et al., 2009](#); Table 2.18 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.18.pdf>) on the general population and one cohort study on alcoholics ([Thygesen et al., 2009](#); Table 2.19 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.19.pdf>) have been identified since [IARC \(2010\)](#). No new meta-analysis or studies on the joint effect of alcohol beverage and virus infection were found.

In the three cohort studies, [Gwack et al. \(2007\)](#) in Republic of Korea, [Ohishi et al. \(2008\)](#) in Japan, and [Allen et al. \(2009\)](#) in the United Kingdom, an association between consumption of alcoholic beverages and cancer of the liver was found. [Hassan et al. \(2008\)](#) reported from a study in USA an increased risk for cancer of the liver in women with increasing alcohol consumption. Among men, the risk for cancer of the liver was only increased among those with an ethanol intake of ≥ 60 ml per day. [Zaridze et al. \(2009\)](#) found an increased risk of cancer of the liver with consumption of alcoholic beverages (usually vodka) among both men and women in the Russian Federation as did [Benedetti et al. \(2009\)](#) from Canada. [Thygesen et al. \(2009\)](#) reported a higher risk of cancer of the liver among both alcoholic men and women compared to the general population. [There were only 8 cases among women.]

2.4.2 Cholangiocarcinoma

Ten studies on the association between consumption of alcoholic beverages and cholangiocarcinoma (CCA) in the general population were identified ([Parkin et al., 1991](#); [Shin et al.,](#)

1996, [Donato et al., 2001](#); [Kuper et al., 2001](#); [Yamamoto et al., 2004](#); [Honjo et al., 2005](#); [Shaib et al., 2007](#); [Hsing et al., 2008](#); [Lee et al., 2008a](#); [Zhou et al., 2008](#)), all of which were case-control studies (Table 2.20 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.20.pdf>). An increased risk for cholangiocarcinoma among heavy drinkers (≥ 80 g/day) was reported in two studies from the Republic of Korea ([Shin et al., 1996](#) for CCA; [Lee et al., 2008a](#) for intrahepatic CCA) and one study from the USA ([Shaib et al., 2007](#) for both intrahepatic and extrahepatic CCA), among current drinkers in a study from China ([Hsing et al., 2008](#) for extrahepatic CCA), and among regular drinkers in Thailand ([Honjo et al., 2005](#) for CCA). In another study in Thailand a non-significant increased risk among regular drinkers was found ([Parkin et al., 1991](#) for CCA). There was no association in three studies on intrahepatic CCA from Italy ([Donato et al., 2001](#)), Japan ([Yamamoto et al., 2004](#)), and China ([Zhou et al., 2008](#)) (Table 2.20 on-line). [Kuper et al. \(2001\)](#) did not find any association between consumption of alcoholic beverages and cholangiocarcinoma in a low-risk Caucasian population in Greece [data not shown due to only six cases].

Cholangiocarcinoma is a recognized complication of primary sclerosing cholangitis. A study among patients with primary sclerosing cholangitis (26 cases of CCA following primary sclerosing cholangitis, 87 controls with primary sclerosing cholangitis) reported alcohol drinking as one of the risk factor for developing CCA ([Chalasani et al., 2000](#)).

2.5 Cancer of the stomach

In the previous *IARC Monograph* ([IARC, 2010](#)), results on the risk for cancer of the stomach associated with the consumption of alcoholic beverages were considered inconsistent. Since then, four cohort studies ([Freedman et al., 2007](#); [Larsson et al., 2007](#); [Sung et al., 2007](#); [Allen](#)

[et al., 2009](#)) and three case-control studies ([Lucenteforte et al., 2008](#); [Benedetti et al., 2009](#); [Zaridze et al., 2009](#)) in the general population, and one cohort study in alcoholics ([Thygesen et al., 2009](#)) have been published.

2.5.1 Cohort studies in the general population

Among cohort studies, no general association between alcohol intake and cancer of the stomach was found in three studies ([Freedman et al., 2007](#); [Larsson et al., 2007](#); [Allen et al., 2009](#)), while [Sung et al. \(2007\)](#) reported a slight increase in risk (Table 2.21 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.21.pdf>).

2.5.2 Cohort studies in special populations (alcohol abusers)

[Thygesen et al. \(2009\)](#) reported a higher risk of cancer of the stomach in alcoholics than in the general population (Table 2.22 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.22.pdf>). The increase was statistically significant in men (68 cases) but not in women (7 cases). [This study provided no information on individual exposures or results adjusted for potential confounders.]

2.5.3 Case-control studies

None of the case-control studies ([Lucenteforte et al., 2008](#); [Benedetti et al., 2009](#); [Zaridze et al., 2009](#); Table 2.23 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.23.pdf>) found an overall association between alcohol intake and risk for cancer of the stomach. [Benedetti et al. \(2009\)](#) reported a statistically significant increase in the risk of cancer of the stomach among those who consumed 1–6 drinks per week, but not among those who drank 7 or more per week.

2.5.4 Types of alcoholic beverage

Analyses by different types of alcoholic beverages are presented in Table 2.24 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.24.pdf>). Larsson *et al.* (2007) found an increased risk for cancer of the stomach with intake of medium or strong beer, while no effects were found with light beer, wine or hard liquor. Freedman *et al.* (2007) reported an increased risk for cancer of gastric cardia among those with high intake of hard liquor while no such association was found in the case of non-cardia gastric adenocarcinoma. Benedetti *et al.* (2009) reported a statistically significant increase in risk for cancer of the stomach among those who consumed 1–6 drinks per week of any of beer, wine or hard liquor, but not with those who drank 7 or more per week.

2.5.5 Confounding

In the previous Monograph, significantly increased risks were reported in some studies, including those from Japan, China, Poland and the Russian Federation. In no study was it possible to stratify or adjust fully for lifetime infection with *Helicobacter pylori*. It was concluded that since most of the population in areas where an association between consumption of alcoholic beverages and stomach cancer emerged had probably been infected by the bacterium, potential confounding by *H. pylori* infection was not a major concern. Of concern, however, was the likelihood that dietary deficiencies exist in those populations and that the consumption of alcoholic beverages might be accompanied by other unfavourable lifestyle factors, such as low socioeconomic class and low intake of fresh fruit, vegetables and various micronutrients (IARC, 2010).

New studies did not provide any additional information of potential confounders.

2.6 Cancer of the pancreas

In the previous *IARC Monograph* (IARC, 2010), it was concluded that there was not strong evidence for an association between the consumption of alcoholic beverages and risk of cancer of the pancreas.

2.6.1 Meta- and pooled analyses

A pooled analysis of 14 cohort studies (Genkinger *et al.*, 2009) and a meta-analysis of 21 case-control studies and 11 cohort studies (one of which was the pooled analysis) (Tramacere *et al.*, 2009) reported a small, statistically significant, increased risk for cancer of the pancreas associated with high intakes of alcoholic beverages (Table 2.25 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.25.pdf>). In the pooled analysis, with over 2000 incident cases of cancer of the pancreas, a relative risk of 1.22 (95%CI: 1.03–1.45) for those drinking ≥ 30 g/day versus none was found, with no significant difference by beverage type (Genkinger *et al.*, 2009). Tramacere *et al.* (2009) reported a relative risk of 1.22 (95%CI: 1.12–1.34) for those drinking ≥ 3 drinks/day [approx. 30 g/day] versus none or occasional drinkers.

2.6.2 Cohort studies in the general population

In addition to the cohort studies included in the pooled analysis by Genkinger *et al.* (2009), the association of alcoholic beverage consumption and risk for cancer of the pancreas has been independently examined in six cohort studies (Table 2.26 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.26.pdf>). A nested case-control study within the Veterans Health Administration Cohort [the control population consisted of all participants without cancer of the pancreas enrolled in the study] found a significant negative association between alcohol use and cancer of the pancreas.

[Only data on current alcohol use were collected by the clinical provider, and duration and intensity of alcohol use were not recorded. It is possible that patients might have stopped drinking due to ill health, thereby causing a spuriously high risk among the non-drinkers ([Khurana et al., 2007](#)).] In another study, high alcohol consumption, defined according to a scoring system that was based on a self-administered questionnaire designed to detect alcoholism and on serum levels of γ -glutamyl transferase [a biomarker of excessive drinking], was associated with an increased risk for cancer of the pancreas ([Johansen et al., 2009](#)). [Data on the amount of alcohol consumption were not available.] In the Million Women Study in the United Kingdom, with approximately 1300 incident cases, there was no association between alcohol intake and risk for cancer of the pancreas among this population of low to moderate drinkers (only 5% drank ≥ 15 drinks/week) ([Allen et al., 2009](#)). In the European Prospective Investigation of nutrition and Cancer there was also no association with alcohol intake ([Rohrmann et al., 2009](#)), although there was some suggestion of an increased risk among those with a high average lifetime intake of spirits (RR for ≥ 10 g/day versus 0.1–4.9 g/day: 1.40; 95%CI: 0.93–2.10). This finding is based on small numbers and should be interpreted with caution, in the NIH-AARP study (based on over 1000 incident cases) there was also a positive association between high alcohol intake and risk for cancer of the pancreas (RR for ≥ 3 versus $> 0 - < 1$ drinks/day: 1.45; 95%CI: 1.17–1.80), which was stronger among those with a high intake of spirits (RR for ≥ 3 drinks/day versus $> 0 - < 1$ drinks/day: 1.62, 95%CI: 1.24–2.10); there was no association for increasing intake of beer or wine, although few participants were heavy wine or beer drinkers ([Jiao et al., 2009](#)). In the Netherlands Cohort Study the increased risk was limited to heavy drinkers (RR for ≥ 30 g/day versus none: 1.57; 95%CI: 1.03–2.39), and was similar in a subgroup of individuals who

reported a stable alcohol intake for the previous five years (RR for ≥ 30 g/day versus none: 1.82, 95%CI: 1.05–3.15), but there was no association with a specific beverage type ([Heinen et al., 2009](#)). The increased risk was observed only during the first 7 years of follow-up and not with longer follow-ups.

2.6.3 Cohort studies in special populations

In one cohort study conducted in the Netherlands there was a significantly higher rate of cancer of the pancreas among male alcohol abusers compared with the national average. Among women, rates of cancer of the pancreas were similar among alcohol abusers and the national population ([Thygesen et al., 2009](#); Table 2.27 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.27.pdf>). [The Working Group noted the low number of cases. This study provided no information on individual exposures or results adjusted for potential confounders.]

2.6.4 Case-control studies

In the previous *IARC Monograph* ([IARC, 2010](#)) reports of 29 case-control studies with quantitative data on the association of alcoholic beverage intake and the risk for cancer of the pancreas were considered. Most of these found no association, although some suggested that heavy alcoholic beverage drinking (e.g. ≥ 15 drinks/week) may be associated with an increased risk, while others found significant reductions in risk with increasing alcoholic beverage intake. Since then, four further case-control studies have been published (Table 2.28 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.28.pdf>). In a case-control study in the USA, with over 800 cases, a significant positive association with heavy consumption of alcoholic beverages and risk for cancer of the pancreas was found (≥ 60 versus < 60 mL ethanol/day: RR, 1.6;

95%CI: 1.1–2.5) ([Hassan et al., 2007](#)). A positive association with high lifetime consumption of alcohol, and which was strongest for intake of spirits, was found in a small study in Canada (with 83 cases) ([Benedetti et al., 2009](#)). In another study in Canada, with over 400 cases, no association with alcohol intake was found ([Anderson et al., 2009](#)). [In this study the range of alcohol intake was narrow and the response rate among the cases was low (24% of all identified cases; 45% of contacted living cases), which may have led to some response bias.] In a study conducted in the Russian Federation with 366 pancreatic cancer deaths no significant association between a very high intake of vodka and death from cancer of the pancreas was found; however, the numbers were small (52 men and 4 women in the highest intake group) and exposure information was obtained from proxies of the decedents [which may have led to some misclassification of exposure] ([Zaridze et al., 2009](#)). [Other studies with a high proportion of proxy respondents may also be prone to recall bias ([Benedetti et al., 2009](#)). On the other hand, given the lethality of the disease, studies that only included self-respondents ([Hassan et al., 2007](#)) may be prone to selection bias if alcohol consumption is associated with tumour aggressiveness.]

2.6.5 Patient characteristics

Some studies have shown higher risks in men than in women ([Heinen et al., 2009](#); [Jiao et al., 2009](#); [Zaridze et al., 2009](#)) [there were too few women in the highest category of alcohol intake to drawn meaningful comparisons.] Most studies, including the meta- and pooled analyses, have found no significant difference in risk estimates between men and women ([Genkinger et al., 2009](#); [Rohrmann et al., 2009](#); [Tramacere et al., 2009](#)). No evidence of a significant interaction between alcohol intake and pancreatic risk was found by either smoking status ([Anderson et al., 2009](#); [Genkinger et al., 2009](#); [Heinen et al., 2009](#);

[Jiao et al., 2009](#); [Johansen et al., 2009](#); [Rohrmann et al., 2009](#)), folate intake ([Genkinger et al., 2009](#); [Heinen et al., 2009](#); [Jiao et al., 2009](#)) or body mass index ([Johansen et al., 2009](#); [Rohrmann et al., 2009](#)), although [Genkinger et al. \(2009\)](#) found that the association of alcohol consumption with risk was stronger among normal-weight individuals compared with overweight and obese individuals.

2.6.6 Potential confounders

Since individuals who consume high amounts of alcohol are also often smokers, it is possible that the positive association observed with alcohol intake may, in part, be due to residual confounding by smoking. In the pooled analysis no association with increasing alcohol consumption among non-smokers was found but a small increased risk among past and current smokers ([Genkinger et al., 2009](#)). Although these differences were not statistically significant, it suggests that residual confounding by smoking cannot be ruled out. Evidence from other smaller studies is inconsistent, perhaps due to the low numbers of heavily exposed cases among non-smokers ([Anderson et al., 2009](#); [Heinen et al., 2009](#); [Johansen et al., 2009](#); [Jiao et al., 2009](#); [Rohrmann et al., 2009](#)). [The Working Group noted that among smokers, it is difficult to disentangle the effects of alcohol from that of smoking due to differences in the amount of cigarettes consumed.]

2.7 Cancer of the lung

A possible link between consumption of alcoholic beverages and risk for cancer of the lung has long been speculated; in the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the available data were inadequate to determine a causal association between the consumption of alcoholic beverages and lung cancer.

Two case-control studies ([Kubík et al., 2004](#); [Benedetti et al., 2009](#)), eight cohort studies ([Takezaki et al., 2003](#); [Nakaya et al., 2005](#); [Chao et al., 2008](#); [Shimazu et al., 2008](#); [Allen et al., 2009](#); [Thun et al., 2009](#); [Thygesen et al., 2009](#); [Toriola et al., 2009](#)), two meta-analyses ([Chao, 2007](#); [Fan & Cai, 2009](#)) and one systematic review ([Wakai et al., 2007](#)) were not considered in the previous IARC Monograph ([IARC, 2010](#)). More detailed analyses with regard to cancer of the lung for one of the case-control studies ([Benedetti et al., 2009](#)) were available in an earlier publication ([Benedetti et al., 2006](#)); therefore, the earlier publication is considered for this evaluation. This section reviews all available data.

A high correlation has been identified between tobacco smoking and alcohol drinking in many populations. As such, careful adjustment for smoking is one of the most important requirements for a valid interpretation for the association between alcohol drinking and cancer of the lung.

2.7.1 Overview of studies

(a) Cohort studies in the general population

Among 29 cohort studies of the general population that provided tobacco smoking-adjusted risk estimates for total alcoholic beverage use, of which one was a pooled analysis of seven cohort studies ([Freudenheim et al., 2005](#)), a significant elevated risk for cancer of the lung associated with alcoholic beverage consumption was reported in 16 ([Klatsky et al., 1981](#); [Pollack et al., 1984](#); [Stemmermann et al., 1990](#); [Chow et al., 1992](#); [Potter et al., 1992](#); [Doll et al., 1994](#); [Murata et al., 1996](#); [Prescott et al., 1999](#); [Lu et al., 2000](#); [Korte et al., 2002](#) [which includes two separate studies: the Cancer Prevention Study (CPS) I and II]; [Balder et al., 2005](#); [Nakaya et al., 2005](#); [Nishino et al., 2006](#); [Chao et al., 2008](#); [Toriola et al., 2009](#)) (the new studies are summarized in Table 2.29 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.29.pdf>).

In some of these studies an increased risk at high levels of consumption was found ([Klatsky et al., 1981](#); [Pollack et al., 1984](#); [Potter et al., 1992](#); [Doll et al., 1994](#); [Murata et al., 1996](#); [Prescott et al., 1999](#); [Lu et al., 2000](#); [Korte et al., 2002](#) [CPS I and II]; [Balder et al., 2005](#); [Nakaya et al., 2005](#); [Chao et al., 2008](#)), while no association at the highest consumption category but with moderate consumption was found in other studies ([Stemmermann et al., 1990](#); [Chao et al., 2008](#), [only for drinking < 1 drink beer per week versus non-drinkers]), among former drinkers ([Nakaya et al., 2005](#); [Nishino et al., 2006](#)), or among binge drinkers ([Toriola et al., 2009](#)). No significant association was observed in the other cohort studies with results adjusted for smoking, including the pooled analysis of seven cohorts ([Kvåle et al., 1983](#); [Kono et al., 1986](#); [Bandera et al., 1997](#); [Yong et al., 1997](#); [Woodson et al., 1999](#); [Breslow et al., 2000](#); [Djoussé et al., 2002](#); [Takezaki et al., 2003](#); [Freudenheim et al., 2005](#); [Rohrmann et al., 2006](#); [Shimazu et al., 2008](#); [Allen et al., 2009](#); [Thun et al., 2009](#)). In some of these studies, levels of alcohol intake among the participants were moderate ([Kono et al., 1986](#); [Breslow et al., 2000](#); [Freudenheim et al., 2005](#); [Allen et al., 2009](#)).

(b) Cohort studies in special populations

The risk for cancer of the lung among alcoholics or patients with alcohol use disorders was examined in seven cohort studies ([Schmidt & Popham, 1981](#); [Adami et al., 1992](#); [Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Sørensen et al., 1998](#); [Boffetta et al., 2001](#); [Thygesen et al., 2009](#)) are summarized in Table 2.30 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.30.pdf>. All reported elevated risk of cancer of the lung. However, due to the lack of control for tobacco smoking in all of the studies, the observed association may be largely explained by the confounding effect of tobacco smoking.

(c) Case-control studies

In all, 22 case-control studies reported tobacco smoking-adjusted odds ratios for total consumption of alcoholic beverages and the risk for cancer of the lung (the new studies are summarized in Table 2.31 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.31.pdf>). In seven population-based studies (Koo, 1988; Bandera *et al.*, 1992; Mayne *et al.*, 1994; Carpenter *et al.*, 1998; Hu *et al.*, 2002; Freudenheim *et al.*, 2003; Benedetti *et al.*, 2006) and 11 hospital-based studies (Williams & Horm, 1977; Herity *et al.*, 1982; Kabat & Wynder, 1984; Mettlin, 1989; Pierce *et al.*, 1989; Rachtan & Sokolowski, 1997; Zang & Wynder, 2001; De Stefani *et al.*, 2002; Pacella-Norman *et al.*, 2002; Ruano-Ravina *et al.*, 2004; Kubík *et al.*, 2004) no significant association between any level of alcoholic beverage consumption and the risk for cancer of the lung was found, while in four hospital-based studies (De Stefani *et al.*, 1993; Dosemeci *et al.*, 1997; Rachtan, 2002; Gajalakshmi *et al.*, 2003) an association was found.

(d) Meta- and pooled analyses

Korte *et al.* (2002) found an increased risk for lung cancer with an ethanol intake of at least 2000 g per month (≥ 5 drinks/day): the relative risk from cohort studies was 1.53 (95%CI: 1.04–2.25) and the odds ratio from case-control studies was 1.86 (95%CI: 1.39–2.49) [the estimated risks for intake of 2000 g/month or more were based on only one study for both cohort and case-control studies]; lower intakes were not associated with increased risk (Table 2.32 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.32.pdf>). [The exposure studied most extensively was the frequency of drinking. Other parameters of alcoholic beverage exposure, such as duration and age at initiation of drinking and the relevant exposure period were not considered.] In another meta-analysis

Fan & Cai (2009) provided estimates for total alcohol drinking, and did not find a significant association with risk of lung cancer. In a pooled analysis of 7 cohort studies, Freudenheim *et al.* (2005) found a slightly greater risk of cancer of the lung with the consumption of ≥ 30 g alcohol per day than with no alcohol consumption (RR, 1.21; 95%CI: 0.91–1.61 in men, RR, 1.16; 95%CI: 0.94–1.43 in women).

2.7.2 Types of alcoholic beverage

Findings from studies examining risk estimates for the consumption of different types of alcoholic beverages (i.e. beer, wine, and hard liquor) have been inconsistent (Pollack *et al.*, 1984; Mettlin, 1989; Bandera *et al.*, 1992; Chow *et al.*, 1992; De Stefani *et al.*, 1993; Carpenter *et al.*, 1998; Prescott *et al.*, 1999; Woodson *et al.*, 1999; De Stefani *et al.*, 2002; Hu *et al.*, 2002; Rachtan 2002; Kubík *et al.*, 2004; Ruano-Ravina *et al.*, 2004; Freudenheim *et al.*, 2005; Benedetti *et al.*, 2006) (the new studies are summarized in Table 2.31 on-line). Risk estimates for different types of alcoholic beverages were also reported in two meta-analyses (Chao, 2007; Fan & Cai, 2009) using results adjusted for smoking (Table 2.32 on-line). Both found a slightly increased risk associated with beer drinking; there was also a slight association between drinking of liquor (Chao, 2007) and spirits (Fan & Cai, 2009) and risk for cancer of the lung. However, when one of the meta-analyses included only the studies with more comprehensive adjustments for smoking (Chao, 2007), there was no significant association.

2.7.3 Smoking status

Several cohort studies have examined the effect of alcoholic beverage consumption among both never smokers and smokers, and the interaction between these two risk factors (Korte *et al.*, 2002; Freudenheim *et al.*, 2005; Nishino *et al.*, 2006; Rohrmann *et al.*, 2006; Chao *et al.*, 2008;

[Shimazu et al., 2008](#); [Thun et al., 2009](#); [Toriola et al., 2009](#); Table 2.33 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.33.pdf>, and Table 2.34 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.34.pdf>). [Korte et al. \(2002\)](#) found an increased risk for cancer of the lung associated with drinking ≥ 500 g of alcohol per month among both never smoker men and women in CPS I but not in CPS II. In a pooled study of seven cohorts, [Freudenheim et al. \(2005\)](#) found an elevated pooled relative risk for alcoholic beverage consumption among never-smoking men but not among never-smoking women. A dose-response was also observed among men with a sixfold increase in risk among never smokers who consumed ≥ 15 g/day (pooled multivariate RR, 6.38; 95%CI: 2.74–14.90; *P* for trend < 0.001).

In contrast, [Nishino et al. \(2006\)](#), [Rohrmann et al. \(2006\)](#), [Shimazu et al. \(2008\)](#), [Thun et al. \(2009\)](#), and [Toriola et al. \(2009\)](#) reported no association among never smokers. [These analyses may have the limitation that most of the cases of cancer of the lung were smokers.] In a detailed analysis examining the effect of consumption of alcoholic beverages by smoking behaviour, [Woodson et al. \(1999\)](#) found no differences in the relative risks across smoking categories (< 20, 20–29, ≥ 30 cigarettes/day) [results were on smokers only]. However, [Shimazu et al. \(2008\)](#) found an increased risk for cancer of the lung among current smokers who drank 300–449 g ethanol per week (hazard ratio (HR), 1.66; 95%CI: 1.04–2.65) as well as those who drank ≥ 450 g/wk (HR, 1.69; 95%CI: 1.05–2.72; *P* for trend = 0.02) compared to current smokers who drank occasionally. [Toriola et al. \(2009\)](#) also found a significant positive association among smokers that was independent of the number of cigarettes smoked or the duration of smoking. However, the analysis was limited to binge drinkers.

Three case-control studies based on populations of never smokers ([Kabat & Wynder, 1984](#);

[Koo, 1988](#); [Hu et al., 2002](#)) found no significant risks for consumption of alcoholic beverages [There is a lack of power to examine the risk associated with heavy drinking, as it is uncommon to find heavy drinkers among never smokers.] In contrast, [Rachtan \(2002\)](#) observed a significantly elevated risk associated with alcoholic beverage intake among women who never smoked and a strong positive dose-response. Other studies on total alcohol intake with results stratified by smoking status have found positive associations between alcohol drinking and risk for cancer of the lung among smokers and no association among non-smokers ([Dosemeci et al., 1997](#); [Zang & Wynder, 2001](#)) or found associations among heavy smokers and no association among non-smokers and low/moderate-smokers combined ([Herity et al., 1982](#); [Bandera et al., 1992](#); [Benedetti et al., 2006](#) [men only]).

There is also some evidence that consumption of alcoholic beverages results in an inverse association with risk of cancer of the lung. Two studies reported an inverse association between wine consumption and lung cancer, one case-control study among non-smokers ([Kubík et al., 2004](#)) [results not adjusted for consumption of other alcoholic beverages], and one cohort study ([Chao et al., 2008](#)) among smokers.

2.7.4 Histological subtypes

Two cohort studies ([Rohrmann et al., 2006](#); [Shimazu et al., 2008](#)), one pooled analysis ([Freudenheim et al., 2005](#)) and eight case-control studies ([Koo, 1988](#); [Dosemeci et al., 1997](#); [Carpenter et al., 1998](#); [Zang & Wynder, 2001](#); [De Stefani et al., 2002](#); [Djoussé et al., 2002](#); [Rachtan, 2002](#); [Benedetti et al., 2006](#)) presented smoking-adjusted risk estimates for consumption of alcoholic beverages by histological type of cancer of the lung (the new studies are summarized in Table 2.35 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.35.pdf>). There appears to be no consistent pattern of

effect estimates by histological type. [Estimates for subtype of cancer of the lung were mostly based on small numbers of cases, which leads to difficulties in interpreting results due to wide confidence intervals and the possibility of chance findings.] Few studies have reported results by histological type among never smokers ([Koo, 1988](#)).

2.7.5 Population characteristics

Several studies conducted analyses stratified by sex using the same exposure categories ([Williams & Horm, 1977](#); [Bandera et al., 1997](#); [Prescott et al., 1999](#); [Korte et al., 2002](#); [Pacella-Norman et al., 2002](#); [Freudenheim et al., 2005](#); [Benedetti et al., 2006](#); [Rohrmann et al., 2006](#)). No significant findings that differed by sex have been reported.

2.8 Cancer of the breast

2.8.1 Cancer of the female breast

The previous *IARC Monograph* ([IARC, 2010](#)) concluded that occurrence of cancer of the female breast was causally associated with the consumption of alcoholic beverages. This conclusion was based on data from more than 100 epidemiological studies, together with a pooled analysis of 53 studies on more than 58000 women with breast cancer, which found a linear increase in risk for breast cancer with increasing levels of alcoholic beverage consumption (increase per 10 g/d of 7.1%, 95%CI: 5.5–8.7%) ([Hamajima et al., 2002](#)).

(a) Cohort studies in the general population

Since [IARC \(2010\)](#), thirteen cohort studies have examined the association of consumption of alcoholic beverages and risk of cancer of the breast (Table 2.36 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.36.pdf>), eight of which showed a significant positive association ([Ericson et al., 2007](#);

[Mørch et al., 2007](#); [Zhang et al., 2007a](#); [Thygesen et al., 2008a](#); [Allen et al., 2009](#); [Duffy et al., 2009](#); [Lew et al., 2009](#); [Li et al., 2009b](#)), and four no significant association ([Trentham-Dietz et al., 2007](#); [Visvanathan et al., 2007](#); [Kabat et al., 2008](#); [Gibson et al., 2009](#)). [In two of these latter studies the number of drinkers was small and there was no quantitative assessment of alcohol intake.] One further study found no association with a predominantly alcohol-based dietary pattern and risk of cancer of the breast ([Engeset et al., 2009](#)) [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.] The Million Women Study in the United Kingdom, with over 28 000 incident cancers, is the largest single study to estimate reliably the risk for cancer of the breast at low to moderate levels of alcohol consumption. A linear increase in risk of cancer of the breast with increasing alcohol intake (increase per 10 g/day [equivalent to about one drink regularly consumed per day] of 12%, 95%CI: 9–14%) was found ([Allen et al., 2009](#)). This estimate is slightly higher than the 7.1% increase in risk reported in the pooled analysis by [Hamajima et al. \(2002\)](#). [[Allen et al. \(2009\)](#) were able to take measurement error into account by repeating the alcohol consumption measure approximately three years after recruitment].

(b) Cohort studies in special populations

Since [IARC \(2010\)](#), [Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the breast among female alcoholics compared with national rates from a cohort study among Danish alcohol abusers (Table 2.37 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.37.pdf>) [This study provided no information on individual exposures or adjusted for potential confounders.]

(c) Case-control studies

The association of consumption of alcoholic beverages and risk for incident cancer of the female breast has been examined in 11 case-control studies (Table 2.38 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.38.pdf>). A significant positive association has been reported from six studies ([Beji & Reis, 2007](#); [Kruk, 2007](#); [Berstad et al., 2008](#); [Kocić et al., 2008](#); [Knight et al., 2009](#); [Newcomb et al., 2009](#)) and a significant inverse association in one ([Zaridze et al., 2009](#)). [This latter study was conducted in the Russian Federation where alcohol consumption is very high relative to other populations and exposure information was obtained from proxies of the decedents (case and control status was based on death certification information). Reasons for the inverse association with very high intake are not clear and information on potential confounders was unavailable.] Null associations were found in four studies ([Terry et al., 2007](#); [Bessaoud & Daurès, 2008](#); [Dolle et al., 2009](#); [Brown et al., 2010](#)), although they either had a very low alcohol intake ([Bessaoud & Daurès, 2008](#); [Dolle et al., 2009](#); [Brown et al., 2010](#)) or did not adjust for potential confounding factors ([Terry et al., 2007](#)).

(d) Other metrics of exposure

Very few investigators have examined whether the frequency of drinking, age at started drinking or the cumulative lifetime intake influences risk; in one cohort study in Denmark some evidence was found that binge drinking at the weekend may additionally increase risk ([Mørch et al., 2007](#)). Another cohort study in Denmark found that risk was attenuated when using updated alcohol information (i.e. most recent intake measured after recruitment), with the suggestion that there may be a long latent period between consumption of alcoholic beverages and development of cancer of the breast ([Thygesen et al., 2008a](#)). In contrast, [Berstad et al. \(2008\)](#)

reported a positive association for recent intake (i.e. in the last five years), but no association with lifetime intake or intake at a young age from a case-control study in the USA.

(e) Types of alcoholic beverage

There is consistent evidence from both cohort and case-control studies that the risk for cancer of the female breast does not vary significantly by beverage type ([Zhang et al., 2007a](#); [Berstad et al., 2008](#); [Bessaoud & Daurès, 2008](#); [Allen et al., 2009](#); [Lew et al., 2009](#); [Li et al., 2009b](#); [Newcomb et al., 2009](#)). Among wine drinkers, the risk does not vary by intake of red wine, white wine or a mixture of both ([Allen et al., 2009](#); [Newcomb et al., 2009](#)).

(f) Other factors affecting risk

There is consistent evidence that the association does not vary by folate intake ([Zhang et al., 2007a](#); [Duffy et al., 2009](#); [Lew et al., 2009](#)) or by menopausal status ([Mørch et al., 2007](#); [Terry et al., 2007](#); [Visvanathan et al., 2007](#); [Zhang et al., 2007a](#); [Kabat et al., 2008](#)), although in two case-control studies there was a slightly stronger association of consumption of alcoholic beverages and risk for cancer of the breast in postmenopausal than in premenopausal women ([Kruk, 2007](#); [Newcomb et al., 2009](#)).

It remains unclear whether the association of consumption of alcoholic beverages with risk of cancer of the breast varies by use of hormone-replacement therapy. In the Copenhagen City Heart Study, and to a lesser extent, the Women's Health Study, a positive association between alcohol intake and risk for cancer of the breast among current users, and no association among non-users of hormone-replacement therapy was found ([Zhang et al., 2007a](#); [Nielsen & Grønbaek, 2008](#)), whereas others have found no such differences ([Bessaoud & Daurès, 2008](#); [Allen et al., 2009](#); [Lew et al., 2009](#)).

Most of the data for an association of consumption of alcoholic beverages on risk for

cancer of the breast comes from Caucasian populations; there is very limited data among Asian populations (Gibson *et al.*, 2009; Brown *et al.*, 2010), perhaps due to the generally low prevalence of alcohol consumption. Most studies that included different ethnic groups estimated risk after adjusting for ethnicity; in two studies that stratified by ethnic group there was no difference in the risk associated with consumption of alcoholic beverages (Berstad *et al.*, 2008; Li *et al.*, 2009b).

There is accumulating evidence that cigarette smoking may increase risk for cancer of the breast (see Monograph on Tobacco Smoking in this Volume), and because drinking and smoking are highly correlated, most studies that have evaluated the association of consumption of alcoholic beverages on risk for cancer of the breast have adjusted for smoking, to a greater or lesser extent. Hamajima *et al.* (2002) found that the association of consumption of alcoholic beverages with risk for cancer of the breast was similar in never, ever and current smokers. No subsequent studies have had sufficient statistical power to evaluate this in more detail, although the evidence to date suggests that the association of consumption of alcoholic beverages on risk of cancer of the breast is unlikely to be confounded by smoking. Another potentially important confounder is body size; in those studies that have examined potential effect modification by body mass index no significant differences have been found (Zhang *et al.*, 2007a; Berstad *et al.*, 2008; Lew *et al.*, 2009).

(g) Contralateral cancer of the breast

The association of consumption of alcoholic beverages with risk for contralateral cancer of the breast was not evaluated in IARC (2010). To date, four cohort (Table 2.39 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.39.pdf>) and one case-control study (Table 2.40 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.40.pdf>)

[pdf](#)) have examined whether consumption of alcoholic beverages increases the risk of a subsequent contralateral cancer of the breast. In one cohort study alcohol consumption at the time of the first diagnosis and during the period between the first and second diagnosis was positively associated with the risk of contralateral cancer of the breast (Li *et al.*, 2009a), although no association was found in other cohort studies (Bernstein *et al.*, 1992; Li *et al.*, 2003b; Trentham-Dietz *et al.*, 2007). In the case-control study women with a contralateral breast cancer were more likely to have drunk regularly and to have drunk for a prolonged period of time compared with women who only had one diagnosis of cancer of the breast, although regular drinking during the period between the first and second diagnosis was not significantly associated with risk (Knight *et al.*, 2009).

(h) Tumour receptor status

The association of consumption of alcoholic beverages and risk for cancer of the breast by estrogen (ER) and progesterone (PR) receptor status has been examined in six cohort studies (Table 2.41 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.41.pdf>). Similar associations for ER+ and ER- tumours were reported by Chlebowski *et al.* (2007), Visvanathan *et al.* (2007), Lew *et al.* (2009) and Setiawan *et al.* (2009). Lew *et al.* (2009) found a slightly stronger association with alcohol intake and ER+/PR+ tumours than for ER+/PR- or ER-/PR- tumours. Li *et al.* (2009b) and Zhang *et al.* (2007a) in contrast reported positive associations for ER+ and PR+ tumours (together with the subgroup of ER+/PR+) and no association with ER- or PR- tumours. Tumour receptor status has also been evaluated in five case-control studies (Table 2.42 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.42.pdf>). In the largest, with approximately 1000 cases with information on receptor status, an increased risk for all

ER+ tumours, and no significant association for ER- tumours, irrespective of PR status, was found; the relative risk per 10 g alcohol/day for ER+/PR+ tumours was 1.14 (95%CI:1.07–1.20), that for ER+/PR- tumours was 1.07 (95%CI: 0.95–1.21) (Deandrea *et al.*, 2008). The association was slightly stronger among pre/perimenopausal women and among women with a high folate intake, although the numbers in these subgroups were small (Deandrea *et al.*, 2008). In a meta-analysis of 16 case-control studies and 3 cohort studies (Table 2.43 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.43.pdf>) an increased risk per 10 g/day increase in alcohol intake for all ER+ tumours was found (12% increased risk), and for the subtypes of ER+/PR+ tumours (11%) and ER+/PR- tumours (15%), and a smaller positive association for all ER- (7%), but no association with ER-/PR- or ER-/PR+ tumours (Suzuki *et al.*, 2008).

There are limited data on the association of consumption of alcoholic beverages with tumours that are characterized as triple-negative or basal-like (defined as ER-/PR-/HER2-), largely because of the recency of available data on HER2 status (human epidermal growth factor receptor). From a case-control study among premenopausal women Dolle *et al.* (2009) reported no association between consumption of alcoholic beverages with triple-negative or non triple-negative tumours, and in another case-control study no significant association with triple-negative or luminal B tumours (ER+ and/or PR+/HER2+) was found, but a stronger positive association for luminal A tumours (ER+ and/or PR+/HER2-) and HER2+ overexpressing tumours (defined as ER-/PR-/HER2+) (Trivers *et al.*, 2009). [The small numbers in some of these subgroups limits interpretation]. No significant differences in drinking status between women with luminal A tumours (the most common tumour type) and women diagnosed with triple-negative or HER2+ overexpressing tumours were

reported by Kwan *et al.* (2009) and Millikan *et al.* (2008) from case-only analyses; one found that women with luminal B tumours were less likely to be drinkers (Kwan *et al.*, 2009), while there was no difference in the other study (Millikan *et al.*, 2008). [The null associations seen for the rarer subtypes of ER+/PR- and ER-/PR+ tumours may reflect limited power of the studies.]

(i) *Histological subtype*

To date, the NIH-AARP (Lew *et al.*, 2009) is the only cohort study to have examined the association of consumption of alcoholic beverages by histological subtype among postmenopausal women; similar positive associations were reported for ductal, lobular and ductal-lobular subtypes (Table 2.44 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.44.pdf>). This is consistent with findings from one case-control study (Nasca *et al.*, 1994; Table 2.45 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.45.pdf>), while a slightly stronger positive association for alcohol intake with the risk for lobular tumours compared with ductal tumours, particularly among postmenopausal women, was found in two others (Li *et al.*, 2003a, 2006). [The low numbers of cases in some subgroups resulted in limited power to detect a significant difference, and these may be chance findings. In addition, it should be noted that the histological data from all of these studies was derived from hospital records and were not subject to central pathology review, leading to potential misclassification due to observer variability.]

2.8.2 *Cancer of the male breast*

It was concluded in the previous IARC Monograph (IARC, 2010) that the evidence for an association of consumption of alcoholic beverages and risk of cancer of the male breast was inconsistent.

(a) Cohort studies

Since [IARC \(2010\)](#), the association between consumption of alcoholic beverages and the risk for cancer of the male breast has been assessed in two cohort studies (Table 2.46 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.46.pdf>). In the NIH-AARP Study no evidence was found that alcohol intake was associated with the risk for cancer of the male breast ([Brinton et al., 2008](#)). In a large cohort of US Army Veterans no association with alcoholism as recorded from hospital records and risk for cancer of the male breast was found ([Brinton et al., 2009](#)).

(b) Studies in special populations

[Thygesen et al. \(2009\)](#) reported similar rates of cancer of the breast among male Danish alcoholics compared with national rates (Table 2.47 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.47.pdf>) [This was based on a very small number of cases and provided no information on individual exposures.]

2.9 Cancer of the uterine cervix

It was concluded in [IARC \(2010\)](#) that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the uterine cervix was sparse. Although some studies of special populations showed positive associations, bias and confounding could not be excluded.

2.9.1 Cohort studies

The association between consumption of alcoholic beverages and risk for cancer of the uterine cervix has been examined in 8 cohort studies, seven of which were carried out in women who were treated for alcohol abuse or alcoholism ([Prior, 1988](#); [Adami et al., 1992](#);

[Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#); [Thygesen et al., 2009](#)) or worked as waitresses ([Kjaerheim & Andersen, 1994](#)), and one in the general population ([Allen et al., 2009](#)) (the new studies are summarized in Table 2.48 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.48.pdf>).

The majority of studies were conducted in Scandinavia ([Adami et al., 1992](#); [Kjaerheim & Andersen, 1994](#); [Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#); [Thygesen et al., 2009](#)), where the use of the unique identification numbers makes it possible to work on large, registry based data. Two cohort studies were conducted in the United Kingdom ([Prior, 1988](#); [Allen et al., 2009](#)). In all seven studies conducted in special populations elevated risk estimates for invasive cancer of the uterine cervix among alcoholic women were found compared to the general population. [None of the studies adjusted for known risk factors for cancer of the uterine cervix, namely human papilloma virus (HPV) infection, number of sexual partners and tobacco smoking, or attendance at cervical cancer screening programmes. It is possible that women with alcohol abuse have other behavioural patterns that may affect risk for cancer of the uterine cervix, such as non-compliance to screening, tobacco smoking and having a higher prevalence of HPV than the general population in their respective countries.]

In the Million Women Study ([Allen et al., 2009](#)) non-drinking women had an elevated risk for cancer of the uterine cervix compared to drinkers. Among drinkers, there was no association between the amount of alcohol consumed and risk for cancer of the uterine cervix. The analyses were adjusted for socioeconomic status, smoking, body mass index, physical activity, oral contraceptives and hormone replacement therapy use, but not for particular risk factors of cancer of the uterine cervix, including HPV infection and factors related to a sexual behaviour such as the

number of lifetime sexual partners or age at first intercourse.

2.9.2 Case-control studies

The association between consumption of alcoholic beverages and cancer of the uterine cervix was evaluated in 12 case-control studies, seven of which were hospital-based (two from Italy, two from Thailand, one from Uganda, one from United Kingdom, one from the USA), three were register or cohort based (from the USA and Zimbabwe), and two were based on both hospital and population controls (one from Lesotho and one large multicentric study from Latin America). No or no significant increased risk for cancer of the uterine cervix among alcoholic drinkers was found in eight studies ([Williams & Horm, 1977](#); [Harris et al., 1980](#); [Marshall et al., 1983](#); [Cusimano et al., 1989](#); [Licciardone et al., 1989](#); [Thomas et al., 2001a, b](#); [Chiaffarino et al., 2002](#)). In the three studies from Africa ([Martin & Hill, 1984](#); [Parkin et al., 1994](#); [Newton et al., 2007](#)), women who drank alcohol had a significant or borderline significant elevated risk for cancer of the uterine cervix. [Adjustment for confounding in these studies was incomplete.] In the study from Latin America, in which adjustment for possible confounders was adequate, there was an elevated risk for cancer of the uterine cervix among occasional drinkers (confidence intervals not given) but no association with heavy drinking ([Herrero et al., 1989](#)).

2.9.3 Evidence of a dose-response

The cohort studies on alcoholics did not provide convincing evidence of a dose-response between risk for cancer of the uterine cervix and duration of exposure, which was roughly estimated as years since cohort enrolment (first hospitalization/clinical treatment for alcoholism).

A case-control study from Latin America ([Herrero et al., 1989](#)), which adjusted for

important risk factors such as tobacco smoking and number of sexual partners, showed an inverse dose-response association. In four other case-control studies in which there was an indication of a higher risk for cancer of the uterine cervix with higher alcohol consumption, the observed association was weak in two ([Harris et al., 1980](#); [Marshall et al., 1983](#)) and significant in two other studies ([Martin & Hill, 1984](#); [Parkin et al., 1994](#)), but adjustment for possible confounders was incomplete. In one study, a positive trend was observed among consumers in the category “wine and other alcoholic beverages” ([Chiaffarino et al., 2002](#)).

2.9.4 Types of alcoholic beverage

The effect of specific types of alcoholic beverages (beer, wine and spirits) on risk for cancer of the uterine cervix was not investigated in the cohort studies.

In almost all case-control studies that evaluated specific types of alcoholic beverage ([Marshall et al., 1983](#); [Martin & Hill, 1984](#); [Chiaffarino et al., 2002](#)) no consistent differences in risk for cancer of the uterine cervix between drinkers and non-drinkers of a certain alcohol type were found. [Williams & Horm \(1977\)](#) found a non-significant higher risk for cancer of the uterine cervix among wine drinkers, while [Marshall et al. \(1983\)](#) found beer drinkers were at higher risk.

2.10 Cancer of the endometrium

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the endometrium was inconsistent.

2.10.1 Cohort studies in the general population

The association between consumption of alcoholic beverages and cancer of the endometrium in the general population has been evaluated in eight cohort studies ([Gapstur et al., 1993](#); [Terry et al., 1999](#); [Folsom et al., 2003](#); [Loerbroks et al., 2007](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)) (the new studies or updates are summarized in Table 2.49 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.49.pdf>). These studies were conducted in North America ([Gapstur et al., 1993](#); [Folsom et al., 2003](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#)) and in Europe, one in the Netherlands ([Loerbroks et al., 2007](#)), one in the United Kingdom ([Allen et al., 2009](#)) and two in Sweden ([Terry et al., 1999](#); [Friberg & Wolk, 2009](#)). Risk estimates adjusted for multiple possible confounders (body size and reproductive factors) were presented in seven reports ([Gapstur et al., 1993](#); [Terry et al., 1999](#); [Loerbroks et al., 2007](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)) while only five of these ([Jain et al., 2000a](#) [an earlier report from the same study as [Kabat et al., 2008](#)] in which results were not adjusted for smoking; [Loerbroks et al., 2007](#); [Setiawan et al., 2008](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)) adjusted the analysis of consumption of alcoholic beverages for smoking. Smoking showed non-significant negative association in almost all studies except for [Friberg & Wolk \(2009\)](#), where the risk estimates for cancer of the endometrium were decreased among never smokers, especially in women drinking more than 10 g of alcohol daily.

There was no clear evidence of association between consumption of alcoholic beverages and the risk for cancer of the endometrium in any of these studies. In four ([Terry et al., 1999](#); [Loerbroks et al., 2007](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#)) some elevated risk for cancer of

the endometrium among drinking women was found. Only [Setiawan et al. \(2008\)](#) reported a statistically significant association, which was among women who consumed more than 2 drinks per day. In one study ([Folsom et al., 2003](#)), an inverse association was found. No association was found in the other studies ([Gapstur et al., 1993](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)).

2.10.2 Cohort studies in special populations

Three earlier cohort studies examined the association between alcoholic beverage intake and the risk for cancer of the endometrium in special populations, namely women hospitalized or being treated for alcohol dependence ([Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#), which was an update of [Adami et al., 1992](#)). [Thygesen et al. \(2009\)](#) conducted the most recent study (Table 2.50 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.50.pdf>).

[Weiderpass et al. \(2001\)](#) found an inverse association between alcoholic beverage consumption and cancer of the endometrium. [The analytical models did not include important covariates that may have confounded the association, such as cigarette smoking and body size.] In the other studies, there was no evidence of an association.

2.10.3 Case-control studies

Case-control studies that have investigated the relationship between alcoholic beverage consumption and the risk for cancer of the endometrium were carried out in North America, Japan and western Europe. Eight of these were hospital-based ([La Vecchia et al., 1986](#); [Cusimano et al., 1989](#); [Austin et al., 1993](#); [Levi et al., 1993](#); [Parazzini et al., 1995a](#); [Kalandidi et al., 1996](#); [Petridou et al., 2002](#); [Hosono et al., 2008](#)), two were based on cases and controls from a cancer survey or registry database ([Williams & Horm, 1977](#); [Kato et al., 1989](#)) and eight were

population-based ([Webster et al., 1989](#); [Shu et al., 1991](#); [Swanson et al., 1993](#); [Goodman et al., 1997](#); [Newcomb et al., 1997](#); [Jain et al., 2000b](#); [McCann et al., 2000](#); [Weiderpass & Baron, 2001](#)). The most recent study ([Hosono et al., 2008](#)) is summarized in Table 2.51 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.51.pdf>)

Eleven studies ([Cusimano et al., 1989](#); [Kato et al., 1989](#); [Webster et al., 1989](#); [Austin et al., 1993](#); [Swanson et al., 1993](#); [Parazzini et al., 1995a](#); [Kalandidi et al., 1996](#); [Newcomb et al., 1997](#); [Weiderpass & Baron, 2001](#); [Petridou et al., 2002](#); [Hosono et al., 2008](#)) were designed to examine the association between consumption of alcoholic beverages, other lifestyle factors such as cigarette smoking, use of hormone replacement therapy and other risk factors in the etiology of cancer of the endometrium. Six studies ([LaVecchia et al., 1986](#); [Shu et al., 1991](#); [Levi et al., 1993](#); [Goodman et al., 1997](#); [Jain et al., 2000b](#); [McCann et al., 2000](#)) were designed to evaluate nutritional factors. Potentially confounding factors were considered in all the studies except for one ([Cusimano et al., 1989](#)), although adjustment may have been incomplete in three studies ([Williams & Horm, 1977](#), [age, race and smoking]; [Shu et al., 1991](#), [pregnancies and weight]; [Levi et al., 1993](#), [only adjusted for age and centre]).

The results of case-control studies were not consistent. In 10 studies little or no association between consumption of alcoholic beverages and the risk for cancer of the endometrium was found ([Kato et al., 1989](#); [Webster et al., 1989](#); [Austin et al., 1993](#); [Swanson et al., 1993](#); [Kalandidi et al., 1996](#); [Goodman et al., 1997](#); [Newcomb et al., 1997](#); [McCann et al., 2000](#); [Weiderpass & Baron, 2001](#); [Petridou et al., 2002](#)). An inverse association was found in three ([Williams & Horm, 1977](#); [Jain et al., 2000b](#); [Hosono et al., 2008](#)), which was significant in two ([Jain et al., 2000b](#); [Hosono et al., 2008](#)) among moderate drinking women. An increased risk for cancer of the endometrium with high consumption of alcoholic beverages

was found by [LaVecchia et al. \(1986\)](#), [Cusimano et al. \(1989\)](#), [Shu et al. \(1991\)](#), [Levi et al. \(1993\)](#) and [Parazzini et al. \(1995a\)](#); in two the association was non-significant ([Cusimano et al., 1989](#); [Shu et al., 1991](#)), in one it was significant ([Parazzini et al., 1995a](#)) and one ([Levi et al., 1993](#)) found a positive association relative to wine and liquor, but not to beer.

2.10.4 Evidence of a dose-response

There was no evidence of a trend of increasing risk for cancer of the endometrium with increasing consumption of alcoholic beverages in the cohort studies, nor a suggestion of a dose-response among long-term drinkers only ([Friberg & Wolk, 2009](#)).

In most case-control studies there was no dose-response relationship between consumption of alcoholic beverages and the risk for cancer of the endometrium. A negative dose-response association with significant trend was observed by [Jain et al. \(2000b\)](#) and [Hosono et al. \(2008\)](#), while one study showed a clear positive dose-response trend ([Parazzini et al., 1995a](#)). In another study, there was an indication of a negative dose-response in the association but no formal test for trend was presented ([Webster et al., 1989](#)).

2.10.5 Types of alcoholic beverage

The effect of specific types of alcoholic beverages (beer, wine, spirits) on the risk for cancer of the endometrium was investigated in three cohort studies, with no clear evidence of heterogeneity between different types of beverages ([Gapstur et al., 1993](#); [Loerbroeks et al., 2007](#); [Setiawan et al., 2008](#)).

Consumption of different alcoholic beverages in relation to risk for cancer of the endometrium was evaluated in seven case-control studies ([Williams & Horm, 1977](#); [Austin et al., 1993](#); [Levi et al., 1993](#); [Swanson et al., 1993](#); [Parazzini](#)

[et al., 1995a](#); [Goodman et al., 1997](#); [Weiderpass & Baron, 2001](#)). [Levi et al. \(1993\)](#) and [Parazzini et al. \(1995a\)](#) found increased risk for cancer of the endometrium with increasing consumption of wine and hard liquor, but not beer. Overall, there were no consistent patterns of association between any specific type of alcoholic beverage and risk for cancer of the endometrium.

2.10.6 Interactions

Only [Setiawan et al. \(2008\)](#) reported detailed results of interaction between other risk factors and consumption of alcoholic beverages for cancer of the endometrium. There was no clear effect modification by body mass index, postmenopausal hormone use, parity, oral contraceptive use or smoking status, though the power to detect such interactions was limited. The Million Women Study Collaborators (2005) investigated alcohol only as an interacting factor with hormone replacement therapy and found no evidence for an effect modification. Results from stratified analyses did not show any effect modification by age, smoking, body mass index, folic acid intake, or postmenopausal hormone use ([Friberg & Wolk, 2009](#)).

2.11 Cancer of the ovary

In the previous *IARC Monograph* ([IARC, 2010](#)), it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the ovary in both cohort and case-control studies was sparse and inconsistent. Since [IARC \(2010\)](#), one cohort study in alcoholics ([Thygesen et al., 2009](#)) and one case-control study ([Kolahdooz et al., 2009](#)) have evaluated the association between consumption of alcoholic beverages and risk of cancer of the ovary.

2.11.1 Cohort studies

A total of five cohort studies have examined the association between consumption of alcoholic beverages and the risk for cancer of the ovary in special populations, women hospitalized or being treated for alcohol dependence, four early ([Adami et al., 1992](#); [Tønnesen et al., 1994](#), [Sigvardsson et al., 1996](#); [Lagiou et al., 2001](#)) and one more recent ([Thygesen et al., 2009](#); Table 2.52 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.52.pdf>); the association in the general population has been examined in seven cohort studies ([Kushi et al., 1999](#); [Kelemen et al., 2004](#); [Schouten et al., 2004](#); [Chang et al., 2007](#); [Kabat et al., 2008](#); [Tworoger et al., 2008](#); [Allen et al., 2009](#)). The studies were conducted in North America (USA and Canada) and Europe (the Netherlands, the United Kingdom and Scandinavia). The reports on studies in special populations presented results adjusted for age and calendar period only, whereas in the population based cohort studies results were adjusted for a large variety of factors.

There was no evidence of an overall association between consumption of alcoholic beverages and the risk for cancer of the ovary in these studies.

2.11.2 Case-control studies

Twenty-four case-control studies investigated the relationship between alcoholic beverage consumption and the risk for cancer of the ovary in North America, Japan, Australia, India, western Europe and Scandinavia, including one recent ([Kolahdooz et al., 2009](#); Table 2.53 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.53.pdf>). Eleven were hospital-based ([West, 1966](#); [Williams & Horm, 1977](#); [Byers et al., 1983](#); [Tzonou et al., 1984](#); [Mori et al., 1988](#); [Hartge et al., 1989](#); [LaVecchia et al., 1992](#); [Nandakumar et al., 1995](#); [Tavani et al., 2001a](#); [Yen et al., 2003](#); [Pelucchi et al., 2005](#)),

one was based on cases and controls who were included in a cancer registry database ([Kato et al., 1989](#)), 11 were population-based ([Gwinn et al., 1986](#); [Polychronopoulou et al., 1993](#); [Godard et al., 1998](#); [Kuper et al., 2000](#); [Goodman & Tung, 2003](#); [McCann et al., 2003](#); [Modugno et al., 2003](#); [Riman et al., 2004](#); [Webb et al., 2004](#); [Peterson et al., 2006](#); [Kolahdooz et al., 2009](#)) and one used controls chosen both among general population and hospital patients ([Whittemore et al., 1988](#)). The recent study ([Kolahdooz et al., 2009](#)) examined dietary patterns, including a predominantly snack and alcohol-based dietary pattern, and cancer of the ovary. [No specific assessment of alcohol intake was presented.] Confounding factors were considered in all studies, although adjustment was more extensive in more newly published studies than in studies published during the 1980s.

Overall, the results of case-control studies do not suggest any association between consumption of alcoholic beverages and risk for cancer of the ovary, although a few studies indicated either positive or negative associations.

2.11.3 Types of alcoholic beverage

In four population-based cohort studies the association with different types of alcoholic beverages was investigated ([Kelemen et al., 2004](#); [Schouten et al., 2004](#); [Chang et al., 2007](#); [Tworoger et al., 2008](#)). Intake of wine during the year before baseline was associated with an increased risk for cancer of the ovary in one study ([Chang et al., 2007](#)), but was not confirmed in the others ([Kelemen et al., 2004](#); [Schouten et al., 2004](#); [Tworoger et al., 2008](#)).

Seven case-control studies evaluated different alcoholic beverages in relation to risk for cancer of the ovary ([Gwinn et al., 1986](#); [LaVecchia et al., 1992](#); [Tavani et al., 2001a](#); [Goodman & Tung, 2003](#); [Modugno et al., 2003](#); [Webb et al., 2004](#); [Peterson et al., 2006](#)). Overall, there were no consistent patterns of association between any

specific type of alcoholic beverage (beer, wine and spirits) and risk for cancer of the ovary.

2.11.4 Interactions

[Kelemen et al. \(2004\)](#), [Schouten et al. \(2004\)](#) and [Chang et al. \(2007\)](#) evaluated their data for possible interaction between alcoholic beverage intake and other variables. [Kelemen et al. \(2004\)](#) found a statistically significant interaction between folate intake and alcohol consumption with regard to risk for cancer of the ovary. A similar association was observed by [Chang et al. \(2007\)](#) for women drinking more than one glass of wine daily. No other consistent interactions were reported. Among the case-control studies, there was no consistent evidence of interaction between alcoholic beverage consumption and different variables known or suspected to be associated with risk of cancer of the ovary, such as reproductive history, education, body size or diet.

2.12 Cancer of the prostate

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the evidence for the association between consumption of alcoholic beverages and risk of cancer of the prostate is inconsistent. Increased risk for cancer of the prostate at elevated levels of consumption of alcoholic beverages was suggested from a few cohort studies, but there was no consistent dose-response relationship and in many cohort studies there was no association. The majority of case-control studies also showed no association between consumption of alcoholic beverages and cancer of the prostate.

2.12.1 Cohort studies in the general population

For studies of cancer of the prostate that were conducted more recently, there should be concern if no attempt is made to distinguish between cases that are detected by screening, with a possibility that many might not have presented clinically during the lifetime of the individual in the absence of screening, and those that present clinically and are more likely to be progressive. Among the 23 cohort studies six studies ([Platz *et al.*, 2004](#); [Baglietto *et al.*, 2006](#); [Sutcliffe *et al.*, 2007](#); [Rohrmann *et al.*, 2008](#); [Gong *et al.*, 2009](#); [Chao *et al.*, 2010](#); Table 2.54 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.54.pdf>) have considered the stage or grade of the disease. None found any association between alcoholic beverage consumption and risk of advanced cases of cancer of the prostate. However in one study ([Gong *et al.*, 2009](#)) a strong association of increased risk of high-grade cancer of the prostate with heavy alcohol consumption in the whole study population was found (RR 2.01; 95%CI: 1.33–3.05), as well as among heavy beer drinkers (RR, 2.89; 95%CI: 1.76–3.76) compared to non-drinkers. In a few of the other cohort studies that did not make a distinction of cancer stage or grade there was an increased risk for cancer of the prostate at elevated levels of alcoholic beverage consumption ([Hirayama, 1992](#); [Schuurman *et al.*, 1999](#); [Putnam *et al.*, 2000](#); [Sesso *et al.*, 2001](#)), but there was no consistent dose–response relationship. Many other cohort studies showed no association. The risk associated with different types of alcoholic beverages was inconsistent, with increased risks for both beer ([Gong *et al.*, 2009](#)) and white wine consumption ([Velicer *et al.*, 2006](#)), as well as null associations ([Sutcliffe *et al.*, 2007](#); [Chao *et al.*, 2010](#)) for all alcoholic beverages. Most studies collected data on consumption of alcoholic beverages only at baseline. Two studies examined lifetime alcohol

use up to baseline ([Rohrmann *et al.*, 2008](#)) and another alcohol use at ages 18 and 45 ([Velicer *et al.*, 2006](#)) and did not find associations.

2.12.2 Cohort studies in special populations

Two of the nine studies of special populations showed an association between alcoholic beverage consumption and cancer of the prostate. [Tønnesen *et al.* \(1994\)](#) and more recently [Thygesen *et al.* \(2009\)](#) (Table 2.55 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.55.pdf>) studying Danish alcohol abusers observed greater numbers of cancers of the prostate compared with the number expected from the general population. None of the studies provided information on individual exposures or adjusted for potential confounders.

2.12.3 Case–control studies

Studies published since [IARC \(2010\)](#) are summarized in Table 2.56 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.56.pdf>. Six of the 38 case–control studies considered aggressiveness of disease. In the study of [Walker *et al.* \(1992\)](#), 90% of the cases were advanced at presentation, and in the study by [Li *et al.* \(2008b\)](#), almost 50% of the cases were advanced and about 40% of moderately differentiated tumour presentation. The majority of the studies showed no association between consumption of alcoholic beverages and cancer of the prostate. Six studies found a positive association ([De Stefani *et al.*, 1995](#); [Hayes *et al.*, 1996](#); [Sharpe & Siemiatycki, 2001](#); [Chang *et al.*, 2005](#); [Gallus *et al.*, 2007](#); [Benedetti *et al.*, 2009](#)). [De Stefani *et al.*, \(1995\)](#) found a borderline elevation of risk for high levels of consumption of beer, but the risk at high levels of total alcohol consumption was not significantly elevated. [Hayes *et al.* \(1996\)](#) found significant elevations in risk for ‘heavy’ and ‘very heavy’ consumers of alcoholic beverages, with higher risks among

those with poorly or undifferentiated tumours, or with regional or distant metastases. [Sharpe & Siemiatycki \(2001\)](#) reported an elevation in risk for those with long duration of drinking, with the greatest elevation in risk for those who started drinking at age < 15 years. An elevated risk with increasing drink/year [with close to significant trend] was reported by [Benedetti et al. \(2009\)](#) among beer drinkers, as well as a borderline increased risk among moderate red wine drinkers. [Gallus et al. \(2007\)](#) reported an increased risk among men with poorly differentiated tumours (Gleason score ≥ 7). This association was not significant for all cancers of the prostate combined (regardless of the stage/differentiation status). [Chang et al. \(2005\)](#) found an association between consumption of alcoholic beverages (in g/week) and risk of cancer of the prostate with a borderline trend; there was no association with advanced cancer, whereas localized cancer showed significant association but without a dose-response relationship. [De Stefani et al. \(2009\)](#) analysed dietary patterns consisting of alcoholic beverages and processed meat and found no significant association with cancer of the prostate.

2.12.4 Meta-analyses

A meta-analysis that included six cohort and 27 case-control studies that were reported before July 1998 resulted in a relative risk estimate of 1.05 (95%CI: 0.98–1.11) for ever consumption of alcoholic beverages and of 1.05 (95%CI: 0.91–1.20) for each additional drink of alcohol per day ([Dennis, 2000](#)). The latter estimate was based on 15 studies reporting amount of alcohol consumed. Based on these 15 studies, the estimated relative risk for 4 drinks/day was 1.21 (95%CI: 1.05–1.39) (Table 2.57 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.57.pdf>). [Middleton-Fillmore et al. \(2009\)](#) conducted a meta-analysis in which 14 cohorts and 21 case-control studies were included, reporting a

weak but statistically significant association of incidence of cancer of the prostate with alcohol consumption levels in population case-control studies (RR, 1.24; 95%CI: 1.14–1.34), but meta-analyses of 7 hospital-based case-control studies and 14 cohort studies found no associations between consumption of alcoholic beverages and cancer of the prostate.

2.13 Cancer of the kidney

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that both cohort and case-control studies provide consistent evidence of no increase in risk for cancer of the kidney with consumption of alcoholic beverages ([IARC, 2010](#)). In several studies, increasing intake of alcoholic beverages was associated with a significantly lower risk for cancer of the kidney. These inverse trends were observed in both men and women and with multiple types of alcoholic beverage.

Since [IARC \(2010\)](#), one cohort (Table 2.58 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.58.pdf>) and three case-control studies (Table 2.59 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.59.pdf>) have been identified.

[Allen et al. \(2009\)](#) reported a decrease in risk for cancer of the kidney associated with moderate alcohol intake in women. The relative risk associated with ≥ 15 drinks per week was 0.66 (95%CI: 0.48–0.92); the reduction in risk per 10 g alcohol/day was 12% (95%CI: 1% to 22%).

[Greving et al. \(2007\)](#) (855 cases) reported an inverse association between alcohol intake measured as gram of ethanol per month and cancer of the kidney. [Pelucchi et al. \(2008\)](#) (1534 cases), in an update of a previous study ([Pelucchi et al. \(2002\)](#)) together with a new study from the same area, found an inverse association between total alcohol intake or intake of wine measured as drinks per day and cancer of the kidney;

however, they did not find any effect of duration (years) of drinking or age of starting. [Benedetti et al. \(2009\)](#) (156 cases) found no effect of alcohol intake on the risk of cancer of the kidney.

2.14 Cancer of the urinary bladder

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the urinary bladder was inconsistent.

One cohort ([Allen et al., 2009](#)) and three case-control studies ([Cao et al., 2005](#); [Jiang et al., 2007](#); [Zaridze et al., 2009](#)) on the general population and one cohort study on alcoholics ([Thygesen et al., 2009](#)) have been identified since *IARC (2010)*.

[Allen et al. \(2009\)](#) found no association between consumption of alcoholic beverages and cancer of the urinary bladder in women (Table 2.60 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.60.pdf>). Likewise, [Thygesen et al. \(2009\)](#) reported no effect of alcohol on cancer of the urinary bladder among alcoholics (Table 2.61 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.61.pdf>).

Two of the case-control studies ([Cao et al., 2005](#); [Zaridze et al., 2009](#)) found no consistent association between consumption of alcoholic beverages and risk for cancer of the urinary bladder (Table 2.62 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.62.pdf>). However, [Jiang et al. \(2007\)](#) in a large case-control study (1671 cases) found a statistically significant reduced risk both in relation to frequency of alcohol intake, duration (in years), and age of initiation. The reduction in risk was particularly large among those who urinated frequently. [The reduced risk for cancer of the urinary bladder among those who urinated frequently may to some extent be due

to a high liquid intake and dilution of potential carcinogens.]

2.15 Cancers of the lymphatic and haematopoietic system

Lymphomas and haematopoietic malignancies comprise a heterogeneous group of malignancies and their respective etiologies are not fully understood. In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that there was *evidence suggesting lack of carcinogenicity* in humans for alcoholic beverages and non-Hodgkin lymphoma (NHL). The results of cohort studies and evidence from some very large case-control studies showed an inverse association or no association between the consumption of alcoholic beverages and the risk for NHL. In general, there was no evidence of substantial differences in the effect of specific beverage types or for specific histological subtypes of NHL. The evidence for an association between consumption of alcoholic beverages and risk for Hodgkin disease was sparse, and no consistent pattern of association was observed for leukaemia and multiple myeloma ([IARC, 2010](#)).

2.15.1 Cohort studies in the general population

In seven cohort studies, associations of consumption of alcoholic beverages and the risk for lymphatic and/or haematopoietic cancers were examined ([Boffetta et al., 1989](#); [Kato et al., 1992](#); [Chiu et al., 1999](#); [Lim et al., 2006](#); [Lim et al., 2007](#); [Allen et al., 2009](#); [Klatsky et al., 2009](#)). Studies published since the previous Monograph ([IARC, 2010](#)) are summarized in Table 2.63 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.63.pdf>).

For NHL specifically, [Chiu et al. \(1999\)](#) found a non-significant inverse association with consumption of alcoholic beverages among postmenopausal women in the USA. This relationship

persisted after adjustment for several potential confounding factors including age, total energy intake, residence (farm, no farm), education, marital status, history of transfusion and diabetes, and intake of red meat and fruit. [The Working Group noted that the level of alcohol intake was very low in this study.] [Lim et al. \(2006\)](#) found weak evidence of an inverse association among Finnish male smokers in a multivariate analysis. The three cohort studies published recently and conducted among retired persons in the USA ([Lim et al., 2007](#)), among middle-aged women in the United Kingdom ([Allen et al., 2009](#)), and in a multiethnic USA population ([Klatsky et al., 2009](#)) have shown significantly decreased risk of NHL among people with moderate alcohol intake. A borderline significant inverse association was also shown for consumers of 7 or more drinks per week who were diagnosed with B-cell lymphoma, chronic lymphocytic lymphoma or small lymphocytic lymphoma, as well as an inverse (although non-significant) association of Hodgkin lymphoma risk with consumption of alcoholic beverages ([Lim et al., 2007](#)).

In a study among American men of Japanese ancestry that also considered several potential lifestyle, medical and dietary confounding factors, consumption of ≥ 30 ml alcohol per day compared with non-drinkers was associated with a threefold higher risk for lymphoma and leukaemia combined ([Kato et al., 1992](#)). In the multiethnic cohort in the USA ([Klatsky et al., 2009](#)) risk for myelocytic leukaemia among regular drinkers compared with never-drinkers plus those reporting < 1 drink/month, and risk for lymphocytic leukaemia among people drinking more than 2 drinks per week versus drinkers who drank < 1 drink/week showed inverse associations (p for trend 0.01 and 0.03, respectively). [Allen et al. \(2009\)](#) did not find any association between alcohol intake and risk of all leukaemias combined.

In the four cohort studies that assessed consumption of alcoholic beverages and the risk

for multiple myeloma, no association was found in three ([Lim et al., 2006](#); [Allen et al., 2009](#); [Klatsky et al., 2009](#)) and in one a lower risk among ever regular drinkers compared with never regular drinkers was found ([Boffetta et al., 1989](#)).

2.15.2 Cohort studies in special populations

Five studies among heavy alcoholic beverage users or brewery workers have investigated the risk for lymphatic and/or haematopoietic cancers ([Hakulinen et al., 1974](#); [Jensen, 1979](#); [Robinette et al., 1979](#); [Schmidt & Popham, 1981](#); [Carstensen et al., 1990](#)).

Three studies examined lymphatic and haematopoietic cancers combined ([Jensen, 1979](#); [Robinette et al., 1979](#); [Carstensen et al., 1990](#)). [Jensen \(1979\)](#) found no significant differences between the observed number of cases among Danish brewery workers compared with the expected number of cases computed from age-, sex-, and area-specific rates. [Carstensen et al. \(1990\)](#) found slightly increased risk for these cancers among Swedish brewery workers compared to the expected cases calculated using age, follow-up time, and area-standardized rates of the Swedish male population. [Robinette et al. \(1979\)](#) found a non-significant decreased risk among chronic alcoholic male USA veterans compared with expected numbers computed from age- and time-specific rates for the US male population.

In two studies, the observed number of cases of lymphoma among alcoholics was lower than that expected based on rates for the local population ([Hakulinen et al., 1974](#); [Schmidt & Popham, 1981](#)).

In studies among alcoholics, the observed number of cases of leukaemia did not differ significantly from those expected in one study ([Hakulinen et al., 1974](#)), and was non-significantly lower in two other studies ([Robinette et al., 1979](#); [Schmidt & Popham, 1981](#)). In studies among brewery workers, [Jensen \(1979\)](#) found

no significant difference between the observed and expected number of leukaemia deaths, while [Carstensen et al. \(1990\)](#) found a 1.6-fold higher risk of mortality among brewery workers compared with those expected from the local population.

2.15.3 Case-control studies

(a) Lymphomas

Associations between consumption of alcoholic beverages and the risk for lymphoma were evaluated in 22 case-control studies ([Williams & Horm, 1977](#); [Cartwright et al., 1988](#); [Brown et al., 1992](#); [Nelson et al., 1997](#); [Tavani et al., 1997](#); [De Stefani et al., 1998](#); [Matsuo et al., 2001a](#); [Tavani et al., 2001b](#); [Briggs et al., 2002](#); [Chiu et al., 2002](#); [Morton et al., 2003](#); [Chang et al., 2004](#); [Willett et al., 2004](#); [Besson et al., 2006a, b](#); [Nieters et al., 2006](#); [Deandrea et al., 2007](#); [Casey et al., 2007](#); [Gorini et al., 2007b](#); [Willett et al., 2007](#); [Monnereau et al., 2008](#); [Benedetti et al., 2009](#)). Studies published since the previous Monograph ([IARC, 2010](#)) are summarized in Table 2.64 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.64.pdf>.

Most case-control studies of consumption of alcoholic beverages and lymphoma focused specifically on NHL and/or its histological subtypes. [Chang et al. \(2004\)](#) found no overall association of NHL risk with moderate consumption of alcoholic beverages, although there was a suggestive possible increased risk of NHL among men. In that study, all cases and controls were free of human immunodeficiency viral infection and several potential confounding factors including age, tobacco smoking and occupational exposure to pesticides were considered. [Briggs et al. \(2002\)](#) also found no difference in the risk for NHL between drinkers and non-drinkers after adjustment for age, ethnicity and smoking status. [Casey et al. \(2007\)](#) found no significant associations of different characteristics of consumption of alcoholic beverages considering drinkers versus

non drinkers, current and former drinking, age at drinking debut, drinking duration or daily intake for all lymphoid neoplasms and B-cell lymphomas. An inverse association for ever alcohol drinking and NHL was observed in a large multicentric study ([Monnereau et al., 2008](#)) with 399 NHL cases (OR, 0.7; 95%CI: 0.5–1.0).

Most individual studies of NHL have limited power to conduct detailed analyses of consumption of alcoholic beverages and risk for this disease, particularly for specific beverage types and histological subtypes. Therefore, data from nine case-control studies conducted in Italy, Sweden, the United Kingdom and the USA were pooled to include 6492 cases of NHL and 8683 controls ([Morton et al., 2005](#)). The analysis showed a significantly lower risk for NHL for ever drinkers when compared to non-drinkers; however, there was no consistent dose-response relationship between risk and frequency of consumption of alcoholic beverages, duration of alcoholic beverage consumption or age at starting drinking. The risk for NHL for current drinkers was lower than that for former drinkers. There was no difference in association by alcoholic beverage type or for the combination of beverages types consumed. For specific subtypes of NHL, no significantly elevated risks were found. The lowest risk associated with ever drinking versus non-drinker was that for Burkitt lymphoma (OR, 0.51; 95%CI: 0.33–0.77). Low risks for diffuse B-cell, follicular and T-cell lymphomas associated with ever drinking were also noted. The findings were unchanged when the analyses were restricted to studies that had a high response rate.

A multicentre case-control study of NHL and consumption of alcoholic beverages included data from five European countries and comprised 1742 cases and 2465 controls ([Besson et al., 2006a](#)). Overall, there were no associations observed for ever drinking, age at starting drinking, duration of drinking or monthly consumption with risk for all NHL or with any

histological subtype; similarly, no associations with risk of NHL were found with any specific type of alcoholic beverage. However, a lower risk associated with regular alcoholic beverage intake was observed for men (OR, 0.76; 95%CI: 0.62–0.93; 691 exposed cases) and for non-Mediterranean countries (OR, 0.73; 95%CI: 0.61–0.86).

Among the nine studies that examined Hodgkin lymphoma specifically ([Williams & Horm, 1977](#); [Tavani et al., 1997](#); [Besson et al., 2006b](#); [Nieters et al., 2006](#); [Deandrea et al., 2007](#); [Gorini et al., 2007b](#); [Willett et al., 2007](#); [Monnereau et al., 2008](#); [Benedetti et al., 2009](#)), a consistent inverse association was found almost in all. In the large multicentre European study, the odds ratio for Hodgkin lymphoma associated with ever regular drinking compared with never regular drinking was 0.61 (95%CI: 0.43–0.87; 81 exposed cases); this association was consistent for younger and older adults ([Besson et al., 2006b](#)). Other multicentre studies have also shown an inverse association of Hodgkin lymphoma risk and frequent alcohol consumption of the order of 0.50 ([Gorini et al., 2007b](#); [Monnereau et al., 2008](#)). [Willett et al. \(2007\)](#) found that the risk of Hodgkin lymphoma was higher among non-drinkers and persons with low alcohol consumption.

Inverse associations were also observed between specific alcoholic beverage types, namely wine and aperitif, and Hodgkin lymphoma ([Gorini et al., 2007b](#); [Monnereau et al., 2008](#)).

(b) Leukaemia

The association of consumption of alcoholic beverages with risk for adult leukaemia was examined in eight case-control studies ([Williams & Horm, 1977](#); [Brown et al., 1992](#); [Wakabayashi et al., 1994](#); [Chang et al., 2004](#); [Pogoda et al., 2004](#); [Rauscher et al., 2004](#); [Gorini et al., 2007a](#); [Monnereau et al., 2008](#)). Studies published since the previous Monograph are summarized in Table 2.65 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.65.pdf>).

No consistent patterns of associations between total consumption of alcoholic beverages and risk for all leukaemias combined were observed. In two studies a non-significant two- to threefold higher risk for acute lymphocytic leukaemia associated with heavy drinking ([Wakabayashi et al., 1994](#)) or with any drinking ([Brown et al., 1992](#)) was found, while in another no association of drinking with risk for this type of leukaemia was found ([Gorini et al., 2007a](#)). Similarly, there was no consistent evidence of associations with acute non-lymphocytic leukaemia, chronic lymphocytic leukaemia or chronic myeloid leukaemia in these studies. [Chang et al. \(2004\)](#) found a positive significant association between high wine intake and risk for chronic lymphocytic leukaemia.

(c) Multiple myeloma

Associations between consumption of alcoholic beverages and the risk for multiple myeloma were examined in nine case-control studies, five in the USA, one in Canada, two in Italy and one in France ([Williams & Horm, 1977](#); [Gallagher et al., 1983](#); [Linnet et al., 1987](#); [Brown et al., 1992](#); [Brown et al., 1997](#); [Deandrea et al., 2007](#); [Gorini et al., 2007b](#); [Hosgood et al., 2007](#); [Monnereau et al., 2008](#)). Studies published since the previous Monograph are summarized in Table 2.66 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.66.pdf>). In the largest studies, there was a statistically significant lower risk for multiple myeloma among drinkers compared with non-drinkers in white men ([Hosgood et al., 2007](#)) and to a lesser extent in black men and white women ([Brown et al., 1997](#)) and among both men and women ([Gorini et al., 2007b](#)), but the latter associations were non-significant. [Brown et al. \(1997\)](#) found a non-significant 2.8-fold higher risk for multiple myeloma for white women who consumed ≥ 22 drinks per week. Non-significantly increased risk of multiple myeloma for consumption of alcoholic beverages was found by [Deandrea et al. \(2007\)](#).

and [Monnereau et al. \(2008\)](#) after adjustment for age, centre, sex and tobacco. No consistent association patterns were observed among the other case-control studies. Most studies collected data on alcoholic beverage consumption from proxy respondents, and some included prevalent cases. In addition, not all studies controlled for the potential confounding effects of tobacco smoking, and only two controlled for other factors such as farming, family history of cancer and occupational exposure to high-risk chemicals ([Brown et al., 1992](#); [Monnereau et al., 2008](#)).

2.16 Other cancers

In the previous *IARC Monograph* ([IARC, 2010](#)) it was noted that the evidence for an association of consumption of alcoholic beverages with risk of other female cancers (vulva and vagina) and cancers of the testis, brain, thyroid, and skin melanoma was generally sparse and/or inconsistent.

2.16.1 Cancers of the vulva and vagina

In two cohort studies the association between consumption of alcoholic beverages and risk for other female cancers was examined. These were carried out in women being treated for alcohol abuse or alcoholism in Sweden ([Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#)). In one study an elevated risk for vaginal cancer but not for vulva cancer was found ([Weiderpass et al., 2001](#)). [Sigvardsson et al. \(1996\)](#) reported high relative risks for both vulva and vaginal cancers combined. In these studies relative risk estimates could not be adjusted for factors that may have confounded the association between alcoholic beverage consumption and vulva and vaginal cancers, such as HPV infections, number of sexual partners and tobacco smoking. It is possible that women who abuse alcohol have other behavioural patterns that may affect risks for these cancers.

Four case-control studies investigated the association between consumption of alcoholic beverages and risk for vulva cancer, conducted in Italy ([Parazzini et al., 1995b](#)) and in the USA ([Williams & Horm, 1977](#); [Mabuchi et al., 1985](#); [Sturgeon et al., 1991](#)); one study from Denmark ([Madsen et al., 2008](#)) investigated both cancer of the vulva and vagina. Studies published since the previous Monograph ([IARC, 2010](#)) are summarized in Table 2.67 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.67.pdf>. Three were hospital-based studies ([Williams & Horm, 1977](#); [Mabuchi et al., 1985](#); [Parazzini et al., 1995b](#)), one was population-based ([Sturgeon et al., 1991](#)), while [Madsen et al. \(2008\)](#) used two sets of controls, population- and hospital-based. Confounding factors were considered in four studies ([Williams & Horm, 1977](#); [Sturgeon et al., 1991](#); [Parazzini et al., 1995b](#); [Madsen et al., 2008](#)), but only two of these provided risk estimates adjusted for both smoking and sexual behaviour ([Sturgeon et al., 1991](#); [Madsen et al., 2008](#)). [Williams & Horm \(1977\)](#), [Mabuchi et al. \(1985\)](#), [Sturgeon et al. \(1991\)](#) and [Parazzini et al. \(1995b\)](#) reported no association between alcoholic beverage consumption and risk for vulva cancer. [Madsen et al. \(2008\)](#) found a higher risk among drinkers compared to non-drinkers, for both vaginal and vulva cancers.

There was no evidence of dose-response for consumption of alcoholic beverages and vulva cancer, in any of these studies, either in terms of frequency of alcohol consumption ([Parazzini et al., 1995b](#)), in terms of years of alcohol consumption ([Madsen et al., 2008](#)), or when providing two defined levels of alcohol consumption ([Williams & Horm, 1977](#)). [Williams & Horm \(1977\)](#), [Mabuchi et al. \(1985\)](#) and [Sturgeon et al. \(1991\)](#) investigated risk of vulva cancer in relation to consumption of different alcoholic beverages. No significant associations were found with any type of alcoholic beverage.

2.16.2 Other sites

No new studies have been identified for cancer of testis, one on brain cancer and thyroid cancer, and three on skin cancer (malignant melanoma, basal cell carcinoma and squamous cell carcinoma).

In a large cohort study of women in the United Kingdom (Allen *et al.*, 2009) no association of consumption of alcoholic beverages was found with brain cancer (Table 2.68 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.68.pdf>), but a significant inverse association with thyroid cancer (Table 2.69 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.69.pdf>).

No association between consumption of alcoholic beverages and malignant melanomas was found by Allen *et al.* (2009) (Table 2.70 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.70.pdf>) or by Benedetti *et al.* (2009) in a case-control study (Table 2.71 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.71.pdf>). In a cohort study in Australia Ansems *et al.* (2008) found no significant association between overall basal cell carcinoma or squamous cell carcinoma risk and total alcohol intake or intake of beer, white wine, red wine or sherry and port (Table 2.70 on-line). Among those with a prior skin cancer history, there was a significant increase in risk of squamous cell carcinoma for above-median consumption of sherry and port compared with abstainers (multivariable adjusted RR, 2.46; 95%CI: 1.06–5.72).

2.17 Parental exposure and childhood cancers

Associations of paternal consumption of alcoholic beverages before pregnancy and/or maternal consumption of alcoholic beverages during pregnancy with risk for haematopoietic

cancers in children were examined in nine case-control studies in Australia, Canada, France, the Netherlands, the United Kingdom and the USA (McKinney *et al.*, 1987; Severson *et al.*, 1993; van Duijn *et al.*, 1994; Shu *et al.*, 1996; Infante-Rivard *et al.*, 2002; Menegaux *et al.*, 2005; Menegaux *et al.*, 2007; MacArthur *et al.*, 2008; Rudant *et al.*, 2008). Studies published since the previous Monograph are summarized in Table 2.72 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.72.pdf>).

No association between maternal alcoholic beverage intake 1 month or 1 year before pregnancy with risk of any childhood leukaemia or lymphoma was reported by Severson *et al.* (1993), Shu *et al.* (1993) and van Duijn *et al.* (1994), whereas a borderline significant association for acute leukaemia and ALL was observed by MacArthur *et al.* (2008) and Infante-Rivard *et al.* (2002) found a positive association for ALL.

For maternal alcoholic beverage consumption during pregnancy, no association was found with leukaemia or lymphoma (McKinney *et al.*, 1987) or with ALL (Rudant *et al.*, 2008), while Infante-Rivard *et al.* (2002) found a reduced risk for ALL when comparing any intake with no intake. Statistically significant two- to 2.4-fold increased risk for acute non-lymphocytic leukaemia were associated with any maternal alcoholic beverage consumption during pregnancy in two studies (van Duijn *et al.*, 1994; Menegaux *et al.*, 2005). Similarly, statistically significant positive associations between maternal alcoholic beverage consumption and risk for ALL (Shu *et al.*, 1993; Menegaux *et al.*, 2005, 2007; MacArthur *et al.*, 2008) and acute myeloid leukaemia (Severson *et al.*, 1993; Shu *et al.*, 1993) were observed. The strongest associations observed in the studies of alcoholic beverages and acute myeloid leukaemia were for children diagnosed at 10 years of age or younger (Severson *et al.*, 1993; Shu *et al.*, 1993). Overall, there was no consistent evidence of dose-response relationships for maternal or

paternal alcoholic beverage intake or for intake of any specific type of alcohol beverage and risk for any childhood haematopoietic cancer. Most studies adjusted for potential confounding factors including maternal age, maternal smoking, and child's sex. Importantly, whether any of the observed associations between maternal or paternal consumption of alcoholic beverages and risk for childhood haematopoietic cancers are attributed to recall bias is unclear.

2.18 Polymorphisms and genetic susceptibility

Studies that identify associations between genetic polymorphisms and inter-individual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

However, when data on genetic susceptibility originate from multiple comparisons in subgroup analyses, false-positive results and inconsistencies across studies can be generated. Furthermore, many of the identified susceptibility genes have no or unknown functional characterization; only for a few genes (e.g. ALDH2) are functional studies available; and generally induction of enzymes is not considered. Such data therefore require careful evaluation.

A challenge in the interpretation of the associations between the polymorphisms affecting alcohol and/or acetaldehyde metabolism and cancer is that the genes coding for more active alcohol oxidizing enzyme and/or less active acetaldehyde oxidizing enzyme, may both promote and inhibit the development of cancer. Carriers of genes enhancing alcohol oxidation and/or inhibiting acetaldehyde oxidation on average consume less alcohol ([Matsuo *et al.*, 2006b, 2007](#); [Zintzaras *et al.*, 2006](#)) and thus may be protected from harmful chronic effects (e.g. cancer) induced by alcohol unless they drink heavily. Thus, in studying the mechanisms of the associations between these polymorphisms and cancer, it is essential to control for differences in alcohol drinking.

2.18.1 Alcohol dehydrogenase-1B (ADH1B)

ADH1B (previously called *ADH2*) is polymorphic, and its superactive *ADH1B*2* allele is highly prevalent among East Asians (54–96%; [Goedde *et al.*, 1992](#)), but relatively rare among Caucasians (1–23%). Individuals with the *ADH1B*1/*1* genotype code less active ADH, which is a risk factor for excessive alcohol consumption in both East Asians and Caucasians ([Zintzaras *et al.*, 2006](#); [Matsuo *et al.*, 2007](#)).

(a) Cancer of the oesophagus

Individuals with the *ADH1B*1/*1* genotype were at increased risk for oesophageal cancer in 15 case-control studies among several populations ([Hori *et al.*, 1997](#); [Yokoyama *et al.*, 1998](#); [Chao *et al.*, 2000](#); [Matsuo *et al.*, 2001b](#); [Yokoyama *et al.*, 2001, 2002](#); [Boonyaphiphat *et al.*, 2002](#); [Yang *et al.*, 2005](#); [Yang *et al.*, 2007](#); [Guo *et al.*, 2008](#); [Hashibe *et al.*, 2008](#); [Lee *et al.*, 2008b](#); [Cui *et al.*, 2009](#); [Ding *et al.*, 2009](#)) and in a cohort study in cancer-free Japanese alcoholics ([Yokoyama *et al.*, 2006b](#)) ([Tables 2.73, 2.74](#)). The difference was not significant in two Japanese studies ([Tanabe *et al.*, 1999](#); [Yokoyama *et al.*, 2006a](#)) and one study in South

Africa ([Li et al., 2008a](#)). [Many studies did not control for the amount of alcohol consumption, which makes it difficult to make firm conclusions about the etiology of the *ADH1B**1/*1 associated cancers.]

(b) *Upper aerodigestive tract cancers combined*

In four Japanese studies ([Yokoyama et al., 2001, 2006b](#); [Asakage et al., 2007](#); [Hiraki et al., 2007](#)), one European study ([Hashibe et al., 2006](#)) and one Indian study ([Solomon et al., 2008](#)) an *ADH1B**1/*1-associated increased risk for upper aerodigestive tract cancers was found in alcohol drinkers. No significant association was found in another European study ([Risch et al., 2003](#); [Tables 2.74, 2.75](#)).

A recent large multicentre study from Europe and Latin America of *ADH* genes and UADT cancer that focused on seven separate *ADH* variants known to change an amino acid (missense substitution) included a total of 3800 cases and 5200 controls ([Hashibe et al., 2008](#)). One variant in *ADH1B* (rs1229984) that codes for fast ethanol metabolism was associated with a strong decreased risk for UADT cancer, after adjusting for amount of alcohol consumed (OR for dominant model, 0.56; 95%CI: 0.47–0.66; $P = 4 \times 10^{-11}$). The odds ratio was 0.45 (95%CI: 0.35–0.57) for oral/pharyngeal cancers combined and 0.71 (95%CI: 0.57–0.88) for laryngeal cancer.

(c) *Cancers of the stomach, colorectum and pancreas*

One Polish study showed no significant effects of the *ADH1B* polymorphism on risk for cancer of the stomach ([Zhang et al., 2007b](#); Table 2.76 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.76.pdf>). For cancer of the colorectum, two Japanese case-control studies of alcohol drinkers found an increased risk in *ADH1B**1/*1 subjects compared with *ADH1B**2 carriers without stratification of *ALDH2* genotypes ([Matsuo et al., 2006a](#); [Yin et al., 2007](#)). However, stratification by *ALDH2*

genotypes rendered the association opposite within the *ALDH2**1/*1 subjects in one of the studies ([Matsuo et al., 2006a](#)), while no such effect was seen in the other study ([Yin et al., 2007](#)). In a Chinese study the *ADH1B**2/*2 genotype tended to increase the risk for cancer of the colorectum regardless of the *ALDH2* genotype ([Gao et al., 2008](#)). Also, a study in Spain reported a non-significant decrease in risk for cancer of the colorectum for the *ADH1B**2/*2 versus *ADH1B**1/*1 ([Landi et al., 2005](#)).

The *ADH1B**2 allele has been associated with an increase in risk for cancer of the pancreas and consumption of alcoholic beverages among Japanese ([Kanda et al., 2009](#)).

(d) *Hepatocellular cancer*

In two studies in Japan and in a study in China it was concluded that the *ADH1B* polymorphism had no significant impact on the risk for hepatocellular carcinoma ([Takeshita et al., 2000b](#); [Sakamoto et al., 2006](#); [Ding et al., 2008](#); Table 2.76 on-line).

(e) *Cancer of the breast*

In a study in Germany ([Lilla et al., 2005](#)), a decreased risk for cancer of the breast with consumption of alcoholic beverages ≥ 12 g ethanol/day compared with no intake was observed in women with the *ADH1B**2 allele, whereas no such association was found in women with the *ADH1B**1/*1 genotype. In four other studies from Japan, United Kingdom and the USA, no significant differences in the risk by *ADH1B* polymorphism were observed ([Cox et al., 2007](#); [Terry et al., 2007b](#); [Visvanathan et al., 2007](#); [Kawase et al., 2009](#); Table 2.76 on-line).

2.18.2 *ADH1C*

ADH1C (previously called *ADH3*) is a major gene polymorphism among Caucasians. The homodimer encoded by the *ADH1C**1 allele catalyses the production of acetaldehyde

Table 2.73 Case-control studies and meta-analyses of *ALDH2*, *ADH1B* and *ADH1C* genotype-associated risk for cancer of the oesophagus

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Hori et al. (1997) , Tokyo, Japan, study period NR	Squamous cell carcinoma	<i>ALDH2</i>			No adjustment was reported
		*1/*1	20	1.0	
		*1/*2	70	4.4 (2.5–7.7)	
		*2/*2	3	0.9 (0.2–3.6)	
		<i>ADH1B</i>			
		*2/*2	40	1.0	
Yokoyama et al. (1998) , Kanagawa, Japan, 1987–97	Oesophagus NOS	*1/*2	33	1.7 (0.9–3.0)	Male alcoholics; because the differences in odds ratio between the incident cases and the prevalent cases were slight, the cases were combined. Adjusted for age, alcohol drinking and cigarette smoking. Possible partial overlap with Yokoyama et al. (2001)
		*1/*1	21	6.2 (2.6–14.7)	
		<i>ALDH2</i>			
		*1/*1	41	1.00	
		*1/*2	46	12.50 (7.23–21.61)	
				NS	
Tanabe et al. (1999) , Hokkaido, Japan, 1994–97	Squamous cell carcinoma	<i>ALDH2</i>			Alcohol consumption and smoking did not differ between the cases and controls.
		*1/*1	8		
		*1/*2	11		
		*2/*2	0		
		<i>ALDH2</i>			
		*1/*1	22	Allele *2 was associated with risk ($P < 0.001$)	
Chao et al. (2000) , Taipei, Taiwan, China, 1997–99	Oesophagus	*1/*2	37	Allele *1 was associated with risk ($P < 0.025$)	Alcoholics and non-alcoholic oesophageal cancer cases and alcoholic and non-alcoholic controls. No adjustment
		*2/*2	0		
		<i>ADH1B</i>			
		*1/*1	17	No significant difference in prevalence of alleles in alcoholics with different diseases and between alcoholic and non-alcoholic oesophageal cancer cases	
		*1/*2	26		
		*2/*2	16		
		<i>ADH1C</i>			
		*1/*1	38		
		*1/*2	21		
		*2/*2	0		

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Matsuo <i>et al.</i> (2001b) , Aichi, Japan, 1999–2000 (cases were first diagnosed as having esophageal cancer between 1984–2000 and visited the study centre in 1999–2000)	Oesophagus NOS	ALDH2			Adjusted for age, sex, drinking, smoking. Heavy drinkers defined as those drinking 75 mL ethanol/d, ≥ 5 d/wk. “Other participants” refers to those who were not heavy drinker
		All participants			
		*1/*1	35	1.00	
		*1/*2	66	3.72 (1.88–7.36)	
		*2/*2	1	0.80 (0.09–6.88)	
		Heavy drinkers			
		*1/*1	22	1.00	
		*1/*2	46	16.4 (4.41–61.2)	
		*2/*2	0	–	
		Other participants			
Yokoyama <i>et al.</i> (2001) , Kanagawa, Japan, 1993–2000	Squamous cell carcinoma	*1/*1	13	1.00	Male alcoholics. Adjusted for age, drinking, smoking, <i>ALDH2</i> and <i>ADH1B</i> genotypes. Possible partial overlap with Yokoyama <i>et al.</i> (1998)
		*1/*2	20	1.68 (0.78–3.62)	
		*2/*2	1	0.42 (0.28–1.25)	
		ALDH2			
		*1/*1	50	1.00	
		*1/*2	62	13.50 (8.06–22.60)	
		ADH1B			
		*1/*2 + *2/*2	56	1.00	
		*1/*1	56	2.64 (1.62–4.31)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Boonyaphiphat <i>et al.</i> (2002) , Songkhla, Thailand, 1997–2000	Squamous cell carcinoma	By alcohol intake			Unlike Japanese and Chinese studies, frequency of inactive <i>ALDH2</i> is low in the Thais: 20% in cases, 18% in controls. Adjusted for age, sex, smoking, betel chewing (drinking, <i>ALDH2</i> and <i>ADH1B</i> genotypes for overall)
		<i>ALDH2</i>			
		Non-drinker			
		*1/*1	40	1.00	
		*1/*2	12	1.56 (0.65–3.70)	
		≤ 60 g/d			
		*1/*1	42	2.16 (1.11–4.21)	
		*1/*2	8	2.52 (0.85–7.46)	
		> 60 g/d			
		*1/*1	79	5.28 (2.70–10.32)	
		*1/*2	20	10.83 (3.37–34.69)	
				Interaction <i>P</i> = 0.031	
		<i>ADH1B</i>			
Itoga <i>et al.</i> (2002) , Chiba, Japan [study period NR]	Oesophagus NOS	Non-drinker			No adjustment was reported
		*1/*2	35	1.00	
		*1/*1	18	0.89 (0.41–1.93)	
		≤ 60 g/d			
		*1/*2	28	2.00 (0.97–4.11)	
		*1/*1	22	2.34 (1.06–5.11)	
		> 60 g/d			
		*1/*2	38	3.35 (1.50–7.02)	
		*1/*1	61	11.46 (5.16–25.45)	
				Interaction <i>P</i> = 0.064	
		Habitual drinkers			
		<i>ALDH2</i> *1	47	1.0	
		<i>ALDH2</i> *2	18	4.9 (<i>P</i> < 0.0001)	
Watanabe <i>et al.</i> (2002) , Kagawa, Japan, 1998–2001	Squamous cell carcinoma	<i>ALDH2</i>			Prevalence of *2 allele was significantly higher in cases than in controls.
		*1/*1	10		
		*1/*2	18		
		*2/*2	1		

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Yokoyama <i>et al.</i> (2002), Tokyo, Chiba, Kanagawa, Osaka, Japan, 2000–01	Squamous cell carcinoma	By alcohol intake			Only male participants. Multivariate odds ratio of <i>ALDH2</i> *1/*2 in comparison with <i>ALDH2</i> *1/*1 was 7.83 (1.33–46.08). However, most men with *2/*2 genotype drank rarely or never and the risk was evaluated based on a small sample size (2 cases/43 controls). For <i>ADH1C</i> genotype the relative risk was associated with less active <i>ADH1C</i> *1/*1 versus active *1/*2 or *2/*2. When the linkage disequilibrium between <i>ADH1B</i> and <i>ADH1C</i> was taken into consideration, the <i>ADH1C</i> genotype did not significantly affect the risk for cancer. Adjusted for age, strong alcoholic beverage, green-yellow vegetables and fruit (and alcohol drinking, <i>ALDH2</i> , <i>ADH1B</i> and <i>ADH1C</i> genotypes for overall association). Cases included in Yokoyama <i>et al.</i> (2001) were excluded from this study.
		<i>ALDH2</i>			
		*1/*1			
		< 22 g/wk	0	0.0 (not calculable)	
		22–197 g/wk	3	1.00	
		198–395 g/wk	23	5.58 (1.54–20.25)	
		≥ 396 g/wk	33	10.38 (2.85–37.84)	
		Former drinker	4	8.81 (1.53–50.76)	
		*1/*2			
		< 22 g/wk	3	0.75 (0.14–4.11)	
		22–197 g/wk	21	5.82 (1.59–21.38)	
		198–395 g/wk	63	55.84 (15.40–202.51)	
		≥ 396 g/wk	73	88.88 (23.97–329.57)	
		Former drinker	9	50.50 (9.18–277.95)	
		*2/*2			
		< 22 g/wk	2	1.44 (0.22–9.54)	
		<i>ADH1B</i>			
		*1/*2 or *2/*2			
		< 22 g/wk	4	0.21 (0.06–0.68)	
		22–197 g/wk	20	1.00	
		198–395 g/wk	68	4.09 (2.25–7.42)	
		≥ 396 g/wk	80	7.01 (3.77–13.04)	
		Former drinker	11	5.73 (2.03–16.20)	
		*1/*1			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Yokoyama <i>et al.</i> (2002) Contd.,		< 22 g/wk	1	4.25 (0.41–43.82)	
		22–197 g/wk	4	3.97 (1.01–15.63)	
		198–395 g/wk	18	33.30 (11.14–99.50)	
		≥ 396 g/wk	26	38.64 (13.27–112.55)	
		Former drinker	2	19.63 (1.65–233.20)	
		ADH1C			
		*1/*1			
		< 22 g/wk	5	0.23 (0.08–0.68)	
		22–197 g/wk	22	1.00	
		198–395 g/wk	69	3.66 (2.04–6.55)	
Yang <i>et al.</i> (2005), Aichi, Japan, 2001–04		≥ 396 g/wk	88	6.64 (3.66–12.05)	
		Former drinker	12	8.44 (2.94–24.25)	
		*1/*2 or *2/*2			
		< 22 g/wk	0	Not calculable	
		22–197 g/wk	2	0.81 (0.17–3.99)	
		198–395 g/wk	17	13.32 (5.28–33.63)	
		≥ 396 g/wk	18	23.83 (7.67–74.06)	
		Former drinker	1	1.01 (0.09–11.93)	
	Oesophagus NOS	Overall analyses			Results from overall analyses were adjusted for age, sex, smoking and alcohol drinking. Results by alcohol intake were adjusted for smoking. <i>P</i> for interaction between alcohol intake and genotypes for <i>ALDH2</i> was 0.03 for ≤ 250 g/wk and < 0.01 for > 250 g/wk alcohol intake. <i>P</i> for interaction for <i>ADH1B</i> was 0.24 for ≤ 250 g/wk and 0.32 for > 250 g/wk alcohol intake
		ALDH2			
		*1/*1		1.00	
		*1/*2		6.43 (4.02–10.3)	
		*2/*2		1.92 (0.23–15.7)	
		ADH1B			
		*2/*2		1.00	
		*1/*2		1.57 (1.04–2.36)	
		*1/*1		0.62 (0.22–1.72)	
		By alcohol intake			
		ALDH2			
		*1/*1			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Yang et al. (2005) , Contd.		Non drinker		1.00	
		≤ 250 g/wk		1.88 (0.42–8.37)	
		> 250 g/wk		4.62 (0.93–23.1)	
		*1/*2			
		Non-drinker		1.00	
		≤ 250 g/wk		9.64 (3.23–28.8)	
		> 250 g/wk		95.4 (28.7–317)	
		<i>ADH1B</i>			
		*2/*2			
		Non-drinker	38	1.00	
Cai et al. (2006) , Taixing, Jiangsu Province, China, 2000	Squamous cell carcinoma	< 1200 g/yr	126	5.03 (1.67–15.1)	
		≥ 1200 g/yr	1	25.8 (8.01–83.3)	
		*1/*2 or *1/*1			
		Non-drinker	74	1.00	
		< 1200 g/yr	85	8.50 (1.90–38.0)	
		≥ 1200 g/yr	6	33.9 (7.34–157)	
		<i>ALDH2</i>			
		*1/*1	119	1.00	
		*1/*2	61	0.76 (0.50–1.16)	
		*2/*2	25	1.72 (0.85–3.48)	
					Adjusted for age, sex, education level, body mass index, and history of smoking and alcohol drinking. An elevation of the risk for ESCC was pronounced most among carriers of <i>ALDH2</i> *2/*2 and <i>XRCC1</i> 399Gln/Gln or Gln/Arg who consumed a low level of dietary selenium (adjusted OR, 4.16; 95% CI: 1.14–15.12).

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Yokoyama et al. (2006a) , Tokyo, Chiba, Kanagawa, Osaka, Japan, 2000–04	Squamous cell carcinoma	By alcohol intake ALDH2 *1/*1 < 22 g/wk 22–197 g/wk 198–395 g/wk ≥ 396 g/wk ALDH2 *1/*2 < 22 g/wk 22–197 g/wk 198–395 g/wk ≥ 396 g/wk ADH1B	12 5 4 4 8 5 2 3	1 0.80 (0.24–2.60) 1.99 (0.52–7.68) 3.16 (0.65–15.48) 0.5 (0.2–1.3) 2.0 (0.5–7.1) 4.7 (0.7–31) 59 (4.7–750) NS	Only female participants. Adjusted for age, smoking, green-yellow vegetables and fruit, hot food and beverages
Hashibe et al. (2006) , Romania, Poland, the Russian Federation, Slovakia, Czech Republic, 2000–02	Squamous cell carcinoma	ADH1B R48H *1/*1 *1/*2 + *2/*2 ADH1C I350V Ile/Ile (slow) Ile/Val Val/Val (fast; *1/*1) ADH1C R272Q Arg/Arg (slow) Arg/Gln Gln/Gln (fast; *1/*1) ALDH2 +82A > G	163 4 42 92 30 42 88 30	1.00 0.19 (0.07–0.53) 1.00 1.61 (1.07–2.43) 1.74 (1.02–2.98) 1.00 1.62 (1.07–2.44) 2.03 (1.18–3.47)	ALDH2 +82A > G, +348C > T and –261C > T showed linkage disequilibrium and were associated with risk for oesophageal squamous-cell carcinoma. Adjusted for age, sex, country, yr of alcohol drinking, pack-yr of tobacco smoking.

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Hashibe <i>et al.</i> (2006) , Contd.	Oesophagus NOS 1999–2003	A/A	82	1.00	Study participants were heavy alcohol drinkers: 123 oesophageal cancer cases and 525 controls with benign tumours. Adjusted for age, sex and smoking. [The reference group was not reported: $ADH1C^{*2/*2}$ or $ADH1C^{*2/*2} + ADH1C^{*1/*1}$.]
		A/G	69	2.11 (1.46–3.05)	
		G/G	15	4.14 (2.03–8.46)	
		$ALDH2 + 348C$			
		> T			
		T/T	83	1.00	
		T/C	71	2.29 (1.59–3.30)	
		C/C	12	3.71 (1.73–7.97)	
		$ALDH2 -261C$			
		> T			
Homann <i>et al.</i> (2006) , Germany, 1999–2003	Oesophagus NOS 1999–2003	T/T	85	1.00	Study participants were heavy alcohol drinkers: 123 oesophageal cancer cases and 525 controls with benign tumours. Adjusted for age, sex and smoking. [The reference group was not reported: $ADH1C^{*2/*2}$ or $ADH1C^{*2/*2} + ADH1C^{*1/*1}$.]
		T/C	71	2.32 (1.61–3.35)	
		C/C	12	3.85 (1.78–8.36)	
		$ADH1C^{*1/*1}$ in heavy drinkers		2.93 (1.84–4.67)	
Yang <i>et al.</i> (2007) , Yanting, Sichuan Province, China, 2003–04	Oesophagus (96% squamous cell carcinoma)	$ADH1B^{*2/*2}$			Adjusted for age, sex, smoking, rapid food eating, quality of drinking-water, consumption of pickled vegetables and fresh fruits, vegetables and eggs. Non-drinkers also included ex-drinkers.
		Non-drinker	37	1.0	
		Current drinker	41	1.88 (0.86–4.15)	
		$*1/*2$ or $*1/*1$			
		Non-drinker	43	1.21 (0.63–2.33)	
		Current drinker	70	3.94 (1.76–8.81)	
		$ALDH2^{*1/*1}$			
		Non-drinker	33	1.0	
		Current drinker	57	3.15 (1.39–7.13)	
		$*1/*2$ or $*2/*2$			
		Non-drinker	47	2.03 (1.03–3.99)	
		Current drinker	54	4.82 (2.06–11.27)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Terry <i>et al.</i> (2007a) , Connecticut, New Jersey and Washington, USA, 1993–95	Squamous cell carcinoma	ADH1C *2/*2	4	1.0	Adjusted for age, gender and geographic site
		*1/*2	10	1.0 (0.3–3.3)	
		*1/*1	9	1.7 (0.5–5.9)	
	Oesophageal and gastric cardia adenocarcinoma	ADH1C *2/*2	17	1.0	Variables for which the results were adjusted were NR
		*1/*2	52	1.2 (0.6–2.5)	
		*1/*1	45	2.0 (1.0–4.2)	
		ALDH2 *1/*1	37	1.00	
	Squamous cell carcinoma	*1/*2	43	2.89 (1.11–5.64)	
		*2/*2	0	–	
		ADH1B *1/*1	17	1.00	
Guo <i>et al.</i> (2008) , Lanzhou, Gansu Province, China, 2004–07	Squamous cell carcinoma	*2/*1	25	3.67 (1.26–8.73)	Variables for which the results were adjusted were NR
		*2/*2	38	1.46 (0.71–2.59)	
		By alcohol intake			
	Squamous cell carcinoma	ALDH2 *1/*1	7	1.00	Variables for which the results were adjusted were NR
		0–200 g/wk	30	2.29 (0.91–5.57)	
		> 200 g/wk			
	Squamous cell carcinoma	*1/*2	7	0.56 (0.20–1.59)	Variables for which the results were adjusted were NR
		0–200 g/wk	36	8.58 (3.28–22.68)	
		> 200 g/wk			
	Squamous cell carcinoma	*2/*2	0	–	Variables for which the results were adjusted were NR
		0–200 g/wk			
		> 200 g/wk			
	Squamous cell carcinoma	ADH1B *1/*2 or *2/*2	13	1.00	Variables for which the results were adjusted were NR
		0–200 g/wk	50	4.75 (2.53–9.38)	
		> 200 g/wk			
	Squamous cell carcinoma	*1/*1	1	1.00 (0.18–9.22)	Variables for which the results were adjusted were NR
		0–200 g/wk	16	27.12 (8.52–70.19)	
		> 200 g/wk			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Lee et al. (2008b) , Taipei and Kaohsiung, Taiwan, China, 2000–05	Squamous cell carcinoma	By alcohol intake ALDH2			Adjusted for age, sex, study hospital, ethnicity, smoking, education, smoking, betel quid chewing, and consumption of fruits and vegetables. Another publication from this study (Lee et al., 2009), reported that heterozygous ALDH2 increased the oesophageal cancer risk more prominently in younger population.
		*1/*1			
		Non-drinker	17	1.0	
		0.1–30 g/d	45	2.2 (1.1–4.5)	
		> 30 g/d	49	7.2 (3.3–15.9)	
		*1/*2			
		Non-drinker	38	1.1 (0.6–2.3)	
		0.1–30 g/d	114	14.5 (7.1–29.6)	
		> 30 g/d	129	102.6 (38.3–274.8)	
		*2/*2			
		Non-drinker	8	1.2 (0.4–3.4)	
		0.1–30 g/d	3	17.3 (1.4–213.7)	
		> 30 g/d	3	– (0 control subject)	
		ADH1B			
		*2/*2			
		Non-drinker	29	1.0	
		0.1–30 g/d	58	3.5 (1.9–6.5)	
		> 30 g/d	53	11.1 (5.0–24.4)	
		*1/*2			
		Non-drinker	26	0.8 (0.4–1.6)	
		0.1–30 g/d	59	4.2 (2.2–7.9)	
		> 30 g/d	64	14.2 (6.6–30.6)	
		*1/*1			
		Non-drinker	8	1.2 (0.4–3.6)	
		0.1–30 g/d	45	10.6 (4.7–23.7)	
		> 30 g/d	64	71.9 (22.6–228.5)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Ding et al. (2008) , Taixing, Jiangsu Province, China, 2005–06	Oesophagus NOS	By alcohol intake			Adjusted for income
		<i>ADH1B</i>			
		Non-drinker			
		*2/*2	50	1.00	
		*1/*2	42	1.31 (0.70–2.46)	
		*1/*1	4	2.10 (0.35–12.54)	
		*1/*2 or *1/*1	46	1.37 (0.74–2.54)	
		Drinker			
		*2/*2	56	1.00	
		*1/*2	54	1.18 (0.64–2.16)	
		*1/*1	15	2.90 (0.85–9.90)	
		*1/*2 or *1/*1	69	1.36 (0.76–2.43)	
		<i>ALDH2</i>			
Li et al. (2008a) , Cape Town, South Africa, 1997–2003	Squamous cell carcinoma	Non-drinker			
		*1/*1	26	1.00	
		*1/*2	43	1.29 (0.65–2.55)	
		*2/*2	27	4.67 (1.63–13.38)	
		*1/*2 or *2/*2	70	1.78 (0.94–3.37)	
		Drinker			
		*1/*1	64	1.00	
		*1/*2	46	2.47 (1.27–4.82)	
		*2/*2	15	8.63 (2.07–35.95)	
		*1/*2 or *2/*2	61	3.08 (1.65–5.78)	
		<i>ADH1B</i>			Results for participants from black racial groups (282 cases and 348 controls). All results for those with mixed ancestry (192 cases and 188 controls) were non-significant. Non-adjusted results.
		*1 allele	265	1.00	
		*2 allele	4	NS	
		*3 allele	13	NS	
		<i>ADH1C</i>			
		*1 allele	153	1.00	
		*2 allele	129	1.80 (<i>P</i> = 0.0004)	
		<i>ALDH2</i>			
		*1 allele	155	1.00	
		*2 allele	27	2.35 (<i>P</i> = 0.008)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Hashibe <i>et al.</i> (2008) , Multicenter study (see Comments), 2000–05	Oesophagus	ADH1B		1	427 cases of oesophageal cancer. Pooled analysis of studies conducted in the Russian Federation (Moscow), Poland (Lodz), Romania (Bucharest), Czech Republic (Prague, Olomouc), Slovakia (Banska Bystrica), France (Paris), Greece (Athens), Italy (Aviano, Padova, Torino), Norway (Oslo), United Kingdom (Edinburgh, Manchester, Newcastle), Spain (Barcelona), Croatia (Zagreb), Cuba, Argentina (Buenos Aires) and Brazil (Goianna, Pelotas, Rio de Janeiro, Sao Paulo) Adjusted for age, sex, centre, cumulative alcohol consumption and smoking
		*1/*1			
		*1/*2 or *2/*2 ADH1C G > A was in linkage disequilibrium with ADH1B		0.34 (0.20–0.56)	
Cui <i>et al.</i> (2009) , Japan (see Comments)	Squamous cell carcinoma	ALDH2			Case samples ($n = 1070$) were from BioBank Japan, a collaborative network of 66 hospitals in Japan. Control samples in the first stage ($n = 938$) were obtained from volunteers in Osaka, Japan. The control groups for the second stage and replication analysis consisted of 1898 individuals who were registered in BioBank Japan as subjects with diseases other than cancers. Adjusted for age, gender, alcohol and smoking. Heterozygous ALDH2 increased the oesophageal cancer risk more prominently in younger population.
		*1/*1	314	1.00	
		*1/*2	735	3.48 (2.99–4.06)	
		*2/*2	17	0.47 (0.28–0.78)	
		ADH1B			
		*2/*2	510	1.00	
		*1/*2	363	1.17 (1.01–1.37)	
		*1/*1	194	4.10 (3.24–5.18)	
		By alcohol intake			
		ALDH2			
		*2/*1 vs 1*1 + *2/*2			
		0–96.5 g/wk		3.35 (2.66–4.22)	
		> 96.5 g/wk		6.20 (4.76–8.09)	
		ADH1B			
		*1/*1 vs *1/*2 + *2/*2			
		0–96.5 g/wk		3.18 (2.28–4.43)	
		> 96.5 g/wk		4.74 (3.21–6.99)	

Table 2.73 (continued)					
Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Meta-analysis					
Lewis & Smith (2005)	Oesophagus	ALDH2*1/*1		1.0	Meta-analysis of the studies: Hori et al. (1997) , Matsuo et al. (2001b) , Boonyaphiphat et al. (2002) , Itoga et al. (2002) , Yokoyama et al. (2002) [Reduced risk with *2/*2 likely due to markedly lower levels of alcohol consumption in *2/*2 versus *1/*1 homozygotes.]
	NOS	ALDH2*1/*2		3.19 (1.86–5.47)	
		ALDH2*2/*2		0.39 (0.16–0.80)	

ALDH2 *1 is more active, ADH1B *1 is less active, and ADH1C *1 is more active alleles than the other allele in the respective genes.
ALDH, aldehyde dehydrogenase; ADH, alcohol dehydrogenase; CI, confidence interval; d, day or days; NOS, not otherwise specified; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

Table 2.74 Cohort study of *ALDH2* and *ADH1B* genotype-associated risk for cancer of the oesophagus and upper aerodigestive tract

Reference, location	Cohort description	Exposure assessment	Cancer and site	Exposure categories	No. of subjects/ squamous-cell carcinoma	Hazard ratio (95% CI)	Adjustment factors	Comments
Yokoyama et al. (2006b) , Kanagawa, Japan	808 Japanese alcoholic men confirmed cancer-free by endoscopic screening during 1993–2005; endoscopic follow-up from 1 to 148 mo (median, 31 mo)	<i>ALDH2</i> , <i>ADH1B</i> genotyping at baseline examination in 556 patients	Upper aerodigestive tract squamous-cell carcinoma	<i>ALDH2</i>			Age	
				*1/*1	484/27	1		
				*1/*2	72/26	11.6 (5.7–23.3)		
				<i>ADH1B</i>				
			Oesophageal squamous-cell carcinoma	*1/*2 + *2/*2	381/28	1		
				*1/*1	175/25	2.0 (1.02–4.0)		
				<i>ALDH2</i>				
				*1/*1	484/14	1		
			Oropharyngolaryngeal squamous-cell carcinoma	*1/*2	72/19	13.0 (5.2–32.1)		
				<i>ADH1B</i>				
			Upper aerodigestive tract squamous-cell carcinoma	*1/*2 + *2/*2	381/18	1		
				*1/*1	175/15	1.6 (0.7–3.9)		
				<i>ALDH2</i>				
				*1/*1	484/17	1		
			Oropharyngolaryngeal squamous-cell carcinoma	*1/*2	72/13	11.7 (4.7–29.5)		
				<i>ADH1B</i>				
				*1/*2 + *2/*2	381/16	1		
				*1/*1	175/14	2.0 (0.8–5.0)		

ADH, alcohol dehydrogenase; *ALDH*, aldehyde dehydrogenase; CI, confidence interval; mo, month or months

from ethanol at a rate 2.5 times faster than the homodimer encoded by the *ADH1C*2* allele ([Bosron & Li, 1986](#)).

(a) *Cancer of the oesophagus*

Associations between *ADH1C* genotype and oesophageal cancer have been investigated in five studies in populations mainly composed of Caucasians. A higher *ADH1C*1/*1*-associated risk was found in four ([Visapää et al., 2004](#); [Hashibe et al., 2006](#); [Homann et al., 2006](#); [Terry et al., 2007a](#); [Table 2.73](#)), in one of which all UADT cancers were combined ([Visapää et al., 2004](#); [Table 2.75](#)). However, no association was observed when the linkage disequilibrium between *ADH1B*2* and *ADH1C*1* was taken into consideration in one study ([Hashibe et al., 2006](#)). Both *ADH1B*2* and *ADH1C*1* were in linkage disequilibrium in an analysis by [Hashibe et al. \(2008\)](#).

In contrast to the overall direction in Caucasian populations, in two Japanese studies it was reported that the *ADH1C*2* allele increases the risk for oesophageal cancer ([Yokoyama et al., 2002](#); [Muto et al., 2005](#)). Again, when the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, no relationship was found between *ADH1C* genotype and UADT cancer risk ([Yokoyama et al., 2002](#)). No significant associations were observed in a Chinese study ([Chao et al., 2000](#)). An association between *ADH1C*2* allele and risk of oesophageal cancer was reported in an African population ([Li et al., 2008a](#)).

(b) *Other upper aerodigestive tract cancers*

In six studies of Caucasians ([Coutelle et al., 1997](#); [Harty et al., 1997](#); [Homann et al., 2006](#); [Hashibe et al., 2006, 2008](#); [Arndt et al., 2008](#)) increased risk of other upper aerodigestive tract cancer cancers associated with the *ADH1C*1/*1* genotype was reported ([Table 2.75](#)). In two other studies of Caucasians ([Schwartz et al., 2001](#); [Peters et al., 2005](#)), two studies from Japan

and India ([Asakage et al., 2007](#); [Solomon et al., 2008](#)) and one Brazilian study of a mixed population ([Nishimoto et al., 2004](#)) opposite results were reported, with the *ADH1C*2/*2* genotype increasing the risk. When the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration ([Asakage et al., 2007](#)), no relationship was found between *ADH1C* genotype and cancer risk. No significant associations were observed in six other studies of Caucasians ([Bouchardy et al., 2000](#); [Olshan et al., 2001](#); [Sturgis et al., 2001](#); [Zavras et al., 2002](#); [Risch et al., 2003](#); [Wang et al., 2005](#)), or in a study of Japan ([Muto et al., 2005](#)).

(c) *Cancers of the stomach and colorectum*

In one study in the USA increased risk of gastric adenocarcinomas associated with the *ADH1C*1/*1* genotype was reported ([Terry et al., 2007a](#)) but in a Polish study no significant effects of the *ADH1C* polymorphism on stomach cancer risk was found ([Zhang et al., 2007b](#)) ([Table 2.76 on-line](#)).

Regarding the risk for cancer of the colorectum, in two European studies an increased risk in *ADH1C*1/*1* carriers compared with *ADH1C*2* subjects was found ([Tiemersma et al., 2003](#); [Homann et al., 2009](#)). However, an increased risk with *ADH1C*2/*2* genotype was reported in another study ([Giovannucci et al., 2003](#)). A trend with the *ADH1C*2/*2* genotype increasing the risk for cancer of the colorectum was also observed in another study of Caucasians [which was perhaps explained by higher alcohol consumption by those with **2/*2* genotype] ([Jung et al., 2008](#)). In two other studies of primarily Caucasians ([van der Logt et al., 2006](#); [Curtin et al., 2007](#)) and a study on Japanese subjects ([Yin et al., 2007](#)) no significant associations between *ADH1C* polymorphism and cancer of the colorectum were found.

Table 2.75 Studies of *ALDH2*, *ADH1B* and *ADH1C* genotype-associated risk for cancers of the head and neck

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Coutelle et al. (1997) , Bordeaux, France, study period NR	Oropharynx, larynx	<i>ADH1C</i>		Study participants were classified as alcoholics and consumed > 100 g ethanol per d for > 10 yr; 21 with oropharyngeal cancer, 18 with laryngeal cancer, and 37 controls with no cancer. ORs adjusted for age. Risk for laryngeal cancer in alcoholics who were <i>GSTμ</i> ⁻ and <i>ADH3*1/*1</i> was 12.9 (95% 1.8–92) compared with those who were <i>GSTμ</i> ⁻ and <i>ADH3*1/*2</i> or <i>*2/*2</i>
	Both cancer sites	<i>*1/*2</i> , <i>*2/*2</i> <i>*1/*1</i>	1.0 3.6 (0.7–10.0)	
	Oropharynx	<i>*1/*2</i> , <i>*2/*2</i> <i>*1/*1</i>	1 2.6 (0.7–10.0)	
	Larynx	<i>*1/*2</i> , <i>*2/*2</i> <i>*1/*1</i>	1 6.1 (1.3–28.6)	
	Oral cavity and pharynx	<i>ADH1C</i>	Alcohol intake	
Harty et al. (1997) , Puerto Rico, 1992–95		<i>ADH1C</i>	Non-drinkers	Patients (<i>n</i> = 137) with histologically confirmed oral cancer, and 146 controls ORs adjusted for sex, age, cigarette use, other tobacco use, fruit and vegetable intake
		<i>*1/*1</i>	1.0	
		<i>*1/*2</i>	0.9 (0.2–3.7)	
		<i>*2/*2</i>	–	
			0–14 drinks/wk	
		<i>*1/*1</i>	1.2 (0.3–5.2)	
		<i>*1/*2</i>	0.9 (0.2–4.2)	
		<i>*2/*2</i>	1.0 (0.1–12.2)	
			15–56 drinks/wk	
		<i>*1/*1</i>	3.5 (0.8–15.8)	
Yokoyama et al. (1998) , Japan, 1987–97	Oropharynx-larynx	<i>*1/*2</i> <i>*2/*2</i>	4.1 (0.9–18.7) 6.3 (1.1–36.8)	Adjusted for age, drinking, smoking. Because the differences in odds ratio between the incident cases and the prevalent cases were small, the cases were combined. Alcoholic beverage drinking not significantly associated with the risk for oral cancer. Adjusted for age, sex, smoking.
		<i>*1/*1</i>	≥ 57 drinks/wk	
		<i>*1/*2</i>	40.1 (5.4–296.0)	
		<i>*2/*2</i>	7.0 (1.4–35.0)	
			4.4 (0.6–33.3)	
			11.1 (5.1–24.4)	
Katoh et al. (1999) , Japan, 1992–98	Oral squamous-cell carcinoma	Overall <i>ALDH2</i>	1.2 (0.7–2.1)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Bouchardy <i>et al.</i> (2000) , France, 1988–92	UADT squamous-cell carcinoma	<i>ADH1C</i>		Hospital-based case–control study. Patients with oral cavity or pharyngeal cancer (<i>n</i> = 121), laryngeal cancer (<i>n</i> = 129), and 172 controls. Patients had histologically confirmed primary SCC. All were regular smokers. Adjusted for age, sex, alcohol drinking and smoking.
	All oral cavity and pharynx	*2/*2	1.0	
		*1/*2	1.1 (0.6–2.2)	
		*1/*1	0.7 (0.4–1.4)	
	Oral cavity	*2/*2	1.0	
		*1/*2	0.9 (0.4–2.0)	
		*1/*1	0.8 (0.4–1.8)	
	Pharynx	*2/*2	1.0	
		*1/*2	1.7 (0.7–4.3)	
	Larynx	*1/*1	0.8 (0.3–2.1)	
*2/*2		1.0		
*1/*2		0.7 (0.4–1.4)		
*1/*1		1.0 (0.5–1.8)		
Nomura <i>et al.</i> (2000)	Oral squamous cell carcinoma	<i>ALDH2</i>		Hospital-based case–control study. Habitual drinking increased the risk for oral cancer (odds ratio [95%CI], 3.9 [2.4–6.3])
		Habitual drinkers	2.9 (1.1–7.8)	
Olshan <i>et al.</i> (2001) , North Carolina, USA, 1994–96	UADT squamous cell carcinoma	<i>ADH1C</i>	Alcohol intake	Patients (<i>n</i> = 182), and 202 controls. Patients had pathologically confirmed SCC of oral cavity, pharynx, larynx. Adjusted for tobacco use, age, sex and race
		*1/*1 + *1/*2	Non-drinkers	
		*2/*2	1.1 (0.3–4.8)	
			1.0	
			1–19 drinks/wk	
		*1/*1 + *1/*2	1.4 (0.3–5.8)	
		*2/*2	1.5 (0.3–8.6)	
			20–59 drinks/wk	
		*1/*1 *1/*2	2.8 (0.6–12.5)	
		*2/*2	2.4 (0.2–29.2)	
		≥ 60 drinks/wk		
	*1/*1 + *1/*2	5.2 (0.9–27.7)		
	*2/*2	– (no controls)		

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Schwartz <i>et al.</i> (2001), Washington, USA, 1985–89	Oral squamous cell carcinoma	<i>ADH1C</i>	Alcohol intake	Population-based case–control study. Oral SCC cases (<i>n</i> = 333) and 541 controls
			< 1 drinks/wk	Distribution of <i>ADH1C</i> among cases and controls:
		*1/*1	2.1 (0.8–5.9)	<i>ADH1C</i> *1/*1: 32.7% vs 36.5%
		*1/*2	1.7 (0.6–4.7)	<i>ADH1C</i> *1/*2: 49.0% vs 43.1%
		*2/*2	1.0	<i>ADH1C</i> *2/*2: 18.3% vs 20.3%
			1–14 drinks/wk	ORs adjusted for age, race and cigarette smoking
		*1/*1	2.0 (0.8–5.3)	
		*1/*2	2.1 (0.8–5.3)	
		*2/*2	1.4 (0.5–4.1)	
			15–28 drinks/wk	
		*1/*1	3.4 (1.1–10.8)	
		*1/*2	3.9 (1.3–11.8)	
		*2/*2	3.4 (1.0–11.5)	
			≥ 29 drinks/wk	
		*1/*1	6.1 (1.9–19.5)	
		*1/*2	8.7 (2.9–26.1)	
		*2/*2	10.0 (2.5–40.2)	
			Overall	
		*1/*1	1.3 (0.8–2.0)	
		*1/*2	1.3 (0.9–2.0)	
		*2/*2	1.0	

Table 2.75 (continued)				
Reference, study location, study period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Sturgis <i>et al.</i> (2001), Houston, TX, USA, 1995–2000	Oral cavity, pharynx	<i>ADH1C</i>		Cases (<i>n</i> = 229), histologically confirmed SCC of the oral cavity and pharynx, matched by age, sex and smoking status with 575 controls. ORs controlled for age, sex, and smoking status.
		*1/*1	Never drinkers	
		*1/*2	1.0	
		*2/*2	1.5 (0.7–3.1)	
			1.2 (0.5–3.0)	
			Former drinkers	
		*1/*1	2.9 (1.3–6.3)	
		*1/*2	2.1 (1.0–4.4)	
		*2/*2	3.4 (1.3–8.6)	
			Current drinkers	
		*1/*1	2.6 (1.2–5.5)	
		*1/*2	2.4 (1.2–4.9)	
		*2/*2	3.6 (1.6–8.1)	
			Total	
		*1/*1	1.0	
		*1/*2	1.0 (0.7–1.4)	
		*2/*2	1.2 (0.8–1.9)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Yokoyama et al. (2001) , Kanagawa, Japan, 1993–2000	Oropharyngo-laryngeal squamous-cell carcinoma	ALDH2 *1/*1	1.00	Adjusted for age, drinking, smoking, <i>ALDH2</i> and <i>ADH1B</i> genotypes
		*1/*2	18.52 (7.72–44.44)	
		ADH1B *1/*2 + *2/*2	1.00	
		*1/*1	6.68 (2.81–15.90)	
	Oral cavity/oropharyngeal squamous-cell carcinoma	ALDH2 *1/*1	1.00	
		*1/*2	20.83 (6.62–65.49)	
		ADH1B *1/*2 + *2/*2	1.00	
		*1/*1	5.48 (1.77–16.96)	
	Epilaryngeal/hypolaryngeal squamous-cell carcinoma	ALDH2 *1/*1	1.00	
		*1/*2	20.83 (6.62–65.49)	
		ADH1B *1/*2 + *2/*2	1.00	
		*1/*1	5.48 (1.77–16.96)	
Yokoyama et al. (2002a) , Tokyo, Chiba, Japan, 1998–99	Multiple primary cancer with oesophageal squamous-cell carcinoma	ALDH2 *2/*2 or *1/*2 vs *1/*1	5.3 (1.1–51.1)	107 patients. Multiple cancers included both multiorgan cancer and multiple intra-oesophageal squamous-cell carcinoma. Adjusted for age, sex, drinking, smoking.
		ADH2 *2/*2 or *1/*2 vs *1/*1	7.4 (1.3–80.1)	
	Multiorgan primary cancer with head and neck squamous-cell carcinoma	ALDH2 *1/*1	1.0	
		*1/*2	5.26 (1.08–51.1)	
	Oesophageal SCC	*2/*2	7.36 (1.29–80.7)	
		ADH2 *1/*1	1.0	Desophageal cancer, <i>n</i> = 48; oropharyngolaryngeal cancer, <i>n</i> = 29; combination, <i>n</i> = 30 ORs for multiple cancer, adjusted for age, drinking, smoking
		*1/*2	5.26 (1.08–51.1)	
		*2/*2	7.36 (1.29–80.7)	
	Oropharyngolaryngeal SCC (alone or in combination)	ADH2 *1/*1	1.0	
		*1/*2	5.26 (1.08–51.1)	
		*2/*2	7.36 (1.29–80.7)	

Table 2.75 (continued)				
Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Zavras <i>et al.</i> (2002) , Athens, Greece, 1995–98	Oral cavity	<i>ADH1C</i>	Alcohol intake	93 cases and 99 controls. Adjusted for sex, smoking and referring hospital.
			Non-drinker	
		*1/*1	1.0	
		*1/*2	0.7 (0.3–2.0)	
		*2/*2	0.4 (0.1–1.8)	
			1–28 drinks/wk	
		*1/*1	1.7 (0.6–4.6)	
		*1/*2	1.0 (0.3–3.0)	
		*2/*2	3.4 (0.7–17.0)	
			> 28–42 drinks/wk	
		*1/*1	1.9 (0.3–11.6)	
		*1/*2	2.2 (0.4–12.3)	
		*2/*2	– (no subjects)	
			> 42 drinks/wk	
		*1/*1	3.0 (0.6–15.8)	
		*1/*2	11.2 (1.1–112.1)	
		*2/*2	– (no subjects)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Risch <i>et al.</i> (2003) , Heidelberg, Germany, 1998–2000	Larynx	ADH1C *1/*2 + *2/*2 *1/*1 *1/*2 + *2/*2 *1/*1 *1/*2 + *2/*2 *1/*1 ADH1B *1/*1 *1/*2 *1/*1 *1/*2 *1/*1 *1/*2	Low intake 1.00 1.14 (0.5–2.6) Medium intake 0.85 (0.4–2.0) 1.21 (0.6–2.5) High intake 1.46 (0.7–3.1) 1.14 (0.6–2.3) Low intake 1.00 0.63 (0.2–2.8) Medium intake 0.94 (0.5–1.7) 1.85 (0.2–14.3) High intake 1.16 (0.7–2.0) 0.89 (0.3–2.5)	Cases (<i>n</i> = 257) of histologically confirmed SCC of the larynx and 251 age- and sex-matched controls. Adjusted for tobacco use. Alcohol intake (gram/d): low, 0–16.95; medium, > 16.95–50.16; high, > 50.16.
Nishimoto <i>et al.</i> (2004) , Sao Paulo, Brazil, 1995–2001	UADT (oral cavity, oropharynx, hypopharynx and larynx) cancers	ADH1C *1/*1 + *1/*2 *2/*2 *1/*1 + *1/*2 *2/*2	Lifetime alcohol intake < 100 kg 1.0 3.8 (1.5–9.7) ≤ 100 kg 1.0 0.5 (0.2–1.2)	Adjusted for age, sex and cancer in first-degree relative
Muto <i>et al.</i> (2005) , Kashiwa, Japan, 1999–2001	Squamous-cell carcinoma, oesophagus and head and neck (multiple cancers only)	ALDH2 *1 allele *2 allele ADH1C *1 allele *2 allele	1.0 5.45 (2.37 – 12.56) 1.0 2.08 (0.86–4.99)	Male and female patients, development of multiple carcinomas, adjusted for age and sex

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Wang et al. (2005) , Iowa, USA, 1994–97 and 2000–02	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	ADHIC*1/*2		Adjusted for age and tobacco pack-yr. “Total” were additionally adjusted for alcohol drinking. Reference group for each drinking level, *2/*2
		Never drinker	0.95 (0.4–2.0)	
		1–21 drinks/wk	0.5 (0.2–1.1)	
		≥ 22 drinks/wk	0.9 (0.4–2.1)	
		Total	0.8 (0.5–1.2)	
		ADHIC*1/*1		
Peters et al. (2005) , USA, 1999–2003	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	Never drinker	0.8 (0.4–1.8)	Adjusted for age, gender, race and smoking. Cutpoint for heavy alcohol is > 30 drinks per wk. Test for heavy drinking x ADH interaction, <i>P</i> = 0.05. <i>ADH1B</i> and <i>ADH1C</i> showed linkage disequilibrium.
		1–21 drinks/wk	0.6 (0.3–1.2)	
		≥ 22 drinks/wk	0.8 (0.3–1.9)	
		Total	0.7 (0.4–1.1)	
		ADHIC*1/*1 + *1/*2		
		Non drinker	1.0	
Hashimoto et al. (2006) , Yamaguchi, Japan, 2002–04	UADT (oral cavity, oropharynx, hypopharynx and larynx) cancer	Light drinker	0.9 (0.6–1.3)	More cases < 66 yr were drinkers than cases ≥ 66 yr.
		Heavy drinker	2.3 (1.4–3.8)	
		ADHIC*2/*2		
		Non drinker	0.8 (0.4–1.8)	
		Light drinker	0.9 (0.6–1.6)	
		Heavy drinker	7.1 (2.3–22.0)	
Homann et al. (2006) , Germany, 1999–2003	All tumours	Case versus controls	Not significantly different	818 patients with alcohol-associated esophageal (<i>n</i> = 123), head and neck (<i>n</i> = 84) and hepatocellular cancer (<i>n</i> = 86) as well as in patients with alcoholic pancreatitis (<i>n</i> = 117), alcoholic liver cirrhosis (<i>n</i> = 217), combined liver cirrhosis and pancreatitis (<i>n</i> = 17) and in alcoholics without gastrointestinal organ damage (<i>n</i> = 174). [The reference group was not reported: <i>ADHIC*2/*2</i> or <i>ADHIC*2/*2 + ADHIC*1/*1</i> .]
		<i>ALDH2</i>	Significantly increased (<i>P</i> < 0.009) in cases < 66 yr compared with cases ≥ 66 yr	
		Case drinkers		
		<i>ALDH2</i>		
		ADHIC*1/*1 in heavy drinkers		
		Malignant versus benign tumour	2.77 (1.89–4.07)	
		Malignant vs benign tumour	2.2 (1.11–4.36)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Hashibe <i>et al.</i> (2006), Czech Republic, Poland Romania, the Russian Federation, Slovakia, 2000–02	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	ADH1B R48H *1/*2 + *2/*2		Reference groups were as following: <i>ADH1B R48H</i> , *1/*1; <i>ADH1C I350V</i> , Ile/Ile; <i>ADH1C R272Q</i> , Arg/Arg; <i>ALDH2</i> +82A > G, A/A; <i>ALDH2</i> +348C > T, T/T; <i>ALDH2</i> –261C > T, T/T. Frequency of alcohol use was as following: Never/light drinkers, ≤ 2 times/wk; Medium/heavy ≥ 3 times/wk. Adjusted for age, sex, country, and pack-yr of tobacco smoking. Overall results were additionally adjusted for yr of alcohol drinking. Results for oral, pharyngeal, laryngeal and oesophageal cancers were also presented in the article. When results were analysed by subsite, strong main effects for <i>ALDH2</i> variants were observed for squamous cell carcinoma of the oesophagus; among other subsites, only the association between <i>ALDH2</i> +82A > G (A/G versus A/A) and pharyngeal cancer remained statistically significant.
		Overall	0.47 (0.32–0.70)	
		Never/light alcohol use	0.57 (0.36–0.91)	
		Medium/heavy use	0.36 (0.17–0.77)	
		<i>P</i> for interaction	0.33	
		ADH1C I350V Val/Val (*1/*1)		
		Overall	1.38 (1.01–1.88)	
		Never/light alcohol use	1.48 (1.02–2.15)	
		Medium/heavy use	1.48 (0.80–2.73)	
		<i>P</i> for interaction	0.52	
		ADH1C R272Q Gln/Gln (*1/*1)		
		Overall	1.49 (1.08–2.05)	
		Never/light alcohol use	1.69 (1.15–2.46)	
		Medium/heavy use	1.42 (0.76–2.66)	
		<i>P</i> for interaction	0.30	
		ALDH2 +82A > G G/G		
		Overall	1.63 (0.94–2.82)	
		Never/light alcohol use	1.70 (0.88–3.29)	
		Medium/heavy use	4.38 (1.32–14.5)	
		<i>P</i> for interaction	0.02	
		ALDH2 +348C > T C/C		
		Overall	1.63 (0.92–2.89)	
		Never/light alcohol use	1.28 (0.65–2.55)	
		Medium/heavy use	5.79 (1.49–22.5)	
		<i>P</i> for interaction	0.009	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Hashibe <i>et al.</i> (2006) Contd.		ALDH2 –261C > T		
		C/C		
		Overall	1.66 (0.93–2.95)	
		Never/light alcohol use	1.29 (0.65–2.58)	
		Medium/heavy use	5.79 (1.49–22.5)	
		<i>P</i> for interaction	0.007	
Asakage <i>et al.</i> (2007) , Tokyo, Chiba, Kanagawa, Osaka, Japan 2000–03	Oral and hypo- and oropharynx	ALDH2	Alcohol intake	Patients with oropharyngeal or oral/oropharynx cancer (<i>n</i> = 53) and with hypopharyngeal cancer (<i>n</i> = 43) and 642 cancer-free men. Moderate-to-heavy drinkers: 22 g/drink, ≥ 9 drinks/wk. Adjusted for age, strong alcoholic beverage use, smoking, green-yellow vegetable use, and subcategory of alcohol drinking. When the linkage disequilibrium between <i>ADH1B</i> and <i>ADH1C</i> was taken into consideration, no relationship was found between <i>ADH1C</i> genotype and cancer risk
		*1/1	Never or light	
		*1/2	1	
			0.56 (0.20–1.59)	
		*1/1	Moderate-heavy	
			2.29 (0.94–5.57)	
		*1/2	8.26 (3.30–20.68)	
		ADH1B	Never or light	
		*1/*2 + *2/*2	1	
		*1/*1	1.00 (0.10–10.22)	
			Moderate-heavy	
		*1/*2 + *2/*2	4.75 (2.44–9.23)	
		*1/*1	26.40 (9.57–72.84)	
		ADH1C	Never or light	
		*1/*1	1	
		*1/*2 + *2/*2	2.34 (0.58–9.48)	
			Moderate-heavy	
		*1/*1	5.64 (2.82–11.31)	
		*1/*2 + *2/*2	17.93 (6.43–50.00)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Hiraki <i>et al.</i> (2007), Aichi, Japan, 2001–04	Squamous cell carcinoma of the lip and oral cavity, pharynx, larynx	<i>ADH1B His/His</i>		Adjusted for age, sex and smoking. No cases of heavy drinkers in <i>ALDH2 Lys/Lys</i> carriers. <i>P</i> trend for heavy drinkers for <i>ADH1B</i> , 0.002 <i>P</i> trend for heavy drinkers for <i>ALDH2</i> , 0.003
		Never drinker	1.0	
		Moderate drinker	1.08 (0.66–1.77)	
		Heavy drinker	1.98 (1.20–3.30)	
		<i>P</i> for trend	0.005	
		<i>ADH1B His/Arg</i>		
		Never drinker	1.22 (0.63–2.35)	
		Moderate drinker	1.06 (0.58–1.94)	
		Heavy drinker	1.66 (1.51–4.71)	
		<i>P</i> for trend drinker	0.056	
		<i>ADH2 Arg/Arg</i>		
		Never drinker	0.50 (0.06–4.11)	
		Moderate drinker	2.46 (0.89–6.73)	
		Heavy drinker	9.52 (3.89–23.3)	
		<i>P</i> for trend	0.008	
		<i>ALDH2 Glu/Glu</i>		
		Never drinker	1.0	
		Moderate drinker	0.66 (0.32–1.36)	
		Heavy drinker	1.41 (0.69–2.89)	
		<i>P</i> for trend	0.058	
		<i>ALDH2 Glu/Lys</i>		
		Never drinker	0.75 (0.37–1.53)	
		Moderate drinker	1.05 (0.50–2.20)	
		Heavy drinker	3.13 (1.46–6.72)	
		<i>P</i> for trend	< 0.001	
		<i>ALDH2 Lys/Lys</i>		
		Never drinker	0.56 (0.22–1.43)	
		Moderate drinker	3.14 (0.45–21.6)	
		Heavy drinker	n/a	
		<i>P</i> for trend	0.44	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Visapää et al. (2004) , Mannheim and Heidelberg, Germany, study period NR	UADT	ADH1C *2/*2 *1/*1	1.00 1.69 (1.12–2.56)	Hospital-based case-control study. Cases (<i>n</i> = 107) of UADT cancer (99 smokers) and 103 control patients (95 smokers) with liver cirrhosis (<i>n</i> = 39), alcoholic pancreatitis (<i>n</i> = 38) or without organ injury (<i>n</i> = 26), whose alcohol intake was similar to that of the UADT patients. Adjusted for alcohol use, smoking, age, sex
Hashibe et al. (2008) , Multicenter study (see Comments), 2000–05	Oral/pharynx	ADH1B *1/*1	1.00	Pooled analysis of studies conducted in the Russian Federation (Moscow), Poland (Lodz), Romania (Bucharest), Czech Republic (Prague, Olomouc), Slovakia (Banska Bystrica), France (Paris), Greece (Athens), Italy (Aviano, Padova, Torino), Norway (Oslo), United Kingdom (Edinburgh, Manchester, Newcastle), Spain (Barcelona), Croatia (Zagreb), Cuba, Argentina (Buenos Aires) and Brazil (Goiania, Pelotas, Rio de Janeiro, Sao Paulo). Mostly Caucasian populations, men and women, adjusted for age, gender, centre, alcohol and tobacco use. The OR (95% CI) for codominant model was 0.59 (0.50–0.69) for all four cancer sites combined.
	Larynx	*1/*2+*2/*2 *1/*1	0.45 (0.35–0.57) 1.00	
	Oral, pharynx, larynx, and oesophagus	*1/*2+*2/*2 *1/*1	0.71 (0.57–0.88) 1.00	
		*1/*2+*2/*2	0.56 (0.47–0.66)	
	Oral/pharynx	ADH7 *1/*1	1.00	
	Larynx	*1/*2+*2/*2 *1/*1	0.70 (0.59–0.84) 1.00	
	Oral, pharynx, larynx, and oesophagus	*1/*2+*2/*2 *1/*1	0.78 (0.59–0.93) 1.00	
		*1/*2+*2/*2	0.68 (0.60–0.78)	
Solomon et al. (2008) , Tamil Nadu, India, study period NR	Squamous-cell carcinoma, oral cavity	ADH1B *2/*1 + *2/*2 *1/*1	Heavy drinkers 1.00 1.62 (1.08–2.14)	
		ADH1C *1/*1 + *1/*2 *2/*2	1 2.65 (1.78–3.53)	
Arndt et al. (2008) , Poznan, Poland, 2006–08	Laryngeal cancer	ADH1C *2/*2 *1/*2 *1/*1	No adjustment was reported 1.00 1.40 (0.68–2.85) 1.53 (0.67–3.46)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Yokoyama <i>et al.</i> (2008) , Japan	Development to multiple carcinomas in oropharyngolarynx	<i>ALDH2</i>		Prospective part of study
		*1/*1	1.0	
		*1/*2	4.3 (1.4–12.9)	
		<i>ADH1B2</i>		
		*1/*2 + *2/*2	1.0	
Meta-analysis Boccia <i>et al.</i> (2009)	Head and neck cancer	<i>ALDH2</i> *1/*1	1.0	Meta-analysis of six Japanese studies. [Reduced risk with *2/*2 likely due to markedly lower levels of alcohol consumption in *2/*2 versus *1/*1 homozygotes.]
		<i>ALDH2</i> *1/*2	1.83 (1.21–2.77)	
		<i>ALDH2</i> *2/*2	0.53 (0.28–1.00)	

ALDH2 *1 is more active, *ADH1B* *1 is less active, and *ADH1C* *1 is more active alleles than the other allele in the respective genes.

ALDH, aldehyde dehydrogenase; *ADH*, alcohol dehydrogenase; CI, confidence interval; mo, month or months; NR, not reported; SCC, squamous cell carcinoma; vs, versus; wk, week or weeks

(d) Hepatocellular cancer

Two European studies investigated associations between *ADH1C* genotype and hepatocellular carcinoma. [Covolo et al. \(2005\)](#) reported negative results and [Homann et al. \(2006\)](#) found a positive association between *ADH1C**1/*1 and the risk for alcohol-associated hepatocellular carcinoma (Table 2.76 on-line).

(e) Cancer of the lung

No significant effect of the *ADH1C* polymorphism on the risk for cancer of the lung was found in one Japanese study ([Minegishi et al., 2007](#)) and one study in the USA ([Freudenheim et al., 2003](#)) (Table 2.76 on-line).

(f) Cancer of the female breast

Six studies conducted in Germany and the USA investigated the relationship between *ADH1C* genotype and the risk for cancer of the female breast. Three of them showed an increased risk in *ADH1C**1/*1 versus *ADH1C**1/*2 and *ADH1C**2/*2 carriers ([Freudenheim et al., 1999](#); [Coutelle et al., 2004](#); [Terry et al., 2006](#); Table 2.76 on-line). In two studies the association was more pronounced among premenopausal women ([Freudenheim et al., 1999](#); [Terry et al., 2006](#)). No significant associations between *ADH1C* polymorphism and the risk for cancer of the female breast were observed in the three other studies ([Hines et al., 2000](#); [Terry et al., 2007b](#); [Visvanathan et al., 2007](#)) as well as in one large pooled study ([Breast Cancer Association Consortium, 2006](#)).

(g) Cancer of the urinary bladder

An increased risk for cancer of the urinary bladder cancer in moderate drinkers of the *ADH1C**1/*1 genotype was reported from a Dutch study ([van Dijk et al., 2001](#)) (Table 2.76 on-line).

2.18.3 Other ADHs

In a pooled study a rare allele of *ADH7* was found to be significantly protective against UADT cancer ([Hashibe et al., 2008](#)). The role of this allele in the functional activity of the enzyme is not yet known.

2.18.4 CYP2E1

CYP2E1 is induced by chronic alcoholic beverage consumption and in addition to ethanol oxidation it plays a role in the metabolic activation of many carcinogens, including *N*-nitrosamines, benzene and aniline. The *CYP2E1* gene contains several single nucleotide polymorphisms, including C1053T (*CYP2E1**5; also referred to as *RsaI* polymorphism), G1293A (*CYP2E1**5; also referred to as *PstI* polymorphism), T7632TA (*CYP2E1**6; also referred to as *DraI* polymorphism) and G71T (*CYP2E1**7).

(a) Cancer of the oesophagus

A *CYP2E1**5B (earlier denoted *c2; *1A is the wild-type allele, earlier denoted *c1) allele-associated risk of oesophageal cancer has been reported from one study of East-Asians ([Tsutsumi et al., 1993](#)). Opposite results, with the *5B allele decreasing the risk for oesophageal cancer, have been observed in four studies of East-Asians ([Tan et al., 2000](#); [Lu et al., 2005](#); [Guo et al., 2008](#); [Qin et al., 2008](#)). The absence of significant results were reported from seven studies of East-Asians ([Morita et al., 1997](#); [Hori et al., 1997](#); [Tanabe et al., 1999](#); [Chao et al., 2000](#); [Gao et al., 2002](#); [Yang et al., 2005](#); [Wang et al., 2006b](#)), and studies of Europeans ([Lucas et al., 1996](#)), South Africans ([Li et al., 2005](#)) and Brazilians ([Rossini et al., 2007](#)) (Table 2.77 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.77.pdf>).

(b) *Other upper aerodigestive tract cancers combined*

In seven studies from East-Asia, India, Brazil and Europe an increased risk for other upper aerodigestive tract cancer cancers in carriers of the *CYP2E1**5B allele was found ([Hildesheim et al., 1997](#); [Hung et al., 1997](#); [Bouchardy et al., 2000](#); [Gattás et al., 2006](#); [Sugimura et al., 2006](#); [Olivieri et al., 2009](#); [Ruwali et al., 2009](#)). In contrast, an inverse association between the *5B allele and oral cancer has been reported in the USA ([Liu et al., 2001](#)). No significant associations were reported from eight European studies ([Jahnke et al., 1996](#); [Lucas et al., 1996](#); [González et al., 1998](#); [Matthias et al., 1998](#); [Zavras et al., 2002](#); [Boccia et al., 2008](#)), three Japanese studies ([Katoh et al., 1999](#); [Morita et al., 1999](#); [Tanabe et al., 1999](#)), and two studies from USA ([Buch et al., 2008](#)) and India ([Soya et al., 2008](#)).

(c) *Cancers of the stomach and colorectum*

In three studies, two of Chinese ([Cai et al., 2001](#); [Wu et al., 2002](#)) and one of Caucasians ([Boccia et al., 2007](#)), increased risk for cancer of the stomach by polymorphic alleles of *CYP2E1* was found. Opposite results with the *5B allele decreasing risk of cancer of the stomach were reported from one study from Brazil ([Nishimoto et al., 2000](#)). Lack of significant associations between the *5B allele and risk of cancer of the stomach has been reported from four studies of East-Asian populations ([Kato et al., 1995, 1997](#); [Gao et al., 2002](#); [Nan et al., 2005](#)).

With regard to cancer of the colorectum, in two studies, one of Hungarians ([Kiss et al., 2000](#)) and one study of Chinese ([Gao et al., 2007](#)), an increased risk for cancer of the colorectum was demonstrated in carriers of the *CYP2E1**5B allele. From one study in Hawaii, USA ([Le Marchand et al., 2002](#)), and one study in Japan ([Morita et al., 2009](#)) an increased risk of cancer of the colorectum with 5' 96-bp insertion variant in *CYP2E1* was reported. In three other studies,

one from China ([Fan et al., 2007](#)) and two from Europe ([Landi et al., 2005](#); [van der Logt et al., 2006](#)), significant associations between *CYP2E1* polymorphism and cancer of the colorectum were not reported. In one study in Japan a decreased risk for rectal cancer in carriers of the *5B allele was found ([Morita et al., 2009](#)).

(d) *Hepatocellular cancer*

A *5B allele-associated increased risk for hepatocellular carcinoma was reported from three studies of Japanese and European populations ([Ladero et al., 1996](#); [Koide et al., 2000](#); [Munaka et al., 2003](#)). No significant association was observed in four other East Asian populations ([Lee et al., 1997](#); [Wong et al., 2000](#); [Yu et al., 2002](#); [Kato et al., 2003](#)). A decreased risk with *5B allele was reported from a Taiwan, China study ([Yu et al., 1995](#)).

(e) *Cancer of the lung*

An increased risk for cancer of the lung associated with the *CYP2E1**5B allele was found in one Japanese study ([Oyama et al., 1997](#)) and one study of mainly Caucasians ([el-Zein et al., 1997c](#)). A similar association was reported in another Japanese study ([Minegishi et al., 2007](#)), but the genotype distribution was not in Hardy-Weinberg equilibrium in the control population [so the finding of an association with cancer of the lung is most likely a false-positive result]. Opposite results with the *5B allele decreasing risk for cancer of the lung have been obtained in studies from Sweden, USA and Republic of Korea ([Persson, et al., 1993](#); [Wu et al., 1997](#); [Le Marchand et al., 1998](#); [Eom et al., 2009](#)). In eight studies, two of East Asians ([Watanabe et al., 1995](#); [Persson et al., 1999](#)), four of mixed South and North American populations ([Kato et al., 1994](#); [Hamada et al., 1995](#); [London et al., 1996](#); [Quiñones et al., 2001](#)), and one of Finns ([Hirvonen et al., 1993](#)), no significant associations were observed.

(f) Cancer of the breast

In one Korean study a non-significant increased risk for cancer of the breast associated with the *5B/*5B genotype was found ([Choi et al., 2003](#)), while in a study from Taiwan, China, an inverse association between the *5B/*5B genotype and breast cancer risk was found ([Wu et al., 2006](#)).

(g) Other cancers

For cancer of the urinary bladder no significant associations to the *5B allele were observed in an Egyptian ([Anwar et al., 1996](#)) and a German population ([Brockmöller et al., 1996](#)). Also for cancer of the kidney (renal cell) and urothelial cancer no significant associations were found in one study from Germany ([Farker et al., 1998a](#)). Three studies on East-Asian populations demonstrated a decreased risk for cancer of the prostate associated with the *5B allele ([Murata et al., 2001](#); [Yang et al., 2006a](#); [Yang et al., 2009](#)). No association between polymorphism in *CYP2E1* and risk of cancer of the pancreas was observed in an East-Asian population ([Lee et al. 2007](#)).

2.18.5 ALDH2

The variant allele *2 that encodes an inactive subunit of *ALDH2* is prevalent among East Asians (28–45%; [Goedde et al., 1992](#)), but is rare in most other populations. Individuals with inactive *ALDH2* generally abstain from heavy alcohol drinking due to subsequent acetaldehydeaemia and alcoholic flushing responses. Most homozygotes for inactive *ALDH2**2/*2 are non-drinkers or occasional drinkers, but substantial percentages of East Asians who are habitual drinkers, including alcoholics, are heterozygous *ALDH2**1/*2.

(a) Cancer of the oesophagus

The *ALDH2**2 allele has been found to be a risk factor for oesophageal cancer in 19 East-Asian studies ([Hori et al., 1997](#); [Yokoyama et al., 1998](#),

[2001, 2002, 2006a, b](#); [Tanabe et al., 1999](#); [Chao et al., 2000](#); [Matsuo et al., 2001b](#); [Boonyaphiphat et al., 2002](#); [Itoga et al., 2002](#); [Watanabe et al., 2002](#); [Yokoyama et al., 2002](#); [Yang et al., 2005, 2007](#); [Cai et al., 2006](#); [Guo et al., 2008](#); [Lee et al., 2008b](#); [Cui et al., 2009](#); [Ding et al., 2009](#); [Tables 2.73, 2.74](#)). The magnitude of the *ALDH2*-associated risk depends on the extent of the association between oesophageal cancer and alcohol consumption. The risk was observed in light-to-moderate drinkers as well as heavy drinkers, but was higher among heavier drinkers including alcoholics than the other drinkers. The findings were also supported by a meta-analysis ([Lewis & Smith, 2005](#)). In two large case-control studies in Taiwan, China ([Lee et al., 2009](#)) and Japan ([Cui et al., 2009](#)) heterozygous *ALDH2* increased the oesophageal cancer risk more prominently in younger populations. Heterozygous *ALDH2* has been consistently reported to be a strong risk factor for multiple cancers in Japanese patients with oesophageal cancer ([Yokoyama et al., 2001, 2002](#); [Muto et al., 2005](#)).

Case-control studies in high-risk rural regions in Mainland China showed modest-positive associations ([Cai et al., 2006](#); [Yang et al., 2007](#); [Ding et al., 2009](#); [Guo et al., 2008](#)) between heterozygous *ALDH2* and oesophageal cancer risk. In these studies, the risks were more distinct where the impact of alcohol consumption on oesophageal cancer was more distinct and when only male populations were evaluated. [Tian et al. \(1998\)](#) reported no significant association between *ALDH2* polymorphism and oesophageal cancer, but this study included only cases of oesophageal squamous carcinoma and the *ALDH2* gene frequencies were compared just to other published data. In addition to the data on East-Asian populations, the association between oesophageal cancer and the *ALDH2**2 allele has been found in a study in South Africa ([Li et al., 2008a](#)). In addition, the +82A > G, +348C > T and –261C > T variants of *ALDH2* (without known functional actions) have been related to

oesophageal cancer in a large pooled European study ([Hashibe et al., 2006](#)).

(b) Other upper aerodigestive tract cancer

In 10 Japanese studies, the *ALDH2**2 allele has been shown to be a risk factor for upper aerodigestive tract cancer ([Yokoyama et al., 1998, 2001, 2002, 2006b, 2008](#); [Nomura et al., 2000](#); [Muto et al., 2005](#); [Hashimoto et al., 2006](#); [Asakage et al., 2007](#); [Hiraki et al., 2007](#); Table 2.75). In one Japanese study significant associations between the *2 allele and oral cancer were not found ([Kato et al., 1999](#)); in this study a significant association between risk of oral cancer and consumption of alcoholic beverages was not found either. A meta-analysis of these Japanese studies showed that heterozygous *ALDH2* increased upper aerodigestive tract cancer risks more strongly in heavy drinkers including alcoholics than the other drinkers ([Boccia et al., 2009](#)). In one Japanese study a higher frequency of heterozygous *ALDH2* in younger drinkers with upper aerodigestive tract cancer was found ([Hashimoto et al., 2006](#)). Heterozygous *ALDH2* has been reported to be a strong risk factor for multiple cancers in Japanese patients with upper aerodigestive tract cancers ([Yokoyama et al., 2001, 2002, 2008](#); [Muto et al., 2005](#)). The other *ALDH2* variants (reported by [Hashibe et al., 2006](#)) did not significantly affect the risk of oral and other upper aerodigestive tract cancers (excluding oesophageal cancer).

(c) Cancers of the stomach, colorectum and pancreas

In two Japanese studies an increased risk for cancer of the stomach by the *ALDH2**2 allele has been reported ([Yokoyama et al., 1998, 2007b](#); Table 2.76 on-line). Such an association was reported from another Japanese study ([Yokoyama et al., 2001](#)) when all gastric cancer cases, including gastric cancer alone or combined with upper aerodigestive tract cancers were considered. However, when only cases of cancer of the stomach alone were included

in the analyses, there was no association with *ALDH2*. In a study of Polish consumers of alcoholic beverages an increased risk for cancer of the stomach by the *ALDH2* +82A > G alleles was found ([Zhang et al., 2007b](#)). No significant associations with the *2 allele were reported from a study from Republic of Korea ([Nan et al., 2005](#)).

Increased risks of colon and/or rectal cancer have been associated with the *2 allele in three East-Asian studies ([Yokoyama et al., 1998](#); [Murata et al., 1999](#); [Matsuo et al., 2002](#)). The *2 allele has also been associated with lower risk in one Chinese ([Gao et al., 2008](#)) and a Japanese ([Yin et al., 2007](#)) study. No significant differences were seen in four Japanese studies ([Takeshita et al., 2000a](#); [Hirose et al., 2005](#); [Otani et al., 2005](#); [Matsuo et al., 2006a](#)).

In one of two Japanese studies [Kanda et al. \(2009\)](#) reported increased risk for the *ALDH2**2 allele for cancer of the pancreas; no significant associations were found by [Miyasaka et al. \(2005\)](#).

(d) Hepatocellular cancer

In four of 11 Japanese and Chinese studies an increased risk for hepatocellular carcinoma in carriers of the *ALDH2**2 allele has been found ([Kato et al., 2003](#); [Munaka et al., 2003](#); [Sakamoto et al., 2006](#); [Ding et al., 2008](#)) (Table 2.76 on-line). Four Japanese ([Shibata et al., 1998](#); [Yokoyama et al., 1998](#); [Koide et al., 2000](#); [Takeshita et al., 2000b](#)) and one Chinese ([Yu et al., 2002](#)) study reported no significant associations between *ALDH2* polymorphism and hepatocellular cancer.

(e) Cancer of the lung

An increased risk for lung cancer associated with *ALDH2**2 alleles has been observed in three studies, two from Japan ([Yokoyama et al., 1998](#); [Minegishi et al., 2007](#)) and one from Republic of Korea ([Eom et al., 2009](#)) (Table 2.76 on-line).

(f) Cancer of the female breast

No significant association between *ALDH2* polymorphism and risk of cancer of the breast has been observed in a Korean ([Choi et al., 2003](#)) and a Spanish population ([Ribas et al., 2008](#)) (Table 2.76 on-line).

2.19 Synthesis*2.19.1 Oral cavity and pharynx*

Data published since the previous *IARC monograph* ([IARC, 2010](#)) support the conclusion that consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and the association is not due to chance, bias or confounding.

2.19.2 Larynx

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the larynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out.

2.19.3 Oesophagus

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) supports the conclusion that consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out. There is now a substantial body of evidence that alcoholic beverage consumption is not associated with adenocarcinoma of the oesophagus.

2.19.4 Upper aerodigestive tract combined

There is evidence that consumption of alcoholic beverages is causally related to cancer of the upper aerodigestive tract, as it is for cancer of the oral cavity and pharynx, larynx and oesophagus separately. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and chance, bias and confounding can be ruled out.

2.19.5 Colon and rectum

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the colorectum. Most of the evidence suggests that consumption of alcoholic beverages is positively associated with both cancer of the colon and cancer of the rectum, and is similar in men and women, although the data are not entirely consistent. Similarly, there is some evidence that risk may only be increased at relatively high levels of intake (i.e. > 30 g/d). There is consistent evidence that risk does not differ by beverage type; whether the risk associated with consumption of alcoholic beverages differs by smoking status or intake of dietary folate is inconsistent.

2.19.6 Liver

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) support the previous conclusion that the consumption of alcoholic beverages is causally related to hepatocellular carcinoma. It is not possible to draw any conclusion concerning consumption of alcoholic beverages and risk of cholangiocarcinoma.

2.19.7 Stomach

Results on the association between consumption of alcoholic beverages and cancer of the stomach are difficult to interpret due to the lack

of information on important confounders, such as possible dietary deficiencies.

2.19.8 *Pancreas*

There is accumulating evidence that high alcohol intake (i.e. ≥ 30 g/d) is associated with a small increased risk for cancer of the pancreas. However, the possibility that residual confounding by smoking may partly explain this association cannot be excluded. Whether the risk associated with heavy alcohol consumption differs by beverage type, smoking status or body mass index is unclear.

2.19.9 *Lung*

Available data are inadequate to determine a causal association between the consumption of alcoholic beverages and cancer of the lung. Although adjustment for tobacco smoking was attempted in many studies, residual confounding cannot be excluded for those analyses that found a positive association with consumption of alcoholic beverages. For those studies that attempted to evaluate risk for cancer of the lung from the consumption of alcoholic beverages in non-smokers, small numbers of cases, or few subjects with high consumption of alcoholic beverages, precluded detection of an association.

2.19.10 *Breast*

Occurrence of cancer of the female breast is causally associated with the consumption of alcoholic beverages. Cancer risk increases proportionately according to the amount of alcohol consumed, with an increase in risk of up to 12% for each additional drink consumed regularly each day (equivalent to about 10 g/d). The risk does not appear to vary significantly by beverage type or smoking status. It remains unclear whether the association of alcohol beverage consumption with risk for cancer of the female breast varies

by use of hormone-replacement therapy or by tumour receptor status.

The evidence that alcoholic beverage consumption is associated with cancer of the male breast remains inconsistent.

2.19.11 *Uterine cervix*

The weak associations noted in some studies for consumption of alcoholic beverages and risk of cancer of the uterine cervix are sufficient to draw any conclusion on causality. Few studies were able to adjust for the known risk factors for the disease.

2.19.12 *Endometrium*

The evidence for an association between consumption of alcoholic beverages and risk for cancer of the endometrium is inconsistent. The majority of studies show no association; the few that show an inverse association were not able to adjust for tobacco smoking.

Among both the cohort and case-control studies, there was no consistent evidence of an interaction between consumption of alcoholic beverages and different variables known or suspected to be associated with cancer of the endometrium, such as use of hormone replacement therapy, body size, age, tobacco smoking, parity, education, physical activity, energy intake and other dietary aspects, oral contraceptive use or menopausal status.

2.19.13 *Ovary*

There is little evidence for an association between consumption of alcoholic beverages and risk for cancer of the ovary. The majority of studies show no association.

2.19.14 Prostate

There is little evidence for an association between consumption of alcoholic beverages and risk of cancer of the prostate. Although in some studies positive associations were found for advanced disease, the majority of studies show no association.

2.19.15 Kidney

There is no causal association between consumption of alcoholic beverages and cancer of the kidney.

2.19.16 Urinary bladder

Overall, the studies on cancer of the urinary bladder suggest no association with consumption of alcoholic beverages.

2.19.17 Haematopoietic malignancies

In cohort studies in the general population, most forms of lymphomas and leukaemias have shown no or inverse associations with consumption of alcoholic beverages; studies that assessed risk for non-Hodgkin lymphoma, the form of lymphomas and leukaemias most studied, generally found an inverse association.

There were consistent inverse associations in case-control studies investigating ever alcohol consumption and risk for Hodgkin lymphoma, with no significant differences between alcoholic beverage types. A large pooled study observed a lower risk of several histological subtypes, such as Burkitt, B-cell, follicular and T-cell lymphomas among ever drinkers.

No clear patterns of association between consumption of alcoholic beverages and risk of all leukaemias combined were shown in case-control studies. Two studies indicated increased risk of acute lymphocytic leukaemia with any or heavy alcohol drinking, and also increased risk of chronic lymphocytic leukaemia among wine

drinkers, but there was no consistent pattern of association for different types of leukaemias. In most studies on multiple myeloma no consistent results were observed.

2.19.18 Other cancers

It is not possible to draw any conclusions regarding the association between intake of alcoholic beverages and risk for cancers of the brain and thyroid, melanoma and non-melanoma skin cancers.

2.19.19 Parental exposure and childhood cancers

Results for the association between maternal consumption of alcohol before or during pregnancy and risk of acute lymphocytic leukaemia, acute lymphocytic leukaemia and acute leukaemia in the offspring are inconsistent.

2.19.20 Polymorphisms and genetic susceptibility

(a) *ADH1B*

The available genetic epidemiological data suggest a positive association between *ADH1B**1/*1 polymorphism and cancer of the oesophagus, and cancers of the upper aerodigestive tract combined. The relationship between *ADH1B* genotype and cancer in other organs is inconclusive because of the small number of studies.

(b) *ADH1C*

The relationship between *ADH1C* genotype and cancer at any site is inconclusive, primarily because of the small number of studies.

(c) *ALDH2*

The available genetic epidemiological data provides ample evidence for a strong contribution of heterozygous *ALDH2* genotype to the

development of alcohol-related cancer in the oesophagus and in the upper aerodigestive tract. While it is often difficult to differentiate clearly between exact locations of tumours in the oropharyngolaryngeal area based on the available published data, there is also strong evidence for a contribution of heterozygous *ALDH2* genotype to the development of alcohol-related cancer in the oropharyngolarynx as a whole, and especially in the hypopharynx. However, the epidemiological studies provide suggestive but inconclusive data for some association of heterozygous *ALDH2* genotype and alcohol-related cancers in the individual oropharyngolaryngeal subsites of the oral cavity, oropharynx and larynx.

The evidence for cancers of the stomach, colorectum, pancreas, liver, breast, bladder and prostate is inconclusive.

3. Cancer in Experimental Animals

Consumption of alcoholic beverages was evaluated in 2007 ([IARC, 2010](#)). The studies described below were considered; no new studies have been published since.

An issue in evaluating bioassays of ethanol is the nutritive value of this substance, which results in a hyperalimentation of alcohol-fed animals. For rigorous evaluation of the carcinogenicity of alcohol by ingestion in experimental animals, controls must be pair fed to equalize caloric intake.

3.1 Oral administration of ethanol in the drinking-water

Study design and results of studies of oral administration of ethanol in drinking-water are presented in [Table 3.1](#).

3.1.1 Rat

Eight groups of 50 male and 50 female Sprague-Dawley rats received either 1% or 3% ethanol or an equicaloric amount of glucose in a semisynthetic liquid diet for 120 weeks ([Holmberg & Ekström, 1995](#)). Males were given 70 mL/day and females 60 mL/day of liquid diet. No tumours developed in male rats. There was a significant ($P < 0.05$) increase in pituitary tumours [not further specified] among 3% ethyl alcohol-treated females (80%) than among high-dose glucose-treated animals (58%). There was also an increase ($P < 0.05$) in mammary gland fibromas, fibroadenomas and adenomas combined, in the 1% ethyl alcohol-treated females compared with the low-dose glucose animals [no incidence provided].

Male Sprague-Dawley rats administered 5% ethanol in the drinking-water for 130 weeks developed hepatocellular carcinomas (8/79 versus 1/80 control rats). Additionally, the authors reported an increase in the incidence of hyperplastic liver nodules in the ethanol group. Pancreatic adenomas, adrenal gland adenomas, and pituitary adenomas occurred in the ethanol group in 18% (14/79), 18% (14/79), and 33% (26/79) of the animals, respectively. No tumours of the pancreas or adrenal gland were found in control rats. Pituitary adenomas were found in 8/80 control rats ([Radike et al., 1981](#)).

In other experiments, the chronic administration of 5% or 10% ethanol had no effect on liver carcinogenesis of Wistar or F344 rats ([Shibayama et al., 1993](#); [Yamagiwa et al., 1994](#); [Wanibuchi et al., 2006](#)).

Sprague-Dawley rats and their offspring received either 10% ethanol or no ethanol in the drinking-water *ad libitum* starting at 39 weeks of age, 7 days before mating or from embryo life (offspring) until death. The intake of fluid was lower in the treated group but no difference in body weight was noted. An increased incidence of total malignant tumours was noted in female

Table 3.1 Carcinogenicity studies on ethyl alcohol administered in the drinking-water to experimental animals

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M) 130 wk Radlike et al. (1981)	5% 7 d/wk 79 animals 80 animals (controls)	Liver	[$P < 0.05$]	Carcinoma Control (1/80) 5% Ethanol (8/79)
		Pituitary gland	[$P < 0.001$]	Adenoma Control (8/80) 5% Ethanol (26/79)
		Adrenal gland	[$P < 0.0001$]	Adenoma Control (0/80) 5% Ethanol (14/79)
		Pancreas	[$P < 0.0001$]	Adenoma Control (0/80) 5% Ethanol (14/79)
		Testes	[NS]	Seminoma Control (0/80) 5% Ethanol (3/79)
		Forestomach	[$P < 0.01$]	Benign Control (1/110) 10% Ethanol (8/110)
			[$P < 0.01$]	Benign and malignant Control (1/110) 10% Ethanol (10/110)
		Head and other sites	[$P = 0.0042$]	Osteosarcoma Control (1/110) 10% Ethanol (12/110)
		Oral cavity, lips and tongue	$P < 0.01$	Carcinoma Control (3/110) 10% Ethanol (15/110)
		Testes	[$P = 0.013$]	Interstitial cell adenoma Control (9/110) 10% Ethanol (23/110)
Rat, Sprague-Dawley (F) 140 wk Soffritti et al. (2002a)	10% 7 d/wk 110 animals 110 animals (controls)	Lymphomas and leukaemias	[$P < 0.0001$]	Control (17/110) 10% Ethanol (46/110)
		Oral cavity, lips and tongue	$P < 0.05$	Carcinoma Control (2/110) 10% Ethanol (12/110)

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M) 179 wk Soffritti et al. (2002a)	10% 7 d/wk 30 animals 49 animals (controls)	Oral cavity, lips and tongue Carcinoma Control (2/49) 10% Ethanol (10/30)	$P < 0.01$	Animals were offspring
Rat, Sprague-Dawley (F) 179 wk Soffritti et al. (2002a)	10% 7 d/wk 39 animals/group 55 animals (controls)	Oral cavity, lips and tongue Carcinoma Control (3/55) 10% Ethanol (16/39)	$P < 0.01$	Animals were offspring
Mouse B6C3F1 (M) 104 wk Beland et al. (2005)	0 (control), 2.5%, 5% 7 d/wk 48 animals/group	Liver Adenoma or Carcinoma Control (12/46) 2.5% Ethanol (16/47) 5% Ethanol (25/48) Adenoma Control (7/46) 2.5% Ethanol (12/47) 5% Ethanol (19/48)	$P < 0.05$ dose-related trend, $P = 0.056$ (5% ethanol) $P < 0.05$ dose-related trend, $P < 0.05$ (5% Ethanol)	
Mouse, ICR (F) 106 wk Watabiki et al. (2000)	10–15% 7 d/wk 20 animals/group	Mammary gland Adenocarcinoma Control (0/20) 10–15% Ethanol (9/20)	$[P = 0.012]$	
Mouse, C57/ BL6APCmin (M) 10 wk Roy et al. (2002)	15% alternating with 20% every other d 12 animals/group	Intestine Adenoma Tumor multiplicity Control (26.8) 15–20% Ethanol (36.9)	$P < 0.05$	

d, day or days; F, female; M, male; NS, not significant; wk, week or weeks

breeders and male offspring. This was due to a significant increase in the incidence of head and neck carcinomas (oral cavity, lips, tongue) in male and female breeders and male and female offspring; benign and combined benign and malignant tumours of the forestomach in male breeders; and combined lymphomas and leukemias in female breeders. Increases in the incidence of interstitial-cell adenomas of the testis and osteosarcomas of the head and other sites were also observed in male breeders ([Soffritti et al., 2002a](#)). [The Working Group noted that some statements reporting increased incidence were not supported by statistical analyses performed by the Working Group].

3.1.2 Mouse

B6C3F₁ male and female mice received 2.5% or 5% of ethanol in drinking-water for 104 weeks. No significant difference in tumour incidence at any site was observed in females. There was a significant dose-related trend for the incidence of hepatocellular adenomas, and hepatocellular adenomas and carcinomas combined in male mice. The administration of 5% ethanol resulted in an increase in the incidence of hepatocellular adenomas ($P < 0.05$) and a marginal increase ($P = 0.056$) in the incidence of hepatocellular adenomas and carcinomas combined in male mice ([NTP, 2004](#); [Beland et al., 2005](#)).

ICR female mice received 10% ethanol in the drinking-water for 2 months and then 15% ethanol in the drinking-water for 23 months. Mammary gland tumours (papillary or medullary adenocarcinomas) were found in 9/20 mice given ethanol in drinking-water compared with 0/20 control mice [$P = 0.012$] ([Watabiki et al., 2000](#)).

C57BL/6^{APC^{min}} male mice received ethanol in drinking-water at doses between 15 and 20% daily for 10 weeks. This treatment increased intestinal adenoma multiplicity ([Roy et al., 2002](#)).

3.2 Oral administration of acetaldehyde in drinking-water

See [Table 3.2](#).

Acetaldehyde was evaluated in 1984 ([IARC, 1985](#)), 1998 ([IARC, 1999](#)), and 2007 ([IARC, 2010](#)).

3.2.1 Rat

Sprague-Dawley male and female rats received acetaldehyde in the drinking-water at doses of 50, 250, 500, 1500 and 2500 mg/L for 161 weeks. With the exception of male rats treated with 1500 mg/L, the administration of acetaldehyde to male Sprague-Dawley rats resulted in a marginal dose-dependent increase in incidence of pancreatic islet cell adenomas. The incidence of pancreatic islet cell adenoma was significantly higher (18%; 9/50) in male rats exposed to the high dose of acetaldehyde (2500 mg/L) compared to 4% (2/50) in the control group. Acetaldehyde caused an increased incidence of head osteosarcomas in the 50 and 2500 mg/L groups. Additionally, ingestion of acetaldehyde resulted in a higher incidence of lymphomas and leukemias in male rats exposed to acetaldehyde at doses of 50 mg/L and 1500 mg/L. Acetaldehyde also caused an increase in lymphomas and leukemias in female rats, 16% in rats exposed to 250 mg/mL compared to 4% in control animals. A higher incidence of mammary gland adenocarcinomas and uterine adenocarcinomas was found in the groups of females exposed to 500 mg/L and 250 mg/L, respectively ([Soffritti et al., 2002b](#)). [The Working Group noted that a variety of tumours were increased. However, no obvious dose–response relationship was observed.]

3.3 Co-carcinogenicity studies on alcohol administered in drinking-water

A comprehensive analysis of the studies on the co-carcinogenicity of ethanol was presented in the previous *IARC Monograph* ([IARC, 2010](#)). Simultaneous administration of alcohol with known carcinogens enhanced tumour development. A selection of positive studies is summarized below.

3.3.1 Rat

Chronic administration of ethanol potentiates the development of tumours in experimental animals induced by chemical agents.

Two groups of 80 Sprague-Dawley rats received either vinyl chloride or vinyl chloride and 5% ethanol in the drinking-water for 130 weeks. Increases in the incidence of liver carcinomas and liver angiosarcomas were observed in the vinyl chloride and ethanol group compared to the vinyl chloride treated control rats. In rats exposed to vinyl chloride and ethanol 15% developed pancreatic adenomas, whereas no tumours were found in control rats ([Radike et al., 1981](#)).

Fischer 344/DuCrj rats were fed 200 ppm 2-amino-3,8-dimethylimidazo[4,5]quinoxaline (MeIQx). After 8 weeks, rats were subdivided to receive either drinking-water or 0.1, 0.3, 1, 3, or 10% ethanol in the drinking-water. In rats administered MeIQx in the diet, the incidence of hepatocellular adenoma, carcinoma and adenoma plus carcinoma was increased by ethanol consumption in a dose-dependent manner ($P < 0.001$) ([Kushida et al., 2005](#)).

Chronic ethanol administration in drinking-water to male F344 rats for 55 weeks after treatment with the chemical carcinogens *N*'-nitroso-*N*-methyl-*N*-nitrosamine (NNN) or 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) increased the incidence of tumours of the oesophagus, oral cavity and

lungs. NNK also induced liver tumours, which were significantly increased by ethanol ingestion ([Nachiappan et al., 1994](#)). Similarly, administration of 5% ethanol to male Wistar rats enhanced the oesophageal tumourigenesis induced by *N*-nitrosomethylbenzylamine ([Tsutsumi et al., 2006](#)). The enhancing effect of ethanol on *N*-nitrosodiethylamine (NDEA)-induced oesophageal carcinogenesis was also observed in male Fischer 344 rats. Two groups of Fischer 344 rats received either 50 ppm NDEA dissolved in 10% ethanol or 50 ppm NDEA solution in water, respectively, for 8 weeks. Rats were maintained on tap water and basal diet for 96 weeks. The incidence of oesophageal papillomas or carcinomas in rats that received NDEA dissolved in 10% ethanol was higher than in rats that received NDEA alone ($P < 0.01$) ([Aze et al., 1993](#)).

Chronic intake of 10% ethanol for 56 weeks enhanced hepatocarcinogenesis induced by oral administration of combined ethinylestradiol and norethindrone acetate in male and especially female Wistar rats ([Yamagiwa et al., 1994](#)). Long-term ethanol treatment had a similar effect in male rats on liver preneoplastic lesions induced by aflatoxin B₁ ([Tanaka et al., 1989](#)), *N*-nitrosomorpholine ([Tatsuta et al., 1997](#)), MeIQx ([Wanibuchi et al., 2006](#)), and NDEA and 2-acetylaminofluorene ([Pires et al., 2008](#)).

The administration of ethanol (15% in the drinking-water) during the initiation and promotion stages of mammary gland carcinogenesis, induced by *N*-methyl-*N*-nitrosourea in female Sprague-Dawley rats, increased the number of mammary adenocarcinomas compared to control rats. Likewise, ethanol intake during the promotion stage resulted in a greater number of mammary adenocarcinomas ([Singletary et al., 1995](#)). The administration of ethyl alcohol to pregnant female Sprague-Dawley rats during gestation significantly increased mammary gland tumours induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) in offspring, as evidenced

Table 3.2 Carcinogenicity studies on acetaldehyde administered with drinking-water to rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours		Significance	Comments
Rat, Sprague-Dawley (M) 161 wk Soffritti et al. (2002b)	50 mg/L 7 d/wk 50 animals/group	Head	Osteosarcoma Control (0/50) Acetaldehyde (5/50)	$P < 0.05$	
	2500 mg/L 7 d/wk 50 animals/group	Head	Osteosarcoma Control (0/50) Acetaldehyde (7/50)	$P < 0.05$	
	50 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (6/50) Acetaldehyde (14/50)	$[P = 0.039]$	
	1500 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (6/50) Acetaldehyde (15/50)	$[P = 0.024]$	
	2500 mg/L 7 d/wk 50 animals/group	Pancreas	Islet cell adenoma Control (2/50) Acetaldehyde (9/50)	$[P = 0.026]$	
	250 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (2/50) Acetaldehyde (8/50)	$[P = 0.046]$	
	500 mg/L 7 d/wk 50 animals/group	Mammary gland	Adenocarcinoma Control (3/50) Acetaldehyde (10/50)	$[P = 0.036]$	
	250 mg/L 7 d/wk 50 animals/group	Uterus	Adenocarcinoma Control (0/50) Acetaldehyde (5/50)	$[P = 0.028]$	

d, day or days; F, female; M, male; wk, week or weeks

by a greater tumour multiplicity ([Hilakivi-Clarke et al., 2004](#)).

3.3.2 Mouse

Treatment of CF-1 male mice with 6% ethanol in the drinking-water increased development of invasive pancreatic adenocarcinoma induced by DMBA ([Wendt et al., 2007](#)).

As part of the study to investigate the effect of ethanol on the carcinogenicity of NDEA, strain A male mice were administered NDEA in the drinking-water with or without 10% ethanol for 4 weeks and were maintained thereafter for 32 weeks on tap-water and basal diet. Ethanol strongly potentiated the tumorigenic effect of NDEA in the forestomach and the lung ([Anderson et al., 1993](#)).

The effect of ethanol on the carcinogenicity of nitrosamines was comprehensively summarized in the previous *IARC Monographs* ([IARC, 1988, 2010](#)).

3.4 Synthesis

Administration of ethanol in the drinking-water increased the incidence of cancers of the head and neck and the liver, benign tumours of the adrenal glands, pituitary gland, testes, and pancreas, osteosarcomas of the head and other sites, forestomach tumours, and combined lymphomas and leukemias in rats and liver tumours and mammary gland adenocarcinomas in mice.

Administration of acetaldehyde in the drinking-water increased the incidence of pancreatic adenomas, combined lymphomas and leukaemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in rats.

Co-administration of ethanol in the drinking-water with several known carcinogens enhanced tumour development in rats and mice.

4. Other Relevant Data

The current knowledge on mechanistic and other data relevant to the carcinogenicity of alcoholic beverages was reported in the recent *IARC Monograph* ([IARC, 2010](#)). A synthesis of these data is presented below.

4.1 Absorption, distribution, metabolism and excretion

The biomedical effects of alcoholic beverages either originate from the properties of the ethanol major component, or from its metabolism. The metabolism of ethanol is depicted in Fig. 4.1. Ethanol is metabolized to acetaldehyde by three major pathways: the alcohol dehydrogenase (ADH) pathway, the microsomal ethanol oxidizing cytochrome P450 (CYP) pathway, and the catalase-H₂O₂ system. Acetaldehyde, to which many deleterious effects of ethanol can be attributed, is oxidized to acetate primarily by acetaldehyde dehydrogenases (ALDHs) ([Vasiliou et al., 2004](#)). The four pharmacokinetic parameters, absorption, distribution, metabolism and excretion, that define the level of ethanol and/or its metabolites in different tissues, are relevant for consideration.

4.1.1 Ethanol

(a) Absorption and distribution

The absorption of orally ingested alcohol starts in the upper digestive mucosa and the stomach, but the bulk is absorbed by simple diffusion in the small intestine into the bloodstream. Hereafter, alcohol is distributed into the body water. The absorption, immediately followed by the distribution phase, largely determines the ascending part and the peak of the blood-alcohol curve. Food in conjunction with alcohol drinking lowers the rate of absorption and diminishes the peak alcohol concentration, while fasting and dehydration create opposite effects. The distribution process produces slightly lower ethanol levels in venous blood ([Jones et al., 2004](#)) and urine ([Jones 2006](#)) compared with arterial blood levels during the absorption phase. More fat and less body water per unit body-mass create higher blood alcohol levels, which explains why women on average reach a 10–15% higher blood-alcohol concentration compared with the same amount of alcohol per body-mass ingested by men ([Goist & Sutker, 1985](#)).

(b) Metabolism and excretion

It is generally believed that more than 90% of the ingested alcohol is oxidized in the liver. The remaining extrahepatic alcohol oxidation and other modes of elimination take place in the gastrointestinal mucosa and bacteria, via oral bacteria, the kidneys and other peripheral tissues, by excretion of body fluids (urine and sweat) and via exhalation. First-pass metabolism, i.e. when the ethanol is oxidized at its first passage through the oral cavity, gut and liver, reduces the amount of ethanol that reaches target organs. The relative contribution of first-pass metabolism to alcohol oxidation is debatable ([Lim et al., 1993](#); [Levitt & Levitt, 2000](#)). However, the smaller the alcohol amount and the slower the alcohol absorption, the greater the relative contribution of first-pass

oxidation in overall alcohol elimination ([Levitt & Levitt, 1998](#)).

(i) *Endogenous alcohol formation*

In addition to ingestion via consumption of alcoholic beverages, small amounts of ethanol are also produced endogenously in normal intermediary metabolism ([Ostrovsky, 1986](#)) and by microbial formation, especially in the gastrointestinal tract ([Krebs & Perkins, 1970](#)). The resulting concentrations in human venous blood are estimated to vary between 0–50 μM ([Jones et al., 1983](#); [Watanabe-Suzuki et al., 1999](#)). Based on case reports ([Kaji et al., 1984](#); [Spinucci et al., 2006](#)) and on data from experimental animals ([Krebs & Perkins, 1970](#)), it has been shown that considerably higher concentrations exist in the gastrointestinal tract. The relevance of endogenous metabolism is further discussed in Section 4.3.1.

(ii) *Alcohol dehydrogenase pathway*

The oxidation of ethanol is largely catalysed by cytosolic ADHs, primarily by the low- K_m variants in the liver. Because of the low K_m (0.05–4.2 mM) ADH quickly becomes saturated and the reaction follows zero-order kinetics with a constant rate for ethanol oxidation. In addition to the enzyme activity, the ADH-mediated ethanol oxidation rate is strictly regulated by the mitochondrial reoxidation of the reduced co-enzyme nicotinamide adenine dinucleotide (NADH) to the oxidized form, nicotinamide adenine nucleotide (NAD^+) ([Zakhari, 2006](#)). This explains why, in spite of huge variations in ADH activity, relatively small effects on the overall alcohol oxidation rate have been observed. The impact of the hepatic redox state is even more apparent under fasting conditions, which are well known to slow down the rate of alcohol oxidation ([Rogers et al., 1987](#)), most likely due to limitations in the mitochondrial reoxidation of NADH ([Lisander et al., 2006](#)). The less alcohol is ingested the larger the

contribution of ADH activity in the regulation of the rate of alcohol oxidation (see Fig. 4.1).

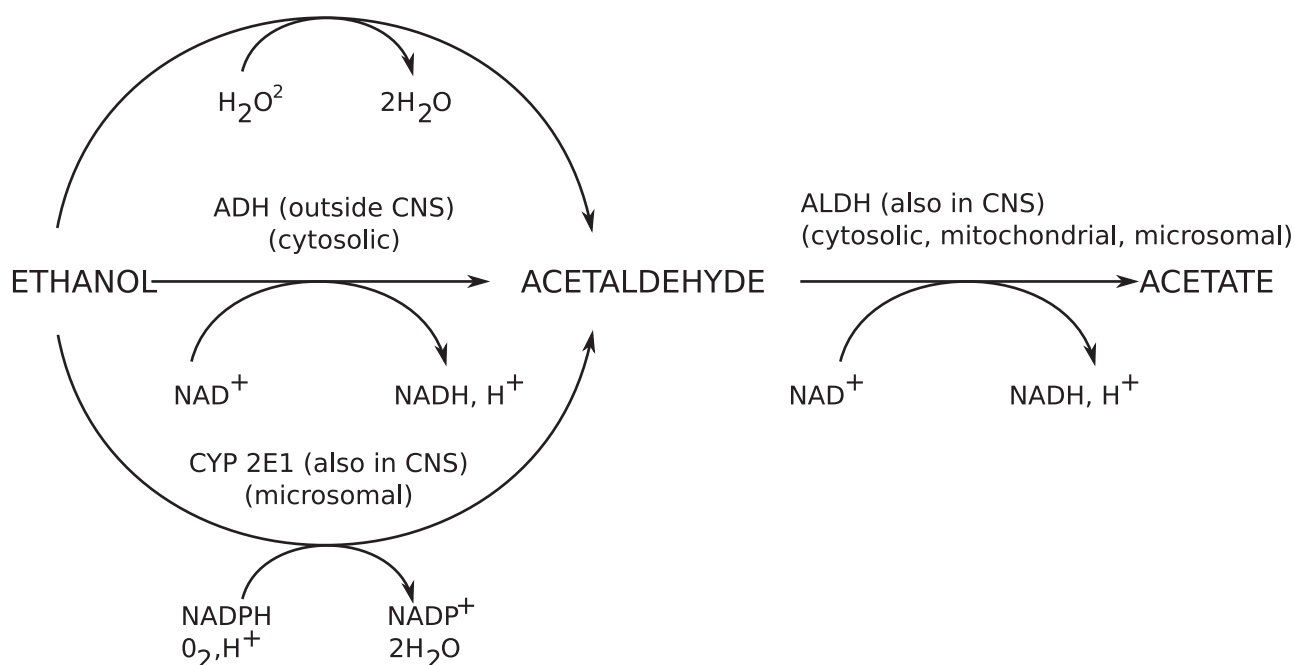
Human ADHs

Three different nomenclature systems have been proposed for the human ADH genes ([Table 4.1](#)). The official nomenclature approved by the Human Genome Organization (HUGO) (www.gene.ucl.ac.uk/nomenclature) will be used here throughout.

Seven human ADHs have been isolated that are divided into five classes on the basis on similarities in their amino acid sequences and kinetic properties ([Table 4.1](#)). They are dimeric enzymes consisting of two 40kDa subunits named α , β , γ , π , χ and either σ or μ . Class I comprises three enzymes: ADH1A, which contains at least one α subunit ($\alpha\alpha$, $\alpha\beta$, or $\alpha\gamma$), ADH1B ($\beta\beta$ or $\beta\gamma$), and ADH1C ($\gamma\gamma$). Class II contains ADH4 ($\pi\pi$). Class III contains ADH5 ($\chi\chi$). Class IV contains ADH7 ($\mu\mu$ or $\sigma\sigma$). Class V contains ADH6 for which there is no subunit designation ([Parkinson & Ogilvie, 2008](#)).

The low- K_m class I ADHs (α , β and γ subunits, formerly called ADH-1, -2, and -3) account for most of the ethanol-oxidizing capacity in the liver and gastrointestinal mucosa ([Lee et al., 2006](#)). Class I ADH is also expressed in several other tissues, such as the upper and lower digestive tracts ([Yin et al., 1993](#); [Seitz et al., 1996](#); [Yin et al., 1997](#); [Jelski et al., 2002](#)), pancreas ([Chiang et al., 2009](#)), lungs ([Engeland & Maret, 1993](#)), breast ([Triano et al., 2003](#)), blood vessels ([Jelski et al., 2009](#)) and salivary glands ([Visapää et al., 2004](#)). In brain no functionally significant class I ADH has been detected ([Estonius et al., 1996](#)).

Allelic variants have been identified in the *ADH1B* and *ADH1C* genes that encode for the β_1 , β_2 , β_3 , γ_1 , and γ_2 subunits, which can combine as homodimers or can form heterodimers with each other and with the α subunit. ADH1B enzymes that differ in the type of β subunit are known as allelozymes, as are ADH1C enzymes that differ in the type of γ subunit. Allelozymes

Fig. 4.1 Ethanol and acetaldehyde metabolism

ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP, cytochrome P450; CNS, central nervous system; NADPH, nicotinamide-adenine dinucleotide phosphate. Adapted from [Vasilou et al. \(2004\)](#).

present different kinetic properties ([Table 4.1](#)) and so differ in their capacity to oxidize ethanol. The allelozymes that are homodimers or heterodimers of $\beta 2$ subunit (encoded by the *ADH1B*2* allele) are especially active ethanol oxidizing enzymes. The *ADH1B*2* allelic variant is found in 90% of the Pacific Rim Asian population and is responsible for the unusually rapid conversion of ethanol to acetaldehyde in this population. *ADH1B*2* is also more common in people of Jewish origin compared to people of other Caucasian descent (where it is found in 0 to < 20%) ([Neumark et al. 1998](#)). The *ADH1B*1* allele is most common in Caucasians (up to 95%) and *ADH1B*3* is found mostly in African and African Americans (~24%). These population differences in *ADH1B* alloenzyme expression potentially contribute to ethnic differences in alcohol consumption and toxicity. Unlike the *ADH1B* allelozymes, the *ADH1C* variants do not

differ much in their ethanol oxidizing activities ([Parkinson & Ogilvie, 2008](#)).

The class II π -ADH (subunit encoded by *ADH4*) also contributes to hepatic ethanol oxidation, especially at higher concentrations ([Edenberg 2007](#); [Birley et al., 2009](#); [Kimura et al., 2009](#)). *ADH4* expression has been found in most epithelial tissues.

Little is known about the functional role of class III, IV and V ADHs (encoded by the genes *ADH5*, 7 and 6, respectively) in the oxidation of alcohol.

Microbial ADHs

There is a large population of microorganisms present in the gastrointestinal tract that may contribute to ethanol oxidation. Another local site for microbial alcohol oxidation is the oral cavity. Microorganisms express numerous forms of ADH, the role of which may become

Table 4.1 Major allele variants and biochemical properties of human alcohol dehydrogenases (ADHs)

Official nomenclature ^a	Former nomenclature ^b	Additional nonstandard nomenclature ^c	Sequence ^d	Allele	Amino Acid differences between alleles	Protein subunit	Class ^e	K _m (mM) ^f	V _{max} (min ⁻¹) ^g
ADH1A	ADH1		NM_000667	ADH1A		α	I	4.0	30
ADH1B	ADH2		NM_000668	ADH1B*1	Arg48, Arg370	β1	I	0.05	4
				ADH1B*2	His48, Arg370	β2	I	0.9	350
				ADH1B*3	Arg48, Cys370	β3	I	40	300
ADH1C	ADH3		NM_000669	ADH1C*1	Arg272, Ile350	γ1	I	1.0	90
				ADH1C*2	Gln212, Val350	γ2	I	0.6	40
				ADH1C*352Thr	^b Thr352	NR	I	NR	NR
ADH4	ADH4	ADH2	NM_000670	ADH4*1		π	II	30	40
				ADH4*2		π	II	NR	NR
ADH5	ADH5	ADH3	NM_000671			χ	III	> 1000	100
ADH6	ADH6	ADH5	NM_000672				V	NR	NR
ADH7	ADH7	ADH4	NM_000673			σ or μ	IV	30	1800

^a Nomenclature approved by the Human Genome Organization (HUGO) Gene Nomenclature Committee (www.gene.ucl.ac.uk/nomenclature/), as used by the National Center for Biotechnology Information (NCBI)

^b Former nomenclature

^c Non-standard nomenclature proposed by [Duester et al. \(1999\)](#)

^d Reference sequence number as listed in the NCBI RefSeq database (www.ncbi.nlm.nih.gov/RefSeq/)

^e ADH proteins have been divided into five classes based on sequence and structural similarities

^f V_{max} indicates how many molecules of ethanol the enzyme will convert to acetaldehyde in 1 minute at saturating ethanol concentrations.

^g K_m indicates the concentration of ethanol at which the enzyme works at 50 percent capacity.

^h *ADH1C*352Thr* has been found in Native Americans as an additional variation on chromosomes with the Val350 characteristics of *ADH1C*2* ([Osier et al. 2002](#)); the protein has not been isolated for study. The kinetic constants are noted for the homodimers of the ADH subunits listed (heterodimers behave as if the active sites were independent).

NR, not reported

Adapted from [Edenberg \(2007\)](#)

even more significant wherever microbial overgrowth occurs ([Salaspuro, 2003](#)).

(iii) Cytochrome P450 oxidation pathway

See Fig. 4.1.

Cytochrome P450 2E1 (CYP2E1) is constitutively expressed in the endoplasmic reticulum of the liver and many other tissues including the brain, in contrast to the expression of ADHs. Its K_m for ethanol is about 10 mM; thus CYP2E1 may assume a greater role in the first-order oxidation reaction at high blood-alcohol levels. Other cytochrome enzymes, CYP1A2 and CYP3A4, also contribute to the oxidation of ethanol, albeit to a lesser extent ([Lieber, 2004](#)). CYP2E1 has the unique property of being induced as a result of chronic alcohol intake, which explains part of the increased alcohol elimination rate after chronic alcohol ingestion ([Lieber, 2004](#)). The CYP2E1-mediated ethanol oxidation is associated with nicotinamide-adenine dinucleotide phosphate (NADPH)-CYP reductase in the endoplasmic reticulum, and reduces molecular oxygen to water as ethanol is oxidized to acetaldehyde. CYP2E1 is unusually 'leaky' and generates reactive oxygen species including hydroxyl radical, superoxide anion, hydrogen peroxide and hydroxyethyl radical. Thus, CYP2E1 is a major source of alcohol-related oxidative stress ([Caro & Cederbaum, 2004](#)).

Genetic variants of CYP2E1

Several allele variants of CYP2E1 have been described in humans (see [Table 4.2](#)).

The allele variant commonly denoted as c2, CYP2E1*5B according to the new recommended nomenclature, has been found more frequently in East Asian individuals (~40%) compared with Caucasians (~8%) ([Garte et al., 2001](#)). Early studies showed an increased CYP2E1 expression and activity in ethanol oxidation associated with the *5B allele ([Hayashi et al., 1991](#); [Tsutsumi et al., 1994](#); [Watanabe et al., 1994](#)), but this finding has not been confirmed in other studies ([Carrière](#)

[et al., 1996](#); [Kim et al., 1996](#); [Powell et al., 1998](#); [Kato et al., 2003](#)), and contrasting results have been reported ([Huang et al., 2003](#)). So it is unclear to what extent the functional activities regarding ethanol oxidation differ from those of the corresponding wild types. Other variants of CYP2E1 polymorphisms, such as CYP2E1*6, have also been shown to be more common in East Asians (ca. 52%) compared with Caucasian individuals (ca. 15%) ([Garte et al., 2001](#)).

(iv) Ethanol oxidation by catalase (Fig. 4.1)

Catalase is constitutively expressed in the peroxisomal part of the endoplasmic reticulum in virtually all tissues. It is an important antioxidant enzyme that detoxifies H_2O_2 into oxygen and water and thus limits the deleterious effects of reactive oxygen species. The functional role of catalase in the oxidation of ethanol in humans is not known. Although catalase-mediated ethanol oxidation is very limited compared with ADH-mediated reactions, it may play a significant role in specific organs and tissues that lack the functional ADH. Based on experimental animal research, catalase seems to contribute to alcohol oxidation in the brain ([Cohen et al., 1980](#); [Zimatkin et al., 2006](#)). As with CYP2E1, catalase also has a high K_m and, thus, the impact on alcohol oxidation would be higher at high alcohol levels. No functional polymorphism regarding alcohol oxidation or its effects has been reported.

(v) Non-oxidative ethanol metabolism

Ethanol can be non-oxidatively metabolized to form fatty-acid ethyl esters (FAEEs), which are toxic for cells ([Laposata & Lange, 1986](#); [Laposata et al., 2002](#)). These esters are formed during the hydrolysis of fatty-acid esters (e.g. triglycerides) in the presence of ethanol. Such esterification activity has been detected in humans mainly with the two high- K_m enzymes fatty-acid ethyl ester synthases (FAEEs) ([Wright et al., 1987](#)) and acyl-coenzyme A:ethanol O-acyltransferase (AEAT) ([Diczfalusy et al., 2001](#)). Highest activities have

Table 4.2 Major allelic variants and biochemical properties of humans cytochrome P450 2E1 (CYP2E1)

Recommended nomenclature ^a	Alternative nomenclature ^a	Protein	Nucleotide changes, Gene	RFLP	Effect	Enzyme activity	
						<i>In_vivo</i>	<i>In_vitro</i>
CYP2E1*1A	CYP2E1*1	CYP2E1.1	None			Normal	Normal
CYP2E1*1B	CYP2E1*2	CYP2E1.1	9896C > G	TaqI-			
CYP2E1*1C		CYP2E1.1	6 repeats in the 5' flanking region				
CYP2E1*1D		CYP2E1.1	8 repeats in the 5' flanking region	DraI and XbaI		Incr. activity after alcohol exposure and in obese subjects	
CYP2E1*2		CYP2E1.2	1132G > A		R76H		Reduced
CYP2E1*3		CYP2E1.3	10023G > A		V389I		Normal
CYP2E1*4		CYP2E1.4	4768G > A		V179I		Normal
CYP2E1*5A		CYP2E1.1	-1293G > C; -1053C > T (c1 > c2); 7632T > A	PstI+ RsaI- DraI-			
CYP2E1*5B	CYP2E1*3	CYP2E1.1	-1293G > C; -1053C > T (c1 > c2)	PstI+ RsaI- DraI-			
CYP2E1*6	CYP2E1*4	CYP2E1.1	7632T > A				
CYP2E1*7A		CYP2E1.1	-333T > A	DraI-			
CYP2E1*7B		CYP2E1.1	-71G > T; -333T > A				
CYP2E1*7C		CYP2E1.1	-333T > A; -352A > G				
not included	CYP2E1*5						
not included	CYP2E1*6						

^a Two different nomenclature systems were developed for the CYP2E1 alleles simultaneously. The authors of both nomenclature systems have agreed in July 2000 that the nomenclature system given in the first column should be the recommended one, see [Ingelman-Sundberg et al. \(2001\)](#); the other nomenclature that was proposed by [Garte & Crosti \(1999\)](#) is given in the second column.

RFLP, restriction fragment length polymorphism

Adapted from <http://www.cypalleles.ki.se/cyp2e1.htm>

been located in the liver and pancreas, and in the liver and duodenum, for FAEs and AEAT, respectively ([Diczfalussy et al., 2001](#)). Lower activities of both enzymes were found in heart, lung, adipose, gall bladder and gastric tissues. Although FAE may be important in the etiology of alcohol-mediated cellular toxicity, especially in the case of long-term accumulation during chronic alcohol intake, the relative contribution to overall alcohol elimination is rather small. In addition to FAEs, alcohol also forms other conjugates, such as ethyl glucuronide, often used as a marker for recent alcohol drinking ([Wurst et al., 2003](#)).

4.1.2 Acetaldehyde

Acetaldehyde is the first metabolite in the oxidation of ethanol (Fig. 4.1). Interindividual variations of the acetaldehyde-mediated effects will depend on the genetic polymorphisms and other factors affecting the metabolism and levels of acetaldehyde, and the effects on the target organs.

(a) Origin of acetaldehyde

(i) Endogenous formation

Several degradation reactions are known to form endogenous acetaldehyde in the human body ([Krebs & Perkins, 1970](#)). Without external alcohol ingestion, acetaldehyde concentrations are below the level of detection, except in the gastrointestinal tract ([Väkeväinen et al., 2000](#)). However, under conditions of inhibited acetaldehyde-oxidation capacity, endogenous acetaldehyde levels may be detected in the blood ([Eriksson, 1985](#)). The relevance of the endogenous acetaldehyde is further discussed in Section 4.3.1.

(ii) Acetaldehyde in alcoholic beverages

A small part of the total acetaldehyde to which the body is exposed comes directly from ingested alcoholic beverages. All alcoholic beverages

contain acetaldehyde in variable amounts: average levels in different types vary between 60 to > 7000 μM ([Lachenmeier & Sohnius, 2008](#)). The magnitude and the significance of exposure to acetaldehyde from alcoholic beverages are further discussed in Section 4.3.1.

(iii) Acetaldehyde formation by oxidation of exogenous ethanol

The major part of the total acetaldehyde to which the body is exposed during alcohol ingestion originates from ethanol oxidation catalysed by the ADH, CYP2E1 and catalase enzymes. The liver and the gut are the primary sites of acetaldehyde formation to such an extent that the rate of alcohol oxidation exceeds the rate of acetaldehyde breakdown, which consequently leads to diffusion of the surplus acetaldehyde into the bloodstream. Under normal conditions, i.e. without reduced capacity for acetaldehyde oxidation or considerably increased acetaldehyde formation, the acetaldehyde produced at other sites is usually directly oxidized within the tissue. The exception is the aerodigestive tract, where acetaldehyde is produced at least partly by microbial alcohol oxidation. Consequently, acetaldehyde can be detected both in breath and saliva during alcohol intoxication ([Eriksson, 2007](#)).

(b) Metabolism

The bulk of the acetaldehyde formed in the liver is directly oxidized by NAD^+ -dependent aldehyde dehydrogenases (ALDHs) to acetate. The efficacy of normal hepatic oxidation of the alcohol-derived acetaldehyde is estimated to be close to 99% ([Eriksson & Fukunaga, 1993](#)). In addition, a minor part of the acetaldehyde is probably oxidized by aldehyde oxidase and CYP2E1. In addition, acetaldehyde reacts with a variety of chemical compounds in the body.

(i) Aldehyde dehydrogenase pathway

Acetaldehyde is metabolized by ALDHs (Fig. 4.1), which are widely expressed in the mitochondria (low- K_m enzyme) and cytosol (high- K_m enzyme) of most tissues ([Crabb, 1995](#)). Oxidation of acetaldehyde is regulated by the rate of acetaldehyde formation, ALDH activity and the cytosolic and mitochondrial redox states. Ethanol consumption is not known to induce *ALDH* expression. Chronic alcohol abuse, especially associated with liver disease, has been reported to reduce the ALDH activity ([Nuutinen et al., 1983](#)).

The major allelic variants of human ALDHs, their respective K_m and their ethnical distribution are summarized in [Table 4.3](#). The high- K_m ALDH1A1 accounts for most of the acetaldehyde-oxidizing capacity in the cytosolic compartment of the liver and other tissues. This enzyme is also abundant in the erythrocytes. Several variant alleles of *ALDH1A1* with potential functional relevance have recently been reported in the promoter ([Spence et al., 2003](#)), intron and untranslated regions ([Lind et al., 2008](#)) ([Table 4.1](#)).

The low- K_m (about 5 μ M for acetaldehyde) ALDH2 is located in the mitochondria and is believed to be responsible for the bulk of the oxidation of the ethanol-derived acetaldehyde. This enzyme is not significantly expressed in the erythrocytes. Of all the polymorphisms in genes encoding enzymes that metabolize alcohol and acetaldehyde, the *ALDH2**2 allele has the greatest functional impact on the human phenotype. This allele is common in East-Asian populations, about 5–10% homozygotes and 30–40% heterozygotes ([Brennan et al., 2004](#)). In these individuals the acetaldehyde levels are elevated, which creates several toxic effects and also euphoric reinforcing reactions ([Eriksson, 2001](#)). The relevance of the elevated acetaldehyde for the development of cancers is discussed in section 4.3.1. In addition to the *2 allele, promoter-region

variants have been reported ([Harada et al., 1999](#)). The functional significance of these other variants remains to be established. The relevance of other ALDHs, including ALDH1B1 and other classes of ALDH, also remains to be elucidated.

(ii) Other pathways in the metabolism and reactions of acetaldehyde

In addition to the ALDH-catalysed reactions, acetaldehyde may also be oxidized to a minor extent by CYP2E1 ([Terelius et al., 1991](#)) and by different oxidases ([Deitrich et al., 2007](#)).

Due to its chemical reactivity, most, if not all, of the ethanol-derived acetaldehyde that is not further oxidized binds to a variety of constituents. These interactions vary between easily reversible and firm covalent bonds. Different kinds of Schiff's base, which are formed by acetaldehyde and the free amino groups of amino acids, peptides and proteins, are the most common products ([Eriksson & Fukunaga, 1993](#), [Niemelä, 2007](#)). Some of these unstable products become stable under reducing conditions, such as during alcohol intoxication. Although only a small fraction of all acetaldehyde formed during ethanol oxidation produces these adducts, they are important in some of the chronic toxic actions of alcohol. The role of the acetaldehyde adducts in the carcinogenic effects of alcohol is further discussed in Sections 4.2.2, 4.3.1 and 4.4.2.

(c) Levels of acetaldehyde in tissues

From the liver, where most of the ethanol-derived acetaldehyde is formed and oxidized, the remaining acetaldehyde, free and/or loosely bound, escapes into the *vena hepatica*, reaching concentrations of approximately 70 μ M under normal conditions ([Eriksson & Fukunaga, 1993](#)). Thereafter, the concentration of acetaldehyde in the blood will be diluted by the *vena cava* blood and further reduced by the circulation in the heart and the lungs before reaching peripheral tissues. Human data show that acetaldehyde levels in pulmonary arterial blood are in the

Table 4.3 Major allelic variants, biochemical properties, and ethnical distribution of human acetaldehyde dehydrogenases (ALDHs)

Gene Locus	Allele	Km μM^a	Ethnic/national distribution ^b	References
<i>ALDH1A1</i>		50	All	Vasiliou et al. (2000)
<i>ALDH2</i>	<i>ALDH2*1</i>	< 5	All	
	<i>ALDH2*2</i>		Asia	Crabb et al. (1989)
	<i>ALDH2*3</i>		Taiwan, People's Republic of China	Novoradovsky et al. (1995)
<i>ALDH1B1</i>	<i>ALDH1B1*1</i>	NR		
(<i>ALDH5</i>)	<i>ALDH1B1*2</i>	NR		Sherman et al. (1993)
<i>ALDH9A1</i>	<i>ALDH9A1*1</i>	30	All	Kurys et al. (1989)
	<i>ALDH9A1*2</i>			Lin (1996)

^a Kinetic constant of the enzyme when acetaldehyde is the substrate

^b The column labelled ethnic/national distribution indicates which populations have high allele frequencies for these variants. The alleles are not limited to those populations.

NR, not reported

Compiled by the Working Group

range of 0–4.4 μM , 30 and 60 minutes after ethanol consumption ([DeMaster et al., 1983](#)) during normal alcohol oxidation. Acetaldehyde in peripheral arterial or venous blood is below the limit of detection (< 1 μM) during normal alcohol intoxication in Caucasian male populations ([Eriksson & Fukunaga, 1993](#)). However, in Caucasian women, acetaldehyde levels of 1–8 μM have been detected during the use of oral contraceptives and during the high-estradiol phase of the normal cycle ([Eriksson et al., 1996](#)).

Except for the blood and the liver, in which acetaldehyde concentration should be approximately the same as in the *vena hepatica*, little is known about acetaldehyde levels in other tissues during normal alcohol oxidation in humans. Acetaldehyde levels should rise in tissues where the ethanol oxidation rate exceeds the capacity of acetaldehyde oxidation. Breath acetaldehyde concentrations of 10–20 and 20–40 nM at blood alcohol levels of about 10 and 20 mM, respectively, imply corresponding tissue acetaldehyde levels of 2–8 μM in the respiratory tract ([Jones, 1995](#); [Eriksson, 2007](#)). Part of this acetaldehyde is derived by microbial ethanol oxidation ([Pikkarainen et al., 1980](#)). Also, acetaldehyde levels in the saliva, which almost exclusively

are derived from microbiological alcohol oxidation, correlate positively with the blood alcohol concentration ([Väkeväinen et al., 2001](#); [Eriksson, 2007](#)). Levels varying between 15 to 25 μM and 20 to 40 μM at corresponding blood ethanol concentrations of 10 to 20 mM, respectively, have been reported ([Homann et al., 1997](#); [Eriksson, 2007](#)). The role of the acetaldehyde concentrations in the upper aerodigestive tract in the carcinogenic effects of alcohol is discussed in Section 4.3.1.

Under certain conditions, such as chronic alcohol consumption especially in combination with increased alcohol oxidation rate and/or liver disease and genetically determined deficiency in the ALDHs, acetaldehyde levels are considerably elevated. Peripheral venous blood acetaldehyde concentrations of 14 μM have been detected during alcohol intoxication (after a dose of 0.8 g per kg) in alcoholics ([Nuutinen et al., 1984](#)). In Asian subjects carrying the *ALDH2* allele, blood acetaldehyde levels above 200 μM have been reported ([Eriksson & Fukunaga, 1993](#)). In addition to *ALDH2* polymorphism, the *ADH1B*2* and *ADH1C*1* variant alleles, which encode more active ADHs, in turn may elevate ethanol-derived acetaldehyde levels. This possibility was suggested by [Visapää et al. \(2004\)](#) who

reported increased acetaldehyde concentrations in saliva of individuals with the *ADH1C*1/*1* genotype. The relevance of the *ALDH* and *ADH* genotypes for the etiology of cancer is further discussed in Section 4.3.1.

4.2 Genotoxicity

4.2.1 Humans

Studies of genotoxic effects of alcoholic beverages have been reviewed ([Obe & Anderson, 1987](#); [IARC, 1988, 2010](#)).

(a) Genotoxic effects in alcoholics

[Maffei et al. \(2000, 2002\)](#) and [Castelli et al. \(1999\)](#) found that alcoholics had significantly more chromosomal aberrations and cells with micronuclei than either non-drinking controls or abstinent alcoholics. The three groups were matched for age, sex and smoking ([Maffei et al., 2002](#)). When centromeric fluorescence in situ hybridization (FISH) was combined with the analysis of micronuclei, the alcoholics showed an increase in the number of lymphocytes with centromere-positive micronuclei, indicating an elevated formation of micronuclei harbouring whole chromosomes, ie, an aneugenic effect ([Maffei et al., 2000](#)). In a combined analysis of three biomonitoring studies, [Iarmarcovai et al. \(2007\)](#) observed a small but significant increase in micronucleus frequency in alcoholic beverage users compared with controls (OR, 1.24; 95%CI: 1.01–1.53).

While the majority of published studies showed no increase in chromosomal alterations in alcoholics following abstinence from ethanol compared to non-drinkers, some studies reported positive results ([De Torok, 1972](#); [Matsushima, 1987](#)). [Gattás & Saldanha \(1997\)](#) compared the frequency of structural or numerical chromosomal aberrations in lymphocytes of alcoholics who had been abstinent for 1 month to 32 years, with those in subjects not consuming alcoholic

beverages. They noted a significant increase in the frequency of cells with structural chromosomal aberrations in the abstinent alcoholics. [Burim et al. \(2004\)](#) observed that the frequencies of chromosomal aberrations in lymphocytes of 29 chronic alcoholics and 11 alcoholics in abstinence were higher than those in 10 control individuals. The level of chromosomal aberrations was not statistically significantly different when smoking and non-smoking alcoholics were compared, which indicated a lack of interaction.

There is some indication that ethanol may lead to chromosomal aneuploidy in human sperm. [Robbins et al. \(1997\)](#) used FISH of the sex chromosomes and chromosome 18 to investigate the potential contribution of common lifestyle exposures to aneuploidy load in sperm from 45 healthy male volunteers. Consumption of alcoholic beverages was significantly associated with increased frequencies of aneuploidy XX18, XY18–18 apparent diploidy, or XX18–18 duplication phenotype, after controlling for caffeine, smoking and donor age.

[Härkönen et al. \(1999\)](#) reported a significant negative association between alcohol intake and sperm aneuploid for chromosomes 1 and 7 (1-1-7 and 1-7-7 constitutions and diploid sperm) among 30 agricultural workers before pesticide exposures, while no statistically significant findings were related to alcohol intake after the exposure. [These inconclusive findings may reflect moderate alcohol consumption (average 6 drinks/week).]

In a case-control study [Kagan-Krieger et al. \(2002\)](#) found no association between self-reported paternal or maternal alcohol consumption and Turner syndrome in offspring.

[Pool-Zobel et al. \(2004\)](#) used the comet assay to study DNA damage and repair in human rectal cells obtained from biopsies and found that male alcoholic beverage abusers had significantly less DNA strand-breaks than male controls. This may be the result of an enhancing effect on endogenous defence, e.g. through upregulation of DNA

repair in response to damage. [Alternatively, a reduced amount of DNA in the comet tails could reflect DNA–protein crosslinks resulting from exposure to endogenous acetaldehyde.]

[van Zeeland *et al.* \(1999\)](#) and [Lodovici *et al.* \(2000\)](#) did not detect any increase in 8-hydroxydeoxyguanosine (8-OHdG) levels [measure of oxidative DNA damage] in leukocyte DNA in relation to alcoholic beverage consumption. In a multicentre study in Europe, [Bianchini *et al.* \(2001\)](#) observed an inverse relationship between alcoholic beverage consumption and levels of 8-OHdG in leukocyte DNA. However, an increased level of 8-OHdG in leukocyte DNA was observed in ALDH2-deficient subjects who consumed alcoholic beverages ([Nakajima *et al.*, 1996](#)).

[Frank *et al.* \(2004\)](#) reported a significant increase in 1,N⁶-ethenodeoxyadenosine DNA adducts in seven subjects diagnosed with alcoholic fatty liver and three diagnosed with alcoholic fibrosis. Patients with alcoholic fibrosis had a much higher level of these adducts than patients with alcoholic fatty liver. [No diagnostic criteria were provided for patients identified as ‘alcoholic’.]

[Wangetal. \(2009\)](#) observed that protein-bound 4-hydroxynonenal [a major lipid peroxidation product] and both 1,N⁶-ethenodeoxyadenosine and 3,N⁴-ethenodeoxycytidine DNA adducts strongly correlated with CYP2E1 expression in fine-needle liver biopsy samples obtained from 14 German patients with alcoholic liver disease ($r = 0.97$, $P < 0.01$). [The results support the assumption that, particularly in non-Asian populations, ethanol-mediated induction of hepatic CYP2E1, leading to highly miscoding DNA lesions derived from lipid peroxidation, may play a central role in hepatocarcinogenesis in patients with alcoholic liver disease.]

A statistically significantly higher frequency of sister chromatid exchange in lymphocytes was observed in Japanese subjects deficient in ALDH2 (at least one *2 allele) compared to those

who were proficient in ALDH2 (*1/*1 genotype) and drank alcohol almost daily; such an effect was not seen in subjects who drank less or did not drink at all ([Morimoto & Takeshita, 1996](#)).

(b) *Effects of polymorphisms for metabolic enzymes*

A significant difference in micronucleus frequency between the ALDH2*2 allele carriers and the individuals carrying the ALDH2*1/*1 genotype was found at all levels of alcohol consumption; the highest micronucleus levels were seen in the ALDH2*2 allele carriers consuming more than 100 g of alcohol per week and more than 3 times a week ([Ishikawa *et al.*, 2003](#)).

In non-smoking regular or occasional Japanese drinkers, the frequency of micronuclei was shown to be higher in ALDH2*2/*2 homozygotes versus ALDH2*2/*1 heterozygotes and in ADH1B*1/*1 homozygotes versus ADH1B*1/*2 heterozygotes. The highest micronucleus levels were seen in regular drinkers carrying both the ALDH2*2 and ADH1B*1 alleles. Nonetheless, due to the low number of subjects, a statistically significant increase of micronuclei was only seen for regular drinkers who carry the more common combination, i.e. ALDH2*2 and ADH1B*2 alleles ([Ishikawa *et al.*, 2007](#)).

Regular drinkers with the CYP2E1*1/*1 genotype showed a significantly higher micronucleus frequency than drinkers carrying the CYP2E1*3 allele; and drinkers with combined ALDH2*2 and CYP2E1*1/*1 genotypes showed the highest micronucleus frequency ([Ishikawa *et al.*, 2006](#)).

4.2.2 *Experimental systems*

(a) *Ethanol*

The genotoxic potential of ethanol has been extensively evaluated in lower organisms, plants, mammalian systems and in human cells, as reviewed previously ([IARC, 1988, 2010](#); [Phillips & Jenkinson, 2001](#)).

Ethanol gave negative results in bacterial mutagenicity tests, even in the presence of exogenous metabolic activation systems. These findings are consistent with the negative findings obtained with acetaldehyde, the primary *in vivo* metabolite of ethanol, in bacterial genotoxicity assays ([IARC, 2010](#)).

Positive results were reported for the induction of DNA strand breaks and chromosome malsegregation by ethanol in fungi and sister chromatid exchange in plants without exogenous metabolic activation. [These findings were obtained at very high concentrations (16000–39100 µg/ml) exceeding those usually recommended as the highest allowable concentrations in genotoxicity testing.]

In mammalian cells *in vitro*, ethanol was not usually able to produce gene mutations or chromosomal aberrations, but one study in mouse preimplantation embryos *in vitro* showed an induction of sister chromatid exchanges and chromosomal aberrations. In these experiments, sister chromatid exchange disappeared in the presence of 4-methylpyrazole, an inhibitor of alcohol dehydrogenase. This suggests that preimplantation embryos are able to convert ethanol to acetaldehyde.

A single study reported ethanol-induced DNA strand breaks in various types of human cells ([Blasiak et al., 2000](#)). The majority of studies showed no induction of chromosome damage by ethanol in human lymphocytes and lymphoblastoid cells *in vitro*. [The Working Group noted that in most of the *in vitro* genotoxicity studies, external metabolic activation systems were not used, which reduces the value of the negative findings.]

Ethanol induced micronuclei in human lymphoblastoid cells without external metabolic activation ([Kayani & Parry, 2010](#)). This effect appeared to be independent of acetaldehyde, since the micronuclei mostly contained whole chromosomes, while those induced by acetaldehyde harboured chromosomal fragments. Thus,

ethanol produced micronuclei *in vitro* by an aneugenic mechanism while acetaldehyde was clastogenic.

In animals *in vivo*, ethanol induced DNA adducts, DNA strand breaks, and sister chromatid exchanges and dominant lethal mutations. No effect of ethanol was seen in the micronucleus or chromosome aberration assays *in vivo*. In rats, exposure to ethanol increased mitochondrial DNA (mt DNA) oxidation and decreased the amount of mt DNA ([Cahill et al., 1997, 2005](#)). Several studies showed that the administration of ethanol to rats and mice leads to changes in the activity and amount of DNA-repair proteins in the liver ([Navasumrit et al., 2001a](#); [Bradford et al., 2005](#)).

The ethanol-induced DNA single-strand breaks in liver parenchymal cells of rat closely matched the timing of CYP2E1 induction and was inhibited by dietary antioxidants ([Navasumrit et al., 2000](#)). Ethanol also increased the level of the lipid peroxidation-derived DNA adduct, ethenodeoxycytidine in rats ([Navasumrit et al., 2001b](#)) and *N*²-ethyl-2'-desoxyguanosine (*N*²EtdG) adducts, not detectable in controls, were seen in liver DNA of ethanol-treated mice ([Fang & Vaca, 1995](#)). Rats and mice fed ethanol showed increased levels of oxidative DNA damage (abasic sites and 8-hydroxydeoxyguanosine) in the liver ([Bradford et al. 2005](#)); this effect was observed in transgenic mice that expressed human CYP2E1, but not in CYP2E1-knockout mice or in the presence of a CYP2E1 inhibitor. Increased levels of 1,*N*⁶-ethenodeoxyadenosine and 3,*N*⁴-ethenodeoxycytidine DNA adducts (measured by immunohistochemistry) were observed in the liver of ethanol-fed lean (Fa/Fa) and obese (fa/fa) Zucker rats ([Wang et al., 2009](#)). The number of hepatocyte nuclei that stained positively for these etheno-DNA adducts correlated significantly with CYP2E1 expression.

(b) Acetaldehyde

Numerous *in vitro* studies have consistently shown that acetaldehyde causes DNA–protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells *in vitro* (Speit *et al.*, 2008; Kayani & Parry, 2010; IARC, 2010). In comparison with other assays, the comet assay requires relatively high concentrations of acetaldehyde to show a positive result, probably reflecting the formation of crosslinks (Speit *et al.*, 2008).

Acetaldehyde induced also DNA protein crosslinks, sister chromatid exchanges, and chromosomal aberrations in rodents *in vivo* (IARC, 2010).

4.2.3 Genotoxicity of acetaldehyde

(a) DNA adduct formation

The structure of acetaldehyde-derived DNA adducts is depicted in Fig. 4.2.

(i) *N*²-Ethyl-2'-deoxyguanosine (*N*²EtdG)

The most abundant DNA adduct that results from the reaction of acetaldehyde is *N*²-ethylidenedeoxyguanosine (*N*²EtidG). This adduct is too unstable to be purified and isolated, but can be converted into the stable adduct *N*²EtdG, by treatment with a reducing agent (sodium cyanoborohydride). The reduction step can also be carried out by a mixture of GSH and ascorbic acid, which may occur *in vivo* (Fang & Vaca, 1995; Wang *et al.*, 2006c).

Fang & Vaca (1997) examined the levels of the *N*²EtdG adduct in a group of Swedish alcohol abusers compared to controls. They found that chronic alcoholics had higher levels of the *N*²EtdG adduct in both lymphocytes and granulocytes compared with controls. The levels of adduct found in both cell types were on the order of one lesion/10⁷ nucleotides. [The Working Group noted that the alcoholic subjects were also heavy smokers, whereas the control subjects were

not. However, the authors reported that *N*²EtdG levels were undetectable in the DNA sample from the one moderate smoker in the control group, and also stated that no adducts were detectable in samples obtained from five additional heavy smokers (> 20 cigarettes/week)].

Inclusion of a reducing agent (cyanoborohydride) in the DNA isolation and digestion solutions allowed *N*²EtidG to be converted quantitatively to *N*²EtdG. Wang *et al.* (2006c) concluded that *N*²EtidG is in fact an endogenous DNA adduct that is present in every animal and human liver DNA at levels in the range of 0.1 lesion/10⁶ normal nucleotides.

Balbo *et al.* (2008) measured the level of *N*²-EtdG in blood leukocyte DNA of two groups of subjects, one consisting of alcohol drinkers and abstainers and the other of heavy drinkers. A significant trend between *N*²-EtdG level and daily alcohol dose was found. In the first group, the mean level of *N*²-EtdG was significantly higher in drinkers (5270 ± 8770 fmol/μmol dG) than in non-drinkers (2690 ± 3040 fmol/μmol dG; *P* = 0.04) after adjusting for potential confounders. Taking into account the dose, the adduct level was higher in younger than older drinkers.

Matsuda *et al.* (1999) reported that detectable levels of *N*²EtdG were found in the urine of healthy Japanese individuals who had abstained from ethanol for at least 1 week. These authors proposed that the lesion resulted from endogenously formed acetaldehyde.

(ii) Other acetaldehyde-derived DNA adducts

In addition to the major adduct *N*²EtidG, three acetaldehyde-derived DNA adducts have been identified. These are: *N*²-(2,6-dimethyl-1,3-dioxan-4-yl) deoxyguanosine (*N*²-Dio-dG); an interstrand crosslink, and two diastereoisomers (R and S) of α-methyl-γ-hydroxy-1,*N*²-propanodeoxyguanosine (α-Me-γ-OH-PdG) (Wang *et al.*, 2000).

[Matsuda et al. \(2006\)](#) analysed the levels of acetaldehyde-derived DNA adducts in DNA samples from peripheral white blood cells of Japanese alcoholic beverage abusers with two different *ALDH2* genotypes: **1/*1* versus **1/*2*. The groups were matched by age, smoking and alcoholic beverage consumption. These authors developed very sensitive and specific liquid chromatograph–mass spectrometry assays for the DNA adducts: *N*²EtdG, α -Me- γ -OH-PdG (both R and S isomers) and *N*²-Dio-dG. The *N*²-Dio-dG adduct was not detected in any of the samples studied. Levels of the other three adducts were significantly higher in **1/*2* carriers than in **1/*1* genotypes.

The formation of the methyl-hydroxypropano-dG adducts can be facilitated by including basic amino acids, histones (which are rich in basic amino acids), or polyamines in the reaction mixture. In the presence of physiologically relevant polyamine concentrations, detectable amounts of these adducts were formed from concentrations as low as 100 μ M acetaldehyde ([Theruvathu et al., 2005](#)). Such concentrations are within the range of acetaldehyde concentrations formed in the saliva of human volunteers who drank alcoholic beverage in a laboratory setting ([Homann et al., 1997](#)). Finally, acetaldehyde can react with malondialdehyde, and the resulting conjugate can form DNA adducts *in vitro* ([Pluskota-Karwatka et al., 2006](#)).

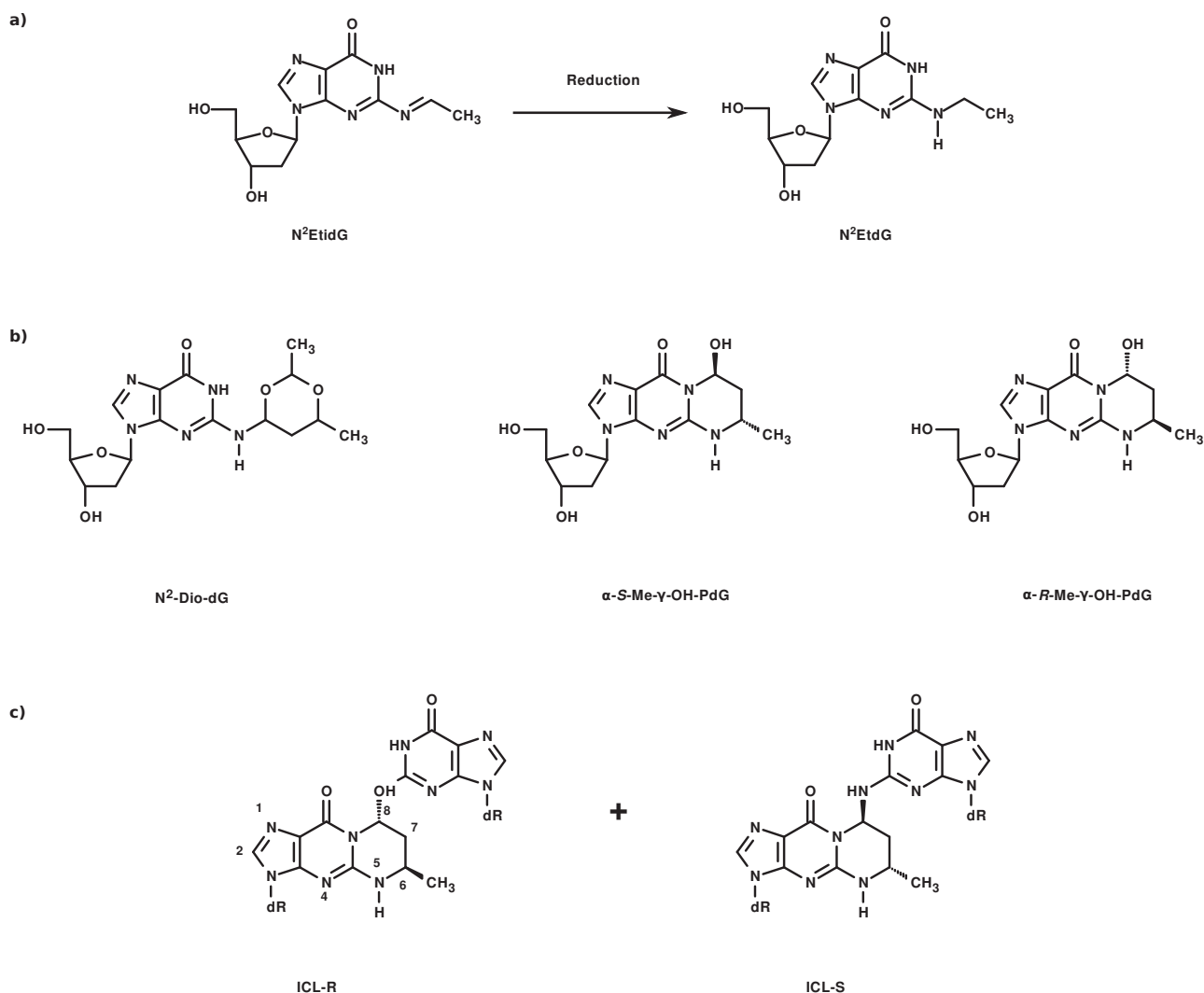
(b) *Mutagenicity of acetaldehyde-derived DNA adducts*

The mutagenic potential of DNA adducts can be tested with single-stranded DNA vectors that contain a single adduct located within a reporter gene. These constructs can then be transfected into cells, allowed to replicate and the resulting replication products analysed for mutations in various ways, depending on the specific nature of the reporter gene. Using such an approach, the *N*²EtdG adduct was only minimally mutagenic to the *supF* gene in the reporter plasmid

pLSX (mean mutant fraction, $0.9 \pm 0.2\%$ for the adduct-containing construct versus $0.4 \pm 0.2\%$ for the lesion-free control) when replicated in *E. coli* ($P = 0.09$). When deoxyuridines were placed on the complementary strand at 5' and 3' positions flanking the adduct, the mutant fractions increased to $1.4 \pm 0.5\%$ for the lesion versus $0.6 \pm 4\%$ for the control ($P = 0.04$) ([Upton et al., 2006](#)). The mutation spectrum generated by the *N*²EtdG adduct included mainly G to T transversions and single base deletions three bases downstream from the adduct. [This study was carried out with *N*²EtdG, whereas, *in vivo*, most probably *N*²EtidG is formed predominantly.]

Two separate studies have shown that methylhydroxypropano-dG adducts result in mutant fractions of 5–11% when inserted into a shuttle vector and replicated in either monkey kidney cells ([Fernandes et al., 2005](#)) or human xeroderma pigmentosum A (XPA) cells ([Stein et al., 2006](#)). In both cases, the predominant mutagenic event observed was a G to T transversion, but G to A and G to C mutations were also found. In comparison, the ethenodeoxyadenosine adduct resulted in mutant fractions as high as 70% in COS7 monkey kidney cells ([Pandya & Moriya, 1996](#)), but the mutant fraction was only 7–14% in human cells ([Levine et al., 2000](#)). [Methodological differences, differences in the host cells used or in the local sequence in the shuttle vectors may be responsible for the results.]

An important feature of the methylhydroxypropano-dG adducts, which is not shared by *N*²EtidG or *N*²EtdG, is that these adducts can undergo ring-opening when located in double-stranded DNA ([Mao et al., 1999](#)). The ring-opened forms of the methylhydroxypropano-dG adducts can react with proteins to generate DNA–protein crosslinks ([Kurtz & Lloyd, 2003](#)). With a deoxyguanosine residue in the opposite strand of the helix, a DNA-intrastrand crosslink can be formed ([Wang et al., 2000](#)). Intrastrand crosslinks generated in this manner are also mutagenic (mutant fraction 3–6%) in mammalian cells, generating

Fig. 4.2 Structure of acetaldehyde-derived DNA adducts

a) The immediate reaction of acetaldehyde with DNA is the unstable Schiff base adduct, N^2 -ethylidene-2-deoxyguanosine (N^2EtdG). This adduct is reduced into the more stable N^2 -ethyl-2-deoxyguanosine (N^2EtdG), the most abundant acetaldehyde-derived DNA adduct.

b) Three additional acetaldehyde-derived DNA adducts: N^2 -(2,6-dimethyl-1,3-dioxan-4-yl) deoxyguanosine ($\text{N}^2\text{-Dio-dG}$) and the two diastereoisomers (R and S) of α -methyl-8-hydroxy-1, N^2 -propanodeoxyguanosine ($\alpha\text{-Me-}\gamma\text{-OH-PdG}$).

c) Structure of R and S interstrand crosslinks (ICL-R) and (ICL-S).

Adapted from [Wang *et al.* \(2006c\)](#) and [Matsuda *et al.* \(2006\)](#).

primarily G to T transversions, as well as deletion and insertion mutations ([Liu et al., 2006](#)). [Matsuda et al. \(1998\)](#) exposed plasmid DNA that contains a *supF* mutation reporter gene to acetaldehyde concentrations up to 1M, and allowed the plasmid to replicate in human XPA cells, which are deficient in nucleotide excision repair. In contrast to the results for the methylhydroxypropano-dG adducts, these authors observed specific tandem GG to TT mutations. The DNA lesions responsible for these mutations are most probably not propano-dG adducts, but the intrastrand crosslinks.

4.3 Synthesis: Mechanistic considerations

Although alcoholic beverages may contain several potentially carcinogenic compounds, this synthesis focuses on the role of ethanol and acetaldehyde in the carcinogenesis associated with alcoholic beverages.

4.3.1 Ethanol-related mechanisms of carcinogenesis

The role of ethanol metabolism in tumour initiation is implied by the associations observed between different forms of cancer and polymorphisms in genes involved in the oxidation of ethanol. Whether, or to what degree, these associations are explained by redox changes, formation of radicals, effects on intermediary metabolism and/or effects on other pro-carcinogens cannot be established from current findings.

(a) Oxidative stress

Ethanol-induced CYP2E1 produces various reactive oxygen species, which lead to the formation of lipid peroxidation products such as 4-hydroxy-nonenal and the condition of oxidative stress. Chronic tissue inflammation and increased iron content exacerbate these actions. The increased reactive oxygen species

and oxidative stress, which damage the DNA and affect its repair, has been associated with ethanol-induced carcinogenesis in many organs, such as the breast, liver and pancreas.

(b) Cirrhosis

Ethanol causes hepatocellular injury that can lead to enhanced fibrogenesis and finally cirrhosis. Liver cirrhosis is strongly associated with an increased risk for developing hepatocellular carcinoma. Ethanol-related hepatocellular carcinoma without pre-existing cirrhosis is rare, which indicates that the pathogenic events that lead to cirrhosis precede those that cause cancer, or that the structural alterations in the liver during cirrhosis, together with other factors, favour the transformation of hepatocytes.

(c) Interaction between alcohol and tobacco smoking

This aspect is discussed in Section 4 of the *Monograph* on Tobacco Smoking in this Volume.

(d) Ethanol and sex hormones

Estrogens and androgens are well known activators of cellular proliferation, which is associated with an increased risk for carcinogenesis. Alcoholic beverage consumption in women causes an increase in the levels of estrogen and androgen, which has been suggested to contribute to the development of breast cancer. ADH-mediated alcohol oxidation, which increases the hepatic redox state, which in turn inhibits catabolism of sex steroids, has been suggested as the mechanism for the alcohol-mediated elevation in steroid levels.

(e) Folate metabolism and DNA methylation

Folate deficiency is associated with different forms of cancer, of which cancer of the colon is the most common. Ethanol per se, and an underlying unhealthy lifestyle associated with high alcoholic beverage consumption, cause

folate deficiency. Several studies have shown interactions between alcohol use and polymorphisms of genes involved in folate metabolism in determining the risk for colon cancer and other cancers. The degree to which the relation between alcohol drinking, folate deficiency and cancer may be explained by the metabolism of ethanol is not known.

Other postulated modes of action of ethanol relevant to its carcinogenicity, such as tumour promotion, induction of the formation of polyunsaturated fatty acids, overproduction of mitogen-activated protein kinases, and effects on vitamin A (retinol) or insulin-like growth factors have not been rigorously established by published studies.

4.3.2 *The role of acetaldehyde in alcohol-induced carcinogenesis*

Over the past decade, epidemiological evidence of enhanced cancer risks among heterozygous carriers of the inactive ALDH enzyme has become much stronger, in particular for oesophageal cancer: practically all studies conducted in East-Asian populations who consumed alcoholic beverages show significantly increased odds ratios for carriers of the inactive ALDH allele. In addition, several studies have demonstrated associations between the polymorphism of ADH1B and upper aerodigestive tract cancers, which have been explained either by more active ADH producing more acetaldehyde or by less active ADH causing prolonged exposure to lower levels of ethanol-derived acetaldehyde. These data imply that acetaldehyde is the key compound in the development of cancers of the oesophagus and other upper aerodigestive tract cancers associated with alcoholic beverage consumption. The considerations that support this suggestion are:

1. there is an established causal relationship between alcoholic beverage consumption

and cancers of the oesophagus, oral cavity, pharynx and larynx;

2. it is generally accepted that ethanol in alcoholic beverages is the principal ingredient that renders these beverages carcinogenic;
3. in the body, ethanol is converted by ADH and CYP2E1 to acetaldehyde, which is oxidized by ALDH to acetate;
4. the formation of acetaldehyde starts in the mouth, mediated mostly by oral bacteria, and continues along the digestive tract;
5. the main production of acetaldehyde occurs in the liver and in the gut. However, the highest levels of acetaldehyde after consumption of alcoholic beverages are found in the saliva of the oral cavity, which is in the vicinity of the target organ sites known to be susceptible to ethanol-induced cancer.
6. the upper digestive tract is also the site that is in first contact with the acetaldehyde content of the alcoholic beverages, which in turn are known to increase the salivary acetaldehyde levels;
7. acetaldehyde is a cytotoxic, genotoxic, mutagenic and clastogenic compound. It is carcinogenic in experimental animals;
8. after alcoholic beverage consumption, carriers of an inactive allele of the ALDH2 enzyme show accumulating levels of acetaldehyde in the peripheral blood, a direct consequence of their enzyme deficiency, and show increased levels of N^2 EtdG and methylhydroxypropano-dG adducts in lymphocyte DNA. The latter adducts have been shown to be formed from acetaldehyde; during DNA replication, these methylhydroxypropano-dG adducts cause mutations;
9. consumers of alcoholic beverages have a higher frequency of chromosomal aberrations, sister chromatid exchange and micronucleus formation in the peripheral lymphocytes than non-consumers. These effects may be attributable to acetaldehyde, which is a clastogen;
10. several of the observations made in ALDH2-deficient individuals have been confirmed in ALDH2-knockout mice.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of alcohol consumption. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma) and female breast. Also, an association has been observed between alcohol consumption and cancer of the pancreas.

For cancer of the kidney and non-Hodgkin lymphoma, there is *evidence suggesting lack of carcinogenicity*.

There is *sufficient evidence* in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages. Acetaldehyde associated with the consumption of alcoholic beverages causes cancers of the oesophagus and of upper aerodigestive tract combined.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethanol.

There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Alcohol consumption is *carcinogenic to humans (Group 1)*.

Ethanol in alcoholic beverages is *carcinogenic to humans (Group 1)*.

Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1)*.

In reaching the second and third evaluations, the Working Group took the following into consideration:

- The epidemiological evidence of the carcinogenicity of alcoholic beverage consumption shows little indication that the carcinogenic effects depend on the type of alcoholic beverage, with ethanol being the common ingredient.
- Upon ingestion of alcoholic beverages, ethanol is converted into acetaldehyde, which is then oxidized to acetate.

- Ethanol and acetaldehyde are both carcinogenic in experimental animals.
- There is sufficient epidemiological evidence showing that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for development of alcohol-related cancers, in particular of the oesophagus and the upper aerodigestive tract.

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CHINESE-STYLE SALTED FISH

Chinese-style salted fish was considered by a previous IARC Working Group in 1992 ([IARC, 1993](#)). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Mode of production

In southern China, about 20 different fish, such as red snapper, threadfin, Spanish mackerel, croaker, Japanese mackerel, are used to prepare salted fish ([Armstrong & Eng, 1983](#); [Poirier et al., 1987](#)). Procedures for preparation of salted fish have been described in detail previously ([IARC, 1993](#)). Briefly, salted fish are prepared by salting, brining, dry-salting, pickle curing, or a combination of these treatments. In brining, fish are placed in a solution of crude salt in water until the fish tissue has absorbed the required amount of salt. For dry-salting, fish are mixed with dry salt and the resultant brine (from dissolution of the salt in the water present in the fish) is allowed to drain away. When pickling or pickle curing the fish is mixed with salt and stored under the brine (pickle) formed when the salt dissolves in the water extracted from the fish.

In southern China, fish are generally not gutted before salting, and only when bigger fish such as red snapper are salted are the guts drawn out through the throat, without making an incision in the belly of the fish. Salting is done with crude salt in wooden vats. After a few days, the fish are immersed in brine and weights (often

large stones placed on top of grass mats) are placed on the surface to prevent the fish from floating, for one to five days. After this the fish are dried under the sun for one to seven days, depending on the size of the fish and the weather. Salted fish prepared in this way are called ‘tough’ or ‘hard meat’ salted fish. Sometimes, fish is allowed to soften by decomposition before salting, to produce ‘soft meat’ salted fish ([Poirier et al., 1989](#); [Yu et al., 1989a](#)). During drying salted fish, insect infestation can be a serious problem, especially in damp weather. In southern China, the average annual temperature and humidity are high and are favourable for the growth of bacteria such as *Staphylococci* ([Armstrong & Eng, 1983](#); [Zou et al., 1994](#)). Salted fish are stored for 4 to 5 months before being consumed.

1.2 Compounds present in salted fish

The previous *IARC Monograph* ([IARC, 1993](#)) reviewed levels of *N*-nitrosamines reported for uncooked salted fish obtained from different countries. The levels of *N*-nitrosodimethylamine in uncooked salted fish ranged from not detected to 388 µg/kg ([Poirier et al., 1989](#)). Some other volatile nitrosamines such as *N*-nitrosodiethylamine, *N*-nitrosopyrrolidine and *N*-nitrosopiperidine were also reported, their levels ranged between

not detected and about 30 µg/kg (Poirier *et al.*, 1989). Twenty samples of salted fish purchased in high- and low-risk areas for nasopharyngeal carcinoma (NPC) were analysed for four volatile *N*-nitrosamines; the highest levels of the sum of the four *N*-nitrosamines (373 µg/kg) were found in samples from the area with the highest NPC mortality (Zou *et al.*, 1992). Salted fish samples were also analysed for total *N*-nitroso compounds determined as the amount of nitric oxide (NO) released from the compounds after treatment with bromhydric acid (HBr) (Haorah *et al.*, 2001). Six types of dried salted fish purchased in the Fujian province of China, on the coast ~500 miles south of Shanghai, contained 3.9 ± 2.0 (range: 1.8–6.0) µmol/kg *N*-nitroso compounds. Upon steaming *N*-nitrosodiethylamine was detected in more samples than in uncooked or fried fish; *N*-nitrosodimethylamine was detected in all of the samples, whether cooked or uncooked (Huang *et al.*, 1981). The average levels of *N*-nitrosamines in steam-cooked salted fish collected from areas with high NPC mortality (1.51 ± 0.23 mg/kg) were significantly higher than those from areas with lower NPC mortality (0.60 ± 0.14 – 0.83 ± 0.18) (Zou *et al.*, 1994).

Fish are rich sources of secondary and tertiary amines, and nitrate and possibly nitrite occur in the crude salt used to pickle them. Steam-cooked, salted fish purchased in various areas in China have been found to contain nitrites (0.15 ± 0.24 mg/kg) and nitrates (6.54 ± 0.43 mg/kg) (Zou *et al.*, 1994). No differences were found in the levels of nitrites or nitrates between areas with different NPC mortality rates.

N-nitroso compounds, including *N*-nitrosamines, can form during the preparation of salted fish. Several factors may affect the levels of *N*-nitroso compounds, including levels of nitrites and nitrates in crude salt, those of nitrogen oxide in the air (when the preparation took place in open air), the growth of nitrate-reducing bacteria and pH. *N*-Nitroso compounds can also be formed after ingestion of foods by

chemical nitrosation under acidic conditions in the stomach (IARC, 2010).

Aqueous food extracts of 116 samples of salted fish from China were analysed for four volatile *N*-nitrosamines before and after strong acid-catalysed nitrosation *in vitro*. After nitrosation, *N*-nitrosodimethylamine levels were increased about 70-fold, while *N*-nitrosopiperidine levels were increased nearly 200-fold (Zou *et al.*, 1994). Six types of dried salted fish purchased in the Fujian province of China contained 6000 ± 3200 (range: 4200–12300) µmol/kg precursors of total *N*-nitroso compounds determined as the amount of NO released after HBr treatment (Haorah *et al.*, 2001). These results confirm that salted fish contains high concentrations of precursors of *N*-nitroso compounds.

1.3 Prevalence of use of Chinese-style salted fish

Chinese-style salted fish is popular in Chinese populations along the south China coast and South-eastern Asian countries, where it is often used as an accompaniment to other dishes or rice. Although the amount consumed at any one time is small (not more than 10 g), the dish may appear at every meal; some people prefer the spoiled parts (Fong & Chan, 1973). Salted fish mixed with rice has also been used as a traditional weaning food, and was often given to infants early and frequently in their life (Topley, 1973; Yu *et al.*, 1981, 1989b). In three studies, 6–53% of individuals reported use during weaning; use in the post-weaning period was slightly lower in each subsequent study (Yu *et al.*, 1986, 1988, 1989b).

Data on prevalence of use are mainly derived from studies on the association with NPC, but in most studies the type of salted fish is not specified. Prevalence of use varies significantly (Table 1.1); in southern Chinese populations 4 to 48% of the adult population have reported eating

Table 1.1 Prevalence of salted fish consumption once weekly or more in Chinese populations^a

Reference	Region or country	Data collection	Number of adult controls ^b	Consumption of salted fish	
				Childhood ^c	Adulthood
Armstrong & Eng (1983)	Malaysia	1980	100	[47%]	[20%]
Yu et al. (1986)	Hong Kong Special Administrative Region	1981–NR	250	[16%]	[8%]
Yu et al. (1988)	Guangxi, Southern China	1984–86	174	4%	NR
Yu et al. (1989b)	Guangzhou, Southern China	1983–85	304	47%	33%
Ning et al. (1990)	Tianjin, Northern China	1985–86	300	3%	NR
Zheng et al. (1994a)	Guangzhou, Southern China	1985–88	195	10%	1–3%
Lee et al. (1994)	Singapore	1988–90	369	16%	4%
Yuan et al. (2000)	Shanghai	1988–91	1032	NR	2%
Zou et al. (2000)	Yangjiang, Southern China	1987–95	192	NR	48%
Ward et al. (2000)	Taiwan, China	1991–94	327	NR	< 5%
			110	31%	NR
Yang et al. (2005)	Taiwan, China	1996–NR	1636	2%	NR
Guo et al. (2009)	Guangxi, Southern China	2004–05	758	NR	4%

^a Prevalence in the control groups from the studies

^b Number of controls with information on salted fish consumption

^c Age 10 years, except [Armstrong & Eng \(1983\)](#) ('Childhood'); [Zheng et al. \(1994a\)](#) (0–3 years). Childhood and adulthood population are the same but were asked their consumption at different time points.
NR, not reported

salted fish more than once weekly. Comparing earlier and later studies shows a decreasing trend in the prevalence of use. Consumption of salted fish in Chinese populations has been declining since the second half of the 20th century, and consumption in weaning and early childhood is now rare ([Zheng et al., 1994a](#); [Yu & Yuan, 2002](#)). Both cultural changes and other methods of preserving food may be responsible for the decrease.

2. Cancer in Humans

2.1 Nasopharyngeal carcinoma

2.1.1 Overview of studies

[Ho \(1967\)](#) estimated that the Tankas (boat people), who consumed Chinese-style salted fish in their daily diet, had twice the incidence

of nasopharyngeal carcinoma (NPC) compared with the land-dwelling Cantonese in Hong Kong Special Administrative Region. Subsequent studies demonstrated that the distinct pattern of NPC incidence among different ethnic or dialect groups in southern China coincided with the prevalence of their consumption of salted fish ([Ho, 1978](#); [Yu et al., 1981](#)), and that high incidence rates of NPC were retained in the Chinese who continued consuming salted fish after they migrated to Malaysia ([Armstrong et al., 1979](#); [Armstrong & Eng, 1983](#)). The peak in incidence rates at ages 45–54 years and decline thereafter suggested that the consumption of salted fish occurred early in life. [Salted fish mixed with soft rice was commonly fed to infants in the weaning and post-weaning period.]

Eight case–control studies on the association of salted fish with NPC, conducted between the 1970s and 1980s, were reviewed in the previous *IARC Monograph* ([IARC, 1993](#)) and are summarized

in Table 2.1 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-07-Table2.1.pdf>) (Henderson *et al.*, 1976; Henderson & Louie, 1978; Geser *et al.*, 1978; Armstrong & Eng, 1983; Yu *et al.*, 1986, 1988, 1989b; Ning *et al.*, 1990; Sriamporn *et al.*, 1992). All but one were conducted on Chinese subjects and consistently demonstrated that consumption of Chinese salted fish was associated with increased risk for NPC. There was a dose-dependent relationship between frequency and duration of consumption and NPC risk. The association was stronger for intake of salted fish during childhood up to 10 years of age compared with intake at older ages.

Since the publication of the previous IARC Monograph (IARC, 1993), an additional 11 case-control studies on the association of Chinese-style salted fish with NPC association have been published in English or Chinese-language articles, all but one in Chinese populations (see Table 2.1 on-line). No cohort studies have been performed. In six studies a significant association between salted fish and NPC was observed (Huang *et al.*, 1993; Zheng *et al.*, 1994a, b; Armstrong *et al.*, 1998; Zou *et al.*, 2000; Guo *et al.*, 2009), in two the association was of borderline significance (Yuan *et al.*, 2000; Yang *et al.*, 2005), while lack of an association was observed in three studies (West *et al.*, 1993; Lee *et al.*, 1994; Ward *et al.*, 2000). Two of the negative studies were performed in populations with a low consumption of Chinese-style salted fish (West *et al.*, 1993; Ward *et al.*, 2000). In the positive studies, the strongest association was seen for intake in early childhood and during weaning, while the association with adult consumption was weaker. Only modestly increased risks were found in the majority of studies, and in the three largest studies (with more than 500 cases), increased risks were only observed for the most exposed individuals.

There are several possible reasons for the smaller risk observed in more recent studies. First, the consumption of salted fish by Chinese

populations, especially feeding young children, has declined in parallel with economic development (Lee *et al.*, 1994; Zheng *et al.*, 1994b). While NPC incidence in certain areas of Southern China has remained stable in recent decades (Jia *et al.*, 2006), the incidence of NPC has declined significantly in Hong Kong Special Administrative Region and Singapore, and a preceding decrease in salted fish consumption may be a contributing factor (Yu & Yuan, 2002). Second, in recent decades the consumption of commercially produced salted fish and other preserved foods has increased and the consumption of home-preserved foods with possible higher nitrite and nitrosamine levels has declined (Ward *et al.*, 2000). Third, compared with later studies (Yuan *et al.*, 2000; Guo *et al.*, 2009; Yang *et al.*, 2005), the cases in some of the earlier studies were younger (Yu *et al.*, 1986, 1988). This is relevant as the effect of salted fish on the risk of NPC seems to be most pronounced in younger onset cases (Yang *et al.*, 2005).

2.1.2 Interaction with other risk factors

(a) Genetic risk factors

The involvement of a genetic factor in the development of NPC is likely and the familial risk of NPC in endemic areas is among the highest of any malignancy (IARC, 1997; Ung *et al.*, 1999) compared to those reported for other cancers (Goldgar *et al.*, 1994). Yang *et al.* (2005) found that the risk of NPC associated with salted fish consumption was strongest in families with three or more affected members in Taiwan, China; however, both genetic factors and shared environment could be responsible. In a study from Guangzhou comparing familial cases of NPC with sporadic cases, no significant differences in salted fish consumption between the two case groups were found (Luo *et al.*, 2009).

(b) Epstein-Barr virus

The association between Epstein-Barr virus (EBV) and undifferentiated NPC is firmly established and EBV is found in all tumour cells from NPC in endemic areas (Hjalgrim *et al.*, 2007). A synergistic effect between EBV and salted fish intake on the risk of NPC is suggested from a study where the association between salted fish and NPC was stronger in EBV VCA IgA positive individuals (Zheng *et al.*, 1994a). In a study of Caucasian NPC patients in the USA, intake of preserved meats with high levels of added nitrites increased the risk of undifferentiated NPC, while the risk of differentiated NPC was unaffected (Farrow *et al.*, 1998). In areas with low NPC incidence, undifferentiated, but not differentiated, NPC is associated with EBV (Hjalgrim *et al.*, 2007).

In studies attempting to control for EBV-infection status, the association between Chinese-style salted fish and NPC remained (Zheng *et al.*, 1994a; Guo *et al.*, 2009).

2.2 Cancer of the stomach

2.2.1 Overview of studies

A total of five case-control studies have investigated the association between Chinese-style salted fish and development of stomach cancer (Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-07-Table2.2.pdf>). Two of the studies were conducted in Southern Chinese populations (Ye *et al.*, 1998; Cai *et al.*, 2003), two studies in Northern Chinese populations (You *et al.*, 1988; Takezaki *et al.*, 2001a) and one study in Malaysia (33% of the controls were Chinese) (Goh *et al.*, 2007). In the two largest studies, with 564 and 272 cases, modest increased risks around 1.4–1.6 were found in the most exposed group (You *et al.*, 1988; Ye *et al.*, 1998). However, the amount of fish consumed in the study from Shandong was small (You *et al.*, 1988). Higher risks were found in two

of the smaller studies (Cai *et al.*, 2003; Goh *et al.*, 2007). A dose-response relationship was found in two smaller studies, with odds ratios ranging from 3.4 to 5.7 in the most exposed individuals (salted fish at least three times/week) (Takezaki *et al.*, 2001a; Cai *et al.*, 2003). Adjustments for smoking and alcohol were missing in two studies (You *et al.*, 1988; Ye *et al.*, 1998), while adjustment for *Helicobacter pylori* status was only performed in one study (Goh *et al.*, 2007).

An increased risk for stomach cancer associated with intake of highly salty foods has been observed in other populations (You *et al.*, 1988; Tsugane & Sasazuki, 2007).

2.2.2 Histology and topography

In the single study reporting histology, all cases were adenocarcinomas (Goh *et al.*, 2007). An equal effect of salted fish consumption was observed on cardia and non-cardia stomach cancer (Cai *et al.*, 2003).

2.2.3 Interactions

Interactions between salted fish consumption and other risk factors for stomach cancer have not been reported. The possible significance of early age at consumption and risk for stomach cancer has not been investigated. Growing evidence has associated EBV infection with a subset (5–10%) of all gastric carcinomas globally (Hjalgrim *et al.*, 2007). Analogous to nasopharyngeal carcinoma, the virus in EBV-positive gastric carcinomas is found in all tumour cells (Imai *et al.*, 1994), and EBV-antibodies are elevated in patients before diagnosis (Levine *et al.*, 1995). However, no studies have investigated the association between salted fish and EBV-positive gastric carcinomas. Nor has a possible interaction between salted fish intake and *Helicobacter pylori* infection been investigated.

2.3 Cancer of the oesophagus

Three studies have investigated the association between Chinese-style salted fish and cancer of the oesophagus (see Table 2.2 on-line). In Hong Kong Special Administrative Region, frequent consumption of salted fish, especially early in life, was associated with an increased risk for oesophageal cancer in univariate analyses, but was much weakened when alcohol and other confounders were taken into account ([Cheng *et al.*, 1992](#)). In a Northern Chinese population consumption of salted fish more than once weekly (the most exposed individuals) was associated with a non-significant 80% increased risk, and there was no significant trend ([Takezaki *et al.*, 2001a](#)). In a Southern Chinese population an increased risk for oesophageal cancer was associated with adult salted fish consumption in women, but not in men, and there was no dose–response relationship from both sexes combined ([Li *et al.*, 2001](#)). In the one study reporting histology, 85% of tumours were squamous cell carcinomas ([Cheng *et al.*, 1992](#)). Information on topography was not provided.

2.4 Other cancers

Consumption of salted fish in Chinese populations has also been associated with an increased risk for cancer of the lung ([Wang *et al.*, 1996](#); [Lu *et al.*, 2003](#)), brain ([Hu *et al.*, 1999](#)), and prostate ([Jian *et al.*, 2004](#)); no such association was seen for lung cancer in two studies in Japan ([Takezaki *et al.*, 2001b](#), [2003](#)). Studies at these sites are too sparse to allow for a systematic evaluation.

2.5 Synthesis

In all five case–control studies salted fish consumption in adulthood is associated with an increased risk for stomach cancer. However, the effect in the largest studies is modest, and adjustment for important confounding risk factors

(including smoking, alcohol and *Helicobacter pylori* status) were missing in several of the studies.

3. Cancer in Experimental Animals

Cantonese-style salted fish and salted fish extracts have been tested for carcinogenicity in three studies in rats and in one study in Syrian golden hamsters. Investigators administered specifically Cantonese-style salted fish to experimental animals ([Table 3.1](#)).

3.1 Oral administration

3.1.1 Rat

In one study, carcinomas of the nasal or paranasal regions developed in 4/10 [not significant] female rats fed steamed Cantonese-style salted fish for six months followed by extract of Cantonese-style salted fish heads as drinking-water for 1–2 years. No such tumours developed in similarly treated males (0/10) or in controls of either sex (0/3 and 0/3) ([Huang *et al.*, 1978](#)). [The working group noted the small number of animals.] In a larger study, malignant nasal cavity tumours of various kinds developed in male and female rats (4/148) fed Cantonese-style salted fish mixed in powdered diet for 18 months and observed until three years of age, but not in controls (0/73) ([Yu *et al.*, 1989a](#)).

Groups of 40–41 offspring (male and female) of rats were exposed to Cantonese-style salted fish mixed in the dams' diet during pregnancy and lactation and were themselves fed Cantonese-style salted fish mixed in diet after weaning for two years; 5 rats of both sexes developed malignant nasal and nasopharyngeal tumours of various kinds. Two offspring of rats exposed to control diet during pregnancy and lactation that were given Cantonese-style salted fish-containing diet after weaning also developed

Table 3.1 Carcinogenicity studies of oral administration of Cantonese-style salted fish in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Inbred WA albino (M, F) up to 24 mo Huang et al. (1978)	Steamed salted fish (30 g/d) for 6 mo, 5 d/wk, followed by salted fish soup (20 mL, 0.2 g fish/mL), 5 d/wk, for 1–2 yr 10 M, 10 F 3 M, 3 F (controls)	Adenocarcinoma of the nasal cavity: M–0/10 F–2/10 Undifferentiated carcinoma of the paranasal sinus: M–0/10 F–1/10 Highly invasive squamous carcinoma in the upper posterior part of the right buccalveolar sulcus: M–0/10 F–1/10 No nasal cavity tumours in controls (0/6)	NR [NS]	Small number of animals
Rat, Inbred Wistar-Kyoto (M, F) 3 yr Yu et al. (1989a)	Steamed Cantonese-style salted fish (48% soft- & 52% hard-type):rat chow, 1:3 or 1:5, for 18 mo Controls given rat chow only 36–37 F or 37 M	Undifferentiated carcinoma in the mid- and left portions of the nasal cavity: (M–1/37) high dose diet Moderately differentiated squamous cell carcinoma in the left lateral nasal cavity: (F–1/37) high dose diet Spindle cell carcinoma in the left lateral nasal cavity: (F–1/37) high dose diet Spindle cell tumour in the left posterior nasal cavity: (M–1/37) low dose diet No tumours in 73 controls	NS	Positive (one sided $P = 0.02$), 4/148 vs historical controls.
Rat, Sprague-Dawley (M, F) 2 yr Zheng et al. (1994c)	Steamed & dried Cantonese-style salted fish (50% soft- & 50% hard-type), 0, 5 or 10% in the diet 40–41 M, F Pregnant rats fed 10% salted fish, 41 new born rats fed 10% salted fish (Group 1) Pregnant rats fed control pellets, 41 new born rats fed 10% salted fish (Group 2) Pregnant rats fed 5% salted fish, 40 new born rats fed 5% salted fish (Group 3) 40 untreated controls	One squamous cell carcinoma (M) and 1 poorly differentiated carcinoma (F) of the nasopharynx; 1 adenocarcinoma (F) and 1 fibrosarcoma (M) of the nasal cavity One squamous cell carcinoma (M) of the nasopharynx and 1 rhabdomyosarcoma (F) of the nasal cavity One soft tissue sarcoma (F) of the nasal cavity No nasal cavity or nasopharyngeal tumours in controls	Positive (P for trend = 0.041)	Positive, 7/122 vs historical controls (one tailed, $P = 0.004$)

d, day or days; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; vs, versus; wk, week or weeks; yr, year or years

malignant nasal or nasopharyngeal tumours. No nasal or nasopharyngeal tumours were found in control offspring born to untreated dams and fed regular pelleted diet throughout life ([Zheng et al., 1994c](#)).

3.1.2 Hamster

No nasal or paranasal tumours were observed in eight male and six female Syrian golden hamsters fed steamed Cantonese-style salted fish for six months and then an extract of Cantonese-style salted fish heads as drinking-water five times per week for 1–2 years ([Huang et al., 1978](#)).

3.2 Synthesis

In three studies in rats fed Cantonese-style salted fish, there was a consistent increased frequency of nasal cavity tumours, which are uncommon neoplasms in rats.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

No data were available to the Working Group.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

The genotoxicity and mutagenicity of Chinese-style salted fish in experimental systems has been reviewed in detail ([IARC, 1993](#)).

(a) Genotoxicity and mutagenicity in bacteria

DMSO extracts of 4 samples of different species of salted fish and 2 samples of dried shrimps were mutagenic in *Salmonella typhimurium* TA 100 and TA 98 in the presence of a metabolic activation system ([Fong et al., 1979](#)). However, n-hexane and ethyl acetate extracts of hard and soft salted dried fish samples obtained in a high risk area for NPC in China were not mutagenic in *S. typhimurium* TA 100 and TA 98 in the absence or presence of rat liver metabolic activation system. Nevertheless, these salted fish samples contained high levels of precursors that upon nitrosation *in vitro* with sodium nitrite under acidic conditions yielded directly-acting genotoxic (probably N-nitroso) compounds ([Tannenbaum et al., 1985](#); [Poirier et al., 1989](#)). Mutagenicity on *S. typhimurium* TA 100 of salted fish obtained from Hong Kong Special Administrative Region increased with increasing nitrite concentration ([Weng et al., 1992](#)).

In one study, urine samples collected from WA rats fed Chinese-style salted fish showed mutagenic activity on *S. typhimurium* TA 100 and TA 98 ([Fong et al., 1979](#)).

(b) Genotoxicity and mutagenicity in experimental animals

(i) DNA adduct

In one study, the levels of 7-methylguanine in the liver and nasopharynx of rats fed 5% or 10% steamed and dried Chinese-style salted fish were analysed by a post-labelling method. There was no significant difference in adduct levels between exposed and control animals, the levels ranging between 3.2–1.2 and 3.3–1.4 per 10⁷ nucleotides, respectively ([Widlak et al., 1995](#)).

(ii) EBV-activation activity

Aqueous extracts of Cantonese-style salted dried fish from China showed a strong activity in EBV reactivation when assayed in Raji cells ([Shao et al., 1988](#)). EBV-reactivation activity was

decreased or showed no change after chemical nitrosation, but it was not correlated with the genotoxicity or nitrosamine levels of the samples ([Poirier et al., 1989](#)).

4.3 Mechanistic considerations

The mechanisms by which consumption of Cantonese-style salted fish induces NPC remain unresolved.

NPC has been classified into three histologic types: keratinizing squamous cell carcinoma (class I), nonkeratinizing carcinoma (class II) and basaloid squamous-cell carcinoma (class III) ([Chan et al., 2005](#)). Distinct etiological factors could be responsible for the three types of NPC. In high incidence areas such as southern China, 99% of NPC are class II whereas class I NPC is predominant in low-incidence regions. The etiological factors of NPC in high incidence areas include EBV, environmental risk factors and genetic susceptibility.

EBV has been classified as a Group 1 carcinogen by IARC, based on sufficient evidence for its carcinogenicity in humans, namely for NPC ([IARC, 1997, 2012](#)). EBV infects primarily B lymphocytes, but also epithelial cells such as oropharyngeal cells, essentially in the lymphoepithelium of the palatine tonsils from Waldeyers ring. The etiological association of NPC with EBV was first suggested on the basis of serological evidence ([Old et al., 1966](#)). Circulating cell-free EBV DNA is detected in the plasma and serum of NPC patients, but not in healthy individuals, and its levels are positively correlated with disease stage and prognosis ([Lin et al., 2004](#)). EBV DNA, RNA and gene products are also present in most tumour cells ([zur Hausen et al., 1970](#)). EBV is detected in cancer cells of virtually all cases of class II NPC in endemic regions. In addition, NPC tumour cells were shown to be clonal expansions of a single EBV-infected progenitor cell ([Raab-Traub & Flynn, 1986](#)). EBV infection alone is, however, not a sufficient

cause of NPC: the ubiquitous EBV infects and persists latently in over 90% of the world population, yet only a small proportion of individuals develop NPC. Although there is little variation in the prevalence of infection or the age at primary infection with EBV throughout China, risk for NPC is more than 20-fold higher in three provinces in southern China ([Zeng, 1985](#)). Therefore environmental and/or genetic factors may also contribute to NPC risk.

On the basis of studies on the natural history of NPC from southern Chinese populations, the following pathogenesis model for NPC has been proposed ([Lo & Huang, 2002](#); [Young & Rickinson, 2004](#)). Clonal cell proliferation with 3p and 9p deletion is frequently detected in dysplastic lesions and even in histologically normal nasopharyngeal epithelia in the absence of EBV infection; loss of heterozygosity (LOH) appear to be an early event in the pathogenesis of NPC in this high-risk area (allelic loss may confer growth advantage and cells may expand to form multiple clonal population within the nasopharynx). These genetic events could result from the consumption of Cantonese-style salted fish and other traditional foods. Samples of Chinese-style salted fish contain high concentrations of several *N*-nitrosamines and their precursors such as *N*-nitrosodimethylamine, *N*-nitrosodiethylamine, *N*-nitrosopyrrolidine and *N*-nitrosopiperidine (see Section 1.2) which were all shown to be carcinogenic in animals ([IARC, 1978, 1993](#); [Tricker & Preussmann, 1991](#)). In addition, increased formation of *N*-nitrosamines occurs after endogenous chemical nitrosation of salted fish with nitrite under acidic conditions (see Section 1.2). *N*-nitrosamino acids excreted in the urine were shown to be increased in subjects living in the high-risk areas of NPC in southern China, compared to those living in the low-risk areas ([Yi et al., 1993](#)). These results suggest exposure to carcinogenic *N*-nitroso compounds, preformed in salted fish or formed endogenously by nitrosation of their precursors.

Polymorphisms in *cytochrome P450* (CYP) 2E1 (CYP2E1) (Hildesheim *et al.*, 1995, 1997; Kongruttanachok *et al.*, 2001) and CYP2A6 (Tiawach *et al.*, 2006) and the absence of *glutathione-S-transferase M1* (GSTM1) and/or GSTT1 (Guo *et al.*, 2008; Zhuo *et al.*, 2009) have been associated with increased risk of NPC in Southern China. Polymorphisms in genes encoding for enzymes involved in *N*-nitrosamine metabolism and detoxification could affect carcinogenesis but exact mechanisms have not been elucidated.

Aqueous extracts of Cantonese-style salted dried fish from China can activate EBV-reactivation (Shao *et al.*, 1988). This is important, since EBV can persist benignly in the body unless it is reactivated. Active EBV can induce many different cellular processes that may lead to carcinogenesis (IARC, 2012). It can for instance, induce genomic instability (Fang *et al.*, 2009) and activation of the NADPH oxidase (Gruhne *et al.*, 2009) and increased expression of inducible nitric oxide synthase (Yu *et al.*, 2002). These enzymes produce reactive oxygen and nitrogen species that damage DNA through formation of 8-oxo-deoxyguanosine and 8-nitroguanine in NPC (Ma *et al.*, 2008; Segawa *et al.*, 2008; Gruhne *et al.*, 2009). Increased lipid peroxidation product (malondialdehyde) was also detected in the blood of NPC patients (Gargouri *et al.*, 2009). These findings indicate that reactivation by Chinese-style salted fish of latent EBV in infected cells may play a substantial role in NPC, by promoting genomic instability via induction of oxidative and nitrative DNA damage. Interestingly, epidemiological data showed that both EBV and Chinese-style salted fish are also associated with gastric carcinoma.

4.4 Synthesis

Possible mechanisms for the association of consumption of Cantonese-style salted fish with risk of NPC are the formation endogenously of

N-nitroso compounds in the human body and/or their formation due to the processing of the fish — i.e. a reaction between secondary and tertiary amines in the fish and nitrate/nitrite in the crude salt used — and activation of the oncogenic Epstein-Barr virus. These two mechanisms are not mutually exclusive.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of Chinese-style salted fish. Chinese-style salted fish causes cancer of the nasopharynx. Also, a positive association has been observed between consumption of Chinese-style salted fish and cancer of the stomach.

There is *sufficient evidence* in experimental animals for the carcinogenicity of Cantonese-style salted fish.

Chinese-style salted fish *is carcinogenic to humans* (Group 1).

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INDOOR EMISSIONS FROM HOUSEHOLD COMBUSTION OF COAL

Indoor combustion of coal was considered by a previous IARC Working Group in 2006 ([IARC, 2010a](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Constituents of coal emissions from household use of coal

1.1.1 Types and forms of coal

Coal is a highly variable fuel, which ranges from high heating-value anthracite through various forms of bituminous coal to intermediates in coal formation, viz. lignite and peat. Each of these types of fuel can contain different levels of moisture, non-combustible inorganic material (ash), sulfur, and sometimes significant levels of other impurities, e.g. arsenic, fluorine, lead and mercury.

Raw coal may be used in many forms, from lumps and briquettes to fine powders. Processing of coal may be as simple as forming coal balls or cakes by hand followed by sun-drying, or it may be a sophisticated procedure, blending coal into a uniform mixture with binders to reduce sulfur and particulate emissions and formed into briquettes designed to burn efficiently and cleanly in special stoves.

1.1.2 Constituents of coal emissions

When using small and simple combustion devices such as household cooking and heating stoves, coals are difficult to burn without substantial emission of pollutants principally due to the difficulty of completely pre-mixing the fuel and air during burning. Consequently, a substantial fraction of the fuel carbon is converted to products of incomplete combustion. For example, typical household coal stoves in China and India divert between more than 10% and up to ~30% of their fuel carbon into products of incomplete combustion ([Smith et al., 2000](#); [Zhang et al., 2000a](#)).

The products that are formed can be present in the gas phase, the particle phase, or both, depending on their volatility. Hence, they represent a complex mixture of particulate and gaseous chemical species, including carbon monoxide, nitrogen dioxide and particulate matter (PM). Products of incomplete combustion include polycyclic aromatic hydrocarbons (PAHs) and a large number of compounds that are precursor components of photochemical smog, such as aldehydes ([Chuang et al., 1992a](#); [Tsai et al., 2003](#)). In addition, many types of coal contain intrinsic

contaminants from their mineral deposits, such as sulfur, arsenic, silica, fluorine, lead or mercury. During combustion, these contaminants are released into the air in their original or oxidized form. In households that use sulfur-rich coals, for example, sulfur dioxide is present at elevated levels. The high temperature of coal combustion leads to emission of large amounts of nitrogen oxides ([Zhang et al., 2000a](#)).

The chemical constituents of coal emissions have been reported as individual chemical compounds (e.g. carbon monoxide, benzene, formaldehyde, PAHs), groups of compounds (e.g. total non-methane hydrocarbon, total organic carbon), elements (e.g. carbon, arsenic), or ions (e.g. fluoride, sulfate) ([IARC, 2010a](#)). The constituents identified to date are summarized in [Table 1.1](#) by compound class, element and ion, respectively. Selected chemicals that are associated with carcinogenicity are discussed below.

(a) *Particles and particle components*

Particles emitted from coal combustion are fine and ultra-fine in size (well below 1 μm in diameter) ([Kleeman et al., 1999](#); [Hays et al., 2002](#)). Fresh coal emissions contain a large number of ultra-fine particles that condense rapidly as they cool and age. The emissions may include larger particles resulting from suspension of ash and solid fuel debris. Combustion-generated particles and ash/debris particles have different chemical composition and particle size. For this reason, there has been a switch in recent studies from measuring total suspended particles (TSP) to measuring inhalable particles ($< 10 \mu\text{m}$, referred to as PM_{10}) or respirable particles ($< 2.5 \mu\text{m}$, referred to as $\text{PM}_{2.5}$).

A large number of chemical species are found in combustion-generated particles and many of these are not stable ([Rogge et al., 1998](#)). Elemental carbon has a characteristic core onto which many metals and organic compounds can be readily adsorbed or absorbed.

Earlier studies also focused on different solvent extracts of particles (soot) emitted from coal combustion. For example, in Xuanwei County, China, particles released from smoky-coal combustion contained the highest amount of organic compounds extractable with dichloromethane, followed by particles released from anthracite (smokeless) coal combustion ([Mumford et al., 1987](#)). Some particles carry stabilized free radicals ([Tian, 2005](#)).

Analytical techniques such as ion chromatography can measure chemicals in the extracts of combustion particles in their dissociated form (ions). The most abundant commonly identified ions in coal emissions are shown in [Table 1.1](#).

(b) *PAHs and substituted PAHs*

Polycyclic aromatic hydrocarbons are formed during incomplete combustion of all carbon-based fuels and organic materials, including coal. At typical ambient temperature, lower molecular-weight PAHs (with 2–4 aromatic rings) are present predominantly in the gas phase while higher molecular-weight PAHs are present predominantly in the particle phase. Because PAHs of higher cancer potency are predominantly present in the particle phase ([IARC, 2010a](#)), combustion particles have often been subject to compositional analysis for PAHs and PAH derivatives. A detailed analysis of PAHs in dichloromethane extracts of soot deposits from coal-burning stoves in several homes of Hunan Province, China, has identified 32 individual PAHs ranging in size from three to eight fused aromatic rings. The PAHs found in the soot deposits included 20 benzenoid PAHs, six fluoranthene benzologues, one cyclopenta-fused PAH, one indene benzologue, three oxygenated PAHs and one ring-sulfur-containing aromatic compound ([Table 1.1](#); [Wornat et al., 2001](#)). Carcinogenic PAHs, methylated PAHs and nitrogen-containing heterocyclic aromatics were detected in the particles emitted from smoky coal combustion, as typically found

Table 1.1 Constituents of coal emissions, by chemical class

Compound	Species
Inorganic compounds	CO, SO ₂ , NO _x
Hydrocarbons	
Alkanes	C ₁ –C ₁₀
Alkenes	C ₂ –C ₁₀ (including 1,3-butadiene)
Aromatics	Benzene, Xylene, Toluene, Styrene
PAHs and substituted PAHs	Acenaphthene Acenaphthylene Acephenanthrylene Anthracene Benz[a]anthracene Benzanthrone Benzo[b]chrysene Benzo[a]coronene Benzo[b]fluoranthene Benzo[k]fluoranthene Benzo[b+j+k]fluorene Benzo[a]fluorine Benzo[b]naphtha[2,1-d]thiophene Benzo[pqr]naphtha[8,1,2-bcd]perylene Benzo[ghi]perylene Benzo[a]pyrene Benzo[e]pyrene Chrysene Coronene Cyclopenta[def]chrysene-4-one Cyclopent[hi]acephenanthrylene Cyclopenta[cd]benzo[ghi]perylene Cyclopenta[bc]coronene Cyclopenta[cd]fluoranthrene Cyclopenta[cd]pyrene Dibenz[a,c]anthracene Dibenz[a,h]anthracene Dibenz[a,j]anthracene Dibenzo[a,e]pyrene Dibenzo[e,l]pyrene Dibenzo[b,k]fluoranthene Dicyclopenta[cd,mn]pyrene Dicyclopenta[cd,jk]pyrene Fluoranthene Fluorene Indeno[123-cd]pyrene Naphtho[1,2-b]fluoranthene Naphtho[2,1-a]pyrene Phenanthrene Picene Pyrene Triphenylene Tribenzo[e,ghi,k]perylene 4-Oxa-benzo[cd]pyrene-3,5-dione
Aldehydes and ketones	Acetaldehyde Acetone Acrolein Benzaldehyde Butyraldehyde Crotonaldehyde Formaldehyde Hexaldehyde Isobutyraldehyde Isovaleraldehyde <i>meta,para</i> -Tolualdehyde <i>ortho</i> -Tolualdehyde Propionaldehyde Valeraldehyde 2-Butanone 2,4-Dimethylbenzaldehyde
Carbon	Elemental and organic
Metals	Na, Mg, Al, K, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Br, Rb, Sr, Yt, Zr, Mo, Pd, Ag, In, Sn, Sb, Ba, La, Au, Hg, Tl, Pb
Non-metals	S, P, Si, Cl, Br
Anions	SO ₄ ²⁻ , Cl ⁻ , NO ₃ ⁻
Cations	NH ₄ ⁺ , K ⁺

From Kauppinen & Pakkanen (1990), Chuang *et al.* (1992a), Miller *et al.* (1994), Zhang & Smith (1999), Watson *et al.* (2001), Wornat *et al.* (2001), Ross *et al.* (2002), Yan *et al.* (2002), Tsai *et al.* (2003), Chen *et al.* (2004, 2005), Ge *et al.* (2004), Lee *et al.* (2005)

in numerous households in Xuanwei County, Yunnan Province, China ([Mumford et al., 1987](#); [Chuang et al., 1992a](#)). In the aromatic fraction, coal combustion particles appeared to contain high concentrations and many species of methylated PAHs ([Chuang et al., 1992a](#)). However, profiles of specific PAHs and their abundance vary largely, depending on the fuel types and combustion conditions ([Tian, 2005](#)).

(c) *Hydrocarbons and partially oxidized organic compounds*

Hydrocarbons identified in coal emissions include alkanes with 1–10 carbons, alkenes with 2–10 carbons (including 1,3-butadiene) and aromatic compounds (e.g. benzene, xylenes, toluene, styrene) ([Table 1.1](#)). Partially oxidized organic compounds identified in coal emissions include alkanols, aldehydes and ketones (carbonyls), carboxylic acids, alkyl esters and methoxylated phenolic compounds ([Rogge et al., 1998](#)).

(d) *Metals*

Some carcinogenic substances were found to be released during the combustion of lignites used in Shenyang City in northern China and smoky coals used in Xuanwei County, China. Lignites from a local Shenyang coal field had very high concentrations of nickel (75 ppm) and chromium (79 ppm) ([Ren et al., 1999, 2004](#)) when compared with the levels reported elsewhere in the world (0.5–50 ppm for nickel and 0.5–60 ppm for chromium) ([Swaine, 1990](#)). Microfibrinous quartz has been found in some smoky coals from Xuanwei County and the resulting coal emissions ([Tian, 2005](#)). In Guizhou Province of China and other areas, particles emitted from burning coal have been reported to contain high levels of chemicals like fluorine, arsenic and mercury ([Gu et al., 1990](#); [Yan, 1990](#); [Shraim et al., 2003](#)).

1.1.3 Emission factors of some carcinogens

The emission factor of a particular chemical species can be measured as the mass of the species emitted per unit mass of fuel combusted or the mass of the species emitted per unit energy produced or delivered through combustion. Few studies conducted to date have quantified emission factors of common pollutants from household stoves used in developing countries.

The available data for several known human carcinogens (benzene, 1,3-butadiene, formaldehyde and benzo[a]pyrene) are summarized in [Table 1.2](#). The sum of PAHs, when ≥ 14 individual PAHs were measured, is also shown. The cited studies measured the PAHs that are most commonly reported in the literature: acenaphthene, acenaphthylene, anthracene, benz[a]anthracene, benzo[b]fluoranthene, benzo[a]pyrene, benzo[ghi]perylene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, fluoranthene, fluorene, indeno[1,2,3-cd]pyrene, naphthalene, phenanthrene and pyrene.

Burning four types of household coal fuel (honeycomb coal briquette, coal briquette, coal powder and water-washed coal powder) in three different coal stoves generated a very wide range of benzene (2.71–1050 mg/kg fuel) ([Tsai et al., 2003](#)) and 1,3-butadiene emission factors ([Table 1.2](#)). The range of emission factors for formaldehyde was smaller.

These patterns of emission factors measured under experimental conditions are, in general, consistent with indoor air concentration profiles measured in households using coal stoves.

1.2 Prevalence of use and exposure

1.2.1 China

(a) *Use and determinants of use of coal*

In China, coal accounts for 70–75% of energy consumption ([Millman et al., 2008](#)).

Table 1.2 Emission factors of carcinogenic compounds from household stoves

Compound	Fuel type	Fuel source	Emission factor ^a (mg/kg fuel)	Emission factor ^{a, b} (mg/MJ)	Reference
Benzene	Coal (4 types)	China	2.71–1050	0.9–390	Tsai et al. (2003)
1,3-Butadiene	Coal (4 types)	China	ND–21.3	ND–7.9	Tsai et al. (2003)
Styrene	Coal (4 types)	China	ND	ND	Tsai et al. (2003)
Formaldehyde	Coal (3 types)	China	2–51	0.9–12	Zhang & Smith (1999)
Acetaldehyde	Coal (3 types)	China	0.8–81	0.3–20	Zhang & Smith (1999)
Naphthalene	Coal briquettes	Viet Nam	44.5		Kim Oanh et al. (1999)
Benzo[a]pyrene	Coal briquettes	Viet Nam	0.30		Kim Oanh et al. (1999)
Benz[a]anthracene	Coal briquettes	Viet Nam	0.11		Kim Oanh et al. (1999)
Dibenz[a,h]anthracene	Coal briquettes	Viet Nam	ND		Kim Oanh et al. (1999)
Sum of PAHs (≥14 individual PAHs)	Coal briquettes	Viet Nam	102	4.4	Kim Oanh et al. (1999)

^a The values are ranges of the means reported in individual studies.

^b Denotes milligrams per megajoule of energy delivered to the pot
ND, not detected (below method detection limit)

Although in-home coal use is banned in all Chinese cities, about 10% of urban households still use coal as their primary source of fuel. In 2004, this corresponded to 27 million tonnes of coal. The use of coal is associated with access to local fuel sources and household income; a greater percentage of households in rural areas tend to use coal than in urban areas. In rural regions with ample and inexpensive coal supplies, virtually all households depend upon coal as their domestic fuel. In aggregate, about 40% of all households in rural China rely on coal for heating or cooking ([National Bureau of Statistics, 2005](#)).

According to the [National Bureau of Statistics \(2005, 2006\)](#), household energy use from coal (raw coal, washed coal and briquettes) in China represented 21% of total energy use in urban areas, and 12.8% in rural areas. An earlier publication by the Ministry of Agriculture ([EBCREY, 1999](#)), by contrast, reported a corresponding value of 34% in rural households.

Occasionally, use of coal for heating does not equate with use of coal for cooking. For example, some households that use coal for heating may use wood for cooking. A recent survey evaluated the specific types of fuels used for cooking

throughout rural China. Overall, about 30% of rural households cook with coal. This distribution varied by geographic region, with coal being used for cooking in 19% of homes in Eastern China, 38% in Central China, 27% in Western China, and 7% in North-eastern China ([National Bureau of Statistics, 2008](#)).

The use of coal varies largely by geographical conditions and socioeconomic status. Coal and other commercial fuels are generally associated with higher incomes. Where coal resources are highest – predominantly in the north – coal use is highest. In a 2003–04 winter survey of rural areas near Xi'an, 16% and 33% of the households, located in a small village, depended mainly on coal for heating and cooking, respectively ([Tonooka et al., 2006](#)). In a study in Shaanxi, Hubei and Zhejiang in China, most households (64%) in Shaanxi reported that they heated with coal in winter, compared to 0.2% in Zhejiang and 28.5% in Hubei ([Sinton et al., 2004](#)). Similarly, 70% of the households in Shaanxi used coal for heating, compared to 1.5% in Zhejiang and 6% in Hubei ([Sinton et al., 2004](#)).

Table 1.3 Levels of indoor air pollutants from coal emissions in Chinese homes

Pollutant	Urban (mg/m ³)	Rural (mg/m ³)
TSP	0.21–2.8	0.01–20
PM ₁₀	0.16–2.7	0.12–26
CO	0.58–97	0.7–87
SO ₂	0.01–5.8	0.01–23
NO _x	0.01–1.8	0.01–1.7
B[a]P	0.3–190	5.3–19000

B[a]P, benzo[a]pyrene; PM, particulate matter; TSP, total suspended particles

From [Sinton *et al.* \(1995\)](#)

(b) Pollutant levels and exposures

Since the 1980s, many studies of indoor air quality in China have been published, measuring particulate matter, benzo[a]pyrene, sulfur dioxide, nitrogen oxide and carbon monoxide ([Table 1.3](#)). The three-province survey ([Sinton *et al.*, 2004](#)) found that in summer when stove use was dominantly for cooking, households that used coal experienced high particulate (PM₄) levels, and traditional stoves emitted higher particulate levels than improved stoves.

Kitchens may not be the sites with the highest average particulate matter levels. In the three-province study ([Sinton *et al.*, 2004](#)), those households that used coal had higher particulate levels in living rooms than in kitchens; heating, smoking and perhaps other factors can result in levels over time that are higher in living rooms than in kitchens, despite the peaks associated with cooking. In another study ([Jin *et al.*, 2005](#)), differences between rooms with and without stoves were small.

A large number of studies monitored benzo[a]pyrene in households in Xuanwei County, Yunnan Province, others reported measurements taken elsewhere ([IARC, 2010a](#)). Indoor levels of benzo[a]pyrene were in a range spanning four orders of magnitude, from 1 ng/m³ to over 10 000 ng/m³ in some of the studies in Xuanwei County, in which bituminous coal led to much higher indoor levels than anthracite coal. In

studies performed in other parts of the country, household averages rarely exceeded 40 ng/m³.

A recent study examined winter levels of PM₄ in households in Guizhou and Shaanxi, in areas where coal is contaminated with fluorine, and found that average levels in kitchen and living areas were from about 200 µg/m³ to 2000 µg/m³ ([He *et al.*, 2005](#)).

1.2.2 Outside China

There is little literature about coal use outside China.

A few measurements of particulate size fractions have been made in households of peri-urban Gujarat (in western India) that use coal ([Aggarwal *et al.*, 1982](#); [Raiyani *et al.*, 1993](#)). During cooking, the proportion of total suspended particulates < 9 µm in aerodynamic diameter was 92%, and 70% were particles < 2 µm in aerodynamic diameter. Particulate PAH size distributions measured in these same indoor environments showed that in houses that used coal, 76% of the PAH mass was contained in particulates < 2 µm aerodynamic diameter ([Raiyani *et al.*, 1993](#)).

In one study, conducted in winter on households in urban Santiago in Chile, levels of PM₁₀ were 250 µg/m³ in the kitchen, and 295 ppb SO₂ ([Cáceres *et al.*, 2001](#)).

2. Cancer in Humans

The Working Group evaluated studies that focused on exposure to coal emissions only without exposure to other solid fuels.

2.1 Studies in China

2.1.1 Cancer of the lung

(a) Overview of studies

Since the previous *IARC Monograph* ([IARC, 2010a](#)), two new case-control studies ([Galeone et al., 2008](#); [Lan et al., 2008](#)) and a re-analysis of a previously published cohort ([Hosgood et al., 2008](#)) were published.

A retrospective cohort study carried out in Xuanwei, China, evaluated the association between lung cancer risk and in-home coal use ([Lan et al., 2002](#)). Among lifetime smoky coal users, households that changed to stoves with chimneys experienced a significantly decreased risk of lung cancer in both men and women compared to individuals that used fire pits. Reduction in lung cancer mortality was also observed among lifetime smoky coal users that changed to portable stoves compared to those that used fire pits, both in men and women ([Hosgood et al., 2008](#)). Both analyses were adjusted for average tons of fuel used annually, years of tobacco smoking, years of cooking, history of spousal lung cancer, family history of lung cancer, as well as other potential confounders.

Several case-control studies ([Koo et al., 1983](#); [Xu et al., 1989](#); [Wu-Williams et al., 1990](#); [Liu et al., 1991](#); [Huang et al., 1992](#); [Sun, 1992](#); [Ger et al., 1993](#); [Lan et al., 1993](#); [Liu et al., 1993](#); [Dai et al., 1996](#); [Du et al., 1996](#); [Lei et al., 1996](#); [Luo et al., 1996](#); [Shen et al., 1996](#); [Wang et al., 1996](#); [Ko et al., 1997](#); [Shen et al., 1998](#); [Zhong et al., 1999](#); [Lan et al., 2000](#); [Zhou et al., 2000](#); [Le et al., 2001](#); [Kleinerman et al., 2002](#); [Galeone et al., 2008](#); [Lan et al., 2008](#)), have evaluated the

association of lung cancer risk with in-home coal use in China (Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-08-Table2.1.pdf>). Four evaluated the effects by histology of lung cancer ([Ger et al., 1993](#); [Luo et al., 1996](#); [Shen et al., 1996](#); [Le et al., 2001](#)). While these studies assessed exposure with different questionnaires and methodologies, in the aggregate, almost every study found in-home coal use to be associated with lung cancer risk in China by some measure of exposure. Notably, lung cancer has been associated with years of coal stove use ([Xu et al., 1989](#); [Wu-Williams et al., 1990](#); [Dai et al., 1996](#)), years of kang use (heated by coal) ([Wu-Williams et al., 1990](#); [Dai et al., 1996](#)), years of cooking or heating with coal as the fuel source ([Xu et al., 1989](#); [Wu-Williams et al., 1990](#); [He et al., 1991](#); [Liu et al., 1991](#); [Lan et al., 2002](#); [Hosgood et al., 2008](#)), amount of coal used ([Lan et al., 1993](#); [Lan et al., 2000](#); [Kleinerman et al., 2002](#); [Hosgood et al., 2008](#)), and quality of ventilation in homes that use coal ([Liu et al., 1993](#); [Ko et al., 1997](#); [Le et al., 2001](#)). The studies were from different areas in China, including northern, southern, Xuanwei and the rest of central China, and Taiwan, China.

(b) Exposure-response evidence

All studies reporting an exposure-response association between coal use and lung cancer controlled for tobacco smoking. [Lan et al. \(1993\)](#) reported a significant exposure-response relationship according to the amount of smoky coal used per year in Xuanwei, China (P for trend < 0.001). Duration of cooking with coal was significantly and positively associated with the risk for lung cancer among women ([Lan et al., 2002](#); [Hosgood et al., 2008](#)). In Gansu, individuals who use coal as their main fuel source were also found to experience higher lung cancer risk, with a significant exposure-response relationship among men (P for trend = 0.04) ([Kleinerman et al., 2002](#)) but not among women. In northern China, lung cancer risk increased in

an exposure–response manner according to the duration of use of heated kang (Xu *et al.*, 1989). Galeone *et al.* (2008) constructed an index of indoor air pollution due to solid fuel use (mainly coal) and found a significant exposure–response relationship.

(c) Type of coal

Various smoky coal types were associated with a range of lung cancer risks with substantial heterogeneity ($P < 0.001$) in Xuanwei, China (Lan *et al.*, 2008). The risk for lung cancer ranged from 24.8 (95%CI: 12.4–49.6) for using smoky coal from the Laibin mine to 0.7 (95%CI: 0.2–3.1) from the Yangliu mine, compared to use of smokeless coal or wood. In this study, indoor benzo[a]pyrene concentrations were highly correlated with the risk for lung cancer.

(d) Histology

In-home coal use has been associated with both adenocarcinomas and squamous-cell carcinomas of the lung (Ger *et al.*, 1993; Luo *et al.*, 1996; Shen *et al.*, 1996; Le *et al.*, 2001); however these studies are based on small sample sizes.

(e) Population characteristics

Most studies have focused on women, as they tend to spend more time at home and consequently have greater exposures to coal combustion products than men. Six studies enrolled only women (Dai *et al.*, 1996; Wang *et al.*, 1996; Ko *et al.*, 1997; Shen *et al.*, 1998; Zhong *et al.*, 1999; Zhou *et al.*, 2000), of which three (Dai *et al.*, 1996; Wang *et al.*, 1996; Shen *et al.*, 1998) were also restricted to non-smokers. [Fuel type was not specified in Zhou *et al.* (2000) but both cases and controls had ‘high level’ of exposure to coal emissions.] In-home coal was associated with lung cancer risk in three studies (Dai *et al.*, 1996; Shen *et al.*, 1998; Zhong *et al.*, 1999). In study populations including men, the risks associated with in-home coal use was generally greater

among women than among men (He *et al.*, 1991; Liu *et al.*, 1991; Liu *et al.*, 1993).

(f) Interactions

The most notable genetic interaction with in-home coal use involves the *GSTM1* null genotype. A meta-analysis found the *GSTM1* null genotype to be associated with lung cancer risk (OR, 1.64; 95%CI: 1.25–2.14; 4 studies) among studies carried out in regions of China that use coal for heating and cooking (Hosgood *et al.*, 2007).

2.2 Studies outside China

2.2.1 Indoor exposures

Two case–control studies that adequately separated the effect of coal from wood or other biomass products evaluated the association of coal use for heating or cooking and cancers of the lung, hypopharynx and larynx (Lissowska *et al.*, 2005; Sapkota *et al.*, 2008; Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-08-Table2.2.pdf>).

In a multicenter study conducted in seven European countries (Czech republic, Hungary, Poland, Romania, the Russian Federation, Slovakia and the United Kingdom), Lissowska *et al.* (2005) evaluated the association of heating and cooking with solids fuels with risk of lung cancer. The study included 2861 cases and 3118 matched population-based controls. In an analysis that evaluated coal use specifically, ever use of coal (either as a cooking or heating fuel) was not significantly related to the risk of lung cancer, after adjusting for tobacco smoking and other factors.

Sapkota *et al.* (2008) conducted a multicenter hospital-based case–control study in India to investigate lifetime fuel usage as risk factors for three different cancer types (1042 hypopharyngeal/laryngeal and 635 lung) and 718 matched controls. Compared with never users, among

those who always used coal for cooking the odds ratios for cancer was 1.92 (95%CI: 0.67–5.54) for the hypopharynx, 2.42 (95%CI: 0.94–6.25) for the larynx, and 3.76 (95%CI: 1.64–8.63) for the lung after adjusting for tobacco smoking and other factors. Among never smokers, the risk for lung cancer was 7.46 (95%CI: 2.15–25.94; based on 11 cases). The risk increased with years of coal usage for cancers of the hypopharynx (*P* for trend = 0.06), larynx (*P* for trend = 0.05) and lung (*P* for trend < 0.01).

2.2.2 Ambient coal smoke exposure from ecological studies

Two ecological studies evaluated the association of coal emissions with lung cancer. A study conducted in Dublin ([Kabir et al., 2007](#)) evaluated the impact of coal burning (black smoke outdoor concentration) on lung cancer mortality using data from 1981 to 2000. In 1990 the use of coal was banned in Dublin. A strong decline in black smoke was noted between the pre- and post-ban periods, from 46.4 µg/m³ in 1981–90 (pre-ban) to 18.2 µg/m³ in 1991–2000 (post-ban). After adjusting for age, sex and smoking, annual mean black smoke concentration was not related to annual death rates from lung cancer. [The Working Group noted that the post-ban period was too short to see any changes in lung cancer mortality.]

Another study evaluated the impact of industrial installations involving combustion of coal and other fuels on the mortality due to lung, laryngeal and bladder cancer in the population of 8073 Spanish towns in 1994–2003 ([García-Pérez et al., 2009](#)). Mortality data were obtained from the National Statistics Institute and population exposure was evaluated by the distance of the centroid of the town to the closest combustion facility. Installations using coal only as the fuel source, within a vicinity of 5 km, was related to an increased risk for lung cancer overall (OR, 1.10; 95%CI: 1.02–1.18) with higher risk in men

(OR, 1.13; 95%CI: 1.05–1.22), for bladder cancer overall (OR, 1.18; 95%CI: 1.01–1.37) and 1.22 (95%CI: 1.03–1.44) in men and for laryngeal cancer (OR, 1.46; 95%CI: 1.21–1.77 in men) after adjusting for smoking and sociodemographic variables. The authors noted that there was no other industry nearby that could bias the risk estimates.

2.3 Synthesis

Several case-control studies from China and a study from India have demonstrated an increased risk for lung cancer associated with exposure to emissions from coal burning, after accounting for potential confounders, including smoking and in analyses restricted to non-smokers. There were higher risks in women than men, and exposure-response relationships were found. A European case-control study did not find a significant effect of indoor coal use for cooking or heating. An ecological study from Europe provided further evidence of an increased risk for lung cancer in the vicinity of coal plants. No major effect was observed on lung cancer mortality after the ban of coal use in Dublin, probably because there was insufficient latency to see a change. Other cancer sites have been studied (larynx, bladder, hypopharynx); however there is not enough evidence to evaluate carcinogenicity with exposure to coal emissions.

In conclusion, there is convincing evidence based on multiple studies, mainly from different parts of China and one in India, that indoor emissions from household combustion of coal (used for heating and cooking) are causally linked to lung cancer in humans.

3. Cancer in Experimental Animals

Soots have been evaluated previously ([IARC, 1985, 2010a](#)).

Coal soot has been tested for carcinogenicity to mice by whole body exposure and coal emissions have been tested by inhalation in both mice and rats. Extracts of coal soot and smoke particles have also been tested by intratracheal, dermal, and subcutaneous administration to mice. A veterinary case–control study has studied sinonasal cancer in pet dogs from households with indoor use of coal.

3.1 Coal emissions and coal soot

3.1.1 Whole-body and inhalation exposure

In one study, whole-body exposure of Buffalo strain mice to coal soot mixed with bedding caused eight lung adenocarcinomas in 100 exposed mice compared to one in 50 controls [not significant] ([Seeling & Benignus, 1936](#)). In a second study, no increase in lung or skin tumours resulted from repeated exposure of mice to a ‘moderate’ cloud of soot in an inhalation chamber for a period of one year ([Campbell, 1939](#)).

Inhalation exposure to coal emissions for periods of 15 to 24 months caused markedly increased incidence of lung cancer in two studies in mice ([Liang et al., 1988](#); [Lin et al., 1995](#)) and one study in rats ([Liang et al., 1988](#); [Table 3.1](#)). Squamous cell lung carcinomas occurred in exposed animals in one of the studies in mice and the study in rats ([Liang et al., 1988](#)).

3.2 Extracts of coal soot

3.2.1 Intratracheal administration

Intratracheal administration of an aqueous detergent extract of coal soot once every 10 days for about 100 days increased lung adenocarcinoma incidence (29/72 versus 7/43, $P < 0.01$) in Kumming mice compared to controls after 18 months ([Yin et al., 1984](#)).

3.2.2 Dermal application

Coal-soot extracts applied repeatedly to mouse skin increased the incidence of skin tumours including squamous cell carcinomas in four studies ([Passey, 1922](#); [Passey & Carter-Braine, 1925](#); [Campbell, 1939](#); [Mumford et al., 1990](#)).

Smoky coal-soot extracts applied to mouse skin followed by repeated dermal applications of the skin tumour promoter 12-O-tetradecanoylphorbol-13-acetate initiated skin tumours in mice in two studies ([Liang & Wang, 1987](#); [Mumford et al., 1990](#); [Table 3.2](#)).

3.2.3 Subcutaneous injection

In one study, a low incidence (17%) of injection-site subcutaneous tumours [histology not specified] developed after 55 weeks in 30 (C57BpxCBA) F_1 male mice given five subcutaneous injections of extracts of brown coal. No tumours were observed in controls ([Khesina et al., 1977](#)).

In two experiments, repeated subcutaneous injections for 10 weeks of extracts of coal soot collected from Xuanwei County, China, increased the incidence of lung cancer (adenocarcinomas, adenosquamous and squamous cell carcinomas) in Kumming mice after 10 months ([Liang et al., 1983, 1984](#); [Table 3.3](#)).

3.3 Veterinary epidemiology

A case–control study in pet dogs found that indoor use of coal was a strong risk factor for sinonasal cancers (adjusted odds ratio, 4.24; 95% confidence interval: 1.30–16.52) ([Bukowski et al., 1998](#)).

Table 3.1 Carcinogenicity studies of inhalation exposure to coal emissions in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Kunming (M, F) 2 yr Lin et al. (1995)	Control air	Lung cancer, 3.6%	–	Purity NR; Age at start NR (weight, 13 ± 1 g)
	Smoke, 60 g coal, daily	Lung cancer, 9.4%	NS	Amounts of coal chosen to simulate normal indoor air conditions for humans in Harbin City, China
	Smoke, 105 g coal, daily	Lung cancer, 12.8%	$P < 0.05$	
	Smoke, 160 g coal, daily	Lung cancer, 24.3%	$P < 0.05$	Exposure assumed to be daily exposure
Mouse, Kunming (M, F) 15 mo Liang et al. (1988)	30 M + 30 F			
	Control air	29/171, total lung cancer (all adenocarcinomas)	–	Age at start NR (weight, 21 g)
	Coal smoke	188/210, total lung cancer (including: 119/210, adenocarcinoma; 45/210 adenocarcinoma; 45/210 squamous-cell carcinoma)	$P < 0.001$	Total suspended particles, 0.91 mg/m ³ (control air) vs 14.38 mg/m ³ (coal smoke). B[a]P, 0.15 µg/m ³ (control air), 50.5 µg/m ³ (coal smoke)
	113 M + 58 F (control) 160 M + 50 F			Bituminous coal incompletely burned to simulate normal indoor air in Xuanwei County, China
Rat, Wistar (M, F) 19 mo Liang et al. (1988)	Control air	1/110, total lung tumours (1 adenocarcinoma)	–	Age at start NR (weight, 105 g)
	Coal smoke	84/125, total lung carcinomas (all squamous cell carcinomas)	$P < 0.001$	Total suspended particles, 0.91 mg/m ³ (control air) vs 14.38 mg/m ³ (coal smoke). B[a]P, 0.15 µg/m ³ (control air), 50.5 µg/m ³ (coal smoke)
	59 M + 51 F (control) 62 M + 63 F			Bituminous coal incompletely burned to simulate normal indoor air in Xuanwei County, China

B[a]P, Benzo[a]pyrene; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; yr, year or years

Table 3.2 Carcinogenicity studies of dermal exposure to coal-soot extracts in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, SENCAR (F) 77 wk Mumford et al. (1990)	0.2 ml, Acetone twice/wk, 52 wk (control) 1 mg smoky coal extract, twice/wk, 52 wk	No skin carcinomas at 52 wk (100% survival) or at 77 wk (78% survival) 38% carcinomas ^a (1.3 per tumour bearing mouse) at 52 wk (88% survival), 88% ^a (1.1 per tumour bearing mouse) at 77 wk (10% survival)	– NR [significant]	Exposure to organic extracts of indoor air particles from burned smoky coal in Xuanwei County, China. B[a]P content, 19.3 µg/m ³ air
40 animals				
Mouse, SENCAR (F) 27 wk Mumford et al. (1990)	Initiation with smoky coal extract, followed one wk after by promotion with TPA (2 µg/mouse in 0.2 ml acetone, twice/wk, 26 wk). Initiation doses: 0 mg 1 mg 2 mg 5 mg 10 mg 20 mg 40 animals	15% with skin papillomas 80% with papillomas 90% with papillomas > 90% with papillomas > 90% with papillomas 100% with papillomas	– NR [significant] NR [significant] NR [significant] NR [significant] NR [significant]	Exposure to organic extracts of indoor air particles from burned smoky coal in Xuanwei County, China. B[a]P content, 19.3 µg/m ³ air Tumour incidence and numbers estimated from graphical presentation of data.
Mouse, Kunming (M) 26 wk Liang & Wang (1987)	Initiation with 0, 1, 5, 10, 20 mg smoky coal soot; promotion with TPA (repeated application of 2 µg/mouse) 40 animals	Skin tumours: 10, 25, 54, 60, 40%	[<i>P</i> < 0.05], 5–20 mg coal soot	Age at start NR (weight, 28.7 g) Extracts of smoky coal soot from Xuanwei County, China

^a mainly squamous cell carcinomasB[a]P, benzo[a]pyrene; F, female; M, male; NR, not reported; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week or weeks

Table 3.3 Carcinogenicity studies of subcutaneous injections of coal soot extracts in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours		Significance	Comments
		Lung cancer ^a			
Mouse, Kunming (M) 10 mo Liang et al. (1983)	Once/wk, 10 wk: 0 mg (control)	1/38	-	-	Age at start NR (weight, 18–26 g) Exposure to cyclohexane extracts of coal soot from Xuanwei County, China.
	500 mg soot extract (total dose)	44/57		$P < 0.001$	
	1000 mg soot extract (total dose) 38–57 animals	36/56		$P < 0.001$	
Mouse, Kunming (M) 311 d Liang et al. (1984)	Once/wk, 10 wk: 0 mg (control)	6/60, all adenocarcinomas	-	-	Age at start NR (weight, 18–22 g) Exposure to Tween 80 – saline extracts of coal soot from Xuanwei County, China.
	119 mg soot extract (total dose)	52/58		$P < 0.001$	
	400 mg soot extract (total dose) ~60 animals	39/59		$P < 0.001$	

^a Lung cancers included squamous cell carcinomas, adenosquamous carcinomas, and adenocarcinomas.
d, day or days; M, male; mo, month or months; NR, not reported; wk, week or weeks

3.4 Synthesis

There is convincing evidence for the carcinogenicity of coal smoke and coal soot in experimental animals, based on the consistent induction of lung cancers in mice and rats exposed to coal emissions by inhalation, and in mice given subcutaneous injections of coal soot extract, and induction of malignant tumours of the skin in mice given repeated dermal applications of coal soot extract.

4. Other Relevant Data

4.1 Inhalable particles

The primary mechanisms for deposition of airborne particles in the respiratory tract are sedimentation, impaction and diffusion (see [IARC \(2010b\)](#) for a review). Deposition by sedimentation and impaction depends on the aerodynamic diameter of the particle, whereas deposition by diffusion depends on its thermodynamic diameter ([ICRP, 1994](#)). Following inhalation, particles may either deposit in the extrathoracic, tracheo-bronchial or pulmonary airways or remain in the air stream and be eliminated upon exhalation. The deposition of particles in the respiratory tract depends primarily on the size of the inhaled particle, the route of breathing (i.e. through the nose and/or mouth) and the breathing pattern (e.g. volume and frequency) ([Bailey *et al.*, 1985](#); [Freedman & Robinson, 1988](#); [ICRP, 1994](#)).

Particles are frequently aggregates or agglomerates of smaller primary particles. The aerodynamic and thermodynamic properties of these aggregates (rather than the primary particles) affect their behaviour in the air and the probability of deposition in the respiratory tract. Once deposited, properties such as the size and surface area of both the aggregate and the primary particle can potentially affect the kinetics of clearance ([ICRP, 1994](#); [Oberdörster, 1996](#)).

The deposition and clearance of particles vary among individuals for several reasons, including age, sex, tobacco smoking status and health status. Pre-existing lung diseases or conditions such as asthma or chronic obstructive pulmonary disease can influence the efficiency and pattern of deposition within the respiratory tract. Deposition and retention determine the initial and retained dose of particles in each region of the respiratory tract and may, therefore, influence the risk for developing diseases specific to those regions of the respiratory tract ([Oberdörster, 1988](#); [ICRP, 1994](#)).

All animal species that are routinely used in particle toxicology, as well as humans, are susceptible to impairment of clearance of poorly soluble particles from the lungs. In rats, impaired clearance is probably one of the first steps necessary to initiate a sequence of events that may lead to lung cancer. Different animal species exhibit differences in particle-induced impairment of clearance, which can result in different lung burdens (expressed as mass or surface area) following exposures to the same particle concentration ([Brown *et al.*, 2005](#); [IARC, 2010b](#)). In cancer bioassays in rats exposed to various types of poorly soluble particles of fine or ultra-fine size, the surface area of the particles may be a better predictor of lung tumours than particle mass ([Oberdörster & Yu, 1990](#); [Driscoll *et al.*, 1996](#)).

Inhaled and deposited particles are cleared more rapidly from the normal lungs of healthy rats than from those of humans. However, at high lung burdens, macrophage-mediated clearance from the rat lung can be impaired and in time, clearance effectively ceases. This phenomenon (termed ‘overload’) is observed with poorly soluble particles generally considered to have low toxicity ([Morrow, 1988](#)). Several studies have shown that rats, but not mice or hamsters, develop excess incidence of lung cancer after chronic inhalation of ‘overloading’ doses of poorly soluble particles. Several authors have discussed this

phenomenon and the challenges it poses for the extrapolation of chronic effects in rats to humans ([Morrow, 1994](#); [Levy, 1995](#); [Watson & Valberg, 1996](#); [ILSI, 2000](#); [Miller, 2000](#); [Oberdörster 2002](#); [Hext *et al.*, 2005](#); [IARC, 2010b](#)).

The events proposed to describe the biological process that starts with particle deposition on critical target cells (e.g. alveolar epithelial cells type II) or tissues within the rat lung and results in lung tumours include:

- sustained inflammation, where the cell population (dominated by activated and probably persistent polymorphonuclear neutrophils) secretes a collection of pro-/anti-inflammatory cytokines, proteases, cytotoxins, fibrogenic and other growth factors;
- production of reactive oxygen species by particle effects or intracellular formation, which may gradually deplete the antioxidant defences; damage DNA directly and potentially induce mutations, promote cell turnover and cell proliferation; events that may enhance the risk for DNA replication error and/or expand a mutated or transformed cell to initiate a tumour ([Castranova, 2000](#); [Knaapen *et al.*, 2004](#)).

Some of these events have been demonstrated in humans exposed to poorly soluble particles, but it is not known to what extent they are operative in humans and whether humans are eventually susceptible to particle-induced lung cancer. Species differences such as breathing conditions, respiratory tract structure and pulmonary defences must be considered when extrapolating toxicological findings from rodents to humans ([Castranova, 2000](#); [Knaapen *et al.*, 2004](#); [Brown *et al.*, 2005](#)). Clear differences in antioxidant defence mechanisms in the lungs also exist between humans and rats, and there is evidence that humans overall are relatively deficient in some of these mechanisms compared with rats ([IARC, 2010b](#)). Studies in rats have shown that, depending on the concentration and duration of exposure, the long-term retention of particles in humans can be greater than that predicted from

rodent studies that used lower concentrations or shorter durations of exposure ([Morrow, 1988, 1992](#); [ILSI, 2000](#)).

Although the degree of sustained inflammation experienced by rats at high lung burdens is not observed in humans, humans may experience sustained inflammation under certain disease conditions, including late-stage interstitial pulmonary fibrosis. Patients who have interstitial pulmonary fibrosis have a high incidence of lung tumours ([Daniels & Jett, 2005](#)).

4.2 Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons are important components of coal emissions (see [IARC \(2010c\)](#) for a review). These compounds are absorbed through the respiratory tract – from where, as adsorbed particulates, they can also be swept back up and swallowed into the gastrointestinal tract and even reach the skin. Smaller molecules (2–3-ring) are absorbed more rapidly than larger ones ([IARC, 2010c](#)).

The rate and extent of absorption by the respiratory tract of PAHs from particles onto which they are adsorbed is generally dependent on particle size, which determines regional deposition in the respiratory tract and the rate of release of PAHs from the particle. Highly lipophilic PAHs released from particles deposited in the conducting and bronchial airways are largely retained for several hours and absorbed slowly by a diffusion-limited process. In contrast, PAHs that are released from particles in alveolar airways are generally absorbed within minutes ([Gerde & Scott, 2001](#); [IARC, 2010c](#)).

Once absorbed, PAHs are distributed widely to most organs and tissues and tend to accumulate in fatty tissue ([WHO, 1998](#); [IARC, 2010c](#)). They are metabolized rapidly to more soluble metabolites, e.g. phenols, dihydrodiols, and phenol dihydrodiols, and in some cases to more reactive species like epoxides, dihydrodiol

epoxides, quinones and tetrols. At least three main pathways of metabolism are involved:

- the cytochrome P450 (CYP) pathway, where PAHs may be (1) metabolized to their bay- and fjord-region diol epoxides with the involvement of epoxide hydrolase ([Xue & Warshawsky, 2005](#)) or (2) undergo cyclopenta-ring oxidation ([IARC, 2010c](#)).
- the cytochrome P450/oxidase pathway, where removal of one electron from the π system by CYPs or oxidases generates a radical cation ([Cavalieri & Rogan, 1992](#); [Xue & Warshawsky, 2005](#)).
- the cytochrome P450/aldo-keto reductase (oxidative) pathway where, following metabolization to dihydrodiols by CYPs and epoxide hydrolase, formation of *ortho*-quinones and generation of reactive oxygen species is ensured by aldo-keto reductases ([Penning et al., 1999](#); [Xue & Warshawsky, 2005](#); [Penning & Drury, 2007](#)).

Many of the above-mentioned metabolites are electrophilic and bind to DNA and proteins, which results in genotoxic effects — primarily through the formation of DNA adducts ([Xue & Warshawsky, 2005](#)). Beyond these phase-I metabolic pathways, PAH metabolites may be eliminated in a conjugated form with either glutathione, sulfate or glucuronic acid via the phase-II metabolism ([WHO, 1998](#); [IARC, 2010c](#)).

Ample evidence, summarized in [IARC \(2010c\)](#), supports a role for PAHs in lung cancer due to exposure to indoor emissions from coal combustion.

A general genotoxic mechanism has emerged in which PAHs such as benzo[a]pyrene are metabolized to electrophilic compounds (e.g. benzo[a]pyrene-7,8-diol-9,10-epoxide) that form adducts in DNA ([Xue & Warshawsky, 2005](#); [IARC, 2010c](#)). If these adducts are not repaired, misreplication converts them primarily into G→T transversion mutations in the *TP53* gene in the lung. An over-representation of G→T transversions

has been found on the non-transcribed strand of DNA in the *TP53* gene in lung tumours from smoky coal-exposed women in China, which is consistent with exogenous exposure and the lack of transcription-coupled DNA repair on that strand, resulting in mutations ([DeMarini et al., 2001](#)). A preference for G→T transversions in the methylated CpG dinucleotides in human lung tumours has been found, in agreement with in-vitro studies that show the same dinucleotide as a target of benzo[a]pyrene diol epoxide ([Casale et al., 2001](#); [DeMarini et al., 2001](#); [Hainaut & Pfeifer, 2001](#); [Pfeifer & Hainaut, 2003](#)).

A study by [Sun et al. \(2007\)](#) found that coal emission-exposed subjects carrying an exon-3 mutation in the microsomal epoxide hydrolase gene had a nearly 2-fold increased risk for lung cancer compared to those with the wild type version of the gene. Thus, metabolism to PAH-epoxides plays an important role in lung cancer associated with coal emissions.

A role for the aldo-keto reductase (AKR) pathway in the formation of mutagenic/carcinogenic metabolites of PAHs has also been found among smoky coal emission-exposed lung cancer patients in China. [Lan et al. \(2004\)](#) found that subjects who had the *AKR1C3-Gln/Gln* genotype had a 1.84-fold increased risk for lung cancer compared with those without the polymorphism. In subjects having the *OGG1-Cys/Cys* or the *OGG1-Ser/Cys* polymorphism, the risk for lung cancer was increased about 1.9-fold relative to *OGG1-Ser/Ser*. Indeed, AKRs convert trans-dihydrodiols to *ortho*-quinones, and [Park et al. \(2008\)](#) have used a yeast system to show that the pattern of *ortho*-quinone-induced mutations in *TP53* in this system is driven by 8-oxo-dGuo formation, whereas the spectrum of mutations is driven by biological selection for dominance. [Park et al. \(2009\)](#) have shown recently that the aryl-hydrocarbon receptor shuttles the AKR-generated *ortho*-quinones into the nucleus.

Consistent with a role for PAHs, studies in smoky coal-exposed women in China have

shown that a polymorphism in nucleotide excision repair (*ERCC2 Gln* at codon 751) reduced lung cancer risk by 60%. A similar reduction was also found for subjects with a particular haplotype in *ERCC2*. A 2-fold increased risk for lung cancer was found for subjects having 1 or 2 copies of the *RAD23B* gene with Val at codon 249 (Shen *et al.*, 2005).

In addition, accumulation of mutations in other key genes (e.g. *KRAS*; Mass *et al.*, 1993; DeMarini *et al.*, 2001; Keohavong *et al.*, 2003), production of reactive oxygen species (Xue & Warshawsky, 2005), photomutagenicity (Yan *et al.*, 2004), together with interruption of gap-junctional intercellular communication (Bláha *et al.*, 2002), cell-cycle dysregulation, increase in cell proliferation, tumour promotion (Tannheimer *et al.*, 1998, 1999; Burdick *et al.*, 2003; Oguri *et al.*, 2003; Plísková *et al.*, 2005), and induction of apoptosis (Ko *et al.*, 2004) can result in tumour formation. PAHs can also have immunosuppressive and haematological effects (Burchiel & Luster, 2001; Booker & White, 2005). Several of the above effects are partly mediated by activation of the aryl-hydrocarbon receptor to which many PAHs can bind (IARC, 2010c).

4.3 Biomarkers and mutagenicity

The available information on the mutagenicity and genotoxicity of smoky-coal emissions from Xuanwei County, China, includes a wide range of end-points that encompass mutations in *KRAS* and *TP53* genes in lung tumours from non-smokers who were exposed to smoky-coal emissions (Li *et al.*, 1997; DeMarini *et al.*, 2001; Keohavong *et al.*, 2003, 2004, 2005). In addition, studies show that such exposures result in the excretion of several PAHs and their metabolites, e.g. methylated- and hydroxyl-PAHs (Mumford *et al.*, 1995; Siwińska *et al.*, 1999) and that exposed individuals exhibit elevated levels of DNA adducts (Gallagher *et al.*, 1993; Mumford *et al.*, 1993; Xu *et al.*, 1997; Casale *et al.*, 2001) and

accumulation of *TP53* protein (Feng *et al.*, 1999; Lan *et al.*, 2001). Recently, mitochondrial DNA content, which is associated with production of reactive oxygen species through oxidative phosphorylation, was found to be elevated in smoky coal-exposed subjects (Bonner *et al.*, 2009).

It was also reported that exposure to coal emissions in Guizhou Province, China, is associated with increased levels of DNA–protein cross-links, unscheduled DNA synthesis (Zhang *et al.*, 2000b), sister chromatid exchange, chromosomal aberrations, micronucleus formation (Zhang *et al.*, 2007a) and *p16* gene deletion and hypermethylation (Zhang *et al.*, 2007b) in peripheral blood lymphocytes. Mutated P53 protein was also elevated in the skin (Hu *et al.*, 2001). [Some of the observed cytogenetic damage were probably due to the elevated levels of arsenic present in this coal].

In many studies, extracts or condensates of coal emissions were found to be mutagenic in *Salmonella* with or without metabolic activation: in strain TA98 in the presence of S9 the potency for smoky-coal could reach 60000 revertants per cubic metre of air (Mumford *et al.*, 1987) and 3000 revertants per milligram of particle (Nakanishi *et al.*, 1997). Bioassay-directed fractionation studies with *Salmonella* have identified that, for smoky-coal, most of the mutagenic activity is due to PAHs and alkylated PAHs (Chuang *et al.*, 1992a, b). Evaluation of the mutation spectrum produced by smoky coal extract in *Salmonella* showed a similar percentage of GC to TA mutations (≈ 77 –86%) as found in the *TP53* (76%) and *KRAS* (86%) genes in lung tumours from smoky coal-exposed women (Granville *et al.*, 2003).

Several studies evaluated populations who are exposed to indoor air pollution from coal for associations between polymorphisms in genes that are involved in xenobiotic metabolism and risk for lung cancer. However, multiple comparisons and generally small sample sizes could have resulted in both false-positive and false-negative findings. There is some evidence that

the *GSTM1*-null genotype was associated with increased risk for lung cancer in some studies in which at least part of the study population was definitely or probably exposed to indoor coal emissions, particularly where exposure to PAHs was suspected to be a contributing agent (Lan *et al.*, 2000; Chen *et al.*, 2006). However, results for polymorphisms in other genes are inconsistent or have been analysed in only one study. Therefore, no conclusion can be made regarding the effect of polymorphisms of genes other than possibly *GSTM1* on risk for lung cancer in these populations.

4.4 Synthesis

Chemical analyses and bioassay-directed fractionation of smoky coal emissions have identified PAHs as an important chemical class that accounts for much of their mutagenicity and carcinogenicity. The epidemiological link between exposure to smoky coal emissions and an increased risk for lung cancer is strengthened mechanistically by the fact that the mutation spectra of the *P53* tumour-suppressor gene and the *KRAS* oncogene in the lung tumours from non-smokers exposed to smoky coal emissions reflect an exposure to PAHs and differs from the mutation spectra found in these genes in lung tumours from cigarette smokers. Thus, the mutation spectra in lung tumours from non-smokers whose cancers are linked to smoky coal emissions reflect the primary DNA damage induced by the most prominent class of mutagens/carcinogens in these emissions.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of indoor emissions from household combustion of coal. Indoor emissions from

household combustion of coal cause cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of coal-derived soot extract.

There is *sufficient evidence* in experimental animals for the carcinogenicity of emissions from combustion of coal.

Indoor emissions from household combustion of coal are *carcinogenic to humans* (Group 1).

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LIST OF ABBREVIATIONS

α -Me- γ -OH-PdG	α -Methyl- γ -hydroxy-1, \underline{N}^2 -propanodeoxyguanosine
16 α -OHE1	16- α -hydroxyestrone
1-OHP or 1-HOP	1-hydroxypyrene
ADH	alcohol dehydrogenase
AEAT	acyl-coenzyme A: ethanol O-acyltransferase
AFRO	WHO African Region
AhR	aryl-hydrocarbon receptor
AIDS	acquired immunodeficiency syndrome
AKR	aldo-keto reductase
ALDH	aldehyde dehydrogenase
AMRO	WHO Region of the Americas
<i>Apc</i>	adenomatous polyposis coli
BaP	benzo[<i>a</i>]pyrene
BMI	body mass index
CalEPA	California Environmental Protection Agency
CDH1	E-cadherin 1
CHEK	checkpoint
CI	confidence interval
CIMP	CpG island methylator phenotype
CML	chronic myeloid leukaemia
COX-2	cyclooxygenase-2
CPS-I	American Cancer Society Cancer Prevention Study I
CPS-II	American Cancer Society Cancer Prevention Study II
CYP	cytochrome P450
DMBA	7,12-dimethylbenz[<i>a</i>]anthracene
DMSO	dimethyl sulfoxide
DRR	direct reversal repair
EBV	Epstein-Barr virus
EGFR	Epidermal growth factor receptor
EHPX	Microsomal epoxide hydrolase
ELISA	enzyme linked immunosorbent assay
EMRO	Eastern Mediterranean Region
EPIC	European Prospective Investigation into Cancer and Nutrition
ERCC	excision repair cross-complementing protein
ER	estrogen receptor
EURO	WHO European Region
FAEE	fatty-acid ethyl ester

FAEES	fatty-acid ethyl ester synthases
FISH	fluorescence in situ hybridization
GSHS	Global School based Student Health Survey
GST	glutathione-S-transferase
GYTS	Global Youth Tobacco Survey
Hb	haemoglobin
HBSC	Health Behaviour in School Aged Children
HCS	high dose cigarette smoke
HEMA	2-hydroxyethyl mercapturic acid
HER	human epidermal growth factor receptor
HPB	4-hydroxy-1-(3-pyridyl)-1-butanone
HPLC	high pressure liquid chromatography
HPMA	3-hydroxypropyl mercapturic acid
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
IGF-2	insulin-like growth factor-2
iso-NNAC	4-(methylnitrosamino)-4-(3-pyridyl)butyric acid
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LCS	low dose cigarette smoke
LOH	loss of heterozygosity
MA	mercapturic acid
MGMT	O ⁶ -methylguanine DNA methyl-transferase
MHBMA	monohydroxybutyl mercapturic acid
MHL1	mutL homologue 1
MINT	methylation in tumour
MNBA	4-(methylnitrosamino)butyric acid
MNPA	3-(methylnitrosamino)propionic acid
MNPhPA	2-(methylnitrosamino)-3-phenylpropionic acid
MNTCA	N-nitroso-2-methylthiazolidine-4-carboxylic acid
MPO	myeloperoxidase
N ² EtdG	N ² -ethyl-2'-deosygnanosine
N ² EtidG	N ² -ethylidene-2'-deosygnanosine
N ² -Dio-dG	N ² -(2,6-demethyl-1,3-dioxan-4-yl)deoxyguanosine
NAA	N-nitrosamino acid
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NAT	N-acetyltransferase
NazCA	N-nitrosoazetidine-4-carboxylic acid
NDEA	N-nitrosodiethylamine
NDMA	N-nitrosodimethylamine
NER	nucleotide excision repair
NHL	non-Hodgkin lymphoma
NHPRO	N-nitrosohydroxyproline
NIH-AARP	National Institutes of Health American Association of Retired People
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N'-nitrososornicotine
NO	nitric oxide
NPIC	N-nitrosopipelic acid

NPIP	N-nitrosopiperidine
NPRO	N-nitrosoproline
NPYR	N-nitrosopyrrolidine
NQO	NAD(P)H quinone oxidoreductase
NTCA	N-nitrosothiazolidine- 4-carboxylic acid
OR	odds ratio
PAHs	polycyclic aromatic hydrocarbons
PGE2	prostaglandin
PheT	<i>r</i> -1, <i>t</i> -2,3, <i>c</i> -4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5,6]pyridine
PM	particulate matter
PM ₁₀	inhalable particles <10 µm
PM _{2.5}	respirable particles <2.5 µm
POB	pyridyloxobutyl
PR	progesterone receptor
RFLP	restriction fragment length polymorphism
RR	relative risk
SEARO	WHO South-East Asian Region
SEER	National Cancer Institute's Surveillance, Epidemiology, and End Results program
SFRP	soluble Frizzled receptor protein
SIR	standardized incidence ratio
SNPs	Single Nucleotide Polymorphisms
SPMA	S-phenyl mercapturic acid
SULT	sulfotransferase
TGF-α	transforming growth factor- α
total NNAL	NNAL and its glucuronides
total NNN	NNN and its glucuronides
TSNA	tobacco-specific N-nitrosamines
TSP	total suspended particles
UDP	uridine diphosphate
UGT	Uridine-5'-diphosphate glucuronosyl transferase (also called uridine-5'-diphosphate glycosyltransferase)
WHO FCTC	WHO Framework Convention on Tobacco Control
WLM	work-level-months
WPRO	WHO Western Pacific Region
XP	Xeroderma pigmentosum
XRCC	X-ray repair cross-complementing protein

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