

# Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies

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# Alcohol Intake and Colorectal Cancer: A Pooled Analysis of 8 Cohort Studies

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**Background:** Epidemiologic studies have generally reported positive associations between alcohol consumption and risk for colorectal cancer. However, findings related to specific alcoholic beverages or different anatomic sites in the large bowel have been inconsistent.

**Objective:** To examine the relationship of total alcohol intake and intake from specific beverages to the incidence of colorectal cancer and to evaluate whether other potential risk factors modify the association.

**Design:** Pooled analysis of primary data from 8 cohort studies in 5 countries.

**Setting:** North America and Europe.

**Participants:** 489 979 women and men with no history of cancer other than nonmelanoma skin cancer at baseline.

**Measurements:** Alcohol intake was assessed in each study at baseline by using a validated food-frequency questionnaire.

**Results:** During a maximum of 6 to 16 years of follow-up across the studies, 4687 cases of colorectal cancer were documented. In categorical analyses, increased risk for colorectal cancer was lim-

ited to persons with an alcohol intake of 30 g/d or greater (approximately  $\geq 2$  drinks/d), a consumption level reported by 4% of women and 13% of men. Compared with nondrinkers, the pooled multivariate relative risks were 1.16 (95% CI, 0.99 to 1.36) for persons who consumed 30 to less than 45 g/d and 1.41 (CI, 1.16 to 1.72) for those who consumed 45 g/d or greater. No significant heterogeneity by study or sex was observed. The association was evident for cancer of the proximal colon, distal colon, and rectum. No clear difference in relative risks was found among specific alcoholic beverages.

**Limitations:** The study included only one measure of alcohol consumption at baseline and could not investigate lifetime alcohol consumption, alcohol consumption at younger ages, or changes in alcohol consumption during follow-up. It also could not examine drinking patterns or duration of alcohol use.

**Conclusions:** A single determination of alcohol intake correlated with a modest relative elevation in colorectal cancer rate, mainly at the highest levels of alcohol intake.

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Alcohol intake is a potentially modifiable behavior that may be related to risk for colorectal cancer (1). Epidemiologic studies on alcohol consumption and risk for colorectal cancer have reported either null or positive associations, with risks that are as much as 5-fold higher among drinkers compared to nondrinkers and with positive associations observed more consistently for rectal than colon cancer (1). Data on risk for cancer at subsites in the colon have been limited. In general, beer intake has been positively related to colorectal cancer, whereas findings for other alcoholic beverages have been inconsistent. Because analyses have varied across studies, it has been difficult to account for discrepancies among studies and in dose-response relationships.

We evaluated the association between alcohol consumption and the incidence of colorectal cancer, including separate examinations by sex, subsites in the large bowel, and other potential risk factors, by analyzing the primary data from 8 large prospective studies from North America and Europe. Results on alcohol use and occurrence of colorectal cancer have been published for only 4 of these studies; for each, follow-up in our analysis is longer than that in the published analysis (2–5).

## METHODS

The Pooling Project of Prospective Studies of Diet and Cancer has been described elsewhere (6). To maximize the quality and comparability of the studies in the project, we formulated general inclusion criteria a priori. For the current analyses, we identified prospective studies (3–5, 7–12) that included at least 50 incident cases of colorectal cancer, assessed long-term dietary intake, had a validation study of the dietary assessment method or a closely related instrument (13–19) (Wolk A. Personal communication), and measured alcohol intake.

The person-time of follow-up in the Nurses' Health Study was divided into 2 segments to take advantage of the more detailed dietary assessment in 1986. In the underlying theory of survival-data analysis, blocks of person-time in different periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people (20).

## Exclusion Criteria

We first applied the exclusion criteria for each study, and then excluded participants with implausible energy intakes ( $>3$  SDs from the study-specific  $\log_e$ -transformed mean energy intake), no information on alcohol intake, or

**Context**

Studies suggest that alcohol consumption increases colorectal cancer risk, but the magnitude of the association and its relationship to type of alcoholic beverage and cancer site are ill defined.

**Contribution**

This pooled analysis of 8 observational studies showed a small absolute increase in colorectal cancer risk with alcohol consumption of 30 g/d or greater (equivalent to 150 mL of wine), with the greatest risk among people who consumed 45 g/d or greater. Risk did not differ by beverage type or for cancer site.

**Cautions**

This analysis relied on a single baseline self-report of alcohol consumption.

**Implications**

Clinicians should factor the small increased risk for colorectal cancer into discussions with patients about alcohol's risks and benefits.

—The Editors

a history of cancer other than nonmelanoma skin cancer at baseline.

**Case Definition**

Incident colorectal cancers were ascertained in each study by self-report with subsequent medical record review (3, 11) or linkage with a cancer registry (8, 21–24) or both

(25). Some studies used additional linkage with a death registry (3, 8, 11, 23–25).

**Dietary Assessment**

Each study provided data on food, nutrient, and alcohol intake as estimated by a baseline food-frequency questionnaire. All studies but 1 measured usual consumption of individual alcoholic beverages (beer, wine, and liquor); in the New York State Cohort, 1 question on the consumption of alcoholic beverages was asked. The format of the questionnaires varied. Some (5, 9) allowed participants to indicate both the frequency of drinking and the usual number of drinks consumed on each occasion; others (3, 4, 11, 12) had participants choose among categories of total usual consumption. Most of the questionnaires assumed a standard drink size, but the Canadian National Breast Screening Study allowed participants to indicate a different drink size from the standard indicated and the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study allowed participants to choose from 1 of 3 portion sizes. Each study calculated alcohol intake in grams per day by using the reported frequency of consumption, quantity consumed, and alcohol content of that beverage. For context, in the United States, we assumed that there is 12.8 g of alcohol in 12 oz (335 mL) of beer, 10.9 g in 4 oz (118 mL) of wine, and 14.0 g in 1.5 oz (44 mL) of 80-proof liquor (26). Spearman correlation coefficients comparing alcohol intake from the dietary questionnaires used in the studies with diet records or 24-hour dietary recalls generally exceeded 0.7 (Wolk A. Personal communication) (16, 17, 19).

Among dietary covariates, no data on nutrients were

**Table 1. Characteristics of the Cohort Studies Included in the Pooled Analysis**

Study	Population	Follow-up Period	Method of Follow-up
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	Randomized clinical trial among men who smoked $\geq 5$ cigarettes/d and lived in southwestern Finland	1985–1995	Cancer and death registry
Canadian National Breast Screening Study	Multicenter randomized, controlled trial of mammography screening for female breast cancer in Canada	1980–1993	Cancer and death registry
Health Professionals Follow-up Study	Male dentists, optometrists, osteopathic physicians, podiatrists, pharmacists, or veterinarians in the United States	1986–1996	Follow-up questionnaire and death registry
Iowa Women's Health Study	Postmenopausal women selected randomly from the 1985 Department of Transportation's driver's license list in Iowa	1986–1998	Cancer and death registry
Netherlands Cohort Study	Men and women from 204 municipal population registries throughout the Netherlands	1986–1993	Cancer registry
New York State Cohort	Male and female residents of New York State who had had the same address and telephone number for the previous 18 years	1980–1987	Cancer registry
Nurses' Health Study a	Female registered nurses in the United States	1980–1986	Follow-up questionnaire and death registry
Nurses' Health Study b	Female registered nurses in the United States	1986–1996	Follow-up questionnaire and death registry
Sweden Mammography Cohort	Mammography screening among women in 2 counties in central Sweden	1987–1998	Cancer registry
Total			

\* Cancer outcomes in the New York State Cohort were identified through linkage with a cancer registry; thus, it is difficult to determine the follow-up rate in the cohort. When a subset of the cohort was followed intensively, loss to follow-up was not related to exposure.

† This value represents a subset of the women included in the Nurses' Health Study a and is not included in the total.

missing. Intake of red meat and milk was assessed, and fewer than 1% of values were missing in most studies.

### Nondietary Covariates

Each study collected information on nondietary covariates by using self-administered questionnaires at baseline. Most studies assessed age; smoking habits; physical activity; education; height; body weight; multivitamin use; and, among women, use of oral contraceptives and postmenopausal hormone replacement therapy. The proportion of missing values generally was less than 5% in each study that measured the covariate. We categorized the covariate information in a consistent manner across studies.

### Statistical Analysis

Alcohol intake was divided into categories by using identical cut-points across the studies. Because the number of cases in higher categories was limited, the cut-point for the highest category was lower in some analyses. To calculate the *P* value for the test for trend, participants were assigned the median value of their category of alcohol, and this value was used as a continuous variable in the study-specific regression models.

Each study was analyzed by using the Cox proportional hazards model. Incidence rate ratios were estimated by using SAS PROC PHREG (27) for all studies except the Canadian National Breast Screening Study and the Netherlands Cohort Study, which were analyzed as case-cohort studies (28) by using Epicure software (29). For all studies, we stratified participants by age at baseline and the year that the baseline questionnaire was returned. Person-

years of follow-up were calculated from the date of return of the baseline questionnaire until the date of diagnosis of colorectal cancer, death, or end of follow-up, whichever came first. We conducted sex-specific analyses; studies that included both sexes were analyzed as two separate cohorts. An indicator variable for missing responses was created for each covariate in a study, if needed. Two-sided 95% CIs were calculated.

To obtain a single pooled estimate, we used a random-effects model to combine  $\log_e$  relative risks from the individual studies (30). The study-specific relative risks were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. In some studies, no cases were included in the categories of higher alcohol intake and the number of noncases in the corresponding category was very small relative to the sample size. We did not include these studies in the pooled estimates for those categories. We tested for heterogeneity among studies by using the *Q* statistic (30, 31).

We tested whether the associations for alcohol from beer, wine, and liquor differed by using a contrast test of the pooled estimates for each beverage and their covariance matrix from the random-effects model. The test statistic follows approximately a chi-square distribution with 2 degrees of freedom (32).

We tested for variation in relative risks by other potential risk factors by using a meta-regression model (33). We also evaluated associations for subsites of the large bowel and used a Wald test to test the null hypothesis of no difference among the  $\log_e$  rate ratios (32, 34).

Table 1—Continued

Estimated Rate of Follow-up	Age Range at Baseline	Size of the Cohort at Baseline	Questions on Alcohol Intake	Cases of Colorectal Cancer
%	<i>y</i>	←	<i>n</i>	→
100	50–69	26 987	6	184
100	40–59	56 837	3	284
>94	40–75	47 673	4	408
98	55–69	34 603	4	796
>95	55–69	120 852	6	1126
–*	15–107	52 913	1	789*
>94	34–59	88 651	3	220
>94	40–65	68 540†	4	420
98	40–76	61 463	5	460
		489 979		4687

Table 2. Distribution of Alcohol Intake

Study	Participants Who Drink Alcohol*				Mean Alcohol Intake among Drinkers $\pm$ SD				Person-Years of Alcohol Intake $\geq 45$ g/d†
	Any Alcohol	Beer	Wine	Liquor	Total Alcohol	Alcohol from Beer	Alcohol from Wine	Alcohol from Liquor	
	← % →				← g/d →				
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	89	71	21	81	20.3 $\pm$ 21.8	9.4 $\pm$ 13.9	4.3 $\pm$ 7.6	12.2 $\pm$ 14.2	9.7
Canadian National Breast Screening Study	77	26	67	52	10.9 $\pm$ 14.5	3.5 $\pm$ 6.2	6.1 $\pm$ 8.8	6.6 $\pm$ 11.5	2.2
Health Professionals Follow-up Study	76	55	59	52	14.8 $\pm$ 16.1	6.5 $\pm$ 10.0	4.8 $\pm$ 6.8	9.2 $\pm$ 12.8	4.2
Iowa Women's Health Study	45	18	30	26	8.7 $\pm$ 12.3	6.5 $\pm$ 11.3	3.0 $\pm$ 4.5	7.1 $\pm$ 10.9	0.9
Netherlands Cohort Study									
Women	68	9	65	13	8.5 $\pm$ 10.6	3.0 $\pm$ 5.0	6.8 $\pm$ 8.6	8.5 $\pm$ 10.4	0.9
Men	85	58	51	58	17.3 $\pm$ 16.7	6.3 $\pm$ 10.0	7.4 $\pm$ 9.7	12.5 $\pm$ 12.9	5.2
New York State Cohort									
Women	78	–	–	–	6.0 $\pm$ 9.4	–	–	–	0.9
Men	89	–	–	–	12.1 $\pm$ 17.1	–	–	–	5.0
Nurses' Health Study									
a	68	22	55	44	9.4 $\pm$ 11.6	5.6 $\pm$ 9.4	4.5 $\pm$ 6.4	6.3 $\pm$ 9.1	1.2
b	64	21	53	37	9.6 $\pm$ 12.1	4.8 $\pm$ 8.8	4.9 $\pm$ 7.0	7.1 $\pm$ 10.5	1.3
Sweden Mammography Cohort	67	52	48	25	3.5 $\pm$ 3.5	1.5 $\pm$ 1.9	2.8 $\pm$ 2.5	1.2 $\pm$ 1.1	0.02
Total									2.2

\* The percentage of participants who drank beer, wine, and liquor does not add up to the percentage of total drinkers because of overlap of intake.

† Person-years for the Canadian National Breast Screening Study and Netherlands Cohort Study were obtained from the subcohort and cases from outside of the subcohort.

### Role of the Funding Source

The research was funded by the National Institutes of Health and by the National Colorectal Cancer Research Alliance. The funding source had no role in the design, conduct, or reporting of the data.

### RESULTS

Of the 8 studies in this analysis, 2 were conducted among health professionals (3, 11), 3 were population-based (4, 5, 9), 2 were conducted in screening programs (8, 12), and 1 was originally a randomized clinical trial (7) (Table 1). During a maximum of 6 to 16 years of follow-up across the studies, 4687 cases of colorectal cancer were documented, of which 3291 (70%) were colon cancer, 1628 were proximal colon cancer, and 1410 were distal colon cancer. Across studies, 45% to 78% of women and 76% to 89% of men consumed alcohol (Table 2). Among drinkers, the mean alcohol intake was 3.5 to 10.9 g/d in women and 12.1 to 20.3 g/d in men.

We calculated study-specific relative risks for alcohol intake and colorectal cancer, which were subsequently pooled. Total alcohol intake was positively associated with risk for colorectal cancer (Table 3). The elevated risk was limited to alcohol intake of 30 g/d or more. The pooled age-adjusted relative risks were 1.21 (95% CI, 1.04 to 1.42) for alcohol intake of 30 to less than 45 g/d and 1.51 (CI, 1.25 to 1.83) for intake of 45 g/d or greater, compared with nondrinkers. The test for heterogeneity among studies was not significant for alcohol consumption of 45 g/d or greater ( $P > 0.2$ ), indicating that the differences in relative risks among the cohorts were compatible with random variation. The relative risks were slightly attenuated after adjustment for other potential risk factors for colorec-

tal cancer. A significant trend also was observed when nondrinkers were excluded from the analysis ( $P < 0.001$ ).

Because metabolism of alcohol is slower in women than men (35), the association with colorectal cancer may differ by sex. However, results were similar for women and men ( $P$  for heterogeneity due to sex for consumption of 45 g/d or greater  $> 0.2$ ). The positive associations for alcohol intake of 30 g/d or greater and colorectal cancer were generally consistent across studies (Figure 1). Additional adjustment for intake of total vitamin E, methionine, fiber, and total fat did not materially change the results (data not shown). Adjustment for age at menarche, menopausal status, parity, and age at first birth did not alter the results among women (data not shown). The findings were similar in analyses that excluded cases diagnosed within the first 4 years of follow-up (data not shown). The pooled relative risks also did not appreciably differ from those obtained when studies were combined into 1 data set (data not shown).

We calculated the population attributable risk, which is the proportion of cases that would be avoided if the risk factor distribution of a high-risk group switched to that of a low-risk group (36, 37), by using the age-adjusted relative risk and the prevalence of alcohol intake of 30 g/d or greater (4% for women and 13% for men) from the analysis that combined studies of the same sex into a single data set. The population attributable risk was 0.9% for women and 5.0% for men.

The association between alcohol consumption and colorectal cancer risk was slightly J-shaped. We hypothesized that this pattern may have occurred because the reference group of nondrinkers included both never-drinkers and past drinkers, and past drinkers may have an elevated



Table 3. Pooled Relative Risks for Colorectal Cancer for Categories of Total Alcohol Intake

Variable	Alcohol Intake						P Value*
	0 g/d	>0 to <5 g/d	5 to <15 g/d	15 to <30 g/d	30 to <45 g/d	≥45 g/d	
Median intake, g/d†	0.0	1.9	9.4	20.8	35.6	57.1	
Cases of colorectal cancer, n	1466	1475	849	485	244	168	
Person-years‡	1 032 388	1 189 623	645 970	255 990	126 763	71 439	
Age-adjusted relative risk (95% CI)	1.00	0.94 (0.85–1.03)	0.98 (0.89–1.08)	1.04 (0.89–1.22)	1.21 (1.04–1.42)	1.51 (1.25–1.83)	<0.001§
Multivariate relative risk (95% CI)							
Overall	1.00	0.94 (0.86–1.03)	0.97 (0.88–1.06)	1.01 (0.86–1.18)	1.16 (0.99–1.36)	1.41 (1.16–1.72)	<0.001§
Women	1.00	0.96 (0.88–1.05)	1.00 (0.89–1.13)	0.99 (0.78–1.25)	1.19 (0.94–1.50)	1.41 (0.98–2.02)	0.05§
Men	1.00	0.87 (0.63–1.19)	0.90 (0.77–1.07)	1.04 (0.82–1.31)	1.11 (0.86–1.45)	1.41 (1.11–1.79)	<0.001§

\* Test for trend.

† Median intake for each category was calculated as  $[\sum(\text{the median intake of each category in each study} \times \text{the number of participants in the category in each study})]/\text{total participants in the category across studies}$ .

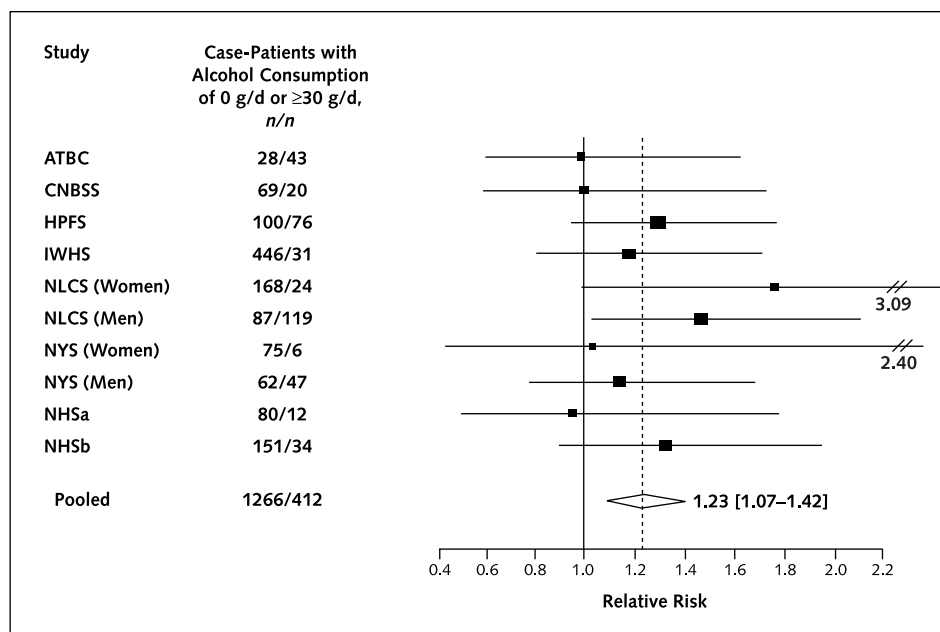
‡ Person-years for the Canadian National Breast Screening Study and Netherlands Cohort Study were obtained from the subcohort and the cases from outside of the subcohort. §  $P > 0.2$  for between-study heterogeneity for the highest intake category and for between-study heterogeneity due to sex for the highest intake category.

|| Multivariate relative risk was adjusted for smoking (never-smoker, past smoker < 20 years' duration, past smoker 20 to 39 years' duration, past smoker ≥40 years' duration, current smoker <25 cigarettes/d and <40 years' duration, current smoker ≥25 cigarettes/d and <40 years' duration, current smoker <25 cigarettes/d and ≥40 years' duration, or current smoker ≥25 cigarettes/d and ≥40 years' duration), body mass index (<23, 23 to <25, 25 to <30, or ≥30 kg/m<sup>2</sup>), education (less than high school graduate, high school graduate, or more than high school graduate), height (<1.60 m, 1.60 to <1.65 m, 1.65 m to <1.70 m, 1.70 m to <1.75 m, or ≥1.75 m for women and <1.70 m, 1.70 to <1.75 m, 1.75 to <1.80 m, 1.80 to <1.85 m, or ≥1.85 m for men), degree of physical activity (low, medium, or high), family history of colorectal cancer (no or yes), use of nonsteroidal anti-inflammatory drugs (no or yes), use of multivitamins (no, yes <6 times/wk, yes ≥6 times/wk, or yes but missing dose for the Health Professionals Follow-up Study, Iowa Women's Health Study, and Nurses' Health Study; no or yes for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Canadian National Breast Screening Study, Netherlands Cohort Study, and New York State Cohort), energy intake (continuous), red meat intake (quartiles), total milk intake (quartiles) and folate intake from food only (quintiles). For women, the relative risks were also adjusted for history of use of oral contraceptives (no or yes) and postmenopausal hormone therapy (ever or never).

risk for colorectal cancer (3, 38). Information on alcohol consumption during the past 5 to 10 years was available from only 4 studies (proportion of past drinkers among nondrinkers, 5% to 56%). For these studies, compared

with nondrinkers (which included never-drinkers and past drinkers), the pooled multivariate relative risks for increasing categories of alcohol intake (0 g/d, >0 to <5 g/d, 5 to <15 g/d, 15 to <30 g/d, 30 to <45 g/d, and ≥45 g/d)

Figure. Study-specific and pooled multivariate relative risks for colorectal cancer for alcohol intake of 30 g/d or greater versus 0 g/d.



The black squares and horizontal lines show the study-specific relative risks and 95% CIs. The area of the black squares indicates the study-specific weight in the pooled analysis. The diamond represents the pooled relative risk and 95% CI. ATBC = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; CNBSS = Canadian National Breast Screening Study; HPFS = Health Professionals Follow-up Study; IWHS = Iowa Women's Health Study; NLCS = Netherlands Cohort Study; NYS = New York State Cohort; NHS = Nurses' Health Study. The Sweden Mammography Cohort was not included because no patients with colorectal cancer and only 36 persons without colorectal cancer consumed 30 or more g of alcohol daily.  $P$  for test for between-study heterogeneity > 0.2.

Table 4. Pooled Relative Risk for Colorectal Cancer for Categories of Alcohol Intakes from Specific Beverages\*

Source of Alcohol	Alcohol Intake			P Value†
	0 g/d	>0 to <30 g/d	≥30 g/d	
<b>Beer</b>				
Cases of colorectal cancer, <i>n</i>	2612	1219	67	
Person-years	1 890 206	1 003 371	47 083	
Age-adjusted relative risk (95% CI)	1.00	1.02 (0.93–1.12)	1.47 (1.13–1.92)	0.06‡
Multivariate relative risk (95% CI)§	1.00	1.01 (0.89–1.13)	1.37 (1.00–1.87)	0.2‡
<b>Wine</b>				
Cases of colorectal cancer, <i>n</i>	2078	1768	52	
Person-years	1 515 247	1 416 395	9019	
Age-adjusted relative risk (95% CI)	1.00	0.98 (0.90–1.06)	1.74 (1.25–2.42)	0.002‡
Multivariate relative risk (95% CI)§	1.00	0.97 (0.89–1.05)	1.82 (1.28–2.59)	0.001‡
<b>Liquor</b>				
Cases of colorectal cancer, <i>n</i>	2392	1347	159	
Person-years	1 767 551	1 088 350	84 761	
Age-adjusted relative risk (95% CI)	1.00	1.00 (0.92–1.09)	1.30 (1.05–1.60)	0.04‡
Multivariate relative risk (95% CI)§	1.00	0.98 (0.88–1.09)	1.21 (0.99–1.47)	0.1‡

\* The New York State Cohort was not included in the analyses on alcohol from beer, wine, and liquor. Person-years for the Canadian National Breast Screening Study and Netherlands Cohort Study were obtained from the subcohort and the cases from outside of the subcohort.

† Test for trend.

‡  $P > 0.2$  for between-study heterogeneity for the highest intake category and for between-study heterogeneity due to sex for the highest intake category.

§ Multivariate relative risk was adjusted for smoking (never-smoker, past smoker < 20 years' duration, past smoker 20 to 39 years' duration, past smoker ≥ 40 years' duration, current smoker < 25 cigarettes/d and < 40 years' duration, current smoker ≥ 25 cigarettes/d and < 40 years' duration, current smoker < 25 cigarettes/d and ≥ 40 years' duration, or current smoker ≥ 25 cigarettes/d and ≥ 40 years' duration), body mass index (< 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m<sup>2</sup>), education (less than high school graduate, high school graduate, or more than high school graduate), height (< 1.60 m, 1.60 to < 1.65 m, 1.65 m to < 1.70 m, 1.70 m to < 1.75 m, or ≥ 1.75 m for women and < 1.70 m, 1.70 to < 1.75 m, 1.75 to < 1.80 m, 1.80 to < 1.85 m, or ≥ 1.85 m for men), degree of physical activity (low, medium, or high), family history of colorectal cancer (no or yes), use of nonsteroidal anti-inflammatory drugs (no or yes), use of multivitamins (no, yes < 6 times/wk, yes ≥ 6 times/wk, or yes but missing dose for the Health Professionals Follow-up Study, Iowa Women's Health Study, and Nurses' Health Study; no or yes for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Canadian National Breast Screening Study, Netherlands Cohort Study, and New York State Cohort), energy intake (continuous), red meat intake (quartiles), total milk intake (quartiles) and folate intake from food only (quintiles) and alcohol intake from the other beverages. For women, the relative risks were also adjusted for history of use of oral contraceptives (no or yes) and postmenopausal hormone therapy (ever or never).

were 1.00, 0.93, 0.90, 0.98, 1.27, and 1.56 (CI, 1.20 to 2.04), respectively. When past drinkers were excluded from the reference group, the corresponding relative risks changed to 1.00, 0.95, 0.92, 0.99, 1.32, and 1.65 (CI, 1.24 to 2.21).

In analyses of each alcoholic beverage, alcohol from beer or wine was significantly associated with an elevated risk for colorectal cancer and alcohol from liquor had a nonsignificant positive association with risk for colorectal cancer (Table 4). The difference among the 3 types of beverage was not statistically significant.

The positive association between alcohol consumption and risk for colorectal cancer was similar across all areas of the large bowel ( $P$  for heterogeneity by subsite for consumption of 45 g/d or greater > 0.2) (Table 5). We also examined associations between alcohol intake from individual beverages and colon cancer and rectal cancer (Table 6). Although all beverages tended to be more strongly related to rectal than to colon cancer, the differences in relative risks between colon cancer and rectal cancer did not differ significantly.

We examined interactions between alcohol intake and other potential factors related to risk for colorectal cancer (Table 7). The positive association between alcohol intake and colorectal cancer was pronounced among persons with a lower body mass index. The elevated risk among leaner persons was somewhat stronger in men than in women ( $P$

for heterogeneity by sex = 0.11). The relative risk for colorectal cancer with an alcohol intake of 30 g/d or greater was 1.60 (CI, 1.07 to 2.41) for women and 3.51 (CI, 1.45 to 8.50) for men with a body mass index less than 22 kg/m<sup>2</sup>. These results did not change materially after exclusion of cases that were diagnosed during the first 3 years of follow-up (data not shown).

The association between alcohol use and colorectal cancer did not vary by other factors (Table 7). However, there was a weak suggestion that the positive association between alcohol consumption and risk for colorectal cancer was restricted to persons who did not take multivitamins. In addition, when examined by levels of methionine intake, the positive association was observed only among persons in the 2 lowest tertiles of intake. The association between alcohol consumption and risk for colorectal cancer did not differ by use of hormone replacement therapy (never, past, or current) among postmenopausal women (data not shown).

## DISCUSSION

In this pooled analysis of cohort studies, alcohol consumption was positively associated with risk for colorectal cancer. The relationship was consistent in women and men and across studies. The positive association existed for proximal colon cancer, distal colon cancer, and rectal can-

Table 5. Pooled Multivariate Relative Risk by Subsite of Colorectal Cancer according to Alcohol Intake\*

Subsite†	Relative Risk (95% CI) by Alcohol Intake						P Value‡	
	0 g/d	>0 to <5 g/d	5 to <15 g/d	15 to <30 g/d	30 to <45 g/d	≥45 g/d	Test for Trend	Test for Trend, Excluding Intake of 0 g/d
Colon (n = 3291)	1.00	0.92 (0.84–1.01)	0.94 (0.84–1.05)	1.01 (0.82–1.24)	1.08 (0.89–1.31)	1.45 (1.14–1.83)	<0.001	0.001
Proximal colon (n = 1628)	1.00	0.90 (0.77–1.04)	0.88 (0.75–1.04)	0.99 (0.80–1.21)	0.98 (0.74–1.29)	1.35 (0.97–1.89)	0.03	0.01
Distal colon (n = 1410)	1.00	0.94 (0.81–1.09)	1.01 (0.85–1.20)	1.02 (0.74–1.40)	1.25 (0.92–1.68)	1.66 (1.17–2.36)	0.04	0.01
Rectum (n = 1370)	1.00	1.01 (0.83–1.22)	0.99 (0.82–1.19)	1.05 (0.83–1.32)	1.42 (1.07–1.88)	1.49 (1.04–2.12)	0.006	0.02

\* Relative risks were adjusted for smoking (never-smoker, past smoker < 20 years' duration, past smoker 20 to 39 years' duration, past smoker ≥40 years' duration, current smoker <25 cigarettes/d and <40 years' duration, current smoker ≥25 cigarettes/d and <40 years' duration, current smoker <25 cigarettes/d and ≥40 years' duration, or current smoker ≥25 cigarettes/d and ≥40 years' duration), body mass index (<23, 23 to <25, 25 to <30, or ≥30 kg/m<sup>2</sup>), education (less than high school graduate, high school graduate, or more than high school graduate), height (<1.60 m, 1.60 to <1.65 m, 1.65 m to <1.70 m, 1.70 m to <1.75 m, or ≥1.75 m for women and <1.70 m, 1.70 to <1.75 m, 1.75 to <1.80 m, 1.80 to <1.85 m, or ≥1.85 m for men), degree of physical activity (low, medium, or high), family history of colorectal cancer (no or yes), use of nonsteroidal anti-inflammatory drugs (no or yes), use of multivitamins (no, yes <6 times/wk, yes ≥6 times/wk, or yes but missing dose for the Health Professionals Follow-up Study, Iowa Women's Health Study, and Nurses' Health Study; no or yes for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Canadian National Breast Screening Study, Netherlands Cohort Study, and New York State Cohort), energy intake (continuous), red meat intake (quartiles), total milk intake (quartiles) and folate intake from food only (quintiles). For women, the relative risks were also adjusted for history of use of oral contraceptives (no or yes) and postmenopausal hormone therapy (ever or never).

† Colon cancers were considered those from the cecum through the sigmoid colon. Tumors from the cecum to the splenic flexure were considered to be proximal colon cancer. The remaining tumors in the colon were defined as distal colon cancers. Rectal cancers included tumors in the rectum and the rectosigmoid junction.

‡ P > 0.2 for between-study heterogeneity for the highest intake category, for between-study heterogeneity due to sex for the highest intake category, and for common effects by subsites (proximal colon, distal colon, and rectum) for the highest intake category.

cer. The risk did not differ significantly by type of alcoholic beverage.

Several mechanisms have been suggested for the effect of alcohol on risk for colorectal cancer. First, acetaldehyde, an oxidation product of alcohol, may be responsible for colorectal carcinogenesis (39, 40). A recent study reported that high levels of acetaldehyde in rat colon degrade folate, a nutrient that is hypothesized to reduce the risk for colorectal cancer (41). Second, alcohol is an antagonist of methyl-group metabolism and may contribute to abnormal

DNA methylation, an early step in colonic carcinogenesis (42, 43). Finally, greater alcohol intake may increase the risk for colorectal cancer indirectly through immune suppression, delay of DNA repair, activation of liver procarcinogens by induction of cytochrome P-450 enzymes, or changes in bile acid composition (44).

Epidemiologic studies on alcohol consumption and colorectal cancer have reported positive or null associations (1). A meta-analysis of 5 cohorts (none of which was included in our analysis) and 22 case-control studies re-

Table 6. Pooled Multivariate Relative Risks by Subsite of Colorectal Cancer according to Intake of Alcohol from Specific Beverages\*

Type of Alcohol and Subsite	Relative Risk (95% CI) by Alcohol Intake			P Value	
	0 g/d	>0 to <15 g/d	≥15 g/d	Test for Trend	Test for Common Effects by Subsite for the Highest Intake Category
<b>Beer</b>					
Colon	1.00	0.96 (0.84–1.10)	1.38 (1.05–1.82)	0.08†	
Rectum	1.00	1.05 (0.88–1.25)	1.59 (1.12–2.25)	0.005‡	>0.2
<b>Wine</b>					
Colon	1.00	0.97 (0.88–1.07)	1.33 (1.00–1.77)	0.03§	
Rectum	1.00	0.96 (0.83–1.11)	1.55 (1.11–2.17)	0.009†	>0.2
<b>Liquor</b>					
Colon	1.00	0.99 (0.88–1.11)	1.06 (0.86–1.30)	>0.2†	
Rectum	1.00	0.97 (0.81–1.16)	1.10 (0.85–1.41)	>0.2†	>0.2

\* Relative risks were adjusted for smoking (never-smoker, past smoker < 20 years' duration, past smoker 20 to 39 years' duration, past smoker ≥40 years' duration, current smoker <25 cigarettes/d and <40 years' duration, current smoker ≥25 cigarettes/d and <40 years' duration, current smoker <25 cigarettes/d and ≥40 years' duration, or current smoker ≥25 cigarettes/d and ≥40 years' duration), body mass index (<23, 23 to <25, 25 to <30, or ≥30 kg/m<sup>2</sup>), education (less than high school graduate, high school graduate, or more than high school graduate), height (<1.60 m, 1.60 to <1.65 m, 1.65 m to <1.70 m, 1.70 m to <1.75 m, or ≥1.75 m for women and <1.70 m, 1.70 to <1.75 m, 1.75 to <1.80 m, 1.80 to <1.85 m, or ≥1.85 m for men), degree of physical activity (low, medium, or high), family history of colorectal cancer (no or yes), use of nonsteroidal anti-inflammatory drugs (no or yes), use of multivitamins (no, yes <6 times/wk, yes ≥6 times/wk, or yes but missing dose for the Health Professionals Follow-up Study, Iowa Women's Health Study, and Nurses' Health Study; no or yes for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Canadian National Breast Screening Study, Netherlands Cohort Study, and New York State Cohort), energy intake (continuous), red meat intake (quartiles), total milk intake (quartiles) and folate intake from food only (quintiles). For women, the relative risks were also adjusted for history of use of oral contraceptives (no or yes) and postmenopausal hormone therapy (ever or never). They were also simultaneously adjusted for the other beverages.

† P > 0.2 for between-study heterogeneity for the highest intake category and for between-study heterogeneity due to sex for the highest intake category.

‡ P > 0.2 for between-study heterogeneity for the highest intake category and P = 0.17 for between-study heterogeneity due to sex for the highest intake category.

§ P > 0.2 for between-study heterogeneity for the highest intake category and P = 0.16 for between-study heterogeneity due to sex for the highest intake category.



Table 7. Pooled Multivariate Relative Risk by Alcohol Intake and Other Risk Factors for Colorectal Cancer\*

Risk Factor	Alcohol Intake					P Value	
	0 g/d	>0 to <5 g/d	5 to <15 g/d	15 to <30 g/d	≥30 g/d	Test for Trend	Test for Interaction for Highest Intake Category
<b>Body mass index</b>							
<22 kg/m <sup>2</sup> (n = 663)	1.00	1.09 (0.87–1.37)	1.28 (0.98–1.68)	1.11 (0.71–1.72)	1.84 (1.27–2.67)	0.003†	
22–25 kg/m <sup>2</sup> (n = 1503)	1.00	0.85 (0.70–1.03)	0.85 (0.71–1.01)	0.96 (0.76–1.22)	1.23 (0.91–1.65)	0.03‡	
≥25 kg/m <sup>2</sup> (n = 2414)	1.00	0.96 (0.86–1.07)	0.92 (0.77–1.10)	1.03 (0.84–1.26)	1.08 (0.88–1.33)	0.04‡	0.03
<b>Multivitamin use§</b>							
Nonusers (n = 2902)	1.00	0.92 (0.79–1.07)	0.94 (0.83–1.07)	1.01 (0.83–1.23)	1.30 (1.10–1.54)	<0.001‡	
Users (n = 917)	1.00	0.96 (0.80–1.14)	0.96 (0.77–1.20)	0.87 (0.65–1.17)	1.06 (0.77–1.44)	>0.2‡	>0.2
<b>Total folate intake  </b>							
1st tertile (n = 1063)	1.00	0.91 (0.75–1.09)	1.01 (0.82–1.24)	0.96 (0.72–1.28)	1.24 (0.96–1.60)	0.07‡	
2nd tertile (n = 1124)	1.00	0.89 (0.71–1.11)	0.96 (0.79–1.18)	1.01 (0.78–1.30)	1.16 (0.87–1.54)	0.2‡	
3rd tertile (n = 914)	1.00	1.00 (0.83–1.19)	0.94 (0.68–1.30)	0.82 (0.55–1.22)	1.19 (0.86–1.64)	0.18‡	>0.2
<b>Methionine intake</b>							
1st tertile (n = 1657)	1.00	0.89 (0.78–1.02)	0.91 (0.77–1.08)	0.91 (0.70–1.17)	1.29 (1.04–1.58)	0.003‡	
2nd tertile (n = 1562)	1.00	1.01 (0.82–1.25)	1.10 (0.92–1.30)	1.00 (0.78–1.27)	1.39 (0.98–1.95)	0.06¶	
3rd tertile (n = 1467)	1.00	0.93 (0.75–1.15)	0.91 (0.74–1.11)	1.19 (0.84–1.70)	0.88 (0.56–1.36)	>0.2**	>0.2
<b>Smoking</b>							
Never (n = 1723)††	1.00	0.89 (0.79–1.00)	0.92 (0.78–1.08)	1.09 (0.85–1.39)	1.17 (0.84–1.63)	0.19‡	
Past (n = 1549)††	1.00	0.95 (0.81–1.13)	0.91 (0.76–1.09)	1.08 (0.88–1.32)	1.26 (1.00–1.58)	0.04‡	
Current (n = 904)	1.00	1.14 (0.86–1.49)	1.14 (0.89–1.45)	0.85 (0.64–1.12)	1.42 (1.11–1.83)	0.007‡	>0.2

\* Relative risks were adjusted for smoking (never-smoker, past smoker < 20 years' duration, past smoker 20 to 39 years' duration, past smoker ≥ 40 years' duration, current smoker < 25 cigarettes/d and < 40 years' duration, current smoker ≥ 25 cigarettes/d and < 40 years' duration, current smoker < 25 cigarettes/d and ≥ 40 years' duration, or current smoker ≥ 25 cigarettes/d and ≥ 40 years' duration), body mass index (< 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m<sup>2</sup>), education (less than high school graduate, high school graduate, or more than high school graduate), height (< 1.60 m, 1.60 to < 1.65 m, 1.65 m to < 1.70 m, 1.70 m to < 1.75 m, or ≥ 1.75 m for women and < 1.70 m, 1.70 to < 1.75 m, 1.75 to < 1.80 m, 1.80 to < 1.85 m, or ≥ 1.85 m for men), degree of physical activity (low, medium, or high), family history of colorectal cancer (no or yes), use of nonsteroidal anti-inflammatory drugs (no or yes), use of multivitamins (no, yes < 6 times/wk, yes ≥ 6 times/wk, or yes but missing dose for the Health Professionals Follow-up Study, Iowa Women's Health Study, and Nurses' Health Study; no or yes for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Canadian National Breast Screening Study, Netherlands Cohort Study, and New York State Cohort), energy intake (continuous), red meat intake (quartiles), total milk intake (quartiles) and folate intake from food only (quintiles). For women, the relative risks were also adjusted for history of use of oral contraceptives (no or yes) and postmenopausal hormone therapy (ever or never).

†  $P > 0.2$  for between-study heterogeneity for the highest intake category and  $P = 0.11$  for between-study heterogeneity due to sex for the highest intake category.

‡  $P > 0.2$  for between-study heterogeneity for the highest intake category and for between-study heterogeneity due to sex for the highest intake category.

§ The Canadian National Breast Screening Study and the Sweden Mammography Cohort were not included in this analysis.

|| The Canadian National Breast Screening Study, the Netherlands Cohort Study, and the Sweden Mammography Cohort were not included in this analysis.

¶  $P = 0.14$  for between-study heterogeneity for the highest intake category and  $P = 0.17$  for between-study heterogeneity due to sex for the highest intake category.

\*\*  $P = 0.15$  for between-study heterogeneity for the highest intake category and  $P > 0.2$  for between-study heterogeneity due to sex for the highest intake category.

†† The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was not included in this analysis.

ported that the relative risks for colorectal cancer in persons who consumed 2 alcoholic beverages daily were 1.32 (CI, 1.16 to 1.51) and 1.07 (CI, 1.02 to 1.12), respectively (45). Associations were stronger in case-control studies that used population controls than those that used hospital controls (44), possibly because alcohol intake is related to many conditions requiring hospitalization.

In separate analyses of colon cancer and rectal cancer, some (46–57) but not all (38, 58–62) studies have reported positive associations between alcohol intake and rectal cancer. The results have been more mixed for colon cancer: Some studies (38, 46, 48–50, 54, 56, 57, 63, 64), but not others (47, 52, 53, 55, 58–62, 65, 66), have found a positive association. However, we found that alcohol intake was positively related to both colon cancer and rectal cancer, suggesting that statistical power might have been problematic in previous studies on colon cancer.

Among alcoholic beverages, beer intake has been related to an increased risk for rectal cancer in most (50–52,

55, 59, 60, 67) but not all (46, 61, 68) studies. The association between beer intake and colon cancer has been inconsistent (46, 49, 50, 52, 55, 59, 61, 63, 64, 68, 69). Most studies have reported no association between wine or liquor intake and colon or rectal cancer (48, 50–52, 60, 61, 63, 67–69); however, a few studies have reported positive associations for colon cancer (46, 55, 63, 64). We found that all 3 types of beverage were somewhat positively associated with colorectal cancer and that the risks among these beverages did not differ significantly. We also found a positive association between intake of wine or beer and risk for both colon and rectal cancers. Thus, our data suggest that the positive association between total alcohol and colorectal cancer is attributable to ethanol itself rather than to a specific beverage.

We found that the association between alcohol consumption and risk for colorectal cancer was stronger among persons with a lower body mass index than in those with a higher body mass index. This effect may be related

to the observation that alcohol intake reduces insulin resistance (70), which is strongly related to obesity (71) and may be related to a higher risk for colorectal cancer (38, 72, 73). Thus, among persons with a higher body mass index, the adverse effect of alcohol on risk for colorectal cancer might be offset by the beneficial effects of alcohol on insulin resistance. Alternatively, because leaner people have higher blood alcohol concentrations in response to a fixed dose of alcohol, the same biological mechanism may be at work.

The effect of alcohol as an antagonist of methyl-group metabolism may be exacerbated by low levels of folate and methionine, which also contribute to DNA hypomethylation (74). We found that the positive association between alcohol use and risk for colorectal cancer was restricted to persons who did not take multivitamins, a major contributor of folate intake. Multivitamins also contain a more bioavailable form of folate than that in foods (75, 76). The positive association between alcohol and colorectal cancer was also not seen in persons who consumed higher amounts of methionine.

We observed a slightly lower risk for colorectal cancer with alcohol intake of 0 to less than 5 g/d compared with nondrinkers, perhaps because the reference group of nondrinkers includes past drinkers, who may differ from never-drinkers (for example, past drinkers may have ceased alcohol intake because of illness). Previous studies have been shown that past drinkers are at higher risk for colorectal cancer than are never-drinkers (3, 38). We had information on past alcohol intake from only 4 studies; however, when we excluded past drinkers from the reference group of nondrinkers, the association was slightly stronger. Therefore, including previous drinkers in the reference group is unlikely to account for the positive association overall.

Our study had several strengths. First, we specified a priori that we would include only prospective studies that used a validated food-frequency questionnaire to estimate dietary intake. Prospective studies are less vulnerable to selection and recall biases that may affect case-control studies of associations between diet and disease. These inclusion criteria also minimized sources of variation across studies due to study design or quality. Results in our analyses were consistent across studies. Second, analysis of the primary data from these studies has several advantages compared with conducting a meta-analysis of the published literature. We could create identical categories for alcohol intake and covariates across studies, removing potential sources of heterogeneity that may occur in a meta-analysis of the published literature. Because the studies were selected to evaluate relationships of diet with cancer in general, rather than of alcohol with colorectal cancer, we also minimized the possibility of including only studies that had significant findings (publication bias). In fact, we included 4 studies that have not published data on alcohol and colorectal cancer.

Our study had several limitations. First, we had only one measure of alcohol consumption at baseline and could not investigate lifetime alcohol consumption, alcohol consumption at younger ages, or changes in alcohol consumption during follow-up. Second, we could not examine drinking patterns or duration of alcohol use. Third, some of the studies did not measure some risk factors for colorectal neoplasia. However, the pooled multivariate results were similar to the age-adjusted results, indicating that this deficiency was not important. Fourth, we did not have information on screening for colorectal cancer. However, during the follow-up period of most of the samples, screening endoscopy and polyp removal were not widespread. Finally, measurement error on alcohol intake may bias the results. However, validation data in our studies have generally supported that alcohol intake was well measured (16, 17, 19) (Wolk A. Personal communication).

Two of the studies also reported strong correlations between alcohol intake and serum high-density lipoprotein cholesterol, a biomarker that cannot be affected by biased reporting (19). Measurement error in other covariates, including dietary covariates, may be a concern. However, because the age-adjusted results were similar to the multivariate results, the influence of measurement error in covariates should be minimal.

In summary, a single determination of alcohol intake was associated with a modest relative elevation in risk for colorectal cancer, mainly for intake of 30 g/d or greater, a level of intake reported by 4% of women and 13% of men. Whether this association is causal depends in part on whether participants in the higher intake groups differ from the other participants in some unmeasured determinants of risk for colorectal cancer, or whether the potential confounding factors for which we adjusted were measured with lesser accuracy in this subset. The associations were consistent across studies, between men and women, and across subsites of the large bowel. Although moderate alcohol consumption has been associated with a reduced risk for cardiovascular disease, alcohol intake has been positively associated with risk for cancers at several sites, including the large bowel. Both the risks and benefits of alcohol intake should be considered in decisions about drinking.

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