Moderate Alcohol Intake and Cancer Incidence in Women

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Background With the exception of breast cancer, little is known about the effect of moderate intakes of alcohol, or of particular types of alcohol, on cancer risk in women.

Methods A total of 1 280 296 middle-aged women in the United Kingdom enrolled in the Million Women Study were routinely followed for incident cancer. Cox regression models were used to calculate adjusted relative risks and 95% confidence intervals (CIs) for 21 site-specific cancers according to amount and type of alcoholic beverage consumed. All statistical tests were two-sided.

Results A quarter of the cohort reported drinking no alcohol; 98% of drinkers consumed fewer than 21 drinks per week, with drinkers consuming an average of 10 g alcohol (1 drink) per day. During an average 7.2 years of follow-up per woman 68 775 invasive cancers occurred. Increasing alcohol consumption was associated with increased risks of cancers of the oral cavity and pharynx (increase per 10 g/d = 29%, 95% CI = 14% to 45%, P_{trend} < .001), esophagus (22%, 95% CI = 8% to 38%, P_{trend} = .002), larynx (44%, 95% CI = 10% to 88%, P_{trend} = .008), rectum (10%, 95% CI = 2% to 18%, P_{trend} = .02), liver (24%, 95% CI = 2% to 51%, P_{trend} = .03), breast (12%, 95% CI = 9% to 14%, P_{trend} < .001), and total cancer (6%, 95% CI = 4% to 7%, P_{trend} < .001). The trends were similar in women who drank wine exclusively and other consumers of alcohol. For cancers of the upper aerodigestive tract, the alcohol-associated risk was confined to current smokers, with little or no effect of alcohol among never and past smokers ($P_{heterogeneity}$ < .001). Increasing levels of alcohol consumption were associated with a decreased risk of thyroid cancer (P_{trend} =.005), non–Hodgkin lymphoma (P_{trend} =.001), and renal cell carcinoma (P_{trend}=.03).

Conclusions Low to moderate alcohol consumption in women increases the risk of certain cancers. For every additional drink regularly consumed per day, the increase in incidence up to age 75 years per 1000 for women in developed countries is estimated to be about 11 for breast cancer, 1 for cancers of the oral cavity and pharynx, 1 for cancer of the rectum, and 0.7 each for cancers of the esophagus, larynx and liver, giving a total excess of about 15 cancers per 1000 women up to age 75.

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Many epidemiological studies have investigated the relationship between drinking alcohol and the risk of cancer. In 2007, the International Agency for Research on Cancer concluded that there is sufficient evidence that alcohol causes cancer of the oral cavity, pharynx, esophagus, larynx, colorectum, liver, and female breast (1). Results from some previous studies suggested that alcohol may reduce the risk of non–Hodgkin lymphoma, thyroid cancer, and renal cell carcinoma, but the findings are inconsistent (2–4). Most of the evidence for an association of alcohol with cancer risk comes from studies of men with high intakes and, with the exception of breast cancer (5), little is known about the risk of cancer associated with more moderate intakes typically consumed by women. Even for breast cancer, little is known about the effects of particular types of alcohol or whether the association differs according to other lifestyle factors such as use of hormone replacement therapy.

The main aim of this report is to describe the relationship of low to moderate levels of alcohol intake, mostly below 21 drinks per week (i.e fewer than 3 drinks per day or 30 g alcohol per day), with subsequent risk of cancer, overall and at particular sites, in a large cohort of women in the United Kingdom. A secondary aim is to examine the associations found by the type of alcoholic drink and to determine whether they are modified by other major risk factors for cancer.

Participants and Methods

Data Collection, Follow-up, and Definitions

The Million Women Study has been described previously (6). In 1996–2001 a total of 1.3 million middle-aged women who attended breast cancer screening clinics in the United Kingdom completed

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a questionnaire that asked for sociodemographic and other personal information, including how much wine, beer, and spirits they drank on average each week. Information on whether the line consumed was red, white or both was also recorded. In a follow-up survey, done about 3 years after recruitment, study participants were again asked to report the usual number of alcoholic drinks consumed per week. The study questionnaires are available on the study web site (www.millionwomenstudy.org). All participants gave written informed consent to take part in the study, and approval was provided by the Oxford and Anglia Multi-Centre Research and Ethics Committee.

All study participants were "flagged" on the National Health Service (NHS) Central Registers, which routinely provide the investigators with information on deaths and incident cancers, and code the cause of death and cancer site according to the the International Classification of Diseases, 10th Revision (ICD-10) (7). For this analysis, we examined the 21 most common cancer sites: oral cavity and pharynx (C00–C14); esophagus (C15); stomach (C16); colon (C18); rectum (C19–C20); liver (C22); pancreas (C25); larynx (C32); lung (C34); malignant melanoma (C43); breast (C50); cervix (C53); endometrium (C54); ovary (C56); renal cell carcinoma (C64); bladder (C67); brain (C71); thyroid (C73); non–Hodgkin lymphoma (C82–C85); multiple myeloma (C90); and leukemia (C91–C93, C95). Cancers of the esophagus were classified according to histological subtype and defined as adenocarcinoma (ICD-10-0 morphology codes under ICD-10 C15: 81903, 81453, 81403, 81443, 82113, 82603, 84803, and 84813) or nonadenocarcinoma (all other morphology codes).

Statistical Analysis

Of the 1 332 425 women potentially eligible for these analyses, we excluded 42 408 who had a cancer (except nonmelanoma skin cancer [ICD-10 C44]) registered before recruitment and a further 9721 who had missing information on alcohol intake, leaving 1 280 296 for the main analyses. The analyses of endometrial and cervical cancer were restricted to women who reported at recruitment not having had a hysterectomy (n = 954 450), and analyses of ovarian cancer were restricted to women who reported not having had a bilateral oophorectomy (n = 1 116 460).

Women were categorized into five groups according to the total number of alcoholic drinks that contained about 10 g alcohol consumed per week, as reported in the recruitment questionnaire (ie, 1 glass of wine, half a pint of beer, or 1 measure of spirits). For wine, a standard glass volume is 125 mL and standard alcohol content is 8.8 g/100 mL for white wine and 9.5 g/100 mL for red wine, for beer a standard volume is 284 mL and alcohol content 3.2 g/100 mL, and for spirits a standard volume is 23 mL and alcohol content 31.7 g/100 mL (8). The categories used in these analyses were 0, less than or equal to 2, 3–6, 7–14, or greater than or equal to 15 drinks per week, the cut points based on an approximately equal distribution among the drinkers, except for the highest category of alcohol intake which was of a priori interest. Women who reported drinking no alcohol at the time they joined the study may be a biased group as some may have stopped drinking due to ill heath. Therefore, women who reported drinking some alcohol, but less than or equal to 2 drinks per week, were taken as the reference group. We adjusted for measurement error in reported alcohol intake using the regression dilution approach (9,10), whereby women were categorized into five levels of alcohol intake, based on consumption reported at recruitment, but the average intake of alcohol (expressed as g/d) in each category was taken to be that reported in the follow-up survey, about 3 years later, using data from 708 265 women. It was assumed that each drink contains 10 g alcohol, and for women who reported at resurvey drinking less than one drink per week, daily consumption was taken to be zero.

Woman-years were calculated from the date of recruitment to the date of any cancer registration (other than nonmelanoma skin cancer), death, or the last date of follow-up, whichever came first. The last date of follow-up in most areas was December 31, 2006; but in the West Midlands and the Thames region it was June 30, 2006; in the North Yorkshire and North West Merseyside regions it was December 31, 2005; and in Scotland it was December 31, 2002. Cancer incidence data were incomplete beyond these dates.

Cox regression models were applied to estimate relative risks (RRs) of each cancer site of interest associated with various measures of alcohol intake, using attained age as the underlying time variable. There was no evidence that the proportional hazard assumption was violated. Data were stratified by region of residence (10 areas covered by 10 cancer registries), and adjustments were made for quintiles of socioeconomic status [using the Townsend deprivation index (11), which includes measures of unemployment, overcrowding, owner–occupier status, and car ownership for the postcode area of each participant, based on the 1991 National Census]; smoking (never, past, or current smokers, <10, 10–19, or ≥20 cigarettes per day); body mass index (<25, 25–29, or ≥30 kg/m^2); physical activity

CONTEXT AND CAVEATS

Prior knowledge

With the exception of breast cancer, there was little information on the cancer risks conferred by alcohol consumption in women.

Study design

Prospective cohort study with alcohol consumption determined on the basis of a questionnaire and information on incidence of specific cancers obtained from a national registry. Cox regression models were used to estimate cancer risks associated with alcohol consumption after adjustment for other risk factors.

Contribution

Increasing but moderate alcohol consumption in women was determined to be associated with an increased risk of cancers of the oral cavity and pharynx, esophagus, larynx, rectum, breast, and liver, and with a decreased risk for thyroid cancer, non–Hodgkin lymphoma, and renal cell carcinoma. No differences in cancer risks were observed between drinkers of wine only and other consumers of alcohol.

Implications

In middle-aged women, moderate alcohol consumption increases the risk of cancer overall; each additional drink regularly consumed per day may account for approximately 15 excess cancers per 1000 women up to age 75 in this age group in developed countries.

Limitations

The study could not address the risk conferred by heavy sustained drinking due to the composition of the cohort.

From the Editors

(strenuous exercise <1 or ≥1 times per week); ever use of oral contraceptives (yes or no); and use of hormone replacement therapy (current, past, or never). There was a relatively low proportion of missing values for each covariate entered in the final model (<1.5% for most variables), and these were assigned to a separate stratum for each variable. However, to assess the effect of any residual confounding on the main findings, sensitivity analyses were performed in which the association of alcohol intake and cancer risk was examined only among those women with complete information on all adjustment variables (n = 1 086 837); the relative risk estimates did not materially change for any cancer endpoint. All variables included in the models were derived from information reported at recruitment, unless otherwise stated. When more than two groups are compared, variances were estimated by treating the relative risks as floating absolute risks, yielding floated confidence intervals (FCIs) (12). The use of floating absolute risks rather than conventional methods does not alter the relative risks but slightly reduces the variances attributed to the relative risks that are not defined as 1.0. This enables the reader to make valid comparisons between any two exposure groups, even if neither is the baseline group. Any comparison between two log relative risks must, therefore, take the variation in each estimate into account [by summing their variances, as described in detail elsewhere (13)]. For any comparison between two alcohol categories, conventional confidence intervals (CIs) were calculated. The test for trend across categories of intake was based on the mean alcohol intake (g/d) reported at resurvey in each group.

The association of alcohol intake and cancer incidence was summarized in the form of a log-linear trend in risk per 10 g/d alcohol (broadly equivalent to one extra drink of alcohol per day or an increase of one unit per day) among drinkers only; statistical heterogeneity of the association of alcohol with cancer risk according to subgroups of type of alcoholic drink, smoking status, and, for breast cancer, use of hormone replacement therapy was assessed using chi-square tests.

Where results are presented in the form of plots, the relative risks and their corresponding confidence intervals or floated confidence intervals are represented by squares and lines, with the area of the square inversely proportional to the variance of the logarithm of the corresponding relative risk. This provides an appropriate indication of the amount of statistical information involved for that particular estimate.

We estimated the excess risk of cancer for every 10 g/d increase in alcohol intake among women in developed countries. This was done by applying the relative risks obtained here to cumulative cancer incidence rates (up to age 75 years for around the year 2000) typically found in developed countries with a low to moderate alcohol intake among women (14), assuming that the relative risks apply to the general population up to age 75 years. We also estimated the proportion of cancers attributable to alcohol in women in the United Kingdom, taking the national average alcohol intake to be 9.3 g/d and assuming that 31% of UK women are nondrinkers (15,16). All statistical tests were two-sided, and all statistical analyses were performed with Stata version 9.0 (Stata, TX).

Results

A total of 1 280 296 middle-aged women recruited in 1996–2001, all of whom were flagged on the NHS Central Registers for automatic notification to the investigators of cancer incidence, were included in these analyses. Overall, the participants were aged 55 years on average at recruitment and had a low to moderate alcohol consumption: 24% reported that they were nondrinkers, 29% reported drinking on average less than or equal to 2 drinks per week, 23% reported drinking 3–6 drinks per week, 19% reported drinking 7–14 drinks per week, and 5% reported drinking greater than or equal to 15 drinks per week. Among drinkers, 98% consumed fewer than 21 drinks per week. The average alcohol intake was 4.4 drinks per week (ie, 6.3 [SD 8.2] g/d) among all women and 7.1 drinks per week (ie, 10 [SD 8.4] g/d) among drinkers (Table 1).

Women who drank alcohol were likely to be younger, leaner, more affluent, and to do strenuous exercise more frequently than nondrinkers (Table 1). Drinkers were also more likely to have ever used oral contraceptives and to be currently using hormone replacement therapy. Among drinkers, the proportion of current smokers increased with increasing alcohol intake. Approximately 30% of the population reported that they drank wine exclusively, with an average alcohol intake of 9.4 (SD 8.1) g/d; 47% drank other alcoholic drinks (defined as women who drank beer and/or spirits exclusively or women who drank a mixture of wine, beer, and/or spirits), with an average alcohol intake of 10.7 (SD 8.6) g/d. Women who drank wine exclusively also tended to be more affluent, to be leaner, or to take strenuous exercise more frequently and were less likely to be current smokers compared with other drinkers (Table 1). Overall, 93% of women who reported at entry that they were nondrinkers also reported in the follow-up survey that they drank no alcohol or less than one drink per week. Among the 7% who reported being nondrinkers at entry but reported 3 years later drinking some alcohol, most (58%) reported that they drank only 1 or 2 drinks per week.

Women were followed up for cancer incidence over 9.2 million person-years, for an average of 7.2 years per woman (Table 1). A total of 68 775 incident cancers were notified by the NHS Central Registers. We calculated the relative risk at individual cancer sites by categories of alcohol consumption at recruitment (Table 2). Nondrinkers had an increased risk for several cancer sites compared with women who drank fewer than or equal to 2 drinks per week; increases were statistically significant for cancers of the oral cavity and pharynx, esophagus, stomach, liver, lung, cervix, endometrium, and renal cell carcinoma. However, because we cannot differentiate between former drinkers and lifelong never drinkers, all subsequent analyses are restricted to drinkers.

Among drinkers, increasing amount of alcohol consumed was statistically significantly associated with increased risks of cancers of the oral cavity and pharynx ($P_{trend} < .001$), esophagus ($P_{trend} = .002$), larynx ($P_{trend} = .008$), rectum ($P_{trend} = .02$), liver ($P_{trend} = .03$), breast ($P_{trend} < .001$), and all cancers combined ($P_{trend} < .001$). When cancer of the esophagus was classified further into nonadenocarcinoma and adenocarcinoma subtypes, alcohol intake was strongly associated with nonadenocarcinoma ($P_{trend} < .001$) and was not associated with adenocarcinoma of the esophagus ($P_{trend} = .2$). There was also evidence for a statistically significant reduction in the risk of thyroid cancer, non–Hodgkin lymphoma, and renal cell carcinoma with increasing alcohol consumption ($P_{trend} = .005$, .001, and .03, respectively). For all other cancer sites, there were no statistically significant trends with alcohol intake.

Table 1. Characteristics of the study population at recruitment, and details of follow-up, according to amount and type of alcohol intake in the Million Women Study*

		Drinkers at recruitment						
		By category of alcohol intake				By type of alcohol		
	Nondrinkers at recruitment†	≤2 drinks per week‡	3–6 drinks per week‡	7–14 drinks per week‡	≥15 drinks per week‡	Drinkers of wine exclusively	Other drinkers§	All women
Characteristic at recruitment								
Number of women	306 760	371 453	293 891	240 894	67 292	378 011	595 519	1 280 296
Alcohol intake, mean (SD), g/d‖	0.4 (1.8)	2.3 (3.3)	6.3 (4.8)	13.8 (7.2)	24.4 (11.4)	9.4 (8.1)	10.7 (8.6)	6.3 (8.2)
Age, mean (SD), y	56.5 (4.5)	56.1 (4.4)	55.6 (4.4)	55.3 (4.3)	55.1 (4.3)	55.8 (4.4)	55.6 (4.4)	55.9 (4.4)
Socioeconomic status (% in lowest quintile)	29.3	18.0	16.3	16.1	15.5	14.1	18.6	19.8
Current smokers (%)	26.2	16.6	17.2	22.4	25.9	15.3	21.2	20.6
Body mass index, mean (SD), kg/m^2	27.2 (5.4)	26.4 (4.7)	26.0 (4.4)	25.4 (4.0)	25.4 (4.1)	25.7 (4.4)	26.1 (4.5)	26.2 (4.7)
Strenuous exercise (% more than once a week)	17.3	19.3	22.0	25.3	27.8	22.7	21.8	21.0
Ever use of oral contraceptives (%)	49.4	57.7	64.3	69.4	73.8	61.0	65.5	60.3
Current use of hormone replacement therapy (%)	28.9	32.7	35.7	38.4	39.5	34.7	36.0	33.9
Follow-up for cancer incidence								
Woman-years of follow-up (in millions)	2.18	2.68	2.11	1.71	0.48	2.74	4.24	9.16
Incident cancers (n)	17 416	19 307	15 183	12 838	4031	19 649	31 710	68 775

* Percentage excludes missing values (proportion of missing values: <1.5% for socioeconomic status, use of oral contraceptives, use of hormone replacement therapy, and smoking status [5.7% for more detailed information on smoking], 3.5% for physical activity, and 5.1% for body mass index).

† Nondrinkers include never drinkers and former drinkers.

‡ One drink or unit is equivalent to about 10 g of alcohol.

§ Other drinkers are defined as drinkers of beer and/or spirits exclusively or a mixture of wine, beer, and/or spirits.

‖ To allow for regression dilution, mean alcohol intake (g/d) in each category is the remeasured value taken 3 years after recruitment (9).

We estimated the change in the absolute incidence of cancer per 10-g/d increase in alcohol intake for the cancers with a statistically significant increase in risk (shown in Figure 1). In around the year 2000, cumulative incidence rates per 1000 women in developed countries by age 75 years were typically 5 for cancers of the oral cavity and pharynx, 3 (liver and esophagus), 1.5 (larynx), 10 (rectum), and 95 (breast) (14). Applying the relative risks shown in Figure 1 to these cumulative incidence rates, we calculated that the excess incidence of cancer up to age 75 years associated with a 10-g increase in alcohol consumption per day is of the order of 1 per 1000 for cancers of the oral cavity and pharynx, 0.7 per 1000 for esophageal cancer, 0.7 per 1000 for cancer of the larynx, 1 per 1000 for rectal cancer, 0.7 per 1000 for liver cancer, and 11 per 1000 for breast cancer. The total excess for these cancers is thus estimated to be about 15 per 1000 women in developed countries up to age 75 years for every additional drink consumed. (The estimated background total cumulative incidence for these cancers is 118 per 1000 up to age 75 years.) We also estimated that in the United Kingdom, alcohol accounts for about 11% of all breast cancers (5000 extra cancers annually), 22% (250 annually) of liver cancers, 9% (500 annually) of rectal cancers, and 25% (1200 annually) of all cancers of the upper aerodigestive tract (defined as cancers of the oral cavity and pharynx, esophagus, and larynx).

Figure 2 shows the estimated increases in relative risk for cancer at sites that we found were statistically significantly associated with alcohol intake or that had been suggested by others to be associated with alcohol intake. Relative risks were calculated per 10-g/d increase in alcohol intake among women who drank wine exclusively and among other drinkers. The differences in risk estimates between those who drank wine exclusively and those who drank only beer and/or spirits or a mixture of alcoholic drinks were not statistically significant for any of the cancer sites examined.

There were 21 971 women with incident breast cancer among the drinkers, and the increase in risk associated with a 10-g/d increase in alcohol intake was similar among women who drank wine exclusively and among other drinkers ($P_{\text{heterogeneity}} = .3$; Figure 3). In addition, there was no evidence of heterogeneity in risk estimates between women who mostly drank white, red, or a mixture of both types of wine (increase in relative risk per 10 g/d alcohol: 9% [95% CI = 3% to 15%], 11% [95% CI = 3% to 19%], and 13% [95% CI = 4% to 24%], respectively; $P_{\text{heterogeneity}} = .8$, or between nonusers and current users of hormone replacement

Table 2. Relative risk (95% floated confidence interval) of incident cancer by alcohol intake reported at recruitment*

Cancer site	All women, n	Nondrinkers†		Women drinking ≤2 drinks per week‡		Women drinking 3–6 drinks per week‡		Women drinking 7–14 drinks per week‡		Women drinking ≥15 drinks per week‡		P_{trend}§
		n	RR (95% FCI)	n	RR (95% FCI)	n	RR (95% FCI)	n	RR (95% FCI)	n	RR (95% FCI)	
All cancers	68 775	17 416	1.04 (1.02 to 1.06)	19 307	1.00 (0.99 to 1.01)	15 183	1.02 (1.00 to 1.03)	12 838	1.05 (1.03 to 1.07)	4031	1.15 (1.11 to 1.18)	<.001
Oral cavity and pharynx	758	201	1.18 (1.02 to 1.36)	179	1.00 (0.86 to 1.16)	158	1.13 (0.97 to 1.32)	142	1.13 (0.96 to 1.34)	78	1.99 (1.59 to 2.50)	<.001
Esophagus	773	239	1.37 (1.20 to 1.57)	178	1.00 (0.86 to 1.16)	157	1.16 (0.99 to 1.36)	139	1.20 (1.02 to 1.42)	60	1.74 (1.34 to 2.25)	.002
Nonadenocarcinoma	395	117	1.56 (1.29 to 1.89)	76	1.00 (0.80 to 1.25)	72	1.22 (0.97 to 1.54)	82	1.56 (1.26 to 1.94)	48	2.99 (2.24 to 4.00)	<.001
Adenocarcinoma	226	76	1.28 (1.01 to 1.63)	60	1.00 (0.77 to 1.29)	55	1.25 (0.96 to 1.62)	27	0.77 (0.53 to 1.13)	8	0.79 (0.39 to 1.59)	.2
Stomach	821	276	1.27 (1.12 to 1.44)	220	1.00 (0.88 to 1.14)	176	1.06 (0.91 to 1.22)	109	0.79 (0.65 to 0.95)	40	1.02 (0.74 to 1.39)	.3
Colon	4169	1047	1.00 (0.94 to 1.07)	1235	1.00 (0.95 to 1.06)	927	0.99 (0.93 to 1.06)	753	1.02 (0.95 to 1.09)	207	1.00 (0.87 to 1.15)	.8
Rectum	2129	496	0.94 (0.86 to 1.03)	621	1.00 (0.92 to 1.08)	479	1.01 (0.92 to 1.11)	402	1.07 (0.97 to 1.18)	131	1.25 (1.06 to 1.49)	.02
Liver	337	114	1.41 (1.16 to 1.72)	83	1.00 (0.80 to 1.24)	58	0.94 (0.72 to 1.21)	59	1.20 (0.93 to 1.55)	23	1.70 (1.12 to 2.56)	.03
Pancreas	1325	378	1.07 (0.97 to 1.20)	382	1.00 (0.90 to 1.11)	255	0.88 (0.78 to 1.00)	237	1.00 (0.88 to 1.14)	73	1.07 (0.85 to 1.35)	.5
Larynx	138	39	1.09 (0.79 to 1.52)	26	1.00 (0.68 to 1.47)	23	1.13 (0.75 to 1.70)	36	1.74 (1.25 to 2.41)	14	2.02 (1.19 to 3.44)	.008
Lung	5203	1735	1.17 (1.12 to 1.23)	1210	1.00 (0.94 to 1.06)	886	0.91 (0.85 to 0.97)	1040	1.06 (1.00 to 1.13)	332	1.01 (0.90 to 1.12)	.2
Malignant melanoma	2459	460	0.80 (0.73 to 0.88)	765	1.00 (0.93 to 1.07)	609	1.00 (0.92 to 1.08)	468	0.96 (0.88 to 1.05)	157	1.17 (1.00 to 1.37)	.3
Breast	28 380	6409	1.00 (0.97 to 1.03)	7841	1.00 (0.98 to 1.02)	6642	1.08 (1.05 to 1.10)	5672	1.13 (1.10 to 1.16)	1816	1.29 (1.23 to 1.35)	<.001
Cervix‖	468	143	1.31 (1.10 to 1.55)	118	1.00 (0.83 to 1.20)	99	1.04 (0.86 to 1.27)	82	0.98 (0.79 to 1.22)	26	1.02 (0.69 to 1.50)	1.0
Endometrium‖	4118	1170	1.06 (1.00 to 1.12)	1264	1.00 (0.95 to 1.06)	897	0.99 (0.92 to 1.05)	597	0.90 (0.83 to 0.97)	190	1.05 (0.91 to 1.22)	.4
Ovary‖	3559	846	0.94 (0.88 to 1.01)	1113	1.00 (0.94 to 1.06)	761	0.89 (0.83 to 0.95)	661	0.97 (0.90 to 1.05)	178	0.94 (0.81 to 1.09)	.6
Renal cell carcinoma	1141	338	1.12 (1.00 to 1.26)	330	1.00 (0.90 to 1.12)	250	1.01 (0.89 to 1.14)	185	0.93 (0.80 to 1.07)	38	0.66 (0.48 to 0.92)	.03
Bladder	928	271	1.06 (0.94 to 1.21)	258	1.00 (0.88 to 1.13)	206	1.05 (0.92 to 1.21)	151	0.91 (0.77 to 1.07)	42	0.86 (0.63 to 1.17)	.2
Brain	908	224	0.94 (0.82 to 1.08)	279	1.00 (0.89 to 1.13)	203	0.96 (0.84 to 1.10)	149	0.90 (0.77 to 1.06)	53	1.17 (0.89 to 1.53)	.9
Thyroid	421	116	1.10 (0.91 to 1.33)	135	1.00 (0.84 to 1.19)	96	0.90 (0.74 to 1.10)	61	0.70 (0.55 to 0.91)	13	0.54 (0.31 to 0.92)	.005
Non–Hodgkin lymphoma	2320	616	1.03 (0.95 to 1.12)	699	1.00 (0.93 to 1.08)	545	1.02 (0.94 to 1.11)	368	0.86 (0.78 to 0.96)	92	0.77 (0.62 to 0.94)	.001
Multiple myeloma	786	213	1.06 (0.92 to 1.22)	244	1.00 (0.88 to 1.14)	159	0.86 (0.74 to 1.01)	134	0.94 (0.79 to 1.12)	36	0.91 (0.66 to 1.27)	.6
Leukemia	993	251	0.98 (0.86 to 1.11)	305	1.00 (0.89 to 1.12)	214	0.93 (0.81 to 1.07)	164	0.92 (0.79 to 1.07)	59	1.19 (0.92 to 1.53)	.6
Other	4917	1468	1.19 (1.12 to 1.25)	1362	1.00 (0.95 to 1.06)	987	0.95 (0.89 to 1.01)	854	1.00 (0.94 to 1.07)	246	1.00 (0.88 to 1.14)	.8

* Adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives, and hormone replacement therapy. RR = relative risk; FCI = floated confidence interval.

† Nondrinkers include never drinkers and former drinkers.

‡ One drink or unit is equivalent to 10-g alcohol.

§ Test for trend was calculated among drinkers only, and categories are scored according to the mean alcohol intake reported at resurvey in each group (2.33, 6.31, 13.84, and 24.39 g/d) (9).

‖ Excluding women who had had a hysterectomy for cancer of the endometrium and cervix and bilateral oophorectomy for cancer of the ovary.

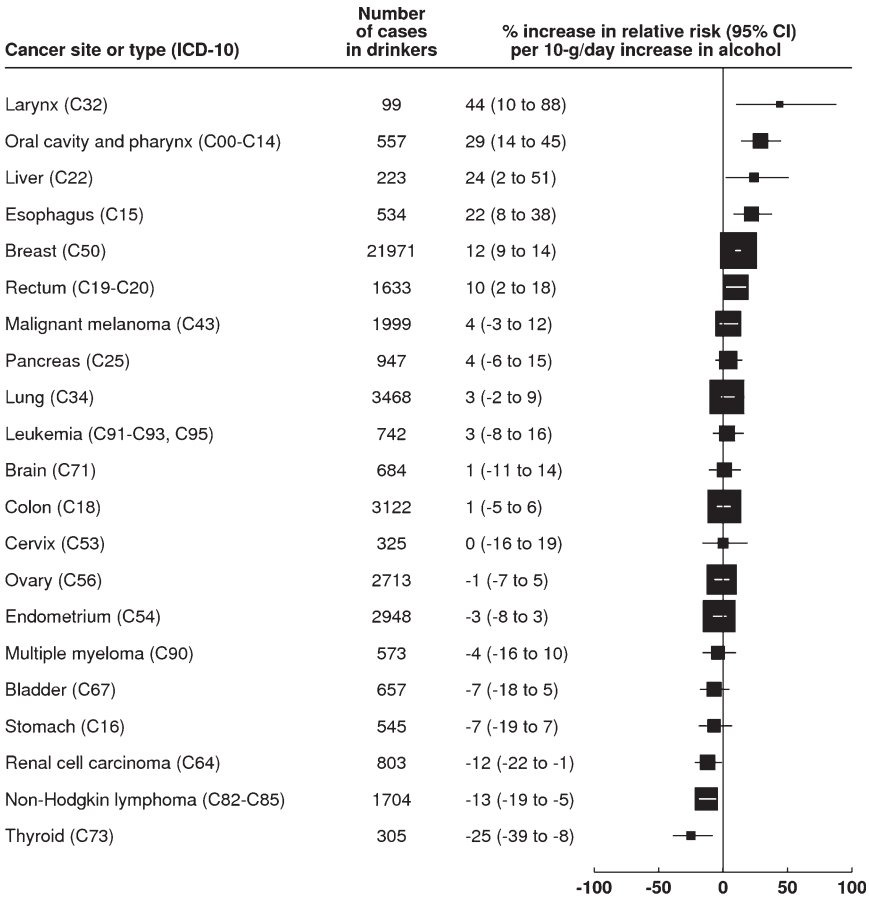

Figure 1. Estimated increase in the relative risk (95% confidence interval) of incident cancer per 10-g/d increase in alcohol intake (drinkers only). Analyses are adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives and hormone replacement therapy. CI = confidence interval. ICD-10 = International Classification of Diseases, 10th Revision (the C00-C97 codes refer to malignant neoplasm codes as defined in ICD-10).

therapy (11% [95% CI = 8% to 14%] and 12% [95% CI = 8% to 15%], respectively; $P_{\text{heterogeneity}} = .8$).

Because smoking is a strong risk factor for cancers of the oral cavity and pharynx, esophagus, and larynx, these cancers of the upper aerodigestive tract were combined giving an overall increase of 27% (95% CI = 17% to 38%) in the relative risk associated with a 10-g/d increase in alcohol, and results were cross-classified by alcohol and tobacco consumption to examine their joint effects (Table 3). Increasing alcohol intake was not associated with an increased risk of cancers of the upper aerodigestive tract in never smokers or past smokers, but was strongly associated with an increased risk among current smokers ($P_{\text{heterogeneity with two degrees of freedom}} < .001$; Figure 4). We next examined the joint association of the type of alcoholic beverage and smoking status on the risk of cancers of the upper aerodigestive tract; the risk associated with alcohol intake in current smokers who drank wine exclusively and in current smokers who drank other alcoholic drinks was similar (increase in RR of 44% [95% CI = 17% to 79%] and 67% [95% CI = 46% to 92%] for a 10-g/d increase in alcohol intake, respectively; $P_{\text{heterogeneity}} = .2$).

Discussion

In this large cohort of middle-aged women in the United Kingdom, a population with low to moderate alcohol consumption where few women regularly drink more than three alcoholic drinks per day, we have shown that the amount drunk is associated with a statistically significantly increased risk of cancers of the oral cavity and pharynx, esophagus, larynx, rectum, liver, breast, and all cancers combined. We also found a statistically significantly reduced risk for thyroid cancer, non–Hodgkin lymphoma, and renal cell carcinoma with increasing alcohol intake. For other cancer sites examined, there was no significant association with alcohol intake.

We estimated that the excess cancer incidence up to age 75 for women in developed countries for every additional 10 g of alcohol (i.e. for every additional drink) regularly consumed per day was typically of the order of 11 per 1000 for breast cancer; 1 per 1000 each for cancers of the oral cavity and pharynx and rectum; and 0.7 per 1000 each for cancers of the esophagus, larynx, and liver, giving a total excess of about 15 per 1000 women up to age 75 years for these cancers. Background incidence rates for these cancers do not vary greatly across most developed countries (14), but where they do, the excess absolute risk would be different. Although the magnitude of the excess absolute risk associated with one additional drink per day may appear small for some cancer sites, the high prevalence of moderate alcohol drinking among women in many populations means that the proportion of cancers attributable to alcohol is an important public health issue. For example, these risk estimates suggest that about 13% of cancers of the breast, upper aerodigestive tract, rectum, and liver in the United Kingdom, that is, 7000 cases annually, are attributable to alcohol and that most of this excess is made up of breast cancer and cancers of the upper aerodigestive tract (with the excess of upper aerodigestive tract cancers confined to smokers).

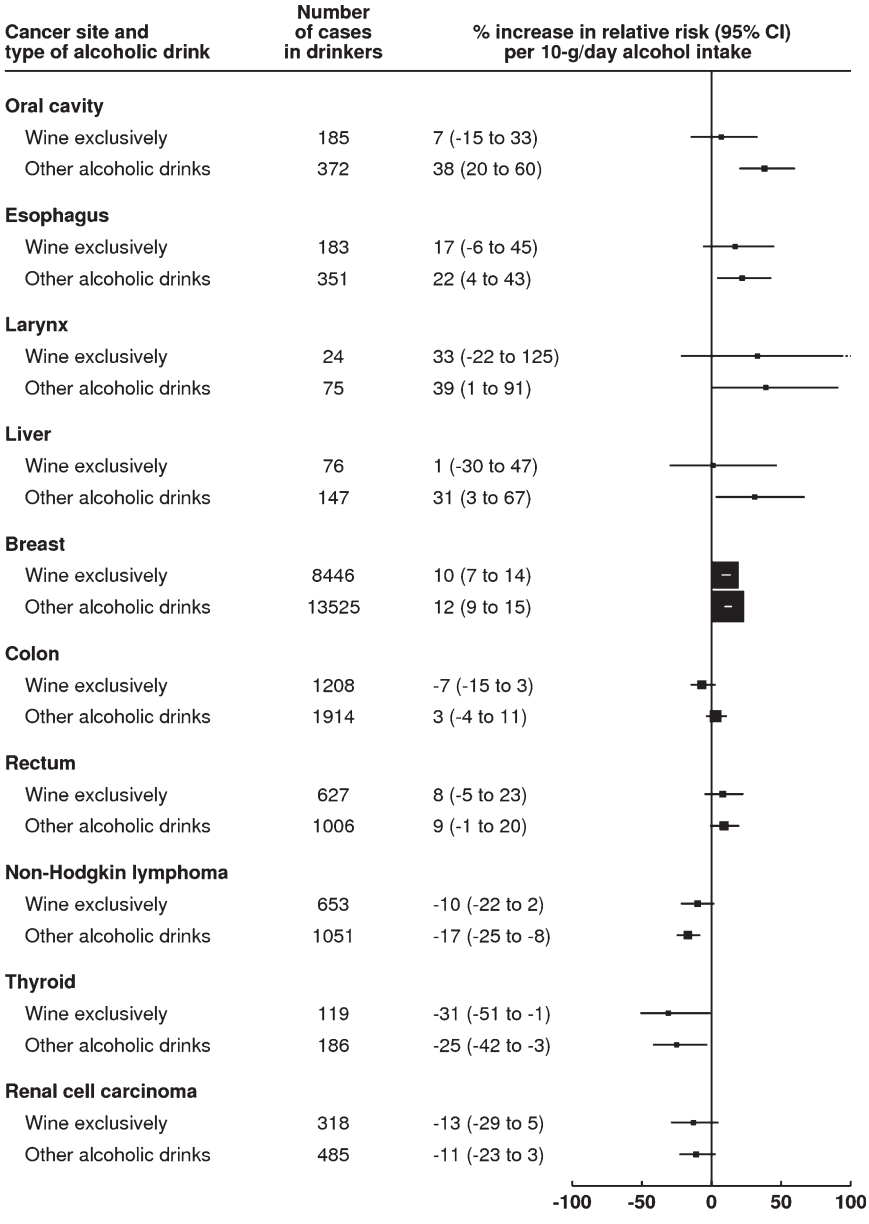

Figure 2. Estimated increase in relative risk (95% confidence interval) for selected cancer sites per 10-g/d increase in alcohol intake and by type of alcohol consumed (drinkers only). Analyses are adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives, and hormone replacement therapy. CI=confidence interval. "Other alcoholic drinks" is defined as drinkers of beer and/or spirits exclusively or a mixture of wine, beer, and/or spirits.

This study has the advantages of having prospectively collected exposure data and complete follow-up for incident cancer. Its large size allows examination of the association of alcohol intake on individual cancer sites. Further, we were able to examine these associations by type of alcoholic beverage, smoking status, and (for breast cancer) use of hormone replacement therapy. Reported alcohol intake was found to be highly reproducible in this study (17), and we addressed regression dilution by using repeat measures of alcohol intake taken approximately 3 years after recruitment (9,10). This cannot address the potential problem of systematic underreporting of alcohol intake that is known to occur in heavy drinkers (18), but this is thought to be less of a problem for low to moderate intake (19). Hence, although some uncertainty remains about the true quantitative effect of alcohol on cancer incidence, systematic underreporting is probably not a major problem here. This study population has an alcohol intake that is comparable to that reported in a national survey of middle-aged women in the United Kingdom (16) and the characteristics of the cohort are broadly similar to that of the female UK population of a similar age (20).

Much of the previous epidemiological evidence of a causal association between alcohol consumption and risk of cancers of the upper aerodigestive tract has been derived from studies of men who were comparatively heavy drinkers (21). The risk of all these cancers is strongly increased among smokers (22). Little has been published on the effect of moderate drinking on the risk of these cancers or on the joint effect with smoking in women. The findings from this study show that a low to moderate alcohol intake is associated with an increased risk of upper aerodigestive tract cancers, but only among current smokers. A similar conclusion was reached in a pooled analysis of 15 case–control studies of head and neck cancer that mostly included men (23). Further, we found that alcohol increased the risk of nonadenocarcinoma but not of adenocarcinoma of the esophagus, which is also consistent with findings

from previous studies (24). Taken together, these results suggest that, in the absence of tobacco smoking, there is little or no effect of moderate alcohol consumption on the risk of cancers of the upper aerodigestive tract. Others have suggested that alcohol may accentuate the known adverse effects of smoking (25) and our data indicate that this is true even at low alcohol intakes. There are several mechanisms through which alcohol might increase risk of cancers of the upper aerodigestive tract among smokers, the most widely accepted being that alcohol may act as a solvent for carcinogens contained in tobacco smoke (26).

We found that the incidence of breast cancer increased with increasing alcohol intakes and that the low to moderate intakes typical of most middle-aged women in the United Kingdom were associated with a statistically significantly increased risk of breast cancer. Our results are consistent with results from a pooled analysis of 53 epidemiological studies worldwide (5), although their finding of a 7.1% (95% CI = 5.5% to 8.7%) increase in risk per 10 g/d of alcohol is slightly lower than our estimate of 12% (95% CI = 9% to 14%), possibly because the pooled analysis did not allow for measurement error. The association of alcohol with breast cancer risk was similar among women who drank wine exclusively and other drinkers, consistent with findings from a meta-analysis of six cohort studies (27). To our knowledge, no other study has examined the association of breast cancer incidence with alcohol intake according to the type of wine consumed and our findings indicate that breast cancer risk is similar in women who drink white wine, red wine, or a mixture of both.

It has been suggested that the association of alcohol intake with breast cancer risk may be stronger in women who are current or past users of hormone replacement therapy compared with never users (28–30), but, similar results from a meta-analysis of the worldwide data and other large studies (5,31–34), we found no such differences. Our risk estimates suggest that about 11% of all breast cancer in women in the United Kingdom, that is, 5000 annually, is attributable to alcohol. Although these results provide no direct evidence about mechanisms of carcinogenesis, there is increasing evidence that moderate alcohol consumption (at the levels studied here) increases circulating concentrations of sex hormones, both in premenopausal and postmenopausal women (35,36).

The International Agency for Research on Cancer concluded that alcohol consumption is causally related to liver and colorectal cancer (1). It is well established that alcohol intake is a cause of chronic liver disease, and previous studies have shown an increased risk of hepatocellular carcinoma among people with a heavy alcohol intake (21,37). The findings from this study suggest that moderate alcohol intake in women is also associated with an increased risk of liver cancer. Our finding that alcohol consumption is weakly associated with an increased risk for cancer of the rectum but probably not with cancer of the colon is consistent with findings from a recent prospective study in Europe (38), although other studies have reported no differences by anatomic subsite (39,40).

The decreased risk for thyroid cancer that we find to be associated with alcohol intake is consistent with results from some studies (41,42), although a meta-analysis of 10 case–control studies (4) and two other cohort studies (43,44) reported no statistically significant associations. Although moderate alcohol consumption has been shown to affect thyroid function (45), the mechanisms by which alcohol may protect against thyroid cancer are unknown. Our finding of a statistically significant reduction in risk for non–Hodgkin

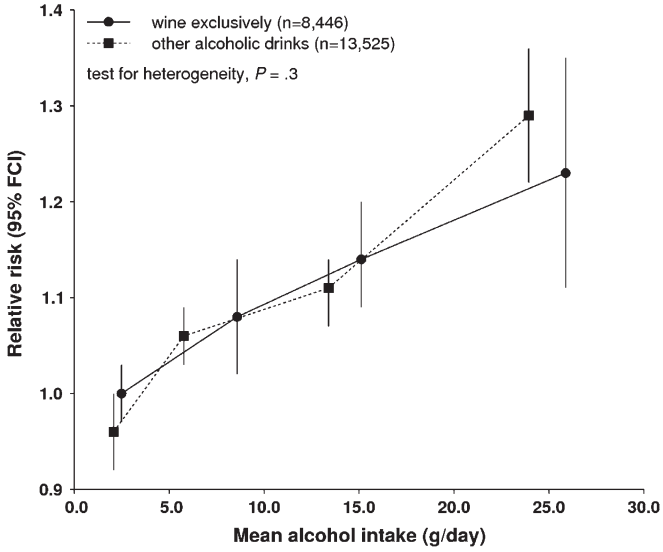

Figure 3. Relative risk (95% floated confidence interval) of breast cancer by amount and type of alcohol consumed (drinkers only). The relative risk is plotted against the mean remeasured value of alcohol intake (g/d) in each category. Analyses are adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives and hormone replacement therapy. FCI = floated confidence interval. "Other alcoholic drinks" is defined as drinkers of beer and/or spirits exclusively or a mixture of wine, beer, and/or spirits.

Table 3. Relative risk (95% floated confidence interval) for cancers of the upper aerodigestive tract by alcohol intake and smoking reported at recruitment (drinkers only)*

Alcohol intake (drinks per week)†	Never smokers		Past smokers		Current smokers	
	No. of cancers	RR (95% FCI)	No. of cancers	RR (95% FCI)	No. of cancers	RR (95% FCI)
≤2	165	1.00 (0.86 to 1.17)	88	1.28 (1.04 to 1.58)	112	2.54 (2.10 to 3.06)
3–6	121	1.04 (0.87 to 1.25)	75	1.22 (0.97 to 1.53)	126	3.57 (2.99 to 4.26)
≥7	83	0.93 (0.75 to 1.16)	116	1.46 (1.22 to 1.75)	257	5.22 (4.60 to 5.92)
P_{trend}‡		.8		.09		<.001

* Includes ICD-10 C00-C14, C15 and C32. All analyses are adjusted for age, region of residence, socioeconomic status, body mass index, physical activity, use of oral contraceptives and hormone replacement therapy. RR = relative risk; FCI = floated confidence interval. ICD-10 = International Classification of Diseases, 10th Revision.

† One drink or unit is equivalent to about 10-g alcohol.

‡ The test for trend was calculated among drinkers only, and categories are scored according to the mean alcohol intake reported at resurvey in each group (2.18, 6.03, and 15.03 g/d in never smokers; 2.59, 6.66, and 16.89 g/d in past smokers; 2.51, 6.81, and 17.73 g/d in current smokers) (9).

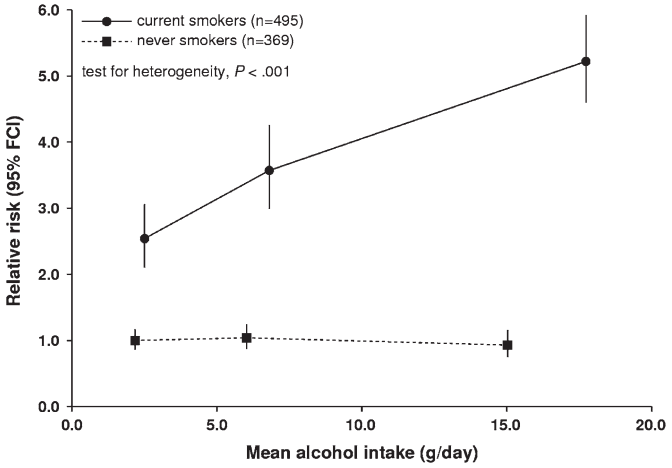

Figure 4. Relative risk (95% floated confidence interval) of cancers of the upper aerodigestive tract (cancer of the oral cavity and pharynx, lanynx and esophagus by alcohol intake and smoking (drinkers only). The relative risk is plotted against the mean remeasured value of alcohol intake (g/d) in each category. Analyses are adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives, and hormone replacement therapy. FCI = floated confidence interval.

lymphoma is consistent with results from a pooled analysis of nine case–control studies (2); to date, two cohort studies have examined this in detail, both of which have reported a statistically significant reduction in risk (46,47). The decrease in risk of renal cell carcinoma associated with moderate alcohol intake is consistent with findings from a recent pooled analysis of 12 prospective studies, seven of which had not previously reported on this association (3). The mechanisms by which moderate alcohol may protect against the risk of non–Hodgkin lymphoma and renal cell carcinoma are also not known.

A limitation of this study is that we were not able to assess the cancer risk for never drinkers and former drinkers separately because the recruitment questionnaire did not discriminate between lifelong nondrinkers and those who had stopped drinking. The increased risk seen in women who were currently nondrinkers compared with light drinkers for many cancer sites suggests that many nondrinkers may be former drinkers who have stopped drinking due to illness, and this may have caused a spuriously high relative risk in this group (48). Because of this, using current nondrinkers as the reference group category may not be appropriate and so nondrinkers were not included in out trend analyses of the association of the amount of alcohol consumed with cancer risk. Although our analyses consider the effect of usual alcohol intake in middle age, we were not able to assess the impact of changes in lifetime alcohol consumption. Finally, the low prevalence of heavy drinking in this cohort meant that we were not able to assess the association of heavy, sustained drinking on subsequent cancer risk.

All risk estimates were adjusted, as far as possible, for potential confounding factors including age, region, socioeconomic factors, smoking, body mass index, physical activity, use of oral contraceptives, and hormone replacement therapy. In particular, we were able to examine the association of alcohol with upper aerodigestive tract cancers by smoking status, thereby minimizing the potential for confounding by this factor. For other cancer sites, stratification by smoking or hormone replacement therapy made little difference to the risk estimates, which suggested that associations with alcohol are unlikely to be confounded by such factors.

In conclusion, regular consumption of low to moderate amounts of alcohol by women increases the risk of cancers of the upper aerodigestive tract, rectum, liver, and breast, all of which have been classified by the International Agency for Research on Cancer to be causally linked to alcohol intake. No statistically significant increases were found between increasing alcohol intake and cancer at other organ sites. Compared with the many studies that have reported an increased risk of various forms of cancer with alcohol intake, far fewer studies have reported that alcohol drinking appears to be associated with a reduced risk of certain other cancers. Further investigations of the possibility that alcohol reduces the risk of thyroid cancer, non–Hodgkin lymphoma, and renal cell carcinoma are warranted.

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