RESEARCH ARTICLE

Lack of Effects of Dietary Folate Intake on Risk of Breast Cancer: An Updated Meta-analysis of Prospective Studies

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Abstract

Background: Epidemiological findings are controversial relating to the relationship between dietary folate intake and the risk of breast cancer. We therefore conducted a meta-analysis of prospective cohort studies to clarify this association. Materials and Methods: PUBMED, EMBASE, and MEDLINE databases were searched for all relevant literature published in English from January 1, 1966 to August 2013. Summary relative risk (RR) and 95% confidence intervals (CIs) were calculated using a fixed or random effects model. Results: Dietary folate intake was not significantly associated with the risk of breast cancer. The combined RR with 95%CI for the highest vs. lowest category dietary intake of folate [fifteen studies; 1,836,566 participants and 24,083 patients with breast cancer] was 0.98 (0.90-1.05). Among subgroup analysis by menstrual status, hormonal status and the consumption of alcohol, methionine and vitamin B12, no significant association was observed for the dietary intake of folate and the risk of breast cancer. Dose-response analysis showed that a 220 μg/day increment in dietary folate intake was not associated with the risk of breast cancer. Conclusions: Our findings indicate that dietary folate intake has no significant effect on the risk of breast cancer.

Keywords: Folate - breast cancer - meta-analysis

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Introduction

Breast cancer is one of the most common malignancies that cause death among females worldwide (Ferlay et al., 2010; Shakeel et al., 2013). As a multifactorial disease, breast cancer is associated not only with environmental and hereditary factors but also dietary factors including folate, vitamin B6, vitamin B12 and alcohol (Ma et al., 2009; Gou et al., 2013; Liu et al., 2013).

Folate, as a methyl donor in one-carbon metabolism, has been shown to mediate carcinogenesis by participating in DNA synthesis, repair, and methylation (Eichholzer et al., 2001; Stevens et al., 2010; Harris et al., 2012). Methionoine and vitamin B12 are also involved in one-carbon metabolism, and any change in the levels of these nutrients could affect one-carbon metabolism, effecting folate availability on this pathway (Zhang et al., 2011).

Studies have investigated the association between dietary folate intake and the risk of breast cancer, but the findings are inconsistent. Although a meta-analysis (Larsson et al., 2007) published in 2007 suggested no association of dietary folate intake with the risk of breast cancer, subsequently seven publications (Cho et al., 2007; Kabat et al., 2008; Larsson et al., 2008; Maruti et al., 2009; Stevens et al., 2010; Shrubsole et al., 2011; Bassett et al., 2013) from February 2007 to 2013 presented different conclusions. Stevens et al. (2010) observed an association of folate dietary intake with decreased risk of breast cancer in postmenopausal women. A negative correlation was seen in one study (Shrubsole et al., 2011) and the remaining (Cho et al., 2007; Kabat et al., 2008; Larsson et al., 2008; Maruti et al., 2009; Bassett et al., 2013) showed no association. Therefore, we performed an updated meta-analysis on a total of 1,854,013 participants and 24,620 breast cancer cases from sixteen prospective studies, to assess further the association of dietary folate intake with the risk of breast cancer.

Materials and Methods

Literature search and selection criteria

We conducted a comprehensive English literature search up to August 2013 by two independent researchers on PUBMED, MEDLINE and EMBASE databases. Search terms "dietary folate intake" or "dietary folic acid consumption" in combination with "breast cancer" or "breast neoplasm" were used. Eligible studies have to meet the following inclusion criteria: 1) prospective study design; 2) the exposure of interest was dietary folate intake; 3) number of incident breast cancer cases and total participants; 4) provided relative risk (RR) or hazard ratio(HR) with 95% confidence interval (CI).

Data extraction and quality assessment

Two independently investigators abstracted data from each eligible publication: the last name of first author, publication year, area where the study carried out, simple size and breast cancer cases, a baseline age of participants,

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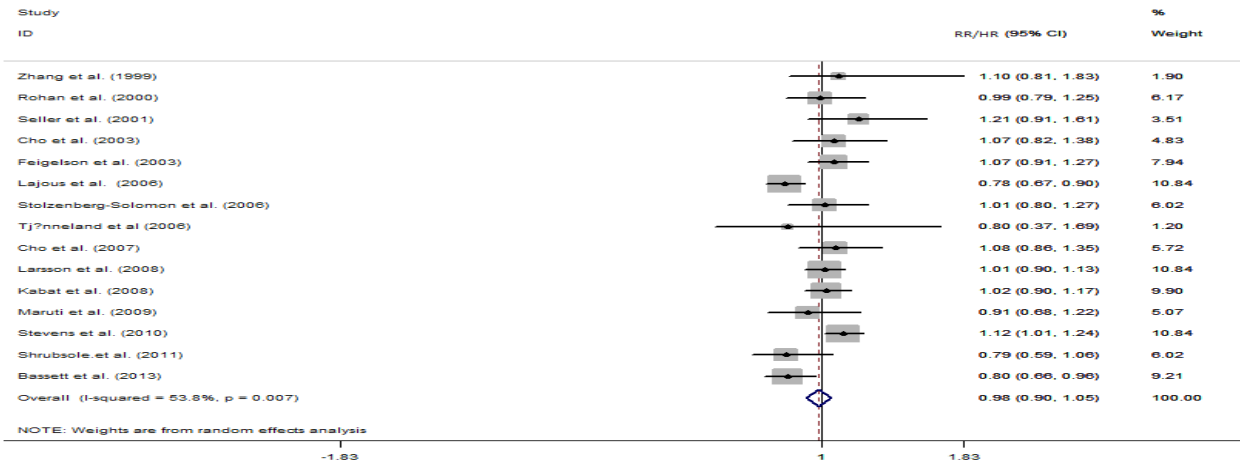

Figure 1. Forest Plot for the Meta-Analysis of the Association Between Dietary Folate Intake and the Risk Breast Cancer(Highest Category *vs* Lowest Category)

follow-up period, RR or HR combination with 95%CI, detailed categories and quantiles of dietary folate intake, methods of estimating dietary intake, adjustments of variables in the analysis. The risk estimates also should be extracted, and which reflecting the greatest degree of control for potential confounders.

The quality of the studies was assessed by two researchers (LM and LN) using the 9-star Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al., 2012). Detailed grading standards of the NOS for case-control or cohort study were listed as follows: selection (maximum score=4), comparability (maximum score=2), and exposure (case-control)/outcome (cohort) assessment (maximum score=3). A high score(≥7) out of a total of nine points indicated high study quality.

Statistical analysis

Since the incidence and mortality rate of breast cancer is relatively low, RR and HR will be approximately equal, and the measure of effect-estimates is referred to as RR in our meta-analysis (Lin et al., 2013).Cochrane Q test and Higgins I-square (I^2) statistics were used to assess heterogeneity among studies. The p-value of 0.1 was used for the Cochrane Q test on testing the heterogeneity, and the values of 25, 50 and 75% of I^2 statistic were used as low, moderate and high heterogeneity, respectively. Based on the test on heterogeneity, the fixed-effects model (Mantel et al., 1959) or random effects mode (DerSimonian et al., 1986) was used to obtain pooled estimates. In addition, we performed meta-regression, subgroup and sensitivity.

For the dose–response analysis, we used the generalized least-squares trend estimation (GLST) method developed by Greenland and Orsini (Greenland et al., 1992; Orsini et al., 2006).The method requires that the average categories of dietary folate dose, number of breast cancer cases, person-years or noncases, and adjusted logarithm of the RR with its SE (Greenland et al., 1992; Berlin et al., 1993). The median value of dietary folate intake in each category was assigned to the corresponding RR for each study when provided in the paper. For studies that reported the range of dietary folate, the midpoint of the interval was chosen. For the lowest category was open ended, the lowest boundary was considered to be zero. For the open-ended upper interval, the value arbitrarily assigned was 20% higher than the low end of the interval (Berlin et al., 1993; Aune et al., 2012) .The does-response results are presented for a 220ug/d increment.

The publication bias among studies was examined with Funnel plots, Egger´s liner regression test (Egger et al., 1997) and Begg´s test (Begg et al., 1994) with a significance level of 0.1. Sensitivity analyses were conducted to assess the stability of individual studies, by excluding any single study each time. In addition, we also performed subgroup analysis based on menstrual status, hormonal status and the consumption of alcohol, methionine and vitamin B12. All statistical analyses were conducted with STATA software (version 12.0; College Station, TX). All statistical tests were two sided and considered statistically significant when <0.05.

Results

Eligible studies and studies characteristics

Our search strategy identified fifteen prospective cohort studies and one nested case-control study, including 1854013 participants and 24620 breast cancer patients. Of those, fifteen studies contained results about dietary intake of folate. Eight studies (Zhang et al., 1999; Sellers et al., 2001; Cho et al., 2003; 2007; Feigelson et al., 2003; Maruti et al., 2009; Stevens et al., 2010; Basset et al., 2013) were conducted in the United States, two articles each in Canada (Rohan et al., 2000; Kabat et al., 2008;) and Australia (Baglietto et al., 2005; Stolzenberg-Solomon et al., 2006) and the rest from China, Swedish, France and Denmark (Lajous et al., 2006; Tjønneland et al., 2006; Larsson et al., 2008; Shrubsole et al., 2011), separately. To estimate dietary folate intake, all studies used the Food Frequency Questionnaire (FFQ). The baseline characteristics of all selected studies were summarized in Table 1. The study quality score ranged from 5 to 8 according to the 9-star Newcastle-Ottawa Scale, and was ≥7 (indicating high quality) for the majority (10/16) of studies.

Dietary folate intake and breast cancer risk

All studies provided detail results on dietary folate intake. The RR or HR for the highest versus lowest

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Table 1. Characteristics of Prospective Studies Included in the Meta-Analysis of Dietary Foate Intake and Breast Cancer Risk

First author, Year Country	subjects	cases	Age (year)	Follow-up period (year)	Dietary assessment	Category ug/day	Adjusted RR/HR 95%CI	Adjustments
Zhang, 1999 USA	88818	3483	30-55	16	126-item FFQ	126 223 329 290 326	— 1.00(ref) — — 1.10(0.81-1.83)	age, parity, length of follow-up, alcohol intake, total energy intake, age at first birth, history of breast cancer in mother or sister, history of begin breast cancer, BMI at age 18 years, height in cm, age at menopause, postmenopausal hormone, use , weight change from age 18 years.
Rohan, 2000 Canada	1020747	1336	40-59	8-13	semiquantitative questionnaire 86-item FFQ	<224.78 224.78-266.83 266.83-305.01 305.01-345.28 >345.28	1.00(ref) 0.98(0.78-1.23) 1.01(0.80-1.28) 0.95(0.76-1.20) 0.99(0.79-1.25)	age, practice of breast self-examination, number of live births, energy intake, age at menarche, menopausal status, randomization group, study center alcohol consumption, family history of breast cancer in a first-degree relative.
Seller, 2001 USA	34387	1586	55-69	12	semiquantitative questionnaire 127-item FFQ	≤172 173-239 240-294 >294	1.00(ref) 0.93(0.76-1.14) 0.98(0.83-1.15) 1.21(0.91-1.61)	age, education, family history of breast cancer, age at menarche, age at menopause, oral contraceptive use, age at first birth, parity, hormone replacement therapy, waist-to-hip ratio, BMI, BMI at age 18, smoking, physical activity, other B vitamins, alcohol, height.
Cho, 2003 USA	90665	714	26-46	8	130-item FFQ	210 260 300 345 429	1.00(ref) 1.18(0.93-1.50) 1.11(0.87-1.42) 1.09(0.86-1.40) 1.07(0.82-1.38)	smoking, height , body mass index , animal fat, parity, age at menarche, alcohol intake, energy, family history of breast cancer, contraceptive use, age at first birth ,history of benign breast disease.
Feigelson, 2003 USA	66561	1303	40-87	5	semiquantitative questionnaire 68-item FFQ	<178.8 178.8-230.9 230.9-294.3 >249.3	1.00(ref) 1.11(0.95-1.30) 1.10(0.93-1.29) 1.07(0.91-1.27)	age, ethanol, dietary folate, methionine, race, age at first birth, age at menopause,history of breast lump, education, multivitamin use, parity, energy, first degree family history of breast cancer, physical activity, HRT use, age at menarche mammographic history, adult weight gain, BMI.
Baglieto, 2005 Australia	17447	537	40-69	13	121-item FFQ	-	1.00(ref) 1.01(0.93-1.1)	age, energy.
Tjønneland, 2006 Denmark	24697	388	50-64	4.7	192-item FFQ	≤250 250-300 300-400 >400	1.00(ref) 0.90(0.55-1.49) 0.69(0.41-1.14) 0.80(0.37-1.69)	total energy , school education , body mass index, age at birth of first child, vitamin C, number of births, parous/ nulliparous, history of benign breast tumour surgery.,
Stolzenberg-Solomn 2006 Australia	25400	691	50-74	4.94	semiquantitative questionnaire FFQ	≤261.3 261.3-307.2 307.2-350.5 350.5-411.9 >411.9	1.00(ref) 0.93(0.73-1.19) 0.73(0.56-0.94) 0.87(0.68-1.11) 1.01(0.80-1.27)	energy, education, mammography screening history , birth control pill use history of benign breast disease , age at menarche, age at first birth ,number of live births, family history of breast cancer, age at menopause, hormonere placement therapy.
Lajous, 2006 France	62739	1812	-	9	208-item FFQ	296 350 392 440 522	1.00(ref) 0.86(0.75-1.00) 0.86(0.75-0.99) 0.80(0.69-0.92) 0.78(0.67-0.90)	age, education, history of benign breast disease, family breast cancer, age at menarche, parity, age at first birth, vitamin supplement use, breastfeeding, years since last use of oral contraceptives, alcohol intake, BMI, years of hormone replacement therapy use, age at menopause, regular mammographic evaluation.
Cho, 2007 USA	90663	1032	26-46	12	130-item FFQ	217 268 309 354 436	1.00(ref) 1.18(0.96-1.44) 1.15(0.93-1.41) 1.16(0.94-1.43) 1.08(0.86-1.35)	smoking, height, parity , age at first birth, BMI, history of benign breast disease, family history of breast cancer, age at menarche, animal fat, oral contraceptive use, intakes of alcohol ,energy.
Kabat, 2008 Canada	889835	2491	40-59	16.4	Semiquantitativ Questionnaire FFQ	<237 237-281 281-321 321-374 >374	1.00(ref) 0.99(0.87-1.13) 1.03(0.91-1.17) 0.98(0.86-1.12) 1.02(0.90-1.17)	age, BMI, smoking, education, oral contraceptive use, menopausal status, intake of calories, family history of breast cancer, history of breast biopsy, age at menarche, parity, hormone replacement therapy, alcohol intake.
Larssm, 2008 Sweden	61433	2952	53.5	17.4	67-item FFQ 96-item FFQ	<200 200-223 224-246 247-276 ≥277	1.00(ref) 0.94(0.84-1.06) 0.99(0.88-1.11) 0.93(0.83-1.05) 1.01(0.90-1.13)	age, education, body mass index, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of breast cancer, history of benign breast disease, intakes of alcohol and total energy.
Maruti, 2009 USA	35023	743	50-76	5	semiquantitative questionnaire 120-item FFQ	210(37-260) 303(260-346) 392(346-450) 541(450-1483)	1.00(ref) 0.94(0.75-1.18) 1.04(0.82-1.33) 0.91(0.68-1.22)	age, race ,family history of breast cancer, mammography within 2 year, preceding baseline, history of breast biopsy, age at menarche , age at first birth, age at menopause, years of combined estrogen and progestin PMH, BMI , total physical activity , alcohol intake in the past year .
Stevens, 2010 USA	70656	3898	50-74	13	68-item FFQ	<166.9 166.9-209.9 209.9-252.8 252.8-312.1 ≥312.1	1.00(ref) 1.10(0.99-1.22) 1.14(1.03-1.26) 1.05(0.95-1.17) 1.12(1.01-1.24)	age, race, education, physical activity, age at first birth, age at menopause, hormone replacement therapy, BMI, multivitamin use, first-family history of breast cancer, age at menarche, energy, parity, history of breast lump, alcohol use.
Shrubsole, 2011 China	74942	918	40-70	7.2	structured questionnaires	194 243 282 328 404	1.00(ref) 0.90(0.71-1.15) 0.89(0.69-1.15) 0.99(0.76-1.28) 0.79(0.59-1.06)	age at baseline , age at menarche , parity, education, use of B vitamin supplements, age at first live birth , height, total daily intakes of energy, vegetables, ER/PR status, physical activity, fat, menopausal status.
Bassett, 2013 USA	20756	936	27-80	16	121-item FFQ	224 286	1.00(ref) 0.8(0.66-0.96)	ethnicity, menopausal status, age at menarche, lactation, education, parity, alcohol consumption, smoking status, physical activity, hormone replacement therapy use, BMI, oral contraceptive use.

*RR=relative risk; HR=hazard rate; CI=confidence interval; FFQ=food-frequency questionnaire; BMI=body mass index

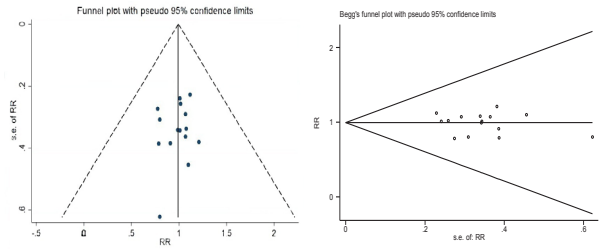

Figure 2. Funnel Plot Analysis and Begg's Test for the Publication Bias

categories of folate dietary intake in each study is shown in Figure 1. The inconsistent results from the included studies were that two researches (Stolzenberg-Solomon et al., 2006; Stevens et al., 2010) investigated a significant positive association between dietary folate intake and the risk of breast cancer, two studies (Lajous et al., 2006; Shrubsol et al., 2011) showed remarkably inverse relationship, and eleven studies (Zhang et al., 1999; Rohan et al., 2000; Sellers et al., 2001; Cho et al., 2003; 2007;n Feigelson et al., 2003; Tjønneland et al., 2006; Kabat et al., 2008; Larsson et al., 2008; Maruti et al., 2009; Bassett et al., 2013) showed no association. The summary RR for breast cancer for the highest versus lowest categories of the folate dietary intake was 0.98 (95%CI 0.90-1.05, Figure 1), indicating that no association was found between dietary folate intake and breast cancer risk.

Sensitivity analysis and heterogeneity assessment

Sensitivity analyses were performed to test the stability of the pooled results. The effect of each study on the overall meta-analysis estimate was assessed by omitting one study at a time, but the pooled RRs were always persistent, demonstrating that our results were robust.

Heterogeneity test showed there was significantly different among the including studies (I^2=53.8%, p=0.007, Q=30.29), therefore, a randomized-effects model was employed to pool them to obtain the overall RR.

Dose–response analysis

Ten cohort studies (Rohan et al., 2000; Sellers et al., 2001; Feigelson et al., 2003; Baglietto et al., 2005; Stolzenberg-Solomon et al., 2006; Larsson et al., 2008; Maruti et al., 2009; Stevens et al., 2010; Shrubsole et al., 2011; Bassett et al., 2013) were eligible for the dose–response analysis, including15904 breast cancers. Dose-response analysis showed that dietary folate intake in increments of 220 μg/day was not associated with the risk of breast cancer (the summary RR=0.96, 95%CI 0.95 to 1.05), and moderate heterogeneity was found (I^2=67.5%, p=0.001).

Publication bias

There was no significant publication bias based on funnel plot (Figure 2). Egger's and Begg's test indicated that there was not a possibility of publication bias for the relationship of dietary folate intake with breast cancer risk (p=0.568 and p=0.488, Figure 2, Table 2).

Meta-analysis results of dietary folate intake by stratification of alcohol intake

Six studies investigated combined effects of dietary folate and alcohol intake on breast cancer. Three of these studies (Zhang et al., 1999; Rohan et al., 2000; Baglietto ett al., 2005) had found marked reductions in breast cancer risk among those who consuming higher alcohol. Three other studies (Cho et al., 2003; Feigelson et al., 2003; Stevens et al., 2010) reported that the relationship between folate intake and breast cancer was not modified by alcohol intake. In our meta-analysis, there was no significant association in breast cancer risk for high versus low folate intake by alcohol stratification (Table 2).

Table 2. Stratified Analyses of Hazard Ratio or Risk Ratio of Breast Cancer with Dietary Folate Intake

Variables	N	Pooled RR/HR (95%CI)	Heterogeneity I^2 (%)	Heterogeneity p value	Begg's test/ Egger's test
Overall	15	0.98(0.90-1.05)	53.8	0.007	0.488/0.568
Menstrual Status[a]					
Premenopausal	4	1.06(0.96-1.16)	0	0.645	0.913
Postmenopausal	10	0.98(0.89-1.07)	56.6	0.014	0.645
ER and PR Status[b]					
ER+/PR+	3	1.05(0.95-1.50)	0	0.987	0.879
ER-/PR-	4	0.91(0.80-1.03)	0	0.795	0.850
Alcohol intake[a]					
Low	6	1.05(0.95-1.15)	0	0.920	0.451
High	6	0.92(0.57-1.27)	83.8	<0.000	0.072
Dietary methionine intake[b]					
Low	3	1.02(0.82-1.22)	0	0.973	0.707
High	3	0.94(0.80-1.08)	0	0.812	0.501
Dietary vitamin B12 intake[a]					
Low	2	0.91(0.68-1.14)	0	0.873	0.221
High	2	0.74(0.36-1.12)	47.7	0.167	0.210

*N: Number of included studies; RR=relative risk; HR= hazard ratio; CI= confidence interval; [a]: A random-effects model was used; [b]: A fixed-effects model was used; Positive:+, Negative:-

Meta-analysis results of dietary folate intake by stratification of menstrual or hormonal status

Meta-analysis results of dietary folate intake and menstrual status, hormonal status are illustrated in Table 2. Subgroup analysis of different menopausal statuses showed the relationship of dietary folate intake with cancer risk did not differ in postmenopausal and premenopausal breast cancer patients (postmenopausal *vs* premenopausal RR=0.98, 95%CI 0.89 to 1.07). The same results were also observed when the stratified analyses were carried out by estrogen receptor (ER) and progesterone receptor (PR) status (Table 2).

Meta-analysis results of dietary folate by stratification of methionine or vitamin B12 intake

Three prospective studies (Stolzenberg-Solomon et al., 2006; Stevens et al., 2010; Shrubsole et al., 2011) have examined whether the association between folate intake and risk of breast cancer is modified by methionine intake. Two prospective studies (Lajous et al., 2006; Shrubsole et al., 2011) have evaluated the association between dietary folate intake and risk of breast cancer by strata of intakes of vitamin B12. In our meta-analysis, there were no significant interactions between dietary folate, methionine and vitamin B12 intake (Table 2).

Discussion

Our meta-analysis was based on prospective cohort studies evaluating the relationship of dietary folate intake

and the risk of breast cancer. We found no evidence to support the association of dietary folate exposure and the risk of breast cancer by using the random-effects model, where the pooled estimate for the highest versus the lowest exposure level was 0.98 (95%CI: 0.90-1.05). We further observed that there was no association in subgroup analysis of menstrual status, hormonal status, the consumption of alcohol, methionine or vitamin B12. In addition, the result from dose-response analysis showed that dietary folate intake in increments of 220 μg/day was not associated with breast cancer risk

Folate has a critical role in DNA methylation (Kim et al., 2004; Nazki et al., 2014). Low folate intake might alter DNA methylation and thereby affect gene expression, DNA integritty and stability (Ma et al., 2009). Folate may also mediate carcinogenesis by an alternative pathway. A form of folate, 5,10-methylene tetrahydrofolate, is a methyl donor that plays an important role in the conversion of dUMP to dTMP. Failure to synthesis dTMP will lead to nucleotide deficiency, and in turn result in inappropriate incorporation of uracil into DNA in place of thymidine, resulting in DNA strand breaks. It has been hypothesized that low dietary folate intake might be associated with breast cancer, affecting the methylation of the ER receptor, which might have an influence on silencing genes (Zhu et al., 1998; Zhang et al., 2005; Gou et al., 2013). However, our meta-analysis result showed that dietary folate intake was not significantly associated with the risk of breast cancer. In fact, a similar result was also seen in meta-analysis studies on the association between dietary folate intake and other malignancies risk, such as ovarian cancer (Li et al., 2013), pancreatic cancer (Bao et al., 2011), and lung cancer (Cho et al., 1999).

Vitamin B12, as cofactors, and methionine may affect carcinogenesis due to their critical roles in the one-carbon metabolism pathway, which plays an important role in DNA synthesis, methylation, and repair. They may also influence folate metabolism and its physiologic effects (Harris et al., 2012). In addition, menstrual status and hormonal status are known risk factors for breast cancer. Further stratified analyses were conducted by menstrual status, hormonal status and the consumption of alcohol, methionine and vitamin B12. We found that those stratified factors didn't change the association of dietary folate intake with breast cancer risk,

Alcohol is likely to affect folate methylation pathways by promoting the degradation, inhibiting the absorption, and increasing the excretion of folate (Kato et al., 1999). Thus, we conducted alcohol stratification analysis based on six prospective studies, and the results indicated that no significant association between high versus low dietary folate intake and breast cancer risk. Similarly, Flood et al. (2002) reported that alcohol consumption couldn't modify the relationship between dietary folate intake and the risk of colorectal cancer. However, a previous meta-analysis (Larsson et al., 2007) in 2007, only including two prospective studies, indicated that high folate intake was associated with a statistically significant decreased risk of breast cancer among women with moderate or high alcohol consumption, but not among women with low or no alcohol consumption. As these results are inconsistent, large prospective studies are warranted to clarify further the interaction of alcohol and dietary folate consumption and the risk of breast cancer.

Begg's and Egger's tests were used to detect the potential publication bias, and no significant discrepancy was seen from the meta-analysis. Our study, consisting of 1,854,013 participants and 24,620 breast cancer patients, included studies that were based on a prospective cohort; therefore, the conclusions are highly credible.

In conclusion, the current meta-analysis demonstrated that there was no association between dietary folate intake and the risk of breast cancer. Also, no differences were observed in the interactions between dietary folate intake and menstrual status, hormonal status and the consumption of alcohol, methionine or vitamin B12 on the risk of breast cancer. Further prospective studies are essential to confirm the observed results.

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