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Associations of dietary folate, vitamin B6, B12 and methionine intake with risk of breast cancer among African American (AA) and European American (EA) women

Zhihong Gong[1], **Christine B. Ambrosone**[1], **Susan E. McCann**[1], **Gary Zirpoli**[1], **Urmila Chandran**[2,3], **Chi-Chen Hong**[1], **Dana H. Bovbjerg**[4], **Lina Jandorf**[5], **Gregory Ciupak**[1], **Karen Pawlish**[6], **Quanjun Lu**[7], **Helena Hwang**[8], **Thaer Khoury**[8], **Bshara Wiam**[8], and **Elisa V. Bandera**[2,3]

[1]Department of Cancer Prevention & Control, Roswell Park Cancer Institute, Buffalo, NY

[2]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

[3]Rutgers School of Public Health, Piscataway, NJ

[4]University of Pittsburgh Cancer Institute, Pittsburgh, PA

[5]Icahn School of Medicine at Mount Sinai, New York, NY

[6]New Jersey State Cancer Registry, New Jersey Department of Health, Trenton, NJ

[7]Department of Nutrition and Food Hygiene, School of Public Health, Zhengzhou University, Zhengzhou, China

[8]Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY

Abstract

African American (AA) women are more likely than European American (EA) women to be diagnosed with breast cancer at younger ages and to develop poor prognosis tumors. However, these racial differences are largely unexplained. Folate and other methyl-group nutrients may be related to breast carcinogenesis, but few studies have examined these associations in AA populations. We examined the associations of dietary intake of these nutrients with breast cancer risk overall, by menopausal and estrogen receptor (ER) status among 1,582 AA (749 cases) and 1,434 EA (744 cases) women using data from a case-control study, the Women's Circle of Health Study. Unconditional multivariable logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs) for the association of each nutrient and breast cancer risk. In AA women, inverse associations were observed for natural food folate intake among premenopausal women (4^{th} vs. 1^{st} quartile: OR=0.57, 95% CI, 0.33–1.00; *P* for trend=0.06) and for ER positive tumors (4^{th} vs. 1^{st} quartile: OR=0.58, 95% CI, 0.36–0.93; *P* for trend=0.03), whereas in EA women, a positive association was observed for intake of synthetic folate (4^{th} vs. 1^{st} quartile: OR=1.53, 95% CI, 1.06–2.21; *P* for trend=0.03). Our findings suggest that natural food folate intake is inversely associated with breast cancer risk and that this association may vary

Corresponding author: Zhihong Gong, PhD, Department of Cancer Prevention & Control, Roswell Park Cancer Institute, Elm & Carlton Sts, Buffalo, NY 14263; Fax: (716) 845-8125; Zhihong.gong@roswellpark.org.

by race, menopausal or ER status. The finding of an increased risk observed among EA women with the highest intake of synthetic folate from fortified foods warrants further investigation.

Keywords

folate; one-carbon nutrients; diet; breast cancer; African American; European American

Introduction

Breast cancer is the most common cancer among women in the US, accounting for approximately 29% of all new cancers and 14% of cancer deaths each year.[1] Although breast cancer incidence is higher in European American (EA) than African American (AA) women overall, AA women are more likely to be diagnosed at younger ages. They are also more likely than EAs, at every age, to develop more aggressive tumors e.g., high grade and estrogen receptor (ER)-negative, and to die from breast cancer.[1,2] These racial differences in breast cancer are largely unexplained.

In addition to obesity and physical activity, dietary factors have been the most studied and widely accepted modifiable risk factor for cancer, although associations between dietary factors and breast cancer remain inconclusive.[3] Identification of food and nutrients that might be associated with an increased or decreased risk of developing breast cancer, particularly those related to premenopausal and ER negative breast tumors that are commonly observed in AA women, is important and may represent a significant opportunity to reduce breast cancer racial disparities. However, few studies have examined associations of diet with breast cancer risk in AA populations or in population-based studies that include adequate AA representation.[4]

Folate is a water soluble B vitamin that participates in one-carbon metabolism as a methyl donor and has been implicated in cancer etiology due to its vital role in methylation reactions, nucleotide synthesis, and DNA replication and repair.[5,6] Other nutrients that play a key role in folate-mediated methyl-group metabolism include vitamins B6 and B12, important enzymatic cofactors, and methionine, a key intermediary compound and also a principal methyl donor for methylation.[7] Although it is clear that folate and other methyl-group nutrients play important roles in maintaining genetic integrity and gene regulation, results have been inconsistent from epidemiologic studies that have examined the association between breast cancer risk and intake of these nutrients, as reviewed in two meta-analyses [8,9] and additional studies after the publication of the two reviews.[10–19] The few studies that have analyzed serum or plasma levels of these nutrients also have not observed a consistent association with breast cancer.[20–23] In addition to the complex role of these nutrients in carcinogenesis and their inconclusive relationship with breast cancer development, none of the studies have focused exclusively on AA populations except for one small case-control study.[24]

In this case-control study designed specifically to study breast cancer racial disparities, we examined associations of dietary intake of folate, vitamins B6, B12, and methionine with

breast cancer risk in a large number of AA and EA women, and further evaluated the association by menopausal and ER status.

Subjects and methods

Study population

Data were from the Women's Circle of Health Study (WCHS), a case-control study designed to evaluate risk factors for early/aggressive breast cancer in AA and EA women. Details of the study design, enrollment criteria, and data collection have been described previously.[25] In brief, cases with incident breast cancer were identified using hospital-based case ascertainment in targeted hospitals within four boroughs of the metropolitan New York City (NYC) area from 2002–2008 and by population-based rapid case ascertainment in seven counties in New Jersey (NJ) from 2006–2012, through the NJ State Cancer Registry, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Eligible cases were English speaking women who self-identified as AA or EA, 20–75 years of age, and recently diagnosed (i.e., within the last 9 months) with primary, histologically confirmed breast cancer with no previous history of cancer other than non-melanoma skin cancer. The average time between diagnosis and enrollment for cases in the study was 8.5 months. Controls were frequency matched to cases by self-reported race and 5-year age groups and were recruited during the same time period as cases from the target population in the same residential area using random digit dialing, supplemented by community recruitment efforts for AA controls in NJ with the help of community partners and advocates [26].

Data collection

Detailed data on demographic characteristics, reproductive and menstrual history, family history of cancer, and lifestyle factors were collected by in-person interviews. Anthropometric measurements and biospecimens were collected by trained interviewers. Pathology data including ER status, grade and stage, were collected and abstracted by trained study staff. This study was approved by institutional review boards at Roswell Park Cancer Institute (RPCI), the Cancer Institute of New Jersey (CINJ, now Rutgers Cancer Institute of New Jersey), Mount Sinai School of Medicine (MSSM; now the Icahn School of Medicine at Mount Sinai), and participating hospitals in New York. Signed informed consent was obtained from each participant prior to interview and data collection.

Dietary intake was assessed using a Food Frequency Questionnaire (FFQ) developed at Fred Hutchinson Cancer Research Center. On the FFQ, women reported their usual frequency of intake and portion size (small, medium, or large with reference to a specified medium portion size for each item) for approximately 125 food and beverages consumed during the 12 months prior to diagnosis for cases and to a comparable reference date for controls. The FFQ also included adjustment questions on cooking methods, food preparation techniques, and consumption of low-fat or fortified foods, given that these factors can affect estimates of nutrient intake. The average daily intake of these nutrients was computed by multiplying the standard serving frequency of each food or beverage item by its nutrient content of the specified standard portion size and then summing the nutrient for all foods and beverages.

Food nutrient content values were obtained from the Nutrient Database, Minnesota Nutrient Data System for Research (University of Minnesota's Nutrition Coordination Center, Minneapolis). This database took into account the US mandated folic acid fortification of grain products, thus natural food folate and synthetic folate (folic acid) from fortified foods were able to be computed separately. Alcohol intake (grams/week) was calculated based on all reported intakes on the FFQ for red wine, white wine, beer, and liquor/mixed drinks.

We included dietary sources of folate (total, natural food folate, synthetic folate from fortified foods), vitamins B6 and B12, and methionine in this analysis. Because synthetic folate (folic acid) is more bioavailable than naturally occurring folate, total dietary folate, expressed in dietary folate equivalents (DFEs), was computed by first multiplying synthetic folate by a conversion factor of 1.7 and then adding intakes of natural food folate.[27] Intake of folate, vitamins B6 and B12 from supplements was not collected, so we were not able to examine intakes of these nutrients from both food sources and supplements.

Exclusions and final sample size

Of the 3,219 (1,732 AA and 1,487 EA) women who participated in the WCHS, we excluded women who did not complete a valid FFQ (n=69) or women with reported total energy intake <400 or >4000 kcal per day because their FFQs were considered to be unreliable (n=134). After all exclusions, 3,016 women remained in this analysis, including 1,582 AAs (749 cases, 833 controls) and 1,434 EAs (744 cases, 690 controls).

Statistical Analysis

Descriptive variables were compared between cases and controls using chi-square tests for categorical variables and t-tests for continuous variables. Multivariable unconditional logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the association of breast cancer associated with each nutrient intake with adjustments for age at diagnosis (continuous), ethnicity (Hispanic or non-Hispanic), country of origin (US born, Caribbean born, other), family history of breast cancer (yes, no), body mass index (BMI, continuous), education (less than or high school graduate, some college, college graduate, and graduate school), age at menarche (continuous), age at first live birth (years <20, 20–24, 25–29, ≥30), age at menopause (<45, 45–49, 50–54, ≥55), parity (continuous), breastfeeding (never, ever), hormone replacement therapy (HRT) use (never, ever), oral contraceptive (OC) use (never, ever), history of benign breast disease (yes, no), cigarette smoking (never smokers, former smokers, and current smokers), alcohol consumption (never drinkers, <15 grams/week, 15–60 grams/week, ≥60 grams/week), and total energy intake (continuous). All analyses were performed separately for AA and EA women. Multiplicative interactions between race and each nutrient were also tested using the likelihood ratio test in the multivariable adjusted logistic regression models.

All nutrients were categorized into quartiles based on the distributions among all controls and race-specific controls. Since using cutpoints for quartiles based on race-specific controls did not substantially change the estimates of these nutrients with breast cancer risk, results presented in tables were from analyses using quartiles based on all controls to facilitate direct comparison of risk estimates between AA and EA women. Tests for linear trend were

conducted by assigning the median intake in each quartile as a continuous variable in multivariable adjusted logistic regression models using the Wald test. Analyses also were conducted to examine whether the associations of each nutrient with breast cancer risk differed by menopausal or ER status. We further examined the joint association of folate intake with intakes of alcohol and other nutrients. Multiplicative interactions were tested by including the cross-product term between the two dichotomously grouped nutrient variables (low- and high-intake based on median intake) in the model and performing the likelihood ratio test.

All statistical tests were two-sided and considered statistically significant for $p<0.05$ and somewhat or borderline significant for p-values ≥ 0.05 and ≤ 0.10. Statistical analyses were conducted using SAS software V9.3 (SAS Institute, Inc., Cary, NC).

Results

Demographic, reproductive, and lifestyle characteristics, and nutrient intake of study participants, stratified by race and case-control status, are presented in Table 1. Compared to controls, both AA and EA cases were slightly older, and more likely to have a Caribbean country origin and to be Hispanic. In AA women, cases were more likely to have a history of benign breast disease, have a later age at menopause, and to be HRT users, whereas controls had slightly higher BMI and were more likely to be current smokers. In EA women, cases were more likely to have a family history of breast cancer and a history of benign breast disease, while controls were more likely to be well educated, ever OC users, to breastfeed their children, and have a higher intake of natural food folate. There were no other significant differences between cases and controls in either AA or EA women. Intakes of folate, vitamins B6, B12, and methionine were different between races. With the exception of vitamin B12, AA women reported lower mean intakes of all of the other nutrients. As expected, modest correlations were found between folate and other nutrients (Supplemental Table 1). Data on ER status were available for 570 (76.1%) of AA and 523 (70.3%) of EA cases; AA cases were more likely than EA cases to be diagnosed with ER negative breast cancer (30.7% versus 16.8%).

Folate, other nutrients and breast cancer in AA women

Associations for risk of breast cancer by quartiles of folate (total, food natural folate, and synthetic folate), vitamins B6, B12, and methionine intake in all AA women and by menopausal status are shown in Table 2. Among AA women overall, no significant association was observed for any of these nutrients. Among premenopausal women, however, natural food folate intake was marginally inversely associated with breast cancer (*P* for trend=0.06). Compared to the lowest quartile of intake, women in the 3rd and 4th quartile of intake had a significant decreased risk of breast cancer (OR=0.51, 95% CI, 0.32–0.84 and OR=0.57, 95% CI, 0.33–1.00, respectively). There was also a suggestion that synthetic folate intake from fortified food sources may be positively associated with breast cancer (*P* for trend=0.08) in premenopausal women, although the association was not statistically significant (4th vs. 1st quartile: OR=1.47). A marginally significant inverse association was also observed for increased methionine intake in premenopausal women (*P*

for trend=0.05). In contrast, high methionine intake was associated with a somewhat positive trend in postmenopausal women (*P* for trend=0.10). No other associations were found in postmenopausal women.

The associations of these nutrients and risk of ER positive and ER negative breast cancer in AA women are summarized in Table 3. Greater intake of natural food folate was inversely associated with risk of ER positive breast cancer (4^{th} vs. 1^{st} quartile: OR=0.58, 95% CI, 0.36–0.93, *P* for trend=0.03). There was also a suggestive but not statistically significant inverse trend (*P* for trend =0.06) for total dietary folate intake with ER positive cancer, which was largely driven by the inverse association from natural food folate intake. In contrast, there was no significant association of any of these nutrients with risk of ER negative breast cancer.

Folate, other nutrients and breast cancer in EA women

Associations of these nutrients with breast cancer risk overall, by menopausal or ER status in EA women are presented in Table 4 and 5. There was a weak inverse trend between greater natural folate intake and breast cancer risk in postmenopausal women (*P* for trend=0.05), although a non-significant reduced risk was observed only among women with the highest level of intake (OR=0.65, 95% CI, 0.33–1.26). Synthetic folate intake was positively associated with breast cancer risk in EA women overall (*P* for trend=0.03), with an increased risk restricted to women in the highest quartile of intake (OR=1.53, 95% CI, 1.06–2.21), which also appeared to be similar in pre- and post-menopausal women. Although not statistically significant, there was some suggestion that methionine intake was weakly inversely associated with risk for postmenopausal women (4^{th} vs. 1^{st} quartile: OR=0.67, 95% CI, 0.31–1.44, *P* for trend=0.11; high vs. low (by median intake): OR=0.66, 95% CI, 0.43–1.01, *P*=0.05; data not shown), and positively associated with risk for premenopausal women (4^{th} vs. 1^{st} quartile: OR=1.93, 95% CI, 0.95–3.91, *P* for trend=0.06). There were no significant associations for any of these nutrients with either ER positive or ER negative breast cancer.

Joint associations of food folate and other related nutrients with breast cancer risk

We examined joint associations of natural food intake and other one-carbon metabolism-related nutrients with risk of breast cancer by menopausal status in AA and EA women. Overall, no statistically significant interactions were observed for any of these associations in the analysis. However, we observed a consistent pattern, suggesting that one nutrient may modify the relationship of another nutrient and cancer in premenopausal AA women (Table 6). The lowest ORs were observed for women who had high natural food folate and high intake of vitamin B6 (OR=0.66, 95% CI, 0.41–1.06), B12 (OR=0.60, 95% CI, 0.37–0.96) or methionine (OR= 0.42, 95% CI, 0.25–0.72) compared to those with low intake of the pair nutrients. Similarly, no significant interaction was observed between natural food folate and alcohol intake in relation to breast cancer risk, however, results suggest that high alcohol intake was more strongly associated with an elevated risk (OR=1.54, 95% CI 0.93–2.54) among women who had low folate intake than higher consumers of alcohol with high folate intake (OR=1.11, 95% CI, 0.62–1.99). No similar patterns were observed for other groups of women, which are thus not shown in the table. Sample sizes were small and limited our

ability to further examine these associations for stratification by both menopausal and ER status.

Associations of folate and other nutrients with breast cancer risk in AA and EA women combined analysis

Although our overall study was fairly large, sample sizes were limited for subgroup analyses, which compromised our power to adequately test some of the hypotheses in these analyses. Moreover, findings in EA did not differ statistically from those in AAs. We therefore also present the results for AA and EA women combined, as shown in Supplemental Tables 2 and 3. In the AA and EA women combined analysis, results show that natural food folate intake was inversely associated with breast cancer risk (*P* for trend=0.04), and intake of synthetic folate (folic acid) from fortified foods was positively associated with breast cancer risk (*P* for trend=0.02) (Supplemental Table 2). Further, results also show that natural food folate intake was inversely associated with risk of ER positive tumors (*P* for trend=0.008), although this relationship was largely driven by the association observed in AA women (Supplemental Table 3).

Discussion

In this case-control study with a large number of AA and EA women, our results suggest that dietary intakes of folate and methionine may be associated with breast cancer risk in certain subgroups, with associations differing somewhat by race, menopausal status, and ER status, as well as by folate source. Specifically, analysis of high intake of natural food folate suggested an inverse association with breast cancer risk, particularly among premenopausal AA women. Furthermore, the reduced risk was observed only for ER positive, but not ER negative breast cancers. In contrast, among EA women, high natural food folate intake was associated with a non-significant reduced risk in postmenopausal women. A positive association between breast cancer risk and synthetic folate intake (folic acid) from fortified foods was observed among EA women overall. There was also some support for an association in premenopausal AA women, although the increased risk was restricted to women with the highest level of intake in both races. Results also suggest that high methionine intake is inversely associated with breast cancer in premenopausal AA and postmenopausal EA women.

In the past 15 years or so, a number of epidemiologic studies, primarily conducted in white women, have examined the role of dietary folate intake and breast cancer risk, with inconsistent findings. Results from case-control studies show that high versus low dietary folate intake is associated with a reduced breast cancer risk, with about half of these studies showing significant inverse associations.[17, 19, 28–32] In contrast, findings from cohort studies are less consistent, with no significant inverse association overall or by menopausal status,[10, 12, 14, 33–38] an inverse association among premenopausal Chinese women,[15] and a significant inverse[11, 39, 40] or positive[16] association among postmenopausal women. A single small case-control study examined the association in AA women and showed that low dietary folate intake was associated with an increased risk in cases with methylated ER, but this was based on small numbers and the association was not statistically significant.[24] The

underlying differences in study designs, study populations, dietary assessment and classification of folate, as well as genetic factors involved in one-carbon metabolism pathways, may contribute to the current inconsistent findings. These potential sources of bias and heterogeneity also make a summary interpretation of the literature on folate and breast cancer difficult.

This is the first large study that specifically examined the association of dietary folate intake and breast cancer risk in AA women and that involved a large number of AA and EA cases and controls within one study. The introduction of mandatory folic acid fortification in US food supplies in 1998 certainly complicates the interpretation of dietary folate findings in many studies, given emerging evidence that folic acid supplementation may be associated with an increased risk of cancer.[41] As our study was conducted in the post-fortification era, we first analyzed total dietary folate, defined as natural food folate plus synthetic folate (folic acid) from fortified foods, which was not statistically associated with breast cancer risk in AA or EA women. We then examined the association of the two type/sources of dietary folate separately. We found high natural folate intake, mostly contributed from vegetables, fruits/juices, and bean/ legumes, was associated with a reduced breast cancer risk among premenopausal AA women and a suggestive non-significant reduced risk limited to postmenopausal EA women with the highest level of intake. Interestingly, we found an opposite, positive association between breast cancer risk and high synthetic folate intake among EA women who had the highest levels of intake, and a likely relationship in premenopausal AA women. Although no studies have reported an increased breast cancer risk associated with high folic acid intake from fortified foods, studies have found inconsistent results on the role of folic acid supplementation in breast cancer, with several cohort studies finding a positive association, [38, 41] while results from randomized clinical trials offered little support for an association [42]. We did not collect information on supplement use, which limited our ability to comprehensively investigate the role of folic acid from both fortified food and supplemental sources on breast cancer risk, therefore future studies are needed to further examine the observed synthetic folate-breast cancer association and to address whether folic acid fortification and supplementation similarly affect breast cancer risk.

It is not entirely clear why associations differ by menopausal status between AA and EA women. This may be due in part to physiologic sufficiency of folate in AA compared to EA women. Studies showed lower serum folate concentrations in AA women than EA women overall,[43] and this is also true in women of childbearing age.[44] Combined with the fact that AAs had lower intakes of micronutrients than EAs, including folate, vitamin B6, and methionine, it is possible that a protective effect of high folate intake may only be observed within subgroups that have the most folate needs, which might be young premenopausal AA women of childbearing age. Similar to our results, a cohort study of Chinese women found an inverse association among premenopausal women.[15] Differential effects of folate intake in these subgroups may also be due to interactions with genetic or environmental factors that may be differentially distributed by race and/or menopausal status.[45] For example, the methylenetetrahydrofolate reductase (MTHFR) 677C>T variant has been associated with decreased folate levels and breast cancer risk,[46,47] thus differences in gene variants related to one-carbon metabolism between two race groups may have contributed to differences in

the results. In addition, observed findings may be related to the specific foods from which natural folate or folic acids are derived, e.g., fruits, vegetables, cereals, or pasta, although associations largely remained when we additionally controlled for total energy intake and certain food or food groups such as total vegetable and fruit intake in the analyses.

Few studies have examined the association between folate and breast cancer by ER and/or by progesterone receptor (PR) status and results have been inconsistent. Some studies observed a stronger or suggestive inverse association for ER−,[12, 14, 15, 18, 48] for ER+/PR−,[12] or for both ER+ and ER− tumors,[17] whereas one study found no association for ER− tumors,[10] and another study observed no overall association for ER+ or ER− tumors,[49] but a suggestive elevated risk for ER− tumors for women with low folate and high alcohol intake. From this limited literature, there appears to be a slightly greater benefit of folate intake for ER− than for ER+ tumors, although several of the studies had limited ER− cases. There have been some data suggesting that methylation of CpG islands on the ER gene is associated with a lack of ER gene expression.[50] However, our study did not support the hypothesis; instead, we observed a significant inverse association between natural folate intake and risk of ER+ tumors in AA women, and no significant association for ER+ or ER− tumors in EA women. The increased risk associated with synthetic folate in EA women was similar by ER status although the estimate appeared to be slightly stronger for ER− tumors. Sample size was relatively small for analyses by ER status, especially for ER− tumors, which limited our power to detect an association for ER− tumors. Future large studies are necessary to further confirm these findings and to investigate potential underlying mechanisms.

In this study, vitamins B6 and B12 were not statistically associated with breast cancer although there were suggestive associations for methionine. Consistent with our findings, several studies reported no association for vitamin B6,[10, 14, 15, 18] vitamin B12,[10, 13–15, 17, 30] or methionine,[10, 15, 17, 30] with few exceptions for a positive[30] or inverse association for vitamins B6, [17] B12 or methionine.[14, 18] Because folate, vitamins B6, B12, methionine and alcohol are all involved in one-carbon metabolism, we examined joint associations of these nutrients. Although the association of natural food folate in premenopausal AA women did not differ significantly by intakes of other methyl-group related nutrients, our results suggest that the strongest reduced risk may occur among women who had both high natural food folate and high methionine intake. Methionine is critical in the production of *S*-adenosylmethionine, an important methyl donor for DNA methylation, and folate plays an integral role in the remethylation of homocysteine to methionine. It is plausible that one nutrient could modify the relationship of another nutrient and cancer risk. This may suggest an added effect and further support our observations that adequate folate-mediated methyl-group metabolism may be associated with a reduced breast cancer risk. Alcohol, a known folate antagonist, is thought to increase breast cancer risk, partly by influencing the absorption and metabolism of folate and interfering with one-carbon metabolism.[51] In our data, there was a suggestion that among certain groups of women, high natural food folate intake may attenuate the increased breast cancer risk from alcohol, which is similar to findings from several[34, 36–39] although not all studies.[12, 18, 52] However, estimates were not statistically significant and findings could be due to chance.

This study had several strengths. We had a large sample size and collected detailed data on diet and other breast cancer risk factors by trained interviewers, minimizing information bias and enabling us to consider various covariates in our analyses. Most importantly, our study is among the first study to examine associations between folate and other related nutrients and breast cancer risk in a large number of AA and EA women. The study also had some limitations. As in other case-control studies, recall or selection bias may be an issue. To help minimize the effects of reverse causation and recall bias, participants were asked to report their usual diet a year prior to diagnosis for cases and a comparable period for controls. Despite these efforts, it is possible that cases and controls may have differentially recalled or reported their diet, which could introduce bias. Consumption of foods rich in folate, vitamins B6, B12 or methionine may be related to a particular dietary pattern and these foods contain other nutrients, which could affect our results, although further adjustments with these factors did not substantially alter results. Another limitation is that we lack information on supplement use, so we were not able to examine total intake of folate and related nutrients from both dietary and supplemental sources. It is also possible that residual confounding may have biased our results, although we controlled for a wide range of potential confounding factors. Finally, it must be emphasized that our findings should be interpreted with caution because the majority of associations are marginally statistically significant and could be due to chance. Nevertheless, as the first large study to examine the association in AA women, our result could be valuable to future studies and contribute to the current literature, especially in AA populations, which is substantially lacking.

In conclusion, our results suggest that associations between folate and breast cancer risk may differ by race, menopausal status, or ER status and provide evidence that high natural food folate, commonly found in vegetables and fruits, is associated with a decreased risk of breast cancer. Although there was no strong evidence of an association with intake of other methyl-group nutrients or interactions with folate and breast cancer risk, lowest ORs were observed in subgroups of AA women who had high folate and other methyl-group nutrients. The increased risk for breast cancer associated with the highest level of intake of synthetic folate from fortified food sources requires further confirmation and additional investigation. Future studies should also evaluate the combined effects of folic acid fortification and supplementation on breast cancer risk. If, indeed, folic acid fortification or supplementation is associated with increased cancer risk, there could be broad public health implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

The evidence for a folate-breast cancer association by menopausal and ER status remains limited, and none has been specifically examined in AAs. This is the first large study designed to examine these associations in AA women and to involve a large number of AA and EA cases and controls. Our findings suggest that folate intake may be associated with breast cancer risk and that this association may vary by race, menopausal and ER status, as well as by folate source.

Table 1

Selected characteristics of African American (AA) and European American (EA) cases and controls in the Women's Circle of Health Study (WCHS)

Characteristics	AA women		*P*-value[1]	EA women		*P*-value[1]
	Cases (n=749)	Controls (n=833)		Cases (n=744)	Controls (n=690)	
Age at interview (yrs)			0.0004			<0.0001
Mean ± SD	51.57±10.26	49.76±9.88		52.18±9.99	49.76±8.69	
Body mass index, kg/m^2			0.009			0.51
Mean ± SD	31.09±6.78	32.04±7.66		27.10±6.35	27.33±7.08	
Parity (live births)			0.56			0.59
Mean ± SD	2.11±1.99	2.06±1.64		1.54±1.38	1.58±1.50	
Age at menarche (yrs)			0.91			0.32
Mean ± SD	12.55±1.88	12.54±1.85		12.51±1.52	12.59±1.54	
Education, n (%)			0.07			<0.0001
<High school	108 (14.4)	101 (12.1)		19 (2.6)	10 (1.4)	
High school graduate	225 (30.0)	209 (25.1)		125 (16.8)	67 (9.7)	
Some college	195 (26.0)	245 (25.1)		163 (21.9)	130 (18.8)	
College graduate	135 (18.0)	169 (20.3)		228 (30.6)	224 (32.5)	
Post-graduate degree	86 (11.5)	109 (13.1)		209 (28.1)	259 (37.5)	
Country of origin, n (%)			<.0001			0.0001
United States	505 (67.4)	662 (79.5)		630 (84.7)	606 (87.8)	
Caribbean countries	183 (24.4)	123 (14.8)		25 (3.3)	2 (0.3)	
Other	61 (8.2)	48 (5.8)		89 (12.0)	82 (11.9)	
Ethnicity, n (%)			0.005			<0.0001
Non-Hispanic	705 (94.1)	808 (97.0)		684 (91.9)	675 (97.8)	
Hispanic	44 (5.9)	25 (3.0)		60 (8.1)	15 (2.2)	
Family history of breast cancer, n (%)			0.16			0.002
No	641 (85.6)	733 (88.0)		571 (76.8)	575 (83.3)	
Yes	108 (14.4)	100 (12.0)		173 (23.2)	115 (16.7)	
History of benign breast disease, n (%)			<.0001			0.0006
No	505 (67.6)	643 (77.3)		426 (57.7)	457 (66.5)	
Yes	242 (32.4)	189 (22.7)		312 (42.3)	230 (33.5)	

Characteristics	AA women		*P*-value[1]	EA women		*P*-value[1]
	Cases (n=749)	Controls (n=833)		Cases (n=744)	Controls (n=690)	
Menopausal status, n (%)			0.57			0.19
Premenopausal	375 (50.1)	429 (51.5)		384 (51.6)	380 (55.1)	
Postmenopausal	374 (49.9)	404 (48.5)		360 (48.4)	310 (44.9)	
Age at menopause (yrs), n (%)			0.003			0.36
≤45	42 (11.2)	54 (13.4)		37 (10.3)	32 (10.3)	
46–49	56 (15.0)	103 (25.5)		71 (19.7)	69 (22.2)	
50–54	214 (57.2)	189 (46.8)		173 (48.1)	156 (50.3)	
>55	62 (16.6)	58 (14.3)		79 (21.9)	53 (17.1)	
Age at first birth (yrs), n (%)			0.25			0.19
Nulliparous (0 birthcount)	112 (15.0)	135 (16.2)		234 (31.4)	203 (29.4)	
≤19	244 (32.6)	278 (33.4)		33 (4.4)	31 (4.5)	
20–24	177 (23.6)	201 (24.1)		134 (18.0)	107 (15.5)	
25–30	124 (16.6)	105 (12.6)		160 (21.5)	141 (20.4)	
>31	92 (12.3)	114 (13.7)		183 (24.6)	208 (30.1)	
Breastfeeding, n (%)			0.76			0.03
Nulliparous	116 (15.5)	140 (16.8)		234 (31.4)	203 (29.4)	
Parous						
Never	313 (41.8)	346 (41.5)		190 (25.5)	145 (21.0)	
Ever	320 (42.7)	347 (41.7)		320 (43.0)	342 (49.6)	
Hormone replacement therapy use, n (%)			0.03			0.19
Never	632 (84.7)	735 (88.4)		550 (73.9)	530 (76.9)	
Ever	114 (15.3)	96 (11.6)		194 (26.1)	159 (23.1)	
Oral contraceptive use, n (%)			0.68			0.02
Never	311 (41.5)	354 (42.6)		255 (34.4)	199 (28.8)	
Ever	438 (58.5)	478 (57.4)		487 (65.6)	491 (71.2)	
Smoking status, n (%)			0.0009			0.14
Never smoker	471 (62.9)	473 (56.8)		376 (50.6)	382 (55.4)	
Former smoker	174 (23.2)	185 (22.2)		279 (37.8)	226 (32.8)	
Current smoker	104 (13.9)	175 (21.0)		88 (11.8)	82 (11.9)	
Alcohol consumption, g/week, n (%)			0.50			0.44

Characteristics	AA women		*P*-value[1]	EA women		*P*-value[1]
	Cases (n=749)	Controls (n=833)		Cases (n=744)	Controls (n=690)	
0	468 (62.6)	492 (59.1)		260 (34.9)	220 (31.9)	
≤15	138 (18.5)	174 (20.9)		153 (20.6)	139 (20.1)	
15.1–60	86 (11.5)	105 (12.6)		141 (19.0)	152 (22.0)	
>60	55 (7.4)	61 (7.3)		190 (25.5)	179 (25.9)	
Total dietary folate (DFE)[2], mcg/day			0.76			0.59
Mean ± SD	484.1±464.8	480.2±464.2		526±251.7	533.6±245.6	
Natural food folate[2]**,** mcg/day			0.56			0.001
Mean ± SD	238.7±140.3	242.7±136.5		247.9±113.9	269.7±138.6	
Synthetic folate[2]**,** mcg/day			0.36			0.13
Mean ± SD	144.3±109.1	139.7±90.3		163.9±112.3	155.2±103.4	
Vitamin B6[2]**, mg/day**			0.70			0.48
Mean ± SD	1.63 ± 0.86	1.62±0.75		1.81± 0.81	1.84±0.79	
Vitamin B12[3]**, mcg/day**			0.15			0.46
Mean ± SD	6.17±6.53	6.67±7.33		5.66±3.79	5.81±4.21	
Methionine[2]**, g/day**			0.45			0.24
Mean ± SD	1.48±0.78	1.51±0.76		1.56±0.66	1.60±0.65	
Estrogen receptor status						<0.0001
ER positive	395 (69.3)			435 (83.2)		
ER negative	175 (30.7)			88 (16.8)		

Abbreviations are as follows: SD, standard deviation; DFE, dietary folate equivalents

[1] *P*-value: T test for continuous variables and chi-square test for categorical variables

[2] Test for difference between races: Nutrient intake in AA women is lower than that in EA women (*P*-value<0.01)

[3] Test for difference between races: Nutrient intake in AA women is greater than that in EA women (*P*-value=0.0009)

Table 2

Association between dietary intake of folate, vitamin B6, B12, methionine and breast cancer risk among all AA women and stratified by menopausal status in the WCHS

	All women				Premenopausal				Postmenopausal			
	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]
Total dietary folate (DFE), mcg/day												
Q1 (≤334.8)	244	246			111	120			134	126		
Q2 (334.9–468.8)	170	193	0.82	0.60–1.12	84	105	0.72	0.46–1.13	86	88	0.92	0.59–1.43
Q3 (468.9–636.4)	162	208	0.77	0.55–1.09	74	104	0.66	0.40–1.10	88	105	0.82	0.50–1.33
Q4 (>636.4)	165	180	0.76	0.49–1.18	102	98	0.67	0.36–1.26	63	82	0.76	0.40–1.44
p for linear trend				0.26				0.27				0.37
Natural folate from food, mcg/day												
Q1 (≤159.6)	236	250			111	123			125	127		
Q2 (159.7–230.6)	189	205	0.88	0.65–1.18	97	116	0.67	0.44–1.02	92	89	1.11	0.72–1.72
Q3 (230.7–315.1)	153	189	0.74	0.53–1.03	68	95	0.51	0.32–0.84	86	95	1.04	0.64–1.68
Q4 (>315.1)	163	183	0.74	0.50–1.09	95	93	0.57	0.33–1.00	68	90	0.92	0.51–1.65
p for linear trend				0.11				0.06				0.83
Synthetic folate from fortified food, mcg/day												
Q1 (≤78.1)	214	228			97	112			118	116		
Q2 (78.2–129.8)	180	208	0.92	0.69–1.25	84	107	0.90	0.57–1.42	96	101	0.95	0.63–1.45
Q3 (129.9–188.6)	159	199	0.93	0.67–1.30	74	106	0.86	0.53–1.42	85	94	1.02	0.64–1.63
Q4 (>188.6)	188	192	1.16	0.80–1.67	116	102	1.47	0.85–2.55	72	90	0.88	0.52–1.49
p for linear trend				0.30				0.08				0.52
Vitamin B6, mg/day												
Q1 (≤1.17)	248	255			110	127			138	128		
Q2 (1.18–1.63)	170	196	0.86	0.63–1.16	82	100	0.82	0.52–1.30	89	97	0.88	0.57–1.34
Q3 (1.64–2.13)	148	199	0.75	0.53–1.07	78	104	0.67	0.40–1.13	70	95	0.82	0.50–1.37
Q4 (>2.13)	175	177	0.94	0.60–1.46	101	96	0.80	0.42–1.53	74	81	1.10	0.58–2.11
p for linear trend				0.72				0.48				0.81
Vitamin B12, mcg/day												
Q1 (≤3.13)	223	227			99	108			125	119		

	All women				Premenopausal				Postmenopausal			
	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]
Q2 (3.14–4.93)	177	201	0.89	0.66–1.20	84	105	0.76	0.49–1.19	93	96	0.99	0.65–1.50
Q3 (4.94–7.08)	136	180	0.79	0.57–1.10	69	89	0.65	0.40–1.06	67	92	0.90	0.57–1.44
Q4 (>7.08)	205	219	0.96	0.68–1.35	119	125	0.71	0.43–1.16	86	94	1.27	0.76–2.11
p for linear trend				0.95				0.26				0.41
Methionine, g/day												
Q1 (≤1.03)	222	244			99	116			123	128		
Q2 (1.04–1.47)	200	200	1.10	0.81–1.48	98	86	1.16	0.73–1.83	103	115	1.09	0.72–1.67
Q3 (1.48–1.96)	146	173	0.94	0.65–1.34	75	103	0.60	0.36–1.02	71	70	1.50	0.87–2.59
Q4 (>1.96)	173	210	0.98	0.62–1.55	99	122	0.63	0.33–1.20	74	88	1.69	0.85–3.36
p for linear trend				0.77				0.05				0.10

Abbreviations: Ca, Cases; Co, Controls; OR, Odds ratio; 95% CI, 95% confidence interval.

*1, 2*Models are adjusted for age, ethnicity, country of origin, education, BMI, age at menarche, menopausal status (when not stratified by this variable), age at menopause (only for postmenopausal women), parity, age at first birth, breastfeeding status, family history of breast cancer, OC use, history of benign breast disease, HRT use, smoking status, alcohol consumption, and total energy intake.

Table 3

Association between dietary intake of folate, vitamin B6, B12, methionine and breast cancer risk among AA women by estrogen receptor (ER) status in the WCHS

Nutrients	Cases		Controls (n)	ER+ vs. Controls		ER− vs. Controls	
	ER+ (n)	ER− (n)		OR[1]	95% CI[2]	OR[1]	95% CI[2]
Total dietary folate DFE, mcg/day							
Q1 (≤334.8)	133	60	246	1.00		1.00	
Q2 (334.9–468.8)	101	33	193	0.82	0.57–1.18	0.78	0.46–1.32
Q3 (468.9–636.4)	74	43	208	0.57	0.38–0.87	1.07	0.61–1.87
Q4 (>636.4)	83	37	180	0.62	0.37–1.06	1.14	0.55–2.34
p for linear trend					0.06		0.60
Natural folate from food, mcg/day							
Q1 (≤159.6)	135	53	250	1.00		1.00	
Q2 (159.7–230.6)	97	48	205	0.73	0.52–1.04	1.10	0.68–1.78
Q3 (230.7–315.1)	82	33	189	0.66	0.44–0.99	0.93	0.53–1.64
Q4 (>315.1)	77	39	183	0.58	0.36–0.93	1.12	0.59–2.10
p for linear trend					0.03		0.87
Synthetic folate from fortified food, mcg/day							
Q1 (≤78.1)	116	56	228	1.00		1.00	
Q2 (78.2–129.8)	101	34	208	0.93	0.65–1.33	0.75	0.45–1.25
Q3 (129.9–188.6)	73	41	199	0.73	0.48–1.09	1.06	0.62–1.82
Q4 (>188.6)	101	42	192	1.08	0.70–1.68	1.25	0.68–2.29
p for linear trend					0.64		0.26
Vitamin B6, mg/day							
Q1 (≤1.17)	132	62	255	1.00		1.00	
Q2 (1.18–1.63)	108	29	196	0.94	0.66–1.35	0.75	0.44–1.29
Q3 (1.64–2.13)	66	41	199	0.54	0.35–0.84	1.17	0.66–2.09
Q4 (>2.13)	85	41	177	0.73	0.42–1.26	1.58	0.76–3.29
p for linear trend					0.14		0.19
Vitamin B12, mcg/day							
Q1 (≤3.13)	124	52	227	1.00		1.00	

Nutrients	Cases		Controls (n)	ER+ vs. Controls		ER− vs. Controls	
	ER+ (n)	ER− (n)		OR[1]	95% CI[2]	OR[1]	95% CI[2]
Q2 (3.14–4.93)	96	37	201	0.81	0.57–1.16	0.87	0.53–1.44
Q3 (4.94–7.08)	74	37	180	0.71	0.48–1.06	1.17	0.69–2.00
Q4 (>7.08)	97	47	219	0.80	0.52–1.23	1.14	0.65–2.00
p for linear trend					0.38		0.50
Methionine, g/day							
Q1 (≤1.03)	116	55	244	1.00		1.00	
Q2 (1.04–1.47)	118	42	200	1.19	0.83–1.70	1.05	0.63–1.76
Q3 (1.48–1.96)	64	38	173	0.78	0.50–1.22	1.23	0.68–2.23
Q4 (>1.96)	93	38	210	1.03	0.59–1.82	1.13	0.52–2.43
p for linear trend					0.77		0.70

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval.

*1, 2*Models are adjusted for age, ethnicity, country of origin, education, BMI, age at menarche, menopausal status, parity, age at first birth, breastfeeding status, family history of breast cancer, OC use, history of benign breast disease, HRT use, smoking status, alcohol consumption, and total energy intake.

Table 4

Association between dietary intake of folate, vitamin B6, B12, methionine and breast cancer risk among all EA women and stratified by menopausal status in the WCHS

	All women				Premenopausal				Postmenopausal			
	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]
Total dietary folate DFE, mcg/day												
Q1 (≤334.8)	167	132	1.00		85	74	1.00		82	58	1.00	
Q2 (334.9–468.8)	181	185	0.85	0.60–1.19	79	102	0.68	0.42–1.12	102	83	0.90	0.54–1.51
Q3 (468.9–636.4)	171	165	0.99	0.68–1.44	96	89	1.07	0.63–1.81	75	76	0.83	0.47–1.47
Q4 (>636.4)	209	197	1.11	0.72–1.70	119	107	1.11	0.60–2.06	90	90	0.96	0.51–1.82
p for linear trend				0.35				0.31				0.94
Natural folate from food, mcg/day												
Q1 (≤159.6)	151	129	1.00		78	76	1.00		73	53	1.00	
Q2 (159.7–230.6)	223	172	1.24	0.88–1.74	110	102	1.13	0.70–1.84	113	70	1.36	0.80–2.32
Q3 (230.7–315.1)	181	185	0.95	0.65–1.40	92	99	0.96	0.57–1.63	89	86	1.01	0.56–1.82
Q4 (>315.1)	173	193	0.89	0.58–1.37	99	95	1.03	0.56–1.88	74	98	0.65	0.33–1.26
p for linear trend				0.24			0.89					0.05
Synthetic folate from fortified food, mcg/day												
Q1 (≤78.1)	161	150	1.00		75	73	1.00		86	77	1.00	
Q2 (78.2–129.8)	182	170	1.20	0.86–1.68	93	89	1.17	0.72–1.89	89	81	1.14	0.70–1.85
Q3 (129.9–188.6)	157	175	0.97	0.68–1.37	81	103	0.80	0.48–1.33	76	72	1.12	0.66–1.88
Q4 (>188.6)	228	184	1.53	1.06–2.21	130	107	1.43	0.83–2.46	98	77	1.48	0.87–2.52
p for linear trend				0.03				0.17				0.17
Vitamin B6, mg/day												
Q1 (≤1.17)	151	124	1.00		79	72			72	52	1.00	
Q2 (1.18–1.63)	194	182	0.98	0.69–1.39	87	110	0.71	0.43–1.17	107	72	1.16	0.68–1.99
Q3 (1.64–2.13)	162	174	0.94	0.63–1.38	97	95	1.11	0.65–1.90	65	79	0.69	0.38–1.26
Q4 (>2.13)	221	199	1.14	0.73–1.77	116	95	1.31	0.70–2.46	105	104	0.84	0.43–1.64
p for linear trend				0.48				0.12				0.37
Vitamin B12, mcg/day												
Q1 (≤3.13)	175	151	1.00		92	86			83	65	1.00	

	All women				Premenopausal				Postmenopausal			
	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]	Ca (n)	Co (n)	OR[1]	95% CI[2]
Q2 (3.14–4.93)	192	178	1.04	0.75–1.44	95	98	0.96	0.61–1.51	97	80	1.15	0.70–1.91
Q3 (4.94–7.08)	180	194	0.91	0.65–1.29	99	111	0.86	0.53–1.38	81	83	1.00	0.58–1.71
Q4 (>7.08)	181	156	1.04	0.71–1.54	93	77	1.01	0.58–1.76	88	79	1.09	0.60–1.96
p for linear trend				0.91				0.97				0.98
Methionine, g/day												
Q1 (≤1.03)	166	135	1.00		77	77			89	58	1.00	
Q2 (1.04–1.47)	205	176	1.08	0.77–1.53	94	98	1.13	0.69–1.84	111	78	1.14	0.67–1.93
Q3 (1.48–1.96)	179	205	0.83	0.56–1.22	105	113	1.27	0.74–2.18	74	92	0.58	0.32–1.06
Q4 (>1.96)	178	163	1.13	0.68–1.87	103	84	1.93	0.95–3.91	75	79	0.67	0.31–1.44
p for linear trend				0.90				0.06				0.11

Abbreviations: Ca, Cases; Co, Controls; OR, Odds ratio; 95% CI, 95% confidence interval.

*1, 2*Models are adjusted for age, ethnicity, country of origin, education, BMI, age at menarche, menopausal status (when not stratified by this variable), age at menopause (only for postmenopausal women), parity, age at first birth, breastfeeding status, family history of breast cancer, OC use, history of benign breast disease, HRT use, smoking status, alcohol consumption, and total energy intake.

Table 5

Association between dietary intake of folate, vitamin B6, B12, methionine and breast cancer risk among EA women by estrogen receptor (ER) status in the WCHS

Nutrients	Cases		Controls (n)	ER+ vs. Controls		ER− vs. Controls	
	ER+ (n)	ER− (n)		OR[1]	95% CI[2]	OR[1]	95% CI[2]
Total dietary folate DFE, mcg/day							
Q1 (≤334.8)	101	16	132				
Q2 (334.9–468.8)	112	22	185	0.86	0.58–1.28	1.06	0.50–2.26
Q3 (468.9–636.4)	100	23	165	1.02	0.66–1.58	1.23	0.55–2.75
Q4 (>636.4)	114	24	197	1.04	0.63–1.72	1.14	0.45–2.92
p for linear trend					0.64		0.78
Natural folate from food, mcg/day							
Q1 (≤159.6)	93	13	129				
Q2 (159.7–230.6)	132	27	172	1.20	0.80–1.78	1.80	0.83–3.93
Q3 (230.7–315.1)	110	25	185	0.93	0.59–1.45	1.33	0.57–3.12
Q4 (>315.1)	92	20	193	0.82	0.49–1.36	1.01	0.97–1.06
p for linear trend					0.19		0.48
Synthetic folate from fortified food, mcg/day							
Q1 (≤78.1)	100	15	150				
Q2 (78.2–129.8)	104	24	170	1.09	0.74–1.60	1.74	0.83–3.63
Q3 (129.9–188.6)	97	19	175	0.96	0.64–1.44	1.21	0.54–2.70
Q4 (>188.6)	126	27	184	1.35	0.88–2.06	1.99	0.89–4.47
p for linear trend					0.15		0.18
Vitamin B6, mg/day							
Q1 (≤1.17)	90	14	124				
Q2 (1.18–1.63)	116	24	182	1.02	0.68–1.53	1.17	0.53–2.59
Q3 (1.64–2.13)	97	25	174	0.96	0.61–1.52	1.18	0.49–2.83
Q4 (>2.13)	124	22	199	1.18	0.70–1.99	0.92	0.34–2.54
p for linear trend					0.49		0.72
Vitamin B12, mcg/day							
Q1 (≤3.13)	108	15	151				

Nutrients	Cases		Controls (n)	ER+ vs. Controls		ER− vs. Controls	
	ER+ (n)	ER− (n)		OR[1]	95% CI[2]	OR[1]	95% CI[2]
Q2 (3.14–4.93)	110	33	178	1.00	0.68–1.47	1.81	0.88–3.70
Q3 (4.94–7.08)	105	22	194	0.90	0.60–1.35	1.14	0.51–2.53
Q4 (>7.08)	104	15	156	1.06	0.67–1.69	0.75	0.29–1.95
p for linear trend				0.80		0.17	
Methionine, g/day							
Q1 (≤1.03)	95	17	135				
Q2 (1.04–1.47)	133	27	176	1.32	0.88–1.99	1.39	0.65–2.98
Q3 (1.48–1.96)	95	20	205	0.81	0.51–1.29	0.76	0.32–1.81
Q4 (>1.96)	104	21	163	1.30	0.70–2.38	1.16	0.38–3.54
p for linear trend				0.90		0.82	

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval.

[1, 2]Models are adjusted for age, ethnicity, country of origin, education, BMI, age at menarche, menopausal status, parity, age at first birth, breastfeeding status, family history of breast cancer, OC use, history of benign breast disease, HRT use, smoking status, alcohol consumption, and total energy intake.

Table 6

Joint association of natural folate and intake of vitamin B6, B12, methionine, and alcohol intake with risk of breast cancer among premenopausal AA women in the WCHS

Other nutrients (median intake)	Natural folate from food (median), mcg/day			
	Low (<230.6)		High (≥230.6)	
	OR[1]	95% CI[2]	OR[1]	95% CI[2]
Vitamin B6, mg/day				
Low (<1.63)	1.00		0.69	0.39–1.24
High (≥1.63)	0.91	0.54–1.55	0.66	0.41–1.06
p for interaction	0.90			
Vitamin B12, mcg/day				
Low (<4.93)	1.00		0.80	0.47–1.60
High (≥4.93)	0.91	0.58–1.43	0.60	0.37–0.96
p for interaction	0.58			
Methionine, g/day				
Low (<1.47)	1.00		0.70	0.41–1.20
High (≥1.47)	0.56	0.34–0.92	0.42	0.25–0.72
p for interaction	0.82			
Alcohol intake, g/week				
Low (<15)	1.00		0.70	0.47–1.04
High (≥15)	1.54	0.93–2.54	1.11	0.62–1.99
p for interaction	0.92			

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval.

[1,2]Models are adjusted for age, ethnicity, country of origin, education, BMI, age at menarche, parity, age at first birth, breastfeeding status, family history of breast cancer, OC use, history of benign breast disease, HRT use, smoking status, alcohol consumption (when not stratified by this variable), and total energy intake.