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Alcohol and risk of breast cancer in Mexican women

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Abstract

BACKGROUND—Little is known about the relationship between alcohol intake and breast cancer risk among Mexican women. This association may be modified by folate and Vitamin B12.

METHODS—A population-based case control study conducted in Mexico recruited 1000 incident breast cancer cases aged 35–69 and 1074 controls matched on age, region, and health care system. In-person interviews were conducted to assess breast cancer risk factors and recent diet using a food frequency questionnaire. Conditional logistic regression models estimated adjusted odds ratios and 95% confidence intervals.

RESULTS—Over one-half (57%) of cases and less than one-half of controls (45%) reported any lifetime alcohol consumption. Compared with never drinkers, women reporting ever drinking (Adjusted OR=1.25, 95% CI=0.99–1.58) had a greater odds of breast cancer. There was evidence for interaction in the association between ever consuming any alcohol and breast cancer by folate (p for interaction=0.04) suggesting women with lower folate intake had a higher odds of breast cancer (Adjusted OR=1.99, 95% CI= 1.26–3.16) compared to women with higher folate intake (OR=1.12, 95% CI = 0.69–1.83).

CONCLUSIONS—Our findings support emerging evidence that any alcohol intake increases risk of breast cancer. Insufficient intake of folate may further elevate risk for developing breast cancer among women who consume alcohol.

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Keywords

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INTRODUCTION

Breast cancer is the second most common type of cancer and the leading cause of cancer death in women worldwide. In Mexico, the estimated age-standardized incidence of breast cancer is 26.4 per 100 000 women (1). Breast cancer is the leading cause of female cancer deaths after cervical cancer among Mexican women; estimated age-standardized mortality from breast cancer is 10.5 of every 100 000 women (2).

Consumption of alcohol is widely reported to be a modest risk factor for breast cancer (3–6); a meta-analysis of data from over 40 reports and 41 477 incident cases of breast cancer estimated that women who consumed one drink per day (defined as 12g) had a 10% (95% CI 6%–14%) increased risk for breast cancer compared to non-drinkers (7). Prospective follow-up for an average of 7.3 years of 1.3 million women further showed that among women who reported recent alcohol consumption, a 12% (95% CI=9% to 14%) elevation in risk was observed for each additional drink (defined as 10g) (8). These findings are consistent with data from a pooled analysis of cohort studies suggesting a dose-response relationship (4).

Despite consistent evidence linking alcohol consumption to breast cancer risk, to-date the mechanisms explaining the relationship are unclear. Several mechanisms have been hypothesized; these include the release of carcinogenic metabolites of alcohol, such as acetaldehyde or reactive oxygen species(9), decreased absorption of essential nutrients(10), and/or the potential influence of alcohol on estrogen metabolism(11).

It has been observed that the effect of alcohol consumption on the risk of breast cancer differs by folate consumption (12). The direct association between alcohol consumption and breast cancer risk may be modified, at least in part, by alcohol's interference with the absorption of folate (13), a micronutrient known to be important in DNA synthesis and repair. Data from the VITAL cohort study of over 35 000 post-menopausal women show that those who consumed 1272 or more dietary folate equivalents per day had a 22% reduction in breast cancer risk, compared to women who consumed less than 345 dietary equivalents (14). Previous epidemiologic studies have suggested that low levels of folate, and other one-carbon methyl group donors such as vitamin B12(15), may form part of the pathway by which alcohol elevates the risk of breast cancer(12,16–18). Similarly, higher intake of folate or multivitamin use has been shown to attenuate the excess risk of breast cancer associated with alcohol consumption (14).

With few exceptions (19,20), studies of the relationship between alcohol consumption and breast cancer risk have been conducted in either the U.S (12,16–18,21–23) or Europe (20,24). Little is known about the relationship between alcohol consumption and the risk for breast cancer among women in Mexico, where both the incidence of breast cancer and the intake of alcohol are relatively low compared to the U.S. (19,25). Given evidence that the association of breast cancer with alcohol intake may be greater among women with low dietary folate intake in European populations(12,16,26), we would expect to observe the same protective effect of folate intake in a case control study conducted in Mexico.

MATERIALS AND METHODS

Study Population

This study, "Risk Factors for Breast Cancer in Mexico: Mammographic Patterns, Peptide C, and Growth Factors, a Multi-Center Study" (CAMA), was conducted by the National Institute of Public Health in Cuernavaca, Mexico. The study used a multicenter, population-based, case-control design, recruiting women between 2004 and 2007 from three regions in Mexico and their surrounding metropolitan areas: Mexico City, Monterrey, and Veracruz. Cases (n = 1074) were women with newly diagnosed, histologically confirmed in situ or invasive breast cancer who were included, regardless of the stage of disease close to their date of diagnosis (median = 3 days). Cases received care from one of twelve participating hospitals from the three major health care systems in Mexico: the Mexican Institute of Social Security (*Instituto Mexicano del Seguro Social* — IMSS, 6 hospitals), the Social Security and Services Institute for State Workers (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado — ISSSTE, 2 hospitals), and the Ministry of Health (*Secretaría de Salud* — SS, 4 hospitals), which offers health care services to individuals who belong to neither of the former systems. Hospitals from all health care systems were included; therefore, the sample is reflective of the socioeconomic diversity of the general population of women living in these regions.

Project nurses stationed at each of the twelve hospitals identified women with newly diagnosed breast cancer using medical records and pathology reports. Cases were excluded if they: a) had received breast cancer treatment (radiotherapy, chemotherapy, or hormone therapy) in the last 6 months; b) were currently using aromatase inhibitors (exemestane, letrozole, anastrozole, or megestrol); c) were pregnant; or d) were HIV positive. The study protocol and data collection instruments were reviewed and approved by the Institutional Review Board at the National Institute of Public Health and by equivalent committees at the collaborating hospitals. .

Controls (n = 1000) were frequency matched to the cases according to age, health-care system, and region. They were selected based on a probabilistic multistage design, with the goal of sampling specific numbers of women in each 5-year age category (range 35–69 years) based on the age distribution of cases reported by the Mexican Tumor Registry in 2002. Within the three study regions, one or more geographic regions (from Spanish, Área Geoestadística Básica, AGEB) was selected for sampling; the selected regions either were part of the catchment area of one health care system (IMSS) or had a similar proportion of women belonging to the ISSTE and SS healthcare system as cases.

Cases and controls provided written informed consent to participate in the study.

Data Collection

Project nurses conducted in-person interviews among the cases, obtained anthropometric measures (height, weight, and waist and hip circumference), and collected blood samples. Among controls, interviewers administered an in-person household survey and scheduled an appointment for a hospital visit during which anthropometric measurements were obtained, mammography screening was performed and a blood sample was taken. The questionnaire was a 243-item instrument that addressed general health and behaviors having a possible association with breast cancer. The health questionnaire collected information on lifetime alcohol consumption, sociodemographic characteristics, reproductive/hormonal factors (e.g. age at menarche and menopause, pregnancies, pregnancy outcomes, lactation history, use of oral contraceptives, and hormone therapy), family history of breast cancer, and smoking history. To measure physical activity, participants were asked about the time spent sleeping and engaging in physical activity (light, moderate, and vigorous) over a usual week prior to

the onset of symptoms. Dietary information was obtained by asking women about their food consumption the year prior to the onset of the symptoms, using a separate 104 item semi-quantitative Food Frequency Questionnaire (FFQ) developed based on consumption data from women living in Mexico City using methods described and used by Willett (27). The relative validity compared to 16 24-hour recalls and reproducibility of the FFQ was assessed in 134 women in Mexico City: deattenuated correlations between the FFQ and 24-hour recalls were 0.52, 0.22, and 0.29 for total energy, folic acid, and vitamin B12, respectively(28). The procedures for secondary analysis of study data were reviewed and approved by the Institutional Review Office at the Fred Hutchinson Cancer Research Center.

Exposure Assessment

Alcohol, vitamin (i.e. folate and vitamin B12), and energy intakes were computed from FFQ responses by multiplying the frequency response by the nutrient content of specified portion sizes. The nutrient database developed by the National Institute of Nutrition in Mexico (29) and, if necessary, the U.S. Department of Agriculture food composition tables (30), were used to calculate intakes (30). Participants were asked to report frequency of consumption in the past year of a typical serving of 104 items, and responses were converted to average daily consumption. Alcohol per day, as measured by the FFQ, was 13.9g per 12oz of beer, 15.4g per 5oz of wine, and 9.3g per 1oz of liquor (29). Never drinkers were defined as those having intakes of 0 grams of alcohol per day.

In addition to FFQ estimates of recent consumption, the health questionnaire queried past drinking habits. Participants were also asked if they ever drank alcohol, the age when they first began drinking, and if they ever drank more than one drink per month for at least one year.

Statistical Analysis

We compared demographic and lifestyle factors that may be associated with breast cancer risk and alcohol intake using chi-square tests or ANOVA as appropriate. Folate and vitamin B12 were categorized into tertiles based on the distribution among controls, and the lowest tertile was considered the referent category.

Conditional logistic regression models were used to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI) for recent and lifetime alcohol use. Model 1 accounted for matching by age category, health care system, and region. Model 2 included matching factors and factors adjusted for in previous literature (body mass index (BMI), family history of breast cancer, age at first pregnancy, number of births, lactation, total energy, physical activity, education, age at menarche, menopausal status, oral contraceptive use (ever/never), smoking (ever, never), fibrocystic disease, and past hormone therapy use(22).

To evaluate whether the associations between recent or lifetime alcohol intake and breast cancer risk were modified by menopausal status, folate, or vitamin B12 intake, formal tests for interaction were performed by entering the product term of the exposure variable by the effect modifier in the model and comparing nested models using the likelihood ratio statistic. All analyses were conducted using STATA (Version 10.1, August 2008, College Station, TX), and P values <0.05 were considered statistically significant.

RESULTS

The study population included 1000 cases with a mean age of 52 matched to 1074 controls having a mean age of 51 (Table 1). A small number of cases (n=29) and controls (n=34) were outside the age range for the study (35–69 years), so the actual age range in the sample

was 28–74 years. The response rate for controls was high in all three regions (87.4% for Mexico City, 90.1% for Monterrey and 97.6% for Veracruz). The majority of women were post-menopausal (59% of cases and 56% of controls). Most breast cancers were invasive; overall, there were only 10 premenopausal and 10 postmenopausal in-situ cases. Cases and controls were similar with respect to likelihood of ever smoking, age at menarche, and ever using oral contraceptives ($P > 0.05$ for all comparisons). Cases had a lower BMI, were more likely to have a family history of breast cancer, had fewer children and were more likely to have children later in life ($P < 0.05$). Cases reported higher energy and nutrient intakes as well as higher levels of light intensity physical activity. Most of the physical activity was classified as light (89% for cases and 84% for controls, data not shown), as opposed to moderate or vigorous intensity.

Almost one-third of cases (29%) reported current alcohol compared to approximately one-fifth (21%) of controls, but differences in propensity to consume any alcohol were not significant after accounting for potential confounders (Table 2, **Model 2** OR=0.98, 95% CI 0.76 to 1.27). When considering the amount of recent alcohol intake, drinking more alcohol was positively related to breast cancer risk, but this association was not statistically significant after multi-variable adjustment (Model 2 P-trend= 0.19). Among women reporting any recent alcohol consumption, 72% drank beer and 61% drank liquor, while only 30% drank wine. Lifetime alcohol use was associated with an increased risk of breast cancer, as women who reported ever drinking one or more drinks a month for at least one year had a 1.74 higher odds of breast cancer (Table 2, **Model 2, 95% CI 1.27–2.39**).

In analyses stratified by menopausal status, there was no evidence for effect modification (P for interaction = 0.83 for current drinking and P for interaction=0.80 for categorized alcohol) (data not shown). Though in stratified analyses the effect was higher and more consistent among premenopausal women compared to post-menopausal women, the statistical test for multiplicative interaction was not significant (P for interaction = 0.37 for ever drinking and P for interaction=0.31 for ever drank >1 drink per month, data not shown).

There was some evidence for interaction in the association between ever consuming any alcohol and breast cancer by folate intake (Table 3, Model 2 P for interaction=0.04). Women in the lowest tertile of folate intake (mean=197 μg/day) had a higher odds of breast cancer (Adjusted OR = 1.99, 95% CI = 1.26–3.16) compared to women with highest tertile of folate intake (mean=532 μg/day) (OR = 1.12, 95% CI = 0.69–1.83). No significant interactions were observed for vitamin B12 intake (Table 3, Model 2 P for interaction = 0.47). Though folate and B12 may act synergistically, the nutrients were highly correlated (Spearman rho = 0.6) and we did not have adequate power to evaluate the possibility of a three-way interaction. There was also no evidence for effect modification in the associations between either folate or vitamin B12 when characterizing alcohol use as ever drinking more than one drink per month (data not shown, Model 2 P for interactions = 0.77 and 0.89 for folate and vitamin B12, respectively).

DISCUSSION

In this population-based case-control study in Mexican women, ever drinking was associated with an increased odds of breast cancer, but no statistically significant association was observed for current drinking, after accounting for confounders. Within a population without a national folate fortification program, folate intake appeared to modify the association between ever consuming any alcohol and breast cancer (P for interaction=0.04). After adjusting for confounders, ever drinking was associated with a two-fold increase in the odds of breast cancer (OR=1.99, 95% CI=1.26–3.16) among women consuming half the Recommended Dietary Allowance of folate (mean=197 μg/d) compared to a 12% increase in

the odds of breast cancer (OR=1.12, 95% CI=0.69–1.83) among women with adequate folate intake (mean=532 μg/d).

Since alcohol is a known folate antagonist and could therefore interfere with DNA repair, several studies have investigated joint associations between alcohol and folate and breast cancer, as recently reviewed (22). Consistent with our findings, the majority of cohort studies provide evidence to support a protective effect of folate on breast cancer among women who consume alcohol (12,16–18). However, data from the Women's Health Initiative Observational study (22) as well as other large cohort studies (23,24) reported no evidence for folate attenuating the association between alcohol consumption and breast cancer in postmenopausal women. In the U.S. and Canada, mandatory fortification programs started in 1998; this, combined with a higher prevalence of vitamin supplementation (14), reduces folate deficiency at the population level, yet complicates folate measurement. Recently, a randomized, controlled trial of combined folate (2.5 mg), Vitamin B6 (50 mg), and Vitamin B12 (1mg) supplementation compared to placebo among women at high risk of cardiovascular disease reported no overall association between supplementation and invasive breast cancer (HR 0.83, 95% CI 0.60–1.14, P=0.24) (21). Vitamin B12, along with riboflavin and Vitamin B6, are cofactors in the folate pathway converting homocysteine into methionine for DNA methylation. Therefore, we might expect similar protective associations between these nutrients and breast cancer risk. In our data, however, we observed no significant associations between Vitamin B12 and breast cancer risk after adjustment for confounders and no significant modification of the effect of alcohol on breast cancer risk according to levels of B12 intake. Prior research has also reported no significant associations between Vitamin B6 and breast cancer risk among premenopausal women (31) or postmenopausal women (14,19,20).

The average annual age-adjusted incidence of breast cancer is lower among women in Mexico compared to the U.S. (26.4 cases versus 101.1 cases per 100,000 women, respectively)(1). Differences in incidence cannot be fully explained by differences in screening practices between countries, as breast cancer mortality is lower in Mexico compared to the U.S. (10.5 versus 19.0 per 100,000 women, respectively)(1). Reproductive and lifestyle factors among women living in Mexico favor a lower risk profile for breast cancer compared to women living in the U.S., as women in Mexico have children at a younger age, are more likely to breast feed, are less likely to use oral contraceptives, and drink less alcohol (32–34). Among women in the U.S., breast cancer incidence also differs among racial/ethnic groups. Hispanic women in the U.S. have a lower incidence of breast cancer than non-Hispanic Whites (35), but breast cancer risk increases with increasing duration of residence in the U.S. (36). The increase in breast cancer incidence that occurs with migration is likely attributable to changes in reproductive, hormonal and lifestyle characteristics (33,34).

Prior epidemiologic research suggests that Hispanic women born in the U.S. drink less than non-Hispanic whites (60.3% vs. 40.1% report no alcohol consumption, respectively), and Hispanic women who immigrated from Mexico or South America reportedly drink even less often (68.9% abstained from alcohol) (37). We are not aware of any published data available to compare associations between alcohol intake and breast cancer risk with other populations living in Central and South America. According to a population-based health survey, <20% of Mexican women reported consuming at least 1 serving of alcohol per month (25). Given the relatively low prevalence of alcohol consumption, large sample sizes are needed to detect small to moderate associations. In our study of 2,074 women, we observed a statistically significant association between alcohol intake and breast cancer. Data from the New Mexico Women's Health Study, a population-based case-control study examining associations between lifetime and recent alcohol use among Hispanic and Non-

Hispanic white women (38), reported no consistent associations between alcohol intake and breast cancer among Hispanic women. The number of Hispanic women interviewed was approximately one-third that of the current study (322 cases and 388 controls). Also, since women in the New Mexico Women's Health Study were interviewed a median of 201 days after diagnosis (and 183 days for non-Hispanic women), changes in alcohol consumption after diagnosis may have attenuated associations. In our study, women were interviewed at the time of diagnosis or shortly thereafter, minimizing bias associated with disease-related changes in dietary behavior.

Limitations should be considered in interpreting our findings. Recall bias is a concern with case-control studies assessing diet. However, interviewing women close to the time of diagnosis may have mitigated differences in the accuracy of recall between cases and controls. FFQs in general are subject to substantial measurement error and this may have limited our ability to accurately measure alcohol and micronutrient intakes. To our knowledge, there are no studies on the accuracy of using USDA food composition tables for estimating nutrient intake in a Mexican population. However, consistent with Hernandez-Avila et al (28), we used food composition tables provided by the National Institute of Nutrition in Mexico and completed tables with the United States Department of Agriculture when necessary. Furthermore, the FFQ used in this study was adapted and tested for use in the Mexican population.

Limited information was collected on supplement use, but the prevalence of any vitamin/mineral supplement use is quite low in this study population. We did not have the opportunity to explore heterogeneity in the association by tumor type, and recent data among supplement users in the VITAL cohort suggest a greater benefit of folate intake for ER −, compared to ER +, breast cancers (14). We did test for interaction by menopausal status and found no evidence for effect modification.

In conclusion, our findings support emerging evidence that even low levels of alcohol intake increase the risk for breast cancer among both pre- and postmenopausal women. Consuming at least the United State's Recommended Dietary Allowance for folate (>400 ug/day) may be particularly important among women who consume alcohol.

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Table 1

Descriptive Statistics of Study Population, CAMA

	Cases n=1000	Controls n=1074
	n (%) or mean ± SD	
Age, yr	52±10	51±9
Postmenopausal	585 (59)	598 (56)
Socioeconomic Level		
Lower	306 (31)	359 (33)
Middle	261 (26)	357 (33)
Upper	433 (43)	358 (33)
Education		
Primary	138 (14)	166 (15)
Secondary	593 (59)	616 (57)
➢ Secondary	268 (27)	292 (27)
BMI, kg/m^2	29.3 ± 5.6	30.6 ± 5.4
Ever smoked at least 100 cigarettes	248 (25)	226 (21)
Marital Status		
Married/Living with Partner	613 (61)	732 (68)
Separated or Divorced	154 (15)	125 (12)
Widow	107 (11)	125 (12)
Single	126 (13)	92 (9)
Family history of breast cancer	63 (6.3)	40 (3.7)
History of fibrocystic disease	150 (15)	83 (8)
Age at menarche, yr	12.8 ± 1.6	12.8 ± 1.6
Age at first pregnancy, yr	22.8 ± 5.6	21.3 ± 4.7
Parity		
Nulliparous	113 (11)	65 (6)
1–2	340 (34)	305 (28)
3–4	351 (35)	384 (36)
≥5	189 (19)	319 (30)
Lactation, months[1]	24.9 ± 30.7	31.7 ± 35.1
Ever use oral contraceptives (OC)	446 (45)	480 (45)
Ever use hormone therapy	150 (15)	106 (10)
Energy Intake, kcal/d	2208±774	1937±672
Alcohol Intake, g/d[2]	1.9 (1.2–3.6)	1.7 (0.6–2.3)
Folate, μg/d	381±176	345±157
Vitamin B12, μg/d	3.7±2.0	3.5±2.0
Physical activity, MET hrs/week[3]	107.9±9.6	106.2±9.0

[1] Among parous women

[2] Median (Inter-quartile range) among drinkers(n=330 cases and n=254 controls)

[3] Estimated from 7-day activity diary that queries all activities (working and leisure)

Table 2

Age and Multivariate-adjusted OR[1] and 95% CI associations between breast cancer and alcohol consumption, CAMA.

	Cases	Controls	Model 1		Model 2	
	n (%)	n (%)	OR	95% CI	OR	95% CI
Recent Alcohol Intake [2]						
Current Drinker						
No	674 (71%)	818 (79%)	**1.00**			
Yes	269 (29%)	222 (21%)	**1.31**	**1.05–1.62**	0.98	0.76–1.27
Alcohol Use, categorical [3]						
Non-drinker	660 (66%)	819 (76%)	**1.00**			
>0–2 g/day	188 (19%)	161 (15%)	**1.42**	**1.11–1.81**	1.19	0.90–1.58
≥2 g/day	152 (15%)	94 (9%)	**1.90**	**1.42–2.53**	1.20	0.85–1.70
Lifetime Alcohol Use[4]						
Ever drank alcohol						
No	402 (43%)	567 (55%)	**1.00**			
Yes	542 (57%)	473 (45%)	**1.53**	**1.27–1.86**	**1.25**	**0.99–1.58**
Ever drink >1 drink per month for ≥ 1 year						
No	768 (81%)	928 (89%)	**1.00**			
Yes	176 (19%)	112 (11%)	**1.91**	**1.47–2.48**	**1.74**	**1.27–2.39**
Age (yr) at first alcohol use						
Nondrinker	402 (44%)	567 (56%)	**1.00**		**1.00**	
>=26	132 (14%)	133 (13%)	**1.37**	**1.00–1.82**	**1.22**	**0.88–1.70**
21–25	126 (14%)	104 (10%)	**1.59**	**1.18–2.15**	**1.24**	**0.86–1.77**
18–20	169 (18%)	124 (12%)	**1.84**	**1.18–2.15**	**1.41**	**1.02–1.96**
<18	90 (10%)	90 (9%)	**1.29**	**0.93–1.81**	**0.92**	**0.61–1.39**
Age (yr) at first alcohol use, among drinkers						
>=26	132 (14%)	133 (13%)	1.00		1.00	
21–25	126 (14%)	104 (10%)	1.00	0.66–1.51	0.87	0.56–1.35
18–20	169 (18%)	124 (12%)	1.36	0.90–2.06	1.04	0.69–1.58
<18	90 (10%)	90 (9%)	1.43	0.97–2.10	0.71	0.44–1.15

[1]Estimated from conditional logistic regression models using data from 1000 cases and 1074 controls (58.5% and 55.7% postmenopausal women, respectively): Model 1 Matching factors only (age, region, and health care institution); Model 2: Model 1+ BMI, family history of breast cancer, age at first pregnancy, number of births, lactation, energy intake, physical activity, education, age at menarche, menopausal status, OC (ever/never),smoking (ever/never), fibrocystic disease, hormone therapy

[2]Recent alcohol (within past year) assessed by Food Frequency Questionnaire

[3]P for trend Model 1 <0.0001; Model 2 =0.19

[4]Lifetime alcohol use assessed using a health questionnaire

Table 3

Odds of breast cancer (OR (95% CI))[1] associated with ever (yes/no) consuming alcohol by tertiles of folate and vitamin B12 intake[2]

	Tertile 1	Tertile 2	Tertile 3	P for interaction[3]
Folate				
Mean±SD, μg/d[2]	197 ±47	317 ±36	532 ±145	
Cases, n (%)	231 (23)	354 (35)	415 (42)	
Controls, n (%)	357 (33)	356 (33)	361 (34)	
Model 1	**2.19 (1.54–3.15)**	**2.42 (1.72–3.40)**	**3.14 (2.26–4.37)**	0.01
Model 2	**1.99 (1.26–3.16)**	**1.70 (1.10–2.63)**	1.12 (0.69–1.83)	0.04
Vitamin B12				
Mean±SD, μg/d[2]	1.6 ±0.5	3.2 ±0.4	5.7 ±1.6	
Cases, n (%)	259 (26)	361 (36)	380 (38)	
Controls, n (%)	357 (33)	357 (33)	360 (34)	
Model 1	**2.00 (1.41–2.85)**	**2.34 (1.68–3.26)**	**2.53 (1.82–3.51)**	0.14
Model 2	**1.56 (1.01–2.43)**	**1.52 (1.02–2.29)**	1.20 (0.78–1.86)	0.47

[1] Estimated from conditional logistic regression models **using data from 1000 cases and 1074 controls (58.5% and 55.7% postmenopausal women, respectively:** Model 1 Matching factors only (age, region, and health care institution) Model 2: Model 1+ BMI, family history of breast cancer, age at first pregnancy, number of births, lactation, energy intake, physical activity, education, age at menarche, menopausal status, OC (ever/never),smoking (ever/never), fibrocystic disease, hormone therapy

[2] Folate and B12 intake were assessed by Food Frequency Questionnaire; Alcohol use assessed by Health Questionnaire.

[3] P for interaction tested whether the association between alcohol consumption and breast cancer was modified by nutrient intake comparing nested models using the likelihood ratio test.