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Original Contribution

Alcohol Consumption and Breast Cancer Risk in Younger Women According to Family History of Breast Cancer and Folate Intake

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To evaluate the association between alcohol consumption and breast cancer risk in younger women, overall and by family history of breast cancer and folate intake, we prospectively followed 93,835 US women aged 27–44 years in Nurses' Health Study II who had alcohol consumption data in 1991. Alcohol consumption and folate intake were measured by food frequency questionnaire every 4 years. We documented 2,866 incident cases of invasive breast cancer between 1991 and 2011. Alcohol consumption was not associated with breast cancer risk overall (for intake of ≥10 g/day vs. nondrinking, multivariate hazard ratio = 1.07, 95% confidence interval: 0.94, 1.22). When the association was stratified by family history and folate intake, a positive association between alcohol consumption and breast cancer was found among women with a family history and folate intake less than 400 μg/day (multivariate hazard ratio = 1.82, 95% confidence interval: 1.06, 3.12; *P*-trend = 0.08). Alcohol consumption was not associated with breast cancer in other categories of family history and folate intake (*P*-interaction = 0.55). In conclusion, in this population of younger women, higher alcohol consumption was associated with increased risk of breast cancer among those with both a family history of breast cancer and lower folate intake.

alcohol drinking; breast cancer; family history; folate; women

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; NHS II, Nurses' Health Study II.

Breast cancer is the most commonly diagnosed invasive cancer in women and a leading cause of cancer mortality in the United States (1). Alcohol consumption is an established and modifiable risk factor for breast cancer (2, 3). However, the association between alcohol consumption and breast cancer risk among younger women (aged <40 years) (4, 5) and premenopausal women (6, 7) is not clear. This is due to the lack of cohort studies in young women. Some previous studies have suggested that breast cancer is etiologically heterogeneous according to age at diagnosis (8, 9). In the United States, the onset of breast cancer has a bimodal peak age distribution, with early onset at ages near 50 years and late onset at ages near 70 years (10). Epidemiologic studies have provided evidence that early-onset breast cancer is more aggressive than late-onset breast cancer (11) and more likely to be attributable to genetic susceptibility than late-onset breast cancer (12–14). However, genetic susceptibility has been estimated to account for less than 33% of early-onset breast cancer (13) and less than 25% of familial breast cancer (15). This indicates that exogenous exposures should be evaluated along with genetic factors to understand the etiology of breast cancer in younger age groups. Because family history of breast cancer may partly represent genetic susceptibility to breast cancer, we hypothesized that younger women with a family history of breast cancer may be more susceptible to breast carcinogenesis by high alcohol consumption. Previous studies regarding effect modification by family history of the association between alcohol consumption and breast cancer risk were inconsistent and were not conducted among younger women (6, 7, 16–18).

Furthermore, heavy alcohol consumption disrupts the absorption and metabolism of folate, and thus could plausibly increase the requirement of folate intake (19, 20). Because DNA hypomethylation and impaired DNA synthesis due to low folate intake can increase the risk of cancer (21), folate

intake needs to be taken into account when analyzing the association between alcohol consumption and breast cancer risk.

Therefore, we prospectively evaluated the association between alcohol consumption and breast cancer risk among younger women in Nurses' Health Study II (NHS II). We also evaluated whether the association differed by family history of breast cancer or folate intake.

METHODS

Study population

NHS II is a prospective cohort study of 116,430 US female registered nurses who were aged 25–42 years at enrollment in 1989. Questionnaires on lifestyle factors, reproductive factors, and medical events have been mailed to participants biennially. The procedures and protocols of the study were approved by the human research committees at Brigham and Women's Hospital and Harvard School of Public Health. A response to the self-administered questionnaire was considered to imply informed consent.

This study included 97,807 women who returned the food frequency questionnaire (FFQ) in 1991, when diet was first measured. Among those, we excluded women who had an implausible daily caloric intake (<800 kcal/day or >4,200 kcal/day) or who left more than 70 food items blank on the FFQ. Among the remaining 95,446 women, we excluded those who reported a diagnosis of any cancer, except nonmelanoma skin cancer, before returning the 1991 questionnaire. Consequently, a total of 93,835 women were included in the analysis. The cumulative response rate among living participants was 95%.

Alcohol and folate intake and other exposure assessments

A semiquantitative FFQ with more than 130 food items was sent to NHS II cohort participants in 1991, 1995, 1999, 2003, and 2007 to assess usual dietary intake and alcohol consumption during the past year. Participants were asked how often, on average, they had consumed each type of food or beverage, as well as 5 types of alcohol (including regular beer (1 glass/bottle/can), light beer (1 glass/bottle/can), red wine (4-ounce (118-mL) glass), white wine (4-ounce glass), and liquor (1 drink/shot)), during the past year. There were 9 response categories ranging from "never or <1/month" to "6+/day."

We calculated total daily alcohol consumption as the product of the daily number of alcoholic drinks consumed and the average alcohol content of each type of alcoholic beverage (12.8 g for regular beer, 11.3 g for light beer, 11.0 g for wine, and 14.0 g for liquor, per standard serving of each alcoholic drink). Total folate intake from foods and supplements was also calculated. The reproducibility and validity of dietary intakes measured by the FFQ have been evaluated in a subsample of participants in the Nurses' Health Study, a similar cohort study of older nurses (22). Alcohol consumption measured by the FFQ was highly correlated with alcohol consumption calculated from multiple diet records ($r = 0.90$) and with high-density lipoprotein levels ($r = 0.40$) (23).

Data on other risk factors for breast cancer, including age, weight, parity and age at first birth, oral contraceptive use, menopausal status and hormone use, personal history of benign breast disease, and smoking status, were obtained from the biennial questionnaires. Questions on height and age at menarche were asked in 1989. Information on history of breast cancer in a mother or siblings was elicited in 1989 and was updated in 1997, 2001, and 2005.

Identification of breast cancer cases

Incident cases of breast cancer are ascertained by biennial follow-up questionnaires and by a search of the National Death Index for deaths due to breast cancer among women who did not respond to the questionnaires. We then obtained permission from cases who reported breast cancer (or next of kin, for those who had died) to review hospital records and pathology reports pertaining to the diagnosis. Pathology reports confirmed more than 98% of self-reported breast cancers (24). Estrogen and progesterone receptor status was confirmed from pathology reports. Cases of carcinoma in situ were excluded from this analysis.

Statistical analyses

We calculated person-time from the date of return of the 1991 questionnaire to the date of diagnosis of breast cancer or other cancer (except nonmelanoma skin cancer), death, or the end of follow-up (June 1, 2011), whichever came first. Because alcohol consumption, both earlier and later in adult life, and cumulative folate intake have previously been associated with breast cancer risk (5, 19), we calculated cumulative averaged intakes of alcohol and folate using the intake data from FFQs administered between 1991 and 2007 to consider long-term intake of alcohol and folate (25). Participants were divided into 4 categories according to their alcohol consumption using prespecified cutoffs (nondrinker, 0.1–4.9 g/day, 5.0–9.9 g/day, or ≥10 g/day). We were unable to assess higher intakes due to the low prevalence of heavy drinkers among younger women in NHS II. All covariates, except height and age at menarche, were updated with information from the most recent questionnaire whenever new data were available.

Hazard ratios and 95% confidence intervals for breast cancer were calculated by dividing the incidence rate for a given category of alcohol consumption by the incidence rate for the nondrinkers. Cox proportional hazards regression was used to control for confounding variables and to handle time-varying covariates efficiently. To finely adjust for confounding by age, calendar time, and any possible 2-way interactions between these 2 time scales, we stratified the analysis jointly by age in months at the start of each follow-up period and calendar year of the current questionnaire cycle. Multivariate models adjusted for oral contraceptive use (never or ever), parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–29 years, parity 1–2 and age at first birth ≥30 years, parity ≥3 and age at first birth <25 years, or parity ≥3 and age at first birth ≥25 years), age at menarche (≤11, 12, 13, or ≥14 years), menopausal status and use of hormone therapy (premenopausal/unknown menopausal status, postmenopausal and never use of hormones, postmenopausal and past hormone use, or postmenopausal and current hormone use), body mass index (weight (kg)/height (m)^2;

<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, or ≥30.0), personal history of benign breast disease (yes or no), height (<62.0, 62.0–64.9, 65.0–67.9, or ≥68.0 inches (<157, 157–164, 165–172, or ≥173 cm)), smoking status (never, past smoker of <25 cigarettes/day, past smoker of ≥25 cigarettes/day, current smoker of <25 cigarettes/day, or current smoker of ≥25 cigarettes/day), family history of breast cancer (yes or no), and intakes of red meat (g/day, continuous) and folate (μg/day, continuous).

We conducted analyses stratified by family history of breast cancer (yes or no), folate intake (<400 μg/day or ≥400 μg/day), and hormone receptor status to examine effect modification of the association between alcohol consumption and breast cancer. We assessed whether the associations between alcohol consumption and breast cancer risk differed by family history, folate intake, or a combination of family history and folate intake using the likelihood ratio test. We added cross-product terms (family history × alcohol, folate × alcohol, or family history × folate × alcohol) for interaction between the stratification factors and alcohol consumption in each Cox model, as continuous variables for alcohol consumption and folate intake, and compared the multivariate regression models with and without the interaction terms. To calculate the *P* value for the test for trend, we assigned to participants the median value of their alcohol consumption category and used this variable as a continuous variable in the regression models. We conducted sensitivity analyses considering alcohol consumption during the premenopausal period only and using dietary folate intake excluding folate from supplements. All statistical analyses were 2-sided and carried out using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). $P < 0.05$ was considered significant.

RESULTS

During follow-up of 93,835 younger women (1,696,068 person-years), 2,866 cases of invasive breast cancer were documented between 1991 and 2011. The average age of the participants in 1991 was 36.4 (standard deviation, 4.6) years, and the average age of breast cancer diagnosis was 45.0 (standard deviation, 4.6) years.

The baseline characteristics of the study participants according to alcohol consumption are presented in Table 1. Compared with nondrinkers, women who consumed higher amounts of alcohol were leaner and had a later age at menarche, fewer children, and lower folate intake, and were more likely to have an older age at first birth, to use oral contraceptives, and to currently smoke. The prevalence of a family history of breast cancer in a mother or sister did not vary by alcohol consumption. A family history of breast cancer in a mother or sister was significantly associated with breast cancer risk (hazard ratio (HR) = 1.73, 95% confidence interval

Table 1. Baseline Characteristics of Potential Risk Factors for Breast Cancer According to Alcohol Consumption in 1991 Among US Women Aged 27–44 Years in Nurses' Health Study II

Characteristic	Alcohol Intake in 1991, g/day							
	0 (*n* = 40,163)		0.1–4.9 (*n* = 36,324)		5.0–9.9 (*n* = 9,148)		≥10.0 (*n* = 8,200)	
	Mean (SD)[a]	%[a]	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years[b]	36.2 (4.7)		35.9 (4.7)		35.9 (4.7)		36.7 (4.6)	
Height, cm[c]	164.6 (6.6)		164.8 (6.6)		165.4 (6.4)		165.6 (6.6)	
Body mass index[d]	25.5 (5.9)		24.3 (5.1)		23.3 (4.0)		23.4 (4.1)	
Age <12 years at menarche		26		24		22		22
Age at first birth, years	25.6 (4.0)		25.9 (4.2)		26.1 (4.4)		26.2 (4.5)	
Parity ≥3		23		20		17		13
Current use of oral contraceptives		8		12		14		14
Benign breast disease (yes)		28		30		30		28
Family history of breast cancer in a mother or sister(s) (yes)		6		6		7		6
Current tobacco use (yes)		9		12		15		23
Alcohol intake, g/day	0.0 (0.0)		2.1 (1.2)		7.1 (1.4)		18.0 (10.7)	
Red meat intake, servings/day	0.8 (0.6)		0.8 (0.5)		0.7 (0.5)		0.8 (0.5)	
Folate intake, μg/day	492.1 (318.8)		475.7 (281.4)		465.1 (260.4)		441.5 (233.4)	

Abbreviation: SD, standard deviation.
[a] Values are standardized to the age distribution of the study population.
[b] Value is not age-adjusted.
[c] 1 inch = 2.54 cm.
[d] Weight (kg)/height $(m)^2$.

Table 2. Relationship Between Cumulative Alcohol Consumption and Risk of Invasive Breast Cancer Among US Women Aged 27–44 Years in Nurses' Health Study II, 1991–2011

Cumulative Average Alcohol Intake, g/day	No. of Cases	Age-Adjusted		Multivariate-Adjusted[a]	
		HR	95% CI	HR	95% CI
0	806	1.00	Referent	1.00	Referent
0.1–4.9	1,334	1.04	0.96, 1.14	1.00	0.92, 1.10
5.0–9.9	377	1.07	0.95, 1.21	0.98	0.87, 1.12
≥10.0	349	1.17	1.03, 1.33	1.07	0.94, 1.22
Per 10-g/day increment		1.09	1.03, 1.15	1.06	1.00, 1.12
P for trend		0.02		0.39	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] A multivariate Cox proportional hazards regression model was used for statistical testing and was stratified by age (in months) and calendar year of the current questionnaire cycle. Results were adjusted for oral contraceptive use (never or ever), the combination of parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–29 years, parity 1–2 and age at first birth ≥30 years, parity ≥3 and age at first birth <25 years, or parity ≥3 and age at first birth ≥25 years), age at menarche (≤11, 12, 13, or ≥14 years), menopausal status and use of hormone therapy (premenopausal/unknown menopausal status, postmenopausal and never use of hormones, postmenopausal and past hormone use, or postmenopausal and current hormone use), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, or ≥30.0), personal history of benign breast disease (yes or no), height (<62.0, 62.0–64.9, 65.0–67.9, or ≥68.0 inches (<157, 157–164, 165–172, or ≥173 cm)), smoking status (never, past smoker of <25 cigarettes/day, past smoker of ≥25 cigarettes/day, current smoker of <25 cigarettes/day, or current smoker of ≥25 cigarettes/day), family history of breast cancer (yes or no), red meat intake (g/day, continuous), and folate intake (μg/day, continuous).

(CI): 1.57, 1.90), as was a family history of breast cancer in both a mother and a sister (HR = 2.68, 95% CI: 1.88, 3.84). Moreover, the breast cancer risk of women with a family history of breast cancer in both a mother and a sister, compared with women without a family history, was suggestively higher among cases diagnosed before age 45 years (HR = 4.08, 95% CI: 1.51, 11.0) than in cases diagnosed at age 45 years or older (HR = 2.55, 95% CI: 1.74, 3.74).

Table 3. Relationship Between Cumulative Alcohol Consumption and Risk of Invasive Breast Cancer According to Family History of Breast Cancer[a] Among US Women Aged 27–44 Years in Nurses' Health Study II, 1991–2011

Cumulative Average Alcohol Intake, g/day	No Family History of Breast Cancer					Family History of Breast Cancer				
	No. of Cases	Age-Adjusted		Multivariate-Adjusted[b]		No. of Cases	Age-Adjusted		Multivariate-Adjusted[b]	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
0	679	1.00	Referent	1.00	Referent	127	1.00	Referent	1.00	Referent
0.1–4.9	1,099	1.04	0.94, 1.14	1.00	0.90, 1.10	235	1.11	0.89, 1.39	1.08	0.86, 1.36
5.0–9.9	292	1.01	0.88, 1.16	0.93	0.81, 1.07	85	1.37	1.03, 1.82	1.31	0.98, 1.75
≥10.0	278	1.13	0.98, 1.30	1.03	0.89, 1.20	71	1.44	1.06, 1.94	1.33	0.97, 1.82
Per 10-g/day increment		1.07	1.01, 1.13	1.04	0.97, 1.10		1.19	1.06, 1.33	1.16	1.03, 1.30
P for trend		0.16		0.89			<0.01		0.04	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] *P* for interaction = 0.16.

[b] A multivariate Cox proportional hazards regression model was used for statistical testing and was stratified by age (in months) and calendar year of the current questionnaire cycle. Results were adjusted for oral contraceptive use (never or ever), the combination of parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–29 years, parity 1–2 and age at first birth ≥30 years, parity ≥3 and age at first birth <25 years, or parity ≥3 and age at first birth ≥25 years), age at menarche (≤11, 12, 13, or ≥14 years), menopausal status and use of hormone therapy (premenopausal/unknown menopausal status, postmenopausal and never use of hormones, postmenopausal and past hormone use, or postmenopausal and current hormone use), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, or ≥30.0), personal history of benign breast disease (yes or no), height (<62.0, 62.0–64.9, 65.0–67.9, or ≥68.0 inches (<157, 157–164, 165–172, or ≥173 cm)), smoking status (never, past smoker of <25 cigarettes/day, past smoker of ≥25 cigarettes/day, current smoker of <25 cigarettes/day, or current smoker of ≥25 cigarettes/day), red meat intake (g/day, continuous), and folate intake (μg/day, continuous).

Among all women, alcohol consumption was not associated with breast cancer risk overall (for alcohol consumption of ≥10 g/day vs. nondrinking, multivariate HR = 1.07, 95% CI: 0.94, 1.22; *P*-trend = 0.39) (Table 2). The association between alcohol consumption and breast cancer risk (≥10 g/day vs. nondrinking) did not vary by estrogen receptor or progesterone receptor status (for tumors with positive estrogen and progesterone receptors, HR = 1.08, 95% CI: 0.90, 1.29; for tumors with negative estrogen and progesterone receptors, HR = 0.95, 95% CI: 0.67, 1.34).

When the association between alcohol consumption and breast cancer risk was stratified by family history of breast cancer in first-degree relatives, the multivariate hazard ratio for breast cancer for alcohol consumption of ≥10 g/day versus nondrinking was 1.33 (95% CI: 0.97, 1.82; *P*-trend = 0.04) among women with a family history of breast cancer and 1.03 (95% CI: 0.89, 1.20; *P*-trend = 0.89) among women with no family history (*P*-interaction = 0.16). When alcohol consumption was evaluated as a continuous variable, there was a positive association between alcohol consumption and breast cancer among women with a family history of breast cancer (Table 3).

When the association between alcohol consumption and breast cancer risk was stratified by folate intake, the multivariate hazard ratio for breast cancer for alcohol consumption of ≥10 g/day versus nondrinking was 1.01 (95% CI: 0.86, 1.20; *P*-trend = 0.99) among women with folate intake of ≥400 μg/day and 1.19 (95% CI: 0.95, 1.47; *P*-trend = 0.08) among those with folate intake of <400 μg/day (*P*-interaction = 0.20). When alcohol consumption was evaluated as a continuous variable, there was a positive association between alcohol consumption and breast cancer among women with folate intake below 400 μg/day (Table 4).

As shown in Table 5, when the association between alcohol consumption and breast cancer risk was further stratified by family history of breast cancer and folate intake, among women with a family history and a low folate intake (<400 μg/day), alcohol consumption of ≥10 g/day was significantly associated with increased breast cancer risk (HR = 1.82, 95% CI: 1.06, 3.12; *P*-trend = 0.08) in comparison with nondrinking. In contrast, among those with no family history and a high folate intake (≥400 μg/day), alcohol consumption was not related to the risk of breast cancer (HR = 0.98, 95% CI: 0.81, 1.18). When alcohol consumption was evaluated as a continuous variable, there was a positive association between alcohol consumption and breast cancer only among women with a positive family history and folate intake below 400 μg/day. However, the *P* value from a test for interaction between alcohol consumption and the combination of family history and folate intake was not significant (*P*-interaction = 0.55). In sensitivity analyses considering alcohol consumption during the premenopausal period only and excluding folate intake from supplements, the associations between alcohol consumption and breast cancer risk did not materially change (data not shown).

DISCUSSION

In this prospective study of younger women, we found that alcohol consumption was not significantly associated with breast cancer risk overall but was associated with an

Table 4. Relationship Between Cumulative Alcohol Consumption and Risk of Invasive Breast Cancer According to Folate Intake[a] Among US Women Aged 27–44 Years in Nurses' Health Study II, 1991–2011

Cumulative Average Alcohol Intake, g/day	High Folate Intake (≥400 μg/day)					Low Folate Intake (<400 μg/day)				
	No. of Cases	Age-Adjusted		Multivariate-Adjusted[b]		No. of Cases	Age-Adjusted		Multivariate-Adjusted[b]	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
0	489	1.00	Referent	1.00	Referent	317	1.00	Referent	1.00	Referent
0.1–4.9	885	1.01	0.90, 1.13	0.98	0.87, 1.10	449	1.10	0.95, 1.27	1.03	0.89, 1.20
5.0–9.9	245	0.98	0.84, 1.14	0.92	0.78, 1.07	132	1.26	1.03, 1.55	1.12	0.91, 1.39
≥10.0	223	1.08	0.92, 1.27	1.01	0.86, 1.20	126	1.34	1.09, 1.65	1.19	0.95, 1.47
Per 10-g/day increment		1.05	0.97, 1.12	1.02	0.95, 1.10		1.15	1.07, 1.25	1.11	1.02, 1.21
P for trend			0.42		0.99			<0.01		0.08

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] *P* for interaction = 0.20.

[b] A multivariate Cox proportional hazards regression model was used for statistical testing and was stratified by age (in months) and calendar year of the current questionnaire cycle. Results were adjusted for oral contraceptive use (never or ever), the combination of parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–29 years, parity 1–2 and age at first birth ≥30 years, parity ≥3 and age at first birth <25 years, or parity ≥3 and age at first birth ≥25 years), age at menarche (≤11, 12, 13, or ≥14 years), menopausal status and use of hormone therapy (premenopausal/unknown menopausal status, postmenopausal and never use of hormones, postmenopausal and past hormone use, or postmenopausal and current hormone use), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, or ≥30.0), personal history of benign breast disease (yes or no), height (<62.0, 62.0–64.9, 65.0–67.9, or ≥68.0 inches (<157, 157–164, 165–172, or ≥173 cm)), smoking status (never, past smoker of <25 cigarettes/day, past smoker of ≥25 cigarettes/day, current smoker of <25 cigarettes/day, or current smoker of ≥25 cigarettes/day), family history of breast cancer (yes or no), and red meat intake (g/day, continuous).

Table 5. Relationship Between Cumulative Alcohol Consumption and Risk of Invasive Breast Cancer According to Family History and Folate Intake Combined[a] Among US Women Aged 27–44 Years in Nurses' Health Study II, 1991–2011

Cumulative Average Alcohol Intake, g/day	No. of Cases	Age-Adjusted		Multivariate-Adjusted[b]	
		HR	95% CI	HR	95% CI
No Family History and High Folate Intake (≥400 μg/day)					
0	412	1.00	Referent	1.00	Referent
0.1–4.9	744	1.02	0.91, 1.16	0.99	0.87, 1.12
5.0–9.9	187	0.91	0.76, 1.08	0.85	0.71, 1.01
≥10.0	178	1.05	0.88, 1.26	0.98	0.81, 1.18
Per 10-g/day increment		1.03	0.95, 1.11	1.00	0.92, 1.09
P for trend			0.99		0.50
No Family History and Low Folate Intake (<400 μg/day)					
0	267	1.00	Referent	1.00	Referent
0.1–4.9	355	1.04	0.88, 1.22	0.97	0.83, 1.15
5.0–9.9	105	1.23	0.98, 1.54	1.09	0.87, 1.38
≥10.0	100	1.28	1.01, 1.61	1.13	0.89, 1.44
Per 10-g/day increment		1.13	1.03, 1.23	1.08	0.98, 1.20
P for trend			0.02		0.19
Family History and High Folate Intake (≥400 μg/day)					
0	77	1.00	Referent	1.00	Referent
0.1–4.9	141	0.96	0.72, 1.29	0.94	0.70, 1.26
5.0–9.9	58	1.30	0.91–1.87	1.27	0.88–1.83
≥10.0	45	1.23	0.84–1.81	1.19	0.79–1.78
Per 10-g/day increment		1.10	0.94, 1.29	1.09	0.92, 1.29
P for trend			0.08		0.12
Family History and Low Folate Intake (<400 μg/day)					
0	50	1.00	Referent	1.00	Referent
0.1–4.9	94	1.44	0.99, 2.08	1.42	0.97, 2.09
5.0–9.9	27	1.53	0.93, 2.52	1.40	0.82, 2.39
≥10.0	26	2.06	1.24, 3.43	1.82	1.06, 3.12
Per 10-g/day increment		1.31	1.11, 1.55	1.26	1.05, 1.51
P for trend			0.01		0.08

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] *P* for interaction = 0.55.

[b] A multivariate Cox proportional hazards regression model was used for statistical testing and was stratified by age (in months) and calendar year of the current questionnaire cycle. Results were adjusted for oral contraceptive use (never or ever), the combination of parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–29 years, parity 1–2 and age at first birth ≥30 years, parity ≥3 and age at first birth <25 years, or parity ≥3 and age at first birth ≥25 years), age at menarche (≤11, 12, 13, or ≥14 years), menopausal status and use of hormone therapy (premenopausal/unknown menopausal status, postmenopausal and never use of hormones, postmenopausal and past hormone use, or postmenopausal and current hormone use), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, or ≥30.0), personal history of benign breast disease (yes or no), height (<62.0, 62.0–64.9, 65.0–67.9, or ≥68.0 inches (<157, 157–164, 165–172, or ≥173 cm)), smoking status (never, past smoker of <25 cigarettes/day, past smoker of ≥25 cigarettes/day, current smoker of <25 cigarettes/day, or current smoker of ≥25 cigarettes/day), and red meat intake (g/day, continuous).

increased risk of breast cancer among those with a family history and a low folate intake.

It has been reported that alcohol consumption contributes to breast cancer risk through the carcinogenic effect of reactive metabolites of alcohol (e.g., acetaldehyde), alcohol's action as a solvent enhancing penetration of carcinogens into cells, or interference with estrogen metabolism influencing hormone levels and estrogen receptors (3, 26, 27). Moreover, consumers of high

levels of alcohol may be more susceptible to carcinogenesis due to the deficiency of essential nutrients in their diet (26, 27). In our younger women, however, no association between alcohol consumption and breast cancer risk was observed, which was consistent with results found among younger women in the previous studies (4–6). This may be due to the possibility that women diagnosed with cancer at young ages may be more affected by genetic susceptibility than by environmental factors such as alcohol consumption. It has been reported that women diagnosed with cancer at young ages have a higher prevalence of family history than older cases (12–14). In our study, a family history of breast cancer was associated with increased risk of breast cancer regardless of age at diagnosis, but a suggestively stronger association was observed in younger women. Another potential explanation is that alcohol consumption in our population was relatively low; only 1.4% of case women reported alcohol consumption of ≥30 g/day in our study. Thus, we were not able to explore higher alcohol consumption levels. In a recent pooled analysis of 20 prospective studies of alcohol and breast cancer, a significant association between alcohol consumption and increased risk of invasive breast cancer was observed in women who consumed alcohol in any amount, although the association was modest among women who consumed less than 30 g/day compared with nondrinkers (7). In addition, the association between alcohol consumption and breast cancer risk could vary by menopausal status or hormone receptor status (28). However, the previous results from pooled analysis on the alcohol–breast cancer association by menopausal status were not consistent (6, 7). In the current study, we did not observe significant heterogeneity in the association between alcohol consumption of ≥10 g/day and breast cancer risk according to estrogen or progesterone receptor status.

Although there was no association between alcohol consumption and breast cancer risk overall, there was some suggestion of a positive association between alcohol consumption and breast cancer risk among women with a family history of breast cancer in first-degree relatives. This suggests that young adult women with a family history of breast cancer might be more susceptible to alcohol consumption. A stronger positive association between alcohol consumption and breast cancer risk among women with a family history of breast cancer has been observed in some studies (16, 17). However, in a pooled analysis of cohort studies, which largely included postmenopausal women, Smith-Warner et al. (6) reported the opposite result—that a significant positive association between alcohol consumption and breast cancer risk was observed only among women without a family history of breast cancer.

There was also some suggestion of a positive association between alcohol consumption and breast cancer risk among women with low folate intake. This finding was in line with previous studies which suggested that, although total folate intake was not associated with overall risk of breast cancer, positive associations between high alcohol consumption and breast cancer risk were attenuated among women with high folate intakes (19, 29–32).

To our knowledge, no previous study has evaluated the association between alcohol consumption and breast cancer by both family history of breast cancer and folate intake. In our study, although the test of interaction between alcohol consumption and the combination of family history and folate intake was not significant, higher alcohol consumption was significantly associated with an increased risk of breast cancer only among women with a family history and low folate intake. If folate intake was high, a significant association between alcohol consumption and breast cancer risk was not apparent, despite the family history of breast cancer, and vice versa. A similar pattern of association has been found for colorectal cancer; compared with nondrinkers with a high folate intake and no family history, the positive association between alcohol drinkers of ≥30 g/day and colorectal cancer was lower among persons who had high folate intake and a family history than among those who had low folate intake and a family history (33).

Major strengths of our study include its large sample size, prospective study design, evaluation of younger women, and repeated measures on diet. We also had prospectively collected information on a wide range of potential confounders of the alcohol–breast cancer association. However, as a limitation, we could not examine the association between heavy alcohol drinking and breast cancer risk due to low consumption of alcohol in this population. Therefore, further study is needed to confirm the association between alcohol consumption and breast cancer risk among younger women with heavier alcohol consumption. In addition, former drinkers who stopped consuming alcohol before participating in NHS II might have been classified as nondrinkers. However, because we used the average intake of alcohol from data repeatedly recorded during the follow-up period, participants who quit drinking during follow-up were not grouped as nondrinkers. Another limitation was limited statistical power to detect a significant interaction, because only 6%–7% of women had a family history of breast cancer.

In conclusion, there was little overall association between alcohol consumption and breast cancer risk in these younger women. However, higher alcohol consumption was related to increased risk of breast cancer among those with both a family history of breast cancer and a low folate intake. Reducing alcohol consumption and increasing folate intake may reduce the risk of breast cancer among women with a family history of breast cancer.

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