American Journal of Epidemiology

Vol. 158, No. 8
Printed in U.S.A.
DOI: 10.1093/aje/kwg221

Joint Association of Alcohol and Folate Intake with Risk of Major Chronic Disease in Women

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Received for publication February 13, 2003; accepted for publication April 9, 2003.

Alcohol interferes with folate metabolism and has opposing effects on the risks of cardiovascular disease and cancer. The authors examined the joint association of alcohol and folate intake with risk of major chronic disease, defined as fatal or nonfatal cardiovascular disease or cancer, or other nontraumatic death. This study included 83,929 women aged 34–59 years with no previous history of cardiovascular disease or cancer who provided dietary data in 1980. During 16 years of follow-up, the authors documented 10,666 new cases of major chronic disease. Overall, heavy drinkers (>30 g/day) with a lower total folate intake (<180 μg/day) had the highest risk; in comparison with abstainers with a folate intake of 400–599 μg/day, the multivariate relative risk was 1.36 (95% confidence interval: 1.10, 1.70). However, the increased risk of major chronic disease associated with heavy drinking was largely diminished among women with a higher folate intake (p for interaction = 0.02). The positive association between heavy alcohol/low folate intake and risk of major chronic disease was most apparent among women younger than age 60 years. Adequate folate intake may be important in the primary prevention of overall major chronic disease in women, especially among younger women consuming more than two alcoholic drinks per day.

alcohol drinking; cardiovascular diseases; chronic disease; effect modifiers (epidemiology); folic acid; neoplasms; women

Abbreviation: CI, confidence interval.

Alcohol interferes with normal folate transport and metabolism by disrupting intestinal absorption, reducing uptake and storage in the liver, increasing urinary loss, inhibiting methionine synthase activity, and activating oxidative catabolism of folate (1). Diminished folate status contributes to elevated blood homocysteine levels, which have been associated with increased risk of cardiovascular disease (2). Diminished folate status can also lead to abnormal DNA synthesis, repair, and methylation, which may increase the risk of cancer (3–5). A statistical interaction between alcohol and folate intake has been observed for risk of coronary heart disease (6), breast cancer (7–9), and colon cancer (10) in large prospective cohort studies. For example, in one study (6), the inverse association between folate intake and risk of coronary heart disease was stronger with increasing levels of alcohol consumption, and the inverse relation between alcohol consumption and risk of coronary heart disease was stronger with increasing levels of folate intake. For breast and colon cancer, alcohol consumption was associated with increased risk only among persons with lower folate intake, and a benefit of higher folate intake was seen primarily among persons with higher alcohol consumption (7–10). The opposing effects of alcohol consumption on the risks of cardiovascular disease and cancer further complicate the overall balance of risks and benefits associated with alcohol and folate intake. Therefore, we examined prospectively the joint associations of alcohol and folate intake with risk of major chronic diseases combined, as well as with cardiovascular disease and cancer separately, in a large cohort of women.

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MATERIALS AND METHODS

The Nurses' Heath Study cohort

The Nurses' Health Study was established in 1976, when 121,700 female registered nurses aged 30–55 years from 11 US states completed a mailed questionnaire designed to study the etiologies of heart disease and cancer. Updated information on lifestyle and disease status has been collected biennially by mailed questionnaire since 1976, and updated information on vitamin supplement use has been collected since 1980. Diet was assessed in 1980, 1984, 1986, 1990, and 1994 using semiquantitative food frequency questionnaires, before mandatory folic acid fortification of cereal-grain products started in 1998.

Dietary assessment

The semiquantitative food frequency questionnaire administered at baseline (1980) included 61 foods, and it was revised and expanded to include approximately twice that number in subsequent cycles (11). Participants were asked to report their average frequency of consumption of selected foods and beverages during the previous year, with a specified commonly used unit or portion size. We computed nutrient intakes by multiplying the consumption frequency of each food by the nutrient content of the portion specified and then summing these products over all of the food items. The food composition values were obtained from the Harvard University Food Composition Database, which was derived from US Department of Agriculture sources (12), and from supplemental manufacturer information. We also asked questions on the frequency and dose of specific vitamin supplements used and the frequency, duration, brand, and type of any multivitamin supplement used. The reproducibility and validity of the dietary questionnaires have been described in detail elsewhere (11).

Total alcohol intake was the sum of the values for three types of beverages: beer, wine, and spirits. We assumed an ethanol content of 13.1 g for a 12-ounce (38-dl) can or bottle of beer, 11.0 g for a 4-ounce (12-dl) glass of wine, and 14.0 g for a standard portion of spirits (13). Total folate intake was the sum of folate intake from both food and vitamin supplement sources.

In validation studies of the dietary instrument, we found that the food frequency questionnaire measured alcohol consumption well; the correlation coefficient for the correlation between alcohol consumption derived from the 1980 questionnaire and that derived from the average of four 1-week diet records was 0.90 (14). We also found that the food frequency questionnaire predicted circulating levels of folate. Correlation coefficients were 0.55 for the correlation between total folate intake calculated from the 1980 questionnaire and erythrocyte folate concentrations measured in 1987 in this cohort (15) and 0.63 for the correlation between total folate intake calculated from the same food frequency questionnaire and plasma folate levels in the Framingham Heart Study (16). In addition, the relation of homocysteine level to dietary folate was virtually the same as its relation to blood levels of folate (16).

Population for analysis

After up to four mailings had been sent, 98,462 women returned the 1980 dietary questionnaire. We excluded from our study women with inadequate assessment of diet (10 or more food items left blank or an implausibly high (>3,500 kcal/day) or low (<500 kcal/day) total energy intake). We also excluded women with a history of cancer (except for nonmelanoma skin cancer) or cardiovascular disease (angina, coronary bypass or angioplasty, myocardial infarction, and stroke), because diagnosis of these conditions can lead to changes in diet and lifestyle. We further excluded women who reported both no alcohol intake at baseline and a substantial decrease in drinking in the previous 10 years (n = 3,120), since these women may have stopped drinking because of illness. After these exclusions, 83,929 participants remained.

Outcome ascertainment

The primary endpoint in this study was incidence of major chronic disease, defined as fatal or nonfatal cardiovascular disease or cancer, or other nontraumatic death—whichever came first. We also examined cardiovascular disease and cancer as separate outcomes. Cardiovascular disease was defined as fatal or nonfatal myocardial infarction or stroke.

We asked all women who reported incident nonfatal myocardial infarction, cancer, or stroke on any biennial follow-up questionnaire to confirm the report and provide permission to review their medical records. Study physicians blinded to the risk factors reviewed the records. Cancer was confirmed according to hospital records and pathology reports. Myocardial infarction was confirmed using the World Health Organization criteria, requiring symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzyme levels (17). Stroke was confirmed using the criteria of the National Survey of Stroke, which require a constellation of neurologic deficits that are sudden or rapid in onset, lasting at least 24 hours or until death (18). Deaths were reported by next of kin, coworkers, or postal authorities or ascertained through a search for nonrespondents using the National Death Index (19); confirmation rates were more than 98 percent. We attempted to confirm the cause of each death by referring medical records or autopsy reports.

Statistical analysis

Each participant contributed follow-up time from the date of returning the 1980 questionnaire to the date of the first event of cardiovascular disease, cancer, or death or June 1, 1996. During the follow-up period, confirmed cases and reported cancers were censored from subsequent follow-up, and the cohort at risk included those who were alive and remained free of cardiovascular disease or cancer at the beginning of each of the eight 2-year follow-up intervals. Thus, each woman could contribute only one major chronic disease event.

To reduce within-subject variation and best represent long-term dietary intake, we used the cumulative average

of dietary intakes from all available questionnaires up to the start of each 2-year follow-up interval (20). For example, 1980 intake was used for follow-up between 1980 and 1984; the average of the 1980 and 1986 intakes was used for follow-up between 1984 and 1986; and the average of the 1980, 1984, and 1986 intakes was used for follow-up between 1986 and 1990. Diet for women who developed angina or underwent coronary bypass or angioplasty was not updated for major chronic disease and cardiovascular disease outcomes, because change in diet after development of the intermediate events of cardiovascular disease might have biased our estimate of the true exposure-disease association. For women who reported other chronic conditions, such as diabetes mellitus, hypercholesterolemia, and hypertension, we used the cumulative average intakes and controlled for these chronic conditions in the multivariate analyses. Intakes of all nutrients (except for alcohol) were energy-adjusted using the residual method (11, 21). Information on nondietary covariates was updated biennially.

We categorized alcohol intake into four groups (0, 0.1–10, 10.1–30, and >30 g/day) and folate intake into five groups (<180, 180–299, 300–399, 400–599, and ≥600 μg/day) to examine the joint associations with alcohol and total folate intake. The alcohol categories used in this study are consistent with those of previously published studies (22–24). We used the previous Recommended Dietary Allowance for folate (180 μg/day) (25) as the cutoff point for the lowest category of folate intake and the current Recommended Dietary Allowance (400 μg/day) (25) as the cutoff point for the reference category. We conducted further stratified analyses to determine whether the combined association of alcohol and total folate intake with risk of major chronic disease was modified by age. We used odds ratios calculated from pooled logistic regression models with eight 2-year time intervals to estimate relative risks (26, 27). In an additional analysis, we used restricted cubic spline regressions with four knots to flexibly model the association between alcohol or folate intake (as a continuous variable) and risk of major chronic disease (28, 29).

In Cox proportional hazards models, including the spline regression models, we adjusted for age, smoking, and other covariates listed in the footnotes of the tables. All p values were two-sided. Tests for trend were conducted using the median value for each category of alcohol or folate intake analyzed as a continuous variable in multivariate models. We performed tests for interaction by entering a cross-product term for the interaction between alcohol and folate intake (as continuous variables using the median value for each category of alcohol and folate intake).

RESULTS

Of the 83,929 participants, 23.8 percent reported no alcohol intake and 4.3 percent reported alcohol intake of more than 30 g/day. For total folate intake, 9 percent reported less than 180 μg/day and 13.7 percent reported at least 600 μg/day.

During the 16 years (1,242,821 person-years) of follow-up, we documented 10,666 incident cases of major chronic disease (2,381 first cardiovascular disease events, 7,478 first diagnoses of cancer, and 807 other nontraumatic deaths mostly related to chronic disease). Breast cancer (42.4 percent), colorectal cancer (9.3 percent), uterine cancer (8.7 percent), and lung cancer (8.1 percent) were the most common cancers in the cohort, and 59.6 percent of cardiovascular disease was coronary heart disease (nonfatal myocardial infarction and fatal coronary heart disease).

We first examined alcohol and total folate intakes independently in relation to risk of major chronic disease, cardiovascular disease, and cancer (table 1). Heavy alcohol consumption (>30 g/day) was not associated with significantly increased risk of major chronic disease because of its opposing effects on the risks of cardiovascular disease and cancer. A lower folate intake (<180 μg/day) was associated with a statistically significant increased risk of cardiovascular disease, but total folate intake was not appreciably associated with risk of cancer or major chronic disease.

We next examined the joint association of alcohol and total folate intake with risk of major chronic disease (table 2). Overall, heavy drinkers with low folate intake (<180 μg/day) had the highest risk; in comparison with abstainers with a folate intake of 400–599 μg/day, the relative risk was 1.36 (95 percent confidence interval (CI): 1.10, 1.70). However, the increased risk of major chronic disease associated with heavy drinking was largely diminished by a higher folate intake (table 2). The test for interaction between alcohol and total folate intake gave a statistically significant result ($p = 0.02$).

The joint associations with alcohol and total folate intake are presented separately for cardiovascular disease (table 3) and cancer (table 4). Although the greatest risk for both cardiovascular disease and cancer among heavy drinkers was observed at the lowest level of folate intake, the dose-response relations were different. Folate intake greater than or equal to 600 μg/day was needed for maximal reduction of the excess cancer risk associated with alcohol drinking (table 4), whereas intake of relatively less folate (<180 μg/day) seemed to be sufficient for a higher level of alcohol consumption to be protective against cardiovascular disease (table 3). The test for interaction between alcohol and total folate intake gave statistically significant results for both cardiovascular disease ($p = 0.03$) and total cancer ($p = 0.01$). Because of the opposite relations of alcohol to the risks of cardiovascular disease and cancer, the joint association of alcohol and folate intake with major chronic disease risk (table 2) lay between the associations for cardiovascular disease and cancer.

Because previous studies have demonstrated alcohol-folate interactions for breast and colon cancer, we also separated total cancer into two subgroups: breast and colon cancer and other cancers (table 4). The pattern of the combined association of alcohol and folate intake was similar for these two cancer groups; however, the increased risk associated with alcohol consumption was much stronger for breast and colon cancer.

Cubic regression splines clearly demonstrated that lower folate intake was associated with markedly higher major chronic disease risk among women who consumed more than 30 g/day of alcohol (figure 1), and higher folate intake appeared to diminish the increased risk of major chronic disease related to heavy alcohol consumption (figure 2). The relations were in concordance with the results of the categorical analyses (table 2).

TABLE 1. Relative risks of major chronic disease, cancer, and cardiovascular disease according to cumulative average alcohol intake and total folate intake, Nurses' Health Study, United States, 1980–1996

	Alcohol intake (g/day)										*p* for trend
	0		0.1–5		5.1–10		10.1–30		>30		
	No. or RR*	95% CI*	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	
						Major chronic disease					
No. of cases	2,584		4,115		1,357		1,948		662		
Person-years of follow-up	296,171		500,617		165,159		227,245		53,630		
Age- and smoking-adjusted RR	1.00†		0.89	0.85, 0.94	0.85	0.80, 0.91	0.84	0.79, 0.89	1.06	0.97, 1.16	—‡
Multivariate RR§	1.00†		0.97	0.93, 1.02	0.96	0.90, 1.03	0.94	0.88, 1.00	1.08	0.98, 1.19	0.38
						Cardiovascular disease					
No. of cases	683		937		265		372		144		
Person-years of follow-up	297,944		503,780		166,244		228,813		54,070		
Age- and smoking-adjusted RR	1.00†		0.75	0.67, 0.82	0.59	0.51, 0.68	0.53	0.47, 0.60	0.65	0.54, 0.79	<0.001
Multivariate RR§	1.00†		0.90	0.81, 0.99	0.80	0.69, 0.92	0.71	0.62, 0.82	0.77	0.63, 0.94	<0.001
						Cancer					
No. of cases	1,695		2,984		1,025		1,447	1,447	454	454	
Person-years of follow-up	298,302		506,847		166,548		228,929	228,929	54,040	54,040	
Age- and smoking-adjusted RR	1.00†		1.00	0.94, 1.06	1.02	0.94, 1.10	1.01	0.94, 1.08	1.24	1.12, 1.38	<0.001
Multivariate RR§	1.00†		1.03	0.97, 1.10	1.06	0.98, 1.15	1.04	0.97, 1.13	1.23	1.10, 1.38	0.002
	Total folate intake (μg/day)										
	<180		180–299		300–399		400–599		≥600		
	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	
						Major chronic disease					
No. of cases	859		3,690		2,199		2,405		1,513		
Person-years of follow-up	113,551		450,635		252,956		254,974		170,705		
Age- and smoking-adjusted RR	1.07	0.99, 1.16	0.99	0.94, 1.04	0.93	0.88, 0.99	1.00†		0.99	0.93, 1.06	0.90
Multivariate RR¶	0.98	0.90, 1.06	0.96	0.91, 1.01	0.93	0.88, 0.99	1.00†		0.97	0.91, 1.03	0.48
						Cardiovascular disease					
No. of cases	239		838		527		480	480	317		
Person-years of follow-up	114,185		453,437		254,565		256,773		171,889		
Age- and smoking-adjusted RR	1.50	1.28, 1.76	1.13	1.01, 1.27	1.13	1.00, 1.28	1.00†		1.05	0.91, 1.21	0.001
Multivariate RR¶	1.25	1.05, 1.48	1.04	0.92, 1.17	1.10	0.97, 1.25	1.00†		1.05	0.91, 1.21	0.21
						Cancer					
No. of cases	563		2,640		1,550		1,777		1,075		
Person-years of follow-up	113,048		453,748		256,751		259,186		171,933		
Age- and smoking-adjusted RR	0.96	0.87, 1.06	0.96	0.90, 1.02	0.89	0.83, 0.95	1.00†		0.96	0.89, 1.04	0.33
Multivariate RR¶	0.96	0.87, 1.07	0.97	0.91, 1.03	0.90	0.84, 0.96	1.00†		0.94	0.87, 1.02	0.83

* RR, relative risk; CI, confidence interval.

† Referent.

‡ The trend test was not applicable because of a U-shaped relation between alcohol intake and risk of major chronic disease in the age- and smoking-adjusted model.

§ The model included indicator variables for age (5-year categories); smoking status (never smoking, past smoking, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day); body mass index (weight (kg)/height $(m)^2$) (<21, 21–22, 23–24, 25–28, and ≥29); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); past or present use of oral contraceptives (yes or no); regular vigorous exercise (<1, 1, 2–3, 4–6, and ≥7 times per week); use of aspirin (<1, 1–6, ≥7 times per week, and dose unknown); parental history of myocardial infarction before age 60 years (yes or no); family history of cancer (yes or no); diabetes mellitus (yes or no); hypercholesterolemia (yes or no); hypertension (yes or no); use of vitamin E supplements (yes or no); quintiles of fiber, saturated fat, polyunsaturated fat, *trans* fat, and total energy intake; and categories of alcohol and total folate intake.

¶ Controlled for all of the variables listed above except fiber intake.

TABLE 2. Relative risk of major chronic disease according to joint levels of cumulative average alcohol intake and total folate intake, Nurses' Health Study, United States, 1980–1996*

	Total folate intake (μg/day)										*p* for trend
	<180		180–299		300–399		400–599		≥600		
	No. or RR†	95% CI†	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	
Alcohol intake of 0 g/day											
No. of cases	250		936		497		514		387		
Person-years of follow-up	33,970		110,999		55,524		54,814		40,863		
Multivariate RR‡	1.00	0.85, 1.16	1.01	0.91, 1.13	0.98	0.87, 1.11	1.00§		1.05	0.92, 1.20	0.58
Alcohol intake of 0.1–10 g/day											
No. of cases	368		1,799		1,203		1,311		790		
Person-years of follow-up	54,009		23,4730		142,259		143,008		91,758		
Multivariate RR‡	0.95	0.83, 1.09	0.96	0.87, 1.07	0.95	0.86, 1.06	1.03	0.93, 1.14	1.00	0.89, 1.12	0.15
Alcohol intake of 10.1–30 g/day											
No. of cases	142		679		391		466		271		
Person-years of follow-up	18,569		83,097		46,020		47,048		32,521		
Multivariate RR‡	1.01	0.83, 1.22	0.95	0.84, 1.07	0.92	0.80, 1.05	1.04	0.92, 1.18	0.91	0.78, 1.05	0.91
Alcohol intake of >30 g/day											
No. of cases	98		269		104		125		66		
Person-years of follow-up	6,756		21,154		9,416		10,477		5,828		
Multivariate RR‡	1.36	1.10, 1.70	1.17	1.01, 1.36	1.00	0.81, 1.24	1.05	0.86, 1.28	1.02	0.79, 1.33	0.06
p for trend	0.004		0.07		0.91		0.62		0.39		

* $p = 0.02$ for the interaction between alcohol and total folate intake.

† RR, relative risk; CI, confidence interval.

‡ The model included indicator variables for age (5-year categories); smoking status (never smoking, past smoking, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day); body mass index (weight (kg)/height (m)^2) (<21, 21–22, 23–24, 25–28, and ≥29); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); past or present use of oral contraceptives (yes or no); regular vigorous exercise (<1, 1, 2–3, 4–6, and ≥7 times per week); use of aspirin (<1, 1–6, ≥7 times per week, and dose unknown); parental history of myocardial infarction before age 60 years (yes or no); family history of cancer (yes or no); diabetes mellitus (yes or no); hypercholesterolemia (yes or no); hypertension (yes or no); use of vitamin E supplements (yes or no); quintiles of saturated fat, polyunsaturated fat, *trans* fat, and total energy intake; and categories of alcohol and total folate intake.

§ Referent.

Younger women are at lower risk of cardiovascular disease, whereas cardiovascular disease risk is proportionally greater among older women (30). Because of the opposing effects of alcohol on the risks of cardiovascular disease and cancer, we also evaluated the combined association of alcohol and total folate intake with major chronic disease risk by age group (<60 years or ≥60 years) (table 5). Heavy alcohol consumption and low folate intake were significantly associated with increased major chronic disease risk among women younger than age 60 years but not among women aged 60 years or more. The test for interaction between alcohol and total folate intake gave a statistically significant result among women younger than age 60 years ($p = 0.01$) but not among women aged 60 years or more ($p = 0.57$).

To exclude the possibility that other beneficial constituents (e.g., anticarcinogens or protective factors for cardiovascular disease) present in multivitamin supple-

TABLE 3. Relative risk of cardiovascular disease according to joint levels of cumulative average alcohol intake and total folate intake, Nurses' Health Study, United States, 1980–1996*

	Total folate intake (μg/day)										*p* for trend
	<180		180–299		300–399		400–599		≥600		
	No. or RR†	95% CI†	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	
Alcohol intake of 0 g/day											
No. of cases	78		238		135		134		98		
Person-years of follow-up	34,228		111,736		55,815		55,104		41,061		
Multivariate RR‡	1.15	0.86, 1.54	0.91	0.73, 1.13	0.99	0.78, 1.26	1.00§		1.04	0.80, 1.35	0.64
Alcohol intake of 0.1–10 g/day											
No. of cases	92		419		288		242		161		
Person-years of follow-up	54,425		236,515		143,029		143,743		92,311		
Multivariate RR‡	0.87	0.66, 1.15	0.88	0.72, 1.07	0.90	0.73, 1.11	0.77	0.62, 0.96	0.86	0.68, 1.09	0.48
Alcohol intake of 10.1–30 g/day											
No. of cases	43		123		78		81		47		
Person-years of follow-up	18,696		83,838		46,250		47,358		32,670		
Multivariate RR‡	1.09	0.77, 1.56	0.64	0.50, 0.83	0.74	0.55, 0.98	0.70	0.52, 0.92	0.61	0.44, 0.86	0.19
Alcohol intake of >30 g/day											
No. of cases	26		58		26		23		11		
Person-years of follow-up	6,836		21,348		9,471		10,568		5,847		
Multivariate RR‡	1.04	0.68, 1.61	0.77	0.56, 1.05	0.83	0.55, 1.27	0.63	0.40, 0.99	0.57	0.31, 1.07	0.09
p for trend	0.73		0.03		0.18		0.04		0.01		

* $p = 0.03$ for the interaction between alcohol and total folate intake.

† RR, relative risk; CI, confidence interval.

‡ The model included indicator variables for age (5-year categories); smoking status (never smoking, past smoking, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day); body mass index (weight (kg)/height $(m)^2$) (<21, 21–22, 23–24, 25–28, and ≥29); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); past or present use of oral contraceptives (yes or no); regular vigorous exercise (<1, 1, 2–3, 4–6, and ≥7 times per week); use of aspirin (<1, 1–6, ≥7 times per week, and dose unknown); parental history of myocardial infarction before age 60 years (yes or no); family history of cancer (yes or no); diabetes mellitus (yes or no); hypercholesterolemia (yes or no); hypertension (yes or no); use of vitamin E supplements (yes or no); quintiles of saturated fat, polyunsaturated fat, *trans* fat, and total energy intake; and categories of alcohol and total folate intake.

§ Referent.

ments or healthy behaviors associated with multivitamin use could contribute to the apparent benefit of folate intake observed in our study, we conducted separate analyses limited to women who did not use supplements and examined the combined associations with alcohol and folate obtained from foods only. Since the range of folate from foods was smaller, folate intake was recategorized into three groups (<180, 180–299, and ≥300 μg/day). With substantially fewer cases, the associations of folate and alcohol intake with risk of major chronic disease, cardiovascular disease, and cancer persisted, though the tests for interaction did not produce statistically significant results. In comparison with abstainers with folate intakes of ≥300 g/day, the relative risk of major chronic disease for heavy drinkers with a low folate intake (<180 μg/day) was 1.56 (95 percent CI: 1.14, 2.13). The corresponding relative risk for cardiovascular disease was 1.38 (95 percent CI: 0.76, 2.50), and the relative risk for total

TABLE 4. Relative risk of cancer according to joint levels of cumulative average alcohol intake and total folate intake, Nurses' Health Study, United States, 1980–1996

	Total folate intake (μg/day)										*p* for trend
	<180		180–299		300–399		400–599		≥600		
	No. or RR*	95% CI*	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	
Total cancer†											
Alcohol intake of 0 g/day											
No. of cases	155		625		319		340		256		
Person-years of follow-up	33,903		111,664		56,098		55,642		40,995		
Multivariate RR‡	1.00	0.82, 1.21	1.06	0.92, 1.21	0.98	0.84, 1.14	1.00§		1.06	0.90, 1.25	0.90
Alcohol intake of 0.1–10 g/day											
No. of cases	254		1,302		871		1,004		578		
Person-years of follow-up	53,819		237,165		144,589		145,256		92,567		
Multivariate RR‡	1.06	0.89, 1.25	1.04	0.93, 1.18	1.01	0.89, 1.15	1.15	1.02, 1.31	1.06	0.93, 1.22	0.23
Alcohol intake of 10.1–30 g/day											
No. of cases	91		517		291		345		203		
Person-years of follow-up	18,554		83,542		46,625		47,681		32,527		
Multivariate RR‡	1.04	0.82, 1.32	1.11	0.97, 1.28	1.01	0.86, 1.18	1.15	0.99, 1.34	1.03	0.87, 1.23	0.86
Alcohol intake of >30 g/day											
No. of cases	63		196		69		88		38		
Person-years of follow-up	6,772		21,378		9,439		10,607		5,844		
Multivariate RR‡	1.58	1.20, 2.07	1.44	1.20, 1.72	1.08	0.83, 1.41	1.22	0.96, 1.54	0.98	0.70, 1.38	0.01
p for trend	0.006		<0.001		0.58		0.26		0.58		
Breast cancer and colon cancer only¶											
Alcohol intake of 0 g/day											
No. of cases	73		311		163		158		121		
Person-years of follow-up	34,020		111,979		56,261		55,824		41,138		
Multivariate RR‡	1.06	0.80, 1.40	1.14	0.94, 1.39	1.06	0.85, 1.32	1.00§		1.09	0.85, 1.38	0.58
Alcohol intake of 0.1–10 g/day											
No. of cases	132		676		438		493		284		
Person-years of follow-up	53,967		237,884		145,032		145,817		92,955		
Multivariate RR‡	1.25	0.98, 1.59	1.17	0.98, 1.40	1.09	0.90, 1.30	1.20	1.00, 1.44	1.12	0.92, 1.37	0.72
Alcohol intake of 10.1–30 g/day											
No. of cases	49		285		140		182		88		
Person-years of follow-up	18,610		83,850		46,814		47,860		32,641		
Multivariate RR‡	1.31	0.94, 1.81	1.36	1.11, 1.66	1.04	0.83, 1.31	1.33	1.07, 1.65	0.96	0.74, 1.25	0.04

Table continues

cancer was 1.63 (95 percent CI: 1.12, 2.37). The relative risk comparing a folate intake of ≥300 μg/day with an intake of <180 μg/day among heavy drinkers was 0.62 (95 percent CI: 0.39, 0.99) for major chronic disease, 0.52 (95 percent CI: 0.21, 1.25) for cardiovascular disease, and 0.62 (95 percent CI: 0.35, 1.08) for cancer.

TABLE 4. Continued

	Total folate intake (μg/day)										*p* for trend
	<180		180–299		300–399		400–599		≥600		
	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	
Alcohol intake of >30 g/day											
No. of cases	27		95		36		42		20		
Person-years of follow-up	6,805		21,461		9,473		10,656		5,862		
Multivariate RR‡	1.76	1.17, 2.65	1.69	1.30, 2.19	1.28	0.88, 1.85	1.38	0.98, 1.94	1.23	0.77, 1.97	0.11
p for trend	0.04		<0.001		0.59		0.04		0.71		
					Other cancers#						
Alcohol intake of 0 g/day											
No. of cases	82		314		156		182		135		
Person-years of follow-up	33,981		112,020		56,273		55,810		41,113		
Multivariate RR‡	0.95	0.73, 1.24	0.98	0.82, 1.19	0.90	0.73, 1.12	1.00§		1.04	0.83, 1.31	0.46
Alcohol intake of 0.1–10 g/day											
No. of cases	122		626		433		511		294		
Person-years of follow-up	53,932		237,875		145,077		145,748		92,878		
Multivariate RR‡	0.90	0.71, 1.15	0.93	0.79, 1.10	0.95	0.80, 1.13	1.11	0.94, 1.32	1.01	0.84, 1.22	0.04
Alcohol intake of 10.1–30 g/day											
No. of cases	42		232		151		163		115		
Person-years of follow-up	18,608		83,847		46,773		47,862		32,620		
Multivariate RR‡	0.82	0.58, 1.16	0.90	0.74, 1.10	0.98	0.79, 1.23	0.99	0.79, 1.22	1.09	0.86, 1.38	0.07
Alcohol intake of >30 g/day											
No. of cases	36		101		33		46		18		
Person-years of follow-up	6,807		21,480		9,483		10,648		5,864		
Multivariate RR‡	1.41	0.98, 2.03	1.23	0.96, 1.58	0.92	0.63, 1.34	1.07	0.77, 1.49	0.78	0.48, 1.27	0.03
p for trend	0.07		0.10		0.80		0.67		0.58		

* RR, relative risk; CI, confidence interval.

† $p = 0.01$ for the interaction between alcohol and total folate intake.

‡ The model included indicator variables for age (5-year categories); smoking status (never smoking, past smoking, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day); body mass index (weight (kg)/height (m)^2) (<21, 21–22, 23–24, 25–28, and ≥29); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); past or present use of oral contraceptives (yes or no); regular vigorous exercise (<1, 1, 2–3, 4–6, and ≥7 times per week); use of aspirin (<1, 1–6, ≥7 times per week, and dose unknown); parental history of myocardial infarction before age 60 years (yes or no); family history of cancer (yes or no); diabetes mellitus (yes or no); hypercholesterolemia (yes or no); hypertension (yes or no); use of vitamin E supplements (yes or no); quintiles of saturated fat, polyunsaturated fat, *trans* fat, and total energy intake; and categories of alcohol and total folate intake.

§ Referent.

¶ $p = 0.048$ for the interaction between alcohol and total folate intake.

$p = 0.05$ for the interaction between alcohol and total folate intake.

Because the biologic functions of folate, methionine, vitamin B_{12}, and vitamin B_6 are closely related and heavy drinking may also increase the possibility of iron deficiency, we added methionine, vitamin B_{12}, vitamin B_6, and iron to the models and found that the results persisted. Because women who consumed more folate were more likely to have

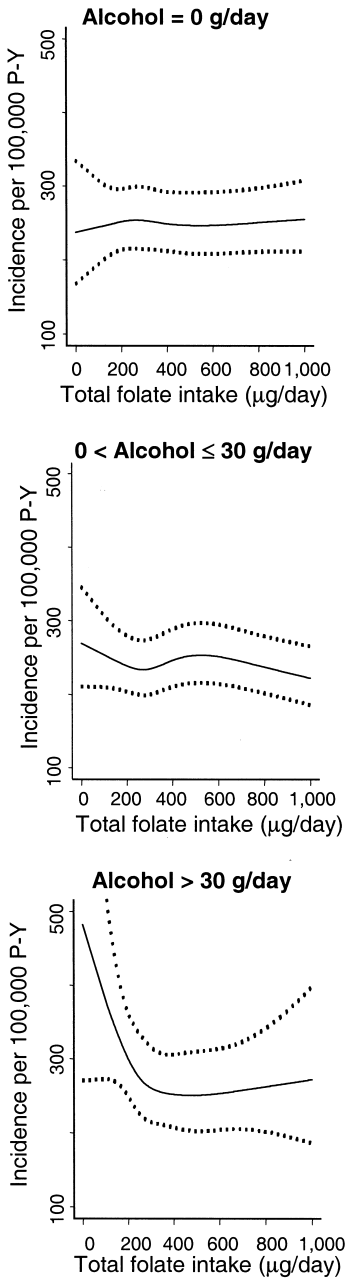

FIGURE 1. Estimated incidence of major chronic disease according to total folate intake, by level of alcohol consumption, Nurses' Health Study, United States, 1980–1996. Dotted lines are 95 percent confidence intervals for the estimated incidence rates. The results, from spline regression models, were adjusted for the same variables as in table 1. Incidence rates were estimated using the reference levels for all covariates represented as sets of indicator variables. Within each level of alcohol, the alcohol variable was set to the median for that group. P-Y, person-years.

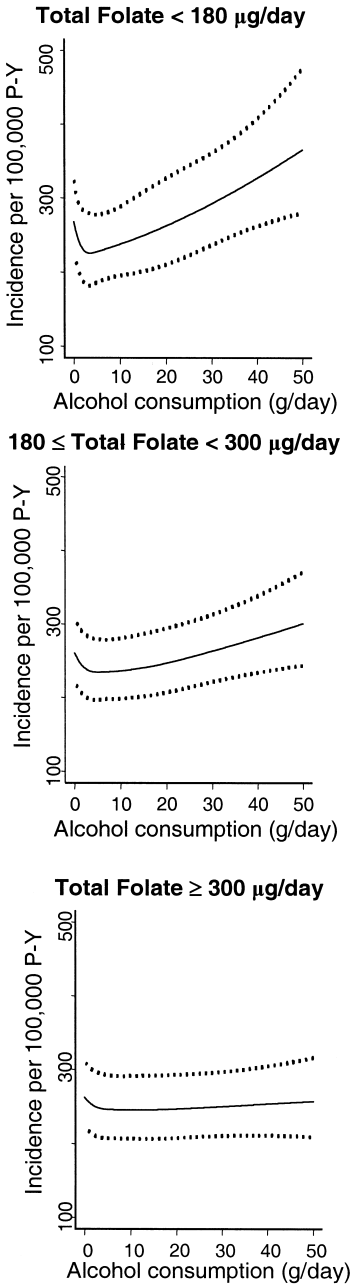

FIGURE 2. Estimated incidence of major chronic disease according to alcohol consumption, by level of total folate intake, Nurses' Health Study, United States, 1980–1996. Dotted lines are 95 percent confidence intervals for the estimated incidence rates. The results, from spline regression models, were adjusted for the same variables as in table 1. Incidence rates were estimated using the reference levels for all covariates represented as sets of indicator variables. Within each level of folate, the folate variable was set to the median for that group. P-Y, person-years.

greater intakes of fiber, β-carotene, lutein/zeaxanthin, preformed vitamin A, and vitamin C, we further adjusted the data for these variables but did not see appreciable differences in our results.

We also examined the joint association of alcohol consumption and multivitamin use with risk of major chronic disease. Heavy drinkers and never users of multivitamins were at highest risk; in comparison with abstainers

TABLE 5. Relative risk of major chronic disease according to joint levels of cumulative average alcohol intake and total folate intake, by age group, Nurses' Health Study, United States, 1980–1996

	Total folate intake (μg/day)										*p* for trend
	<180		180–299		300–399		400–599		≥600		
	No. or RR*	95% CI*	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	No. or RR	95% CI	
Age, <60 years†											
Alcohol intake of 0 g/day											
No. of cases	185		595		257		240		213		
Person-years of follow-up	30,725		90,884		41,360		39,651		31,179		
Multivariate RR‡	1.11	0.91, 1.35	1.14	0.98, 1.33	1.03	0.86, 1.23	1.00§		1.16	0.96, 1.39	0.82
Alcohol intake of 0.1–10 g/day											
No. of cases	287		1,161		591		680		420		
Person-years of follow-up	49,465		192,865		104,382		103,445		68,046		
Multivariate RR‡	1.09	0.92, 1.31	1.08	0.94, 1.25	0.98	0.84, 1.14	1.15	0.99, 1.34	1.08	0.92, 1.27	0.52
Alcohol intake of 10.1–30 g/day											
No. of cases	106		420		209		241		148		
Person-years of follow-up	16,730		67,361		33,520		33,349		24,731		
Multivariate RR‡	1.09	0.87, 1.38	1.04	0.88, 1.22	1.00	0.83, 1.21	1.16	0.97, 1.39	0.94	0.77, 1.16	0.64
Alcohol intake of >30 g/day											
No. of cases	70		168		47		64		31		
Person-years of follow-up	5,792		16,596		6,616		7,481		4,479		
Multivariate RR‡	1.57	1.19, 2.06	1.34	1.10, 1.64	0.99	0.72, 1.36	1.09	0.82, 1.44	0.94	0.64, 1.37	0.01
p for trend	0.02		0.18		0.97		0.69		0.09		
Age, ≥60 years¶											
Alcohol intake of 0 g/day											
No. of cases	65		341		240		274		174		
Person-years of follow-up	3,245		20,115		14,164		15,163		9,684		
Multivariate RR‡	0.91	0.69, 1.20	0.89	0.75, 1.04	0.96	0.80, 1.14	1.00§		0.96	0.79, 1.16	0.32
Alcohol intake of 0.1–10 g/day											
No. of cases	81		638		612		631		370		
Person-years of follow-up	4,545		41,864		37,877		39,563		23,713		
Multivariate RR‡	0.78	0.61, 1.01	0.84	0.73, 0.97	0.93	0.80, 1.07	0.93	0.80, 1.07	0.93	0.79, 1.09	0.10
Alcohol intake of 10.1–30 g/day											
No. of cases	36		259		182		225		123		
Person-years of follow-up	1,840		15,736		12,500		13,699		7,790		
Multivariate RR‡	0.99	0.69, 1.41	0.87	0.73, 1.04	0.85	0.70, 1.03	0.94	0.78, 1.12	0.90	0.72, 1.12	0.73
Alcohol intake of >30 g/day											
No. of cases	28		101		57		61		35		
Person-years of follow-up	964		4,558		2,799		2,996		1,348		
Multivariate RR‡	1.13	0.76, 1.66	0.99	0.79, 1.26	1.00	0.75, 1.34	1.03	0.77, 1.37	1.12	0.78, 1.60	0.76
p for trend	0.13		0.22		0.83		0.74		0.60		

* RR, relative risk; CI, confidence interval.

† $p = 0.01$ for the interaction between alcohol and total folate intake.

‡ The model included indicator variables for age (5-year categories); smoking status (never smoking, past smoking, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day); body mass index (weight (kg)/height (m)^2) (<21, 21–22, 23–24, 25–28, and ≥29); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); past or present use of oral contraceptives (yes or no); regular vigorous exercise (<1, 1, 2–3, 4–6, and ≥7 times per week); use of aspirin (<1, 1–6, ≥7 times per week, and dose unknown); parental history of myocardial infarction before age 60 years (yes or no); family history of cancer (yes or no); diabetes mellitus (yes or no); hypercholesterolemia (yes or no); hypertension (yes or no); use of vitamin E supplements (yes or no); quintiles of saturated fat, polyunsaturated fat, *trans* fat, and total energy intake; and categories of alcohol and total folate intake.

§ Referent.

¶ $p = 0.57$ for the interaction between alcohol and total folate intake.

and current users of multivitamins, the relative risk was 1.26 (95 percent CI: 1.08, 1.47). Heavy drinking was not associated with increased risk among current multivitamin users; in comparison with abstainers, the relative risk was 1.05 (95 percent CI: 0.89, 1.23).

DISCUSSION

Results from this large prospective cohort study with 16 years of follow-up indicate that the joint effects of alcohol and folate intake substantially affect the overall health of women. Heavy alcohol intake and lower folate intake were associated with an increased risk of major chronic diseases combined. The increased risk of major chronic disease, particularly cancer, associated with heavy alcohol consumption was largely diminished by higher folate intake. Moreover, a higher level of alcohol consumption, even at levels exceeding 30 g/day, was associated with a further reduction in cardiovascular disease risk when folate intake was higher, but the expected benefit of alcohol with regard to cardiovascular disease was not observed when folate intake was low.

The joint association of alcohol and folate intake with risk of major chronic disease depended largely on the balance of the association of alcohol and folate intake with risk of cardiovascular disease and cancer. In comparison with women aged 60 years or more, heavy alcohol intake and low folate intake appeared to be more detrimental for women younger than age 60 years, who were at lower risk of cardiovascular disease. In the younger women, more folate was needed to reduce the increased major chronic disease risk, because a higher level of folate appeared to be needed to optimize risk of cancer than for cardiovascular disease.

Although multivitamin supplements are a major source of folate, the observed benefit of high folate intake is unlikely to be confounded by other beneficial constituents of multivitamins or by healthy behaviors associated with multivitamin use, because the risk pattern of the combined associations of alcohol and folate intake remained for each of the three disease outcomes even after multivitamin users had been excluded. Several other micronutrients considered to be related to a healthy diet, such as β-carotene, lutein/zeaxanthin, preformed vitamin A, and total vitamin C, were not associated independently with our disease outcomes and were therefore unlikely to confound or explain our results.

There are possible biases that may limit these findings. In this study, dietary intake and multivitamin use were self-reported, which raises the issue of misclassification. However, in addition to the prospective study design, the repeated measurements of diet and multivitamin use assessed by means of a validated food frequency questionnaire minimized the likelihood of bias due to error in the measurement of folate or alcohol. Confounding due to unmeasured and imperfectly measured confounders is impossible to eliminate. Although the sample size for this study was large, only 0.5 percent of this cohort simultaneously reported alcohol consumption of >30 g/day and total folate intake of <180 μg/day, which limited our power to detect a significant interaction between alcohol and folate intake. Nevertheless, we still found a statistically significant interaction of alcohol and total folate intake for major chronic disease, cardiovascular disease, and total cancer.

Our findings regarding the joint associations of alcohol and folate intake with risk of cardiovascular disease and cancer not only reflect the biochemical interactions between alcohol and folate metabolism but also are consistent with previous findings on joint associations with different diseases and even with different cancer sites. A significant interaction of alcohol-folate intake was observed for breast cancer in previous studies (7–9, 31). An interaction of alcohol-folate intake was also observed for colon cancer in men (10, 32) and for precancerous adenomas in women in this cohort (15). Breast and colon cancer accounted for 42.4 percent and 7.7 percent of total cancer cases in this cohort, respectively. To address whether our results for total cancer risk may have been mostly accounted for by these two cancers, we also examined the joint effects of alcohol and folate intake on other cancers after excluding breast and colon cancer. We observed a pattern for other cancers that was similar to, though somewhat weaker than, the pattern for breast and colon cancer. High folate intake appeared beneficial for breast and colon cancer risk among moderate drinkers. The consistent presence of similar patterns of alcohol-folate interaction for different diseases (cardiovascular disease and cancer) and cancer sites indicates that folate deficiency might be one important common mechanism by which heavy alcohol consumption causes human cancer and increases cardiovascular disease risk. Because the joint associations of alcohol and folate intake appear to be different in both magnitude and direction for cardiovascular disease and cancer, the study of major chronic disease provides an overall measure of the risks and benefits of alcohol and folate intake.

Combined with those of other studies, our results suggest that the role of folate should be expanded from prevention of megaloblastic anemia and neural tube defects to prevention of cancer, cardiovascular disease, and possibly other chronic diseases. Increasing one's folate intake, especially among women who consume alcohol regularly, to the level of the current Recommended Dietary Allowance (≥400 μg/day) may provide an important benefit in reducing the overall risk of chronic disease. It has been estimated that mandatory fortification of cereal-grain products with folic acid, introduced by the Food and Drug Administration in 1998, will add approximately 100 μg of folic acid per day to the average diet (33). Although the amount of folate obtained from cereal-grain products may play a role in reducing the total risk of chronic diseases, it may still be suboptimal. Even after fortification, only 25 percent of adult women in the general population will have a dietary folate intake above 400 μg/day. On the basis of our findings, some women would have unnecessary and preventable chronic diseases due to insufficient folate intake.

Our findings suggest that adequate folate intake may be important in the primary prevention of major chronic disease in women, especially among younger women consuming more than two alcoholic drinks per day. Because the risks of cardiovascular disease and cancer differ in men and women, the findings of this study cannot be directly applied to men, and further studies in men are needed.

ACKNOWLEDGMENTS

This study was supported by research grants CA87969 and HL36798 from the National Institutes of Health.

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