

Carcinogenicity of alcoholic beverages

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In February, 2007, 26 scientists from 15 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to reassess the carcinogenicity of alcoholic beverages and of ethyl carbamate (urethane), a frequent contaminant of fermented foods and beverages. These assessments will be published as volume 96 of the IARC Monographs.¹ This paper reports on the assessment of alcoholic beverages. Details on the assessment of ethyl carbamate can be found at <http://monographs.iarc.fr/>.

Although moderate alcohol consumption has some health benefits,² the WHO identified the consumption of alcohol as one of the top-10 risks for worldwide burden of disease.³ In 2002, more than 1.9 billion adults (≥ 15 years of age) around the world were estimated to be regular consumers of alcoholic beverages, with an average daily consumption of 13 g of ethanol (about one drink).⁴ In general, men drink alcohol more often and in larger quantities than women. On the basis of production data, per-capita consumption is highest in eastern Europe and the Russian Federation. In Africa, South America, and Asia, alcohol consumption is comparatively lower, but a large proportion of alcohol is produced locally and remains unrecorded. Over the past 40 years, alcohol consumption has remained stable in most regions of the world, except in the western Pacific region—predominantly China—where it has increased by about five times. In addition to ethanol and water, alcoholic beverages can contain many different substances derived from fermentation, contamination, and from the use of additives or flavours.

The Working Group reviewed the epidemiological published work on the possible association between alcohol consumption and cancer at 27 ana-

tomical sites. Many studies of different design and in different populations around the world have consistently shown that regular alcohol consumption is associated with an increased risk for cancers of the oral cavity, pharynx, larynx, and oesophagus.^{5–7} Daily consumption of around 50 g of alcohol increases the risk for these cancers by two to three times, compared with the risk in non-drinkers. Additionally, the effects of drinking and smoking seem to be multiplicative. Furthermore, in populations that are deficient in the activity of aldehyde dehydrogenase, an enzyme involved in the catabolism of ethanol, much higher risks for oesophageal cancer after alcohol consumption have been reported than in populations with a fully active enzyme.⁸

A large number of cohort and case-control studies provide strong evidence that the consumption of alcohol is an independent risk factor for primary liver cancer. Cirrhosis and other liver diseases often occur before the cancer becomes manifest and patients with these disorders generally reduce their alcohol intake. Therefore, the effect of alcohol consumption on the risk for liver cancer is difficult to quantify.⁹

More than 100 epidemiological studies that assessed the association between alcohol consumption and breast cancer in women consistently found an increased risk with increasing alcohol intake. A pooled analysis of 53 studies on more than 58 000 women with breast cancer showed that daily consumption of about 50 g of alcohol is associated with a relative risk of about 1.5 (95% confidence interval 1.3–1.6), compared with that in non-drinkers.¹⁰ For regular consumption of even 18 g of alcohol per day the relative risk is significantly increased.¹⁰

The association between alcohol consumption and colorectal cancer

has been reported on by more than 50 prospective and case-control studies. Pooled results from eight cohort studies¹¹ and data from recent meta-analyses provide evidence for an increased relative risk of about 1.4 for colorectal cancer with regular consumption of about 50 g of alcohol per day, compared with that in non-drinkers. This association seems to be similar for colon cancer and for rectal cancer.^{11,12}

By contrast, both cohort and case-control studies provide consistent evidence of no increase in risk for renal-cell cancer with increasing alcohol consumption. In several studies, increasing alcohol intake was associated with a significantly lower risk for renal-cell cancer. This inverse trend was seen in both men and women.^{13,14} Furthermore, two prospective cohort studies and several large case-control studies showed an inverse association or no association between alcohol consumption and non-Hodgkin lymphoma; most studies showed a lower risk in drinkers than in non-drinkers.^{15,16} For cancers of the lung and stomach, there were suggestions that alcohol consumption might be associated with an increased risk, but confounding by smoking and dietary habits could not be ruled out. For other cancers, the evidence of an association between alcohol consumption and cancer risk was generally sparse or inconsistent.

In animals, administration of ethanol in drinking-water caused a dose-related increase in the incidence of hepatocellular adenomas and carcinomas in male mice,¹⁷ an increased incidence of head and neck carcinomas in male and female rats, an increased incidence of fore-stomach carcinomas, testicular interstitial-cell adenomas, and osteosarcomas of the head, neck, and other sites in male rats,¹⁸ and of

mammary adenocarcinomas in female rats.¹⁹ In most of the studies in which ethanol was co-administered with known carcinogens, it enhanced the carcinogenic effect. The Working Group concluded that there is “sufficient evidence” for the carcinogenicity of ethanol in animals.²⁰

The major alcohol-metabolising enzymes in humans are the alcohol dehydrogenases (ADH) that oxidise alcohol (ethanol) to acetaldehyde, and the aldehyde dehydrogenases (ALDH) that detoxify acetaldehyde to acetate. The variant allele ALDH2*2, which encodes an inactive subunit of the enzyme ALDH2, is dominant and highly prevalent in certain populations of Asian ethnicity (28–45%), but rare in other ethnic groups.²¹ Most homozygous carriers of this allele (ALDH2*2/*2) are abstainers or infrequent drinkers, because the enzyme deficiency would cause a strong facial flushing response, physical discomfort, and severe toxic reactions. In heterozygous carriers (ALDH2*1/*2, with about 10% residual ALDH2 activity) these acute adverse effects are less severe, but when alcohol is consumed these carriers are at high risk for several alcohol-related aerodigestive cancers. For example, genetic epidemiological studies provide strong evidence that the heterozygous genotype contributes substantially to the development of oesophageal cancer related to alcohol consumption, with relative risks—compared with carriers of the homozygous ALDH2*1/*1 genotype, which encodes the active enzyme—of up to 12 for heavy drinkers.²² Compared with those with the ALDH2*1/*1 genotype, the heterozygous carriers have higher levels of acetaldehyde in blood and saliva after alcohol drinking, and in a recent study higher levels of acetaldehyde-related DNA adducts have been measured in their lymphocytes.²³

Overall, the Working Group confirmed that alcoholic beverages are “carcinogenic to humans” (Group 1),²⁰ and concluded that the occurrence of malignant tumours of the oral cavity,

pharynx, larynx, oesophagus, liver, colorectum, and female breast is causally related to alcohol consumption. For renal-cell cancer and non-Hodgkin lymphoma the Working Group concluded that there is “evidence suggesting lack of carcinogenicity” for alcohol drinking.²⁰

The addition of breast cancer and colorectal cancer, two of the most common cancers worldwide, to the list of cancers causally related to alcohol consumption suggests that the proportion of cancers attributable to alcohol consumption is higher than previously estimated. Because these associations were generally noted with different types of alcoholic beverage, and in view of the carcinogenicity of ethanol in animals, the Working Group also classified ethanol in alcoholic beverages as “carcinogenic to humans” (Group 1).²⁰

The Working Group agreed that the substantial mechanistic evidence in humans deficient in aldehyde dehydrogenase indicates that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to causing malignant oesophageal tumours.

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- IARC. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 96. Alcoholic beverage consumption and ethyl carbamate (urethane). Lyon: International Agency for Research on Cancer (in press).
- WHO. WHO Global Status Report on Alcohol 2004. Geneva: World Health Organization, Department of Mental Health and Substance Abuse.
- Ezzati M, Rodgers A, Lopez AD, et al. Mortality and burden of disease attributable to individual risk factors. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. Comparative quantification of health risks. Global and regional burden of disease attributable to selected major risk factors. Volume 2. Geneva: World Health Organization, 2004: 2141–66.
- WHO. WHO Global Alcohol Database. <http://www.who.int/globalatlas/default.asp> (accessed March 2, 2007).
- Boeing H. Alcohol and risk of cancer of the upper gastrointestinal tract: first analysis of the EPIC data. In: Riboli E, Lambert R, eds. Nutrition and lifestyle: opportunities for cancer prevention. IARC Sci Publ 156. Lyon: International Agency for Research on Cancer, 2002: 151–54.
- Talamini R, Bosetti C, La Vecchia C, et al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. *Cancer Causes Control* 2002; **13**: 957–64.

- Znaor A, Brennan P, Gajalakshmi V, et al. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer* 2003; **105**: 681–86.
- Yokoyama A, Omori T. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. *Alcohol* 2005; **35**: 175–85.
- Bagnardi V, Blangiardo M, La Vecchia C, et al. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* 2001; **85**: 1700–05.
- Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 2002; **87**: 1234–45.
- Cho E, Smith-Warner SA, Ritz J, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med* 2004; **140**: 603–13.
- Moskal A, Norat T, Ferrari P, Riboli E. Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. *Int J Cancer* 2007; **120**: 664–71.
- Hu J, Mao Y, White K. Diet and vitamin or mineral supplements and risk of renal cell carcinoma in Canada. *Cancer Causes Control* 2003; **14**: 705–14.
- Hsu CC, Chow WH, Boffetta P, et al. Dietary risk factors of kidney cancer in eastern and central Europe. *Am J Epidemiol* 2007 (in press).
- Morton LM, Zheng T, Holford TR, et al. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. *Lancet Oncol* 2005; **6**: 469–76.
- Besson H, Brennan P, Becker N, et al. Tobacco smoking, alcohol drinking and non-Hodgkin's lymphoma: a European multicenter case-control study (EpiLymph). *Int J Cancer* 2006; **119**: 901–08.
- US National Toxicology Program. Toxicology and Carcinogenesis Studies of Urethane + Ethanol (CAS Nos. 51-79-6 & 64-17-5) in F344/N Rats and B6C3F1 Mice (drinking-water studies). NTP Technical Report No. 510. Bethesda: National Institutes of Health, 2004.
- Soffritti M, Belpoggi F, Cevolani D, et al. Results of long-term experimental studies on the carcinogenicity of methyl alcohol and ethyl alcohol in rats. *Ann N Y Acad Sci* 2002; **982**: 46–69.
- Watabiki T, Okii Y, Tokiyasu T, et al. Long-term ethanol consumption in ICR mice causes mammary tumor in females and liver fibrosis in males. *Alcohol Clin Exp Res* 2000; **24**: 1175–225.
- IARC. Preamble to the IARC monographs on the evaluation of carcinogenic risks to humans. <http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf> (accessed March 2, 2007).
- Goedde HW, Agarwal DP, Fritze G, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet* 1992; **88**: 344–46.
- Lewis SJ, Smith GD. Alcohol, ALDH2, and esophageal cancer: a meta-analysis which illustrates the potentials and limitations of a Mendelian randomization approach. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1967–71.
- Matsuda T, Yabushita H, Kanaly RA, et al. Increased DNA damage in ALDH2-deficient alcoholics. *Chem Res Toxicol* 2006; **19**: 1374–78.

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Conflicts of interests

DWC is a member of the Medical Advisory Council of the Alcoholic Beverages Medical Research Foundation. All other members of the Working Group declared no conflicts of interests.

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None

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None