Folate Intake and Risk of Breast Cancer by Estrogen and Progesterone Receptor Status in a Swedish Cohort

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Abstract

Background: **Folate is a B vitamin involved in one-carbon metabolism and has been postulated to influence the risk of breast cancer. However, epidemiologic studies of folate intake in relation to breast cancer risk are inconclusive. We examined the association between dietary folate intake and the risk of breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumor in the Swedish Mammography Cohort.**

Methods: **Our study population consisted of 61,433 women who completed a food frequency questionnaire at baseline (1987-1990) and again in 1997. Cox proportional hazards models were used to estimate rate ratios (RR) with 95% confidence intervals (95% CI).**

Results: **During an average of 17.4 years of follow-up, 2,952 incident cases of invasive breast cancer were ascertained. We observed no association between dietary folate intake and risk of total breast cancer or ER+/PR+ or ER-/PR- tumors. The multivariate RR of total breast cancer comparing extreme quintiles of folate intake was 1.01 (95% CI, 0.90-1.13; P_{trend} = 0.84). However, folate intake was inversely associated with risk of ER+/PR- breast cancer (n = 417 cases; RR for highest versus lowest quintile, 0.79; 95% CI, 0.59-1.07; P_{trend} = 0.01). Results did not vary by alcohol intake or menopausal status.**

Conclusions: **These findings do not support an overall association between folate intake and risk of breast cancer but suggest that folate intake may be inversely associated with ER+/PR− tumors.** (Cancer Epidemiol Biomarkers Prev 2008;17(12):3444–9)

Introduction

Folate is a water-soluble B vitamin that has been postulated to be associated with cancer risk. Biological reactions requiring folate, known as one-carbon metabolism, include DNA synthesis and DNA methylation (1, 2). An inadequate folate intake may predispose individuals to cancer through aberrations in these processes. In fact, epidemiologic studies have suggested that a low folate intake or status may increase the risk of certain cancers, and the evidence is most convincing for gastrointestinal cancers (3, 4). Epidemiologic studies of folate intake in relation to risk of breast cancer have been inconclusive. Whereas retrospective case-control studies generally have shown an inverse association between folate intake and breast cancer risk, the majority of prospective studies have found no overall association (5, 6). However, some prospective studies (7-12) have suggested that an adequate folate intake may be important in the prevention of breast cancer specifically among women with high alcohol consumption.

The relation between folate intake and breast cancer may vary by hormone receptor status of the breast tumor (13). However, only four prospective studies have reported findings for folate and breast cancer risk by hormone receptor status and the results are mixed (14-17).

To evaluate further the potential role of folate intake in the development of breast cancer, we analyzed data from a population-based cohort of Swedish women. We examined whether the association varied by estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumor, alcohol consumption, or menopausal status. Whereas folic acid (synthetic form of folate) fortification of grain products was mandated in the United States in 1998 (18), no such fortification program has been initiated in Sweden, which allows an analysis that is not influenced by fortification.

Materials and Methods

Study Cohort. The Swedish Mammography Cohort was established in 1987 to 1989 in Västmanland County and in 1988 to 1990 in Uppsala County in central Sweden. All women born between 1917 and 1948 in Västmanland County and between 1914 and 1948 in Uppsala County received a mailed invitation to be screened by mammography. Enclosed with this invitation was a six-page questionnaire that elicited information on diet, body size, reproductive factors, family history of breast cancer, and others; a completed questionnaire was obtained from 66,651 women, representing 74% of the source population. In the late autumn of 1997, all cohort members who were still alive and residing in the study area received a new questionnaire that was expanded to include about 350 items concerning diet and other lifestyle factors (including smoking); 39,227 (70%) women completed the second questionnaire.

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From the baseline cohort of 66,651 women, we excluded women with an incorrect or a missing national registration number as well as those lacking date on the questionnaire, date of moving out of the study area, or date of death. After additional exclusion of women with implausible values for total energy intake (3 SDs from the mean value for $\log_e$-transformed energy intake) and those with a cancer diagnosis (except nonmelanoma skin cancer) before baseline, the analytic cohort consisted of 61,433 women. Among these women, 26,403 were premenopausal, 2,574 were perimenopausal, and 32,456 were postmenopausal. For analyses using information from the second questionnaire, 36,664 women were eligible after excluding those with implausible energy intake on the second dietary questionnaire as well as those who had been diagnosed with cancer between baseline and January 1, 1998. The study was approved by the ethics committees at the Uppsala University Hospital and the Karolinska Institutet.

Assessment of Diet. A food frequency questionnaire (FFQ) with 67 and 96 food items was used to assess diet at baseline and in 1997, respectively. In these questionnaires, women were asked to report how often, on average, they had consumed each food item during the previous 6 months (baseline FFQ) or the previous year (1997 FFQ). The questionnaires had eight mutually exclusive predefined categories for frequency of consumption, ranging from ''never/seldom'' to ''≥3 times per day'' (1997 FFQ) or ''≥4 times per day'' (baseline FFQ). Dietary folate intake was calculated by multiplying the frequency of consumption of each food item by its folate content per age-specific serving using food composition values obtained from the Swedish National Food Administration Database (19). The age-specific serving sizes were based on mean values obtained from 213 randomly selected women from the study area who weighed and recorded their food intake for an average of 27.8 days. The 1997 questionnaire also asked for information on the use of dietary supplements, including specific folic acid supplements, B-vitamin supplements, and multivitamins. We calculated total folate intake by summing intake of folate from foods and dietary supplements.

The validity of the baseline dietary questionnaire was assessed previously by comparing responses from the FFQ with responses from four 1-week dietary records (3-4 months apart) among 129 women randomly chosen from the cohort.[3] Pearson correlation coefficients between the FFQ and the dietary records were 0.5 for dietary folate and 0.9 for alcohol. The validity of the second FFQ has been reported previously (20); the Spearman correlation coefficient for total folate intake between the FFQ and the average of fourteen 24-h recall interviews was 0.5.

Case Ascertainment and Follow-up. We ascertained histologically confirmed incident cases of invasive breast cancer by linkage with the national and regional Swedish cancer registers. The completeness of cancer follow-up was estimated to be almost 100% (21). Information on ER and PR status of breast tumors was obtained by reviewing pathology laboratory work logs stored at Uppsala University Hospital (from 1987 to 1994) and by linkage with the clinical database (the Quality Register) at the Regional Oncology Centre in Uppsala (from January 1992 to December 2007), which was based on the patients' original medical records. ER and PR status was evaluated by using an Abbott immunoassay until 1997 and an immunohistochemical method thereafter. Cases with ≥0.1 fmol/μg cytosol DNA were considered hormone receptor positive when using the Abbott immunoassay. By the immunohistochemical method, cases were considered as receptor positive when the percentage of positive cells was ≥10% and receptor-negative when the percentage of positive cells was <10%. The Department of Pathology and Cytology at Uppsala University Hospital and Västerås Central Hospital were involved in this evaluation. Information on dates of death for deceased participants was obtained from the Swedish Death Registry.

Statistical Analysis. Person-time of follow-up was calculated from the date of enrollment until the date of breast cancer diagnosis, death from any cause, or December 31, 2007, whichever occurred first. In analyses of ER/PR status, for women in Västmanland County, person-time of follow-up was counted from January 1998 because routine evaluation of ER and PR status was implemented in Västmanland County first in 1997. For analyses using data from the second questionnaire, the follow-up of all women began in January 1998. Folate intake was adjusted for total energy using the residual method (22) and categorized into quintiles.

To account for changes in diet during follow-up and to better represent long-term dietary intake, we used a cumulative average approach (23). Specifically, breast cancer incidence from baseline to 1997 was related to estimated folate intake at baseline, and breast cancer incidence from 1998 to December 2007 was related to the average folate intake at baseline and in 1997; for women who did not complete the second questionnaire, data from the baseline questionnaire were used for the whole follow-up. We also related folate intake in 1997 to breast cancer incidence from 1998 to December 2007.

Cox proportional hazards models (24) were used to estimate rate ratios (RR) and 95% confidence intervals (95% CI) for the association between folate intake and breast cancer risk. To control as finely as possible for age and calendar time, and possible two-way interactions between these two timescales, we stratified the models by age in months at start of follow-up and year of enrollment. In multivariate models, we further adjusted for education (primary school, high school, university) and potential risk factors for breast cancer, including body mass index (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), height (in cm), parity (nulliparous, 1-2, ≥3), age at first birth (nulliparous, <26, 26-30, ≥31 years), age at menarche (≤12, 13, ≥14 years), age at menopause (<51, ≥51 years), use of oral contraceptives (ever/never), use of postmenopausal hormones (ever/never), family history of breast cancer (yes/no), and intakes of alcohol (nondrinkers, <3.4, 3.4-9.9, ≥10.0 g/d) and total energy (kcal/d). We tested the proportional hazards assumption using the likelihood ratio test and found no departure from the assumption.

[3] A. Wolk, unpublished data.

Because alcohol intake may modify the relation between folate intake and breast cancer (5), we conducted analyses stratified by alcohol intake (nondrinkers, 0.1-9.9, ≥10.0 g/d). We also performed analyses by menopausal status. To test for trend, we assigned the median value to each quintile of folate intake and treated this value as a continuous variable in the model. All statistical analyses were conducted using SAS version 9.1 (SAS Institute). All P values were two-sided.

Results

In this cohort of Swedish women, the mean ± SD daily intake of dietary folate at baseline was 234 ± 50 μg, ranging from 177 ± 18 μg in the lowest quintile to 315 ± 49 μg in the highest quintile. Baseline distributions of risk factors for breast cancer by quintiles of dietary folate intake are presented in Table 1. Compared with women with a low folate intake, those with higher intakes were slightly older and more likely to have a postsecondary education and to have used oral contraceptives and postmenopausal hormones. Other characteristics did not vary appreciably across quintiles of folate intake.

Among 61,433 women followed-up for 1,071,164 person-years (mean, 17.4 years), a total of 2,952 incident cases of invasive breast cancer were diagnosed. Information on ER and PR status was available for 2,062 cases (information about ER/PR status was available for women in Västmanland County first in 1997). Among them, 1,286 (62.4%) cases were ER+/PR+, 417 (20.2%) were ER+/PR-, 266 (12.9%) were ER-/PR-, and 93 (4.5%) ER−/PR+.

The association between long-term dietary folate intake (assessed at baseline and in 1997) and incidence of breast cancer are shown in Table 2. We observed no association between folate intake and risk of total breast cancer or ER+/PR+ or ER-/PR- tumors. However, there was an inverse association between folate intake and risk of ER+/PR- breast cancer (P_{trend} = 0.01). The association between folate intake and breast cancer was not modified by alcohol intake (Table 3). In analyses stratified by menopausal status, the multivariate RRs of total breast cancer for an increment of 100 μg/d folate intake were 1.04 (95% CI, 0.93-1.17) among premenopausal women (n = 1,244 cases) and 0.97 (95% CI, 0.88-1.07) among postmenopausal women (n = 1,584 cases). The corresponding RRs for ER+/PR- breast tumors were 0.87 (95% CI, 0.65-1.16) for premenopausal women (n = 209 cases) and 0.71 (95% CI, 0.53-0.95) for postmenopausal women (n = 185 cases). Excluding all cases diagnosed during the first 3 years of follow-up did not change the results materially.

We used information from the second questionnaire to examine the relation between total folate intake (from foods and supplements combined) and breast cancer risk (information on supplement use was not available at baseline). In 1997, 24.5% of participants reported use of multivitamins and 1.0% used folic acid supplements. During 346,162 person-years of follow-up, from January 1998 to December 2007, we ascertained 1,008 incident invasive breast cancer cases. The multivariate RR comparing the highest quintile of total folate intake (mean intake, 552 μg/d) with the lowest quintile (mean intake, 192 μg/d) was 1.06 (95% CI, 0.87-1.28) for total breast cancer and 0.78 (95% CI, 0.53-1.15) for ER+/PR− tumors. Total folate intake was not associated with risk of ER+/PR+ or ER−/PR− tumors.

Discussion

In this large population-based prospective cohort of Swedish women, we found no association between folate intake and total breast cancer risk. However, there was an inverse association between folate intake and risk of developing ER+/PR- breast cancer. The results did not vary appreciably by alcohol intake or menopausal status.

Our findings are consistent with recent meta-analyses of prospective studies in which no overall association between folate intake or blood folate levels and risk of breast cancer was observed (5, 6). Since those meta-analyses, three additional prospective studies on folate and breast cancer risk have been published (15, 17, 25). Among those, a statistically significant inverse association between dietary and total folate intake and breast

Table 1. Age-standardized baseline characteristics of 61,433 women in the Swedish Mammography Cohort by quintiles of energy-adjusted dietary folate intake in 1987-1990

Characteristics	Quintile of folate intake (μg/d)				
	<200 (177)*	200-223 (212)	224-246 (235)	247-276 (260)	≥277 (315)
Age (y)	53.3	53.3	53.5	54.0	54.8
Postsecondary education (%)	9.0	11.3	13.4	15.0	16.4
Body mass index (kg/m^2)	24.7	24.7	24.7	24.7	25.0
Age at menarche (y)	13.3	13.3	13.2	13.2	13.2
Age at menopause (y)	50.4	50.6	50.8	50.8	50.9
Age at first birth (y)†	23.6	24.0	24.2	24.4	24.3
No. children†	2.4	2.4	2.4	2.4	2.4
Oral contraceptive use (%)	52.8	53.5	54.2	54.6	55.2
Postmenopausal hormone use (%)	40.5	43.5	45.0	46.4	47.2
Family history of breast cancer (%)	6.6	7.4	7.4	7.1	7.6
Total energy intake (kcal/d)	1,552	1,624	1,615	1,593	1,521
Alcohol intake (g/d)	2.6	2.6	2.6	2.5	2.3

NOTE: All values are means if not otherwise indicated.
*Mean values in parentheses.
†Among parous women only.

Table 2. RR (95% CI) of breast cancer by quintiles of long-term dietary folate intake among 61,433 women in the Swedish Mammography Cohort, 1987-2007

	Quintile of folate intake (μg/d)					P_{trend}*	100 μg/d increment in folate intake
	<200	200-223	224-246	247-276	≥277		
All invasive tumors							
Cases	577	560	596	577	642		
Person-years	211,726	213,590	215,023	214,797	216,029		
Age-adjusted RR (95% CI)	1.00	0.95 (0.84-1.07)	1.00 (0.89-1.12)	0.94 (0.84-1.06)	1.02 (0.91-1.14)	0.94	0.99 (0.92-1.06)
Multivariate RR (95% CI) †	1.00	0.94 (0.84-1.06)	0.99 (0.88-1.11)	0.93 (0.83-1.05)	1.01 (0.90-1.13)	0.84	0.99 (0.92-1.06)
ER+/PR+ tumors							
Cases	241	212	243	272	318		
Age-adjusted RR (95% CI)	1.00	0.85 (0.70-1.02)	0.92 (0.77-1.10)	0.97 (0.81-1.16)	1.04 (0.88-1.23)	0.29	1.06 (0.95-1.17)
Multivariate RR (95% CI) †	1.00	0.85 (0.71-1.03)	0.92 (0.77-1.10)	0.97 (0.81-1.16)	1.03 (0.87-1.23)	0.35	1.05 (0.94-1.17)
ER+/PR- tumors							
Cases	82	80	88	64	103		
Age-adjusted RR (95% CI)	1.00	0.89 (0.65-1.21)	0.93 (0.68-1.25)	0.61 (0.44-0.85)	0.87 (0.65-1.17)	0.05	0.83 (0.68-0.99)
Multivariate RR (95% CI) †	1.00	0.85 (0.62-1.16)	0.86 (0.64-1.18)	0.56 (0.40-0.78)	0.79 (0.59-1.07)	0.01	0.78 (0.64-0.95)
ER-/PR- tumors							
Cases	53	60	46	46	61		
Age-adjusted RR (95% CI)	1.00	1.09 (0.75-1.58)	0.80 (0.54-1.19)	0.75 (0.51-1.12)	0.90 (0.62-1.30)	0.19	0.92 (0.73-1.17)
Multivariate RR (95% CI) †	1.00	1.07 (0.74-1.56)	0.80 (0.53-1.20)	0.76 (0.51-1.14)	0.92 (0.63-1.35)	0.27	0.95 (0.74-1.21)

*The test for trend was calculated by using median intake of folate in each quintile as a continuous variable.
† Adjusted for 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, and intakes of alcohol and total energy.

cancer risk was found in a cohort of 11,699 postmenopausal Swedish women (including 392 cases) followed up for 9.5 years (25). No association between dietary or total folate intake and risk of breast cancer was observed in the Nurses' Health Study II cohort of 90,663 premenopausal women (including 1,032 cases; ref. 17) or in a nested case-control study (848 cases and 848 controls; ages ≥45 years) within the Women's Health Study (15). However, in the Women's Health Study, plasma folate concentrations were significantly positively associated with the risk of premenopausal breast cancer (15). The inconsistent findings may be due to different validity of the dietary measurement. The validity of estimated folate intake was quite high in the Swedish Malmö Diet and Cancer cohort in which an inverse relation between folate intake and breast cancer risk was observed (25).

Two previous prospective studies observed an inverse association between folate intake and breast cancer risk specifically among women with moderate to high alcohol consumption (>14 g/d; refs. 7, 8). Other prospective studies have suggested that adequate folate intakes may attenuate the excess risk of breast cancer associated with high alcohol consumption (9-12). In the present study, the association between folate intake and breast cancer risk did not vary by alcohol consumption. However, because alcohol consumption in our Swedish population was low (alcohol intake in the highest category was ≥10 g/d; median intake in that category was 12.4 g/d), we were not able to evaluate the association among women with higher alcohol consumption.

Folate plays an important role in DNA methylation (1). Hence, low folate status may alter DNA methylation and thereby influence gene expression and DNA integrity and stability (1). Zhu et al. (13) hypothesized that methyl-deficient diets (low in folate and methionine) may be associated primarily with breast cancer with methylated ER gene CpG island. ER CpG island methylation has been related to lack of ER gene expression in ER- breast tumors (26, 27). Findings from our study do not support the

Table 3. RR (95% CI) of total breast cancer by quintiles of long-term dietary folate and alcohol intake among 61,433 women in the Swedish Mammography Cohort, 1987-2007

Alcohol intake	Quintile of folate intake (μg/d)					P_{trend}*	100 μg/d increment in folate intake
	<200	200-223	224-246	247-276	≥277		
Nondrinkers							
Cases	204	146	156	115	144		
Multivariate RR (95% CI) †	1.00	0.88 (0.71-1.10)	1.07 (0.86-1.34)	0.82 (0.64-1.04)	1.01 (0.81-1.27)	0.93	1.06 (0.93-1.21)
0.1-9.9 g/d							
Cases	337	379	402	431	460		
Multivariate RR (95% CI) †	1.00	0.97 (0.84-1.13)	0.98 (0.84-1.13)	0.97 (0.83-1.12)	0.99 (0.86-1.15)	0.78	0.97 (0.89-1.06)
≥10.0 g/d							
Cases	36	35	38	31	38		
Multivariate RR (95% CI) †	1.00	0.73 (0.42-1.28)	1.07 (0.62-1.86)	1.02 (0.57-1.82)	1.18 (0.67-2.07)	0.64	1.23 (0.85-1.79)

*The test for trend was calculated by using median intake of folate in each quintile as a continuous variable.
†Adjusted for 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, and total energy intake.

hypothesis that folate intake is associated with risk of ER- breast cancer. Instead, we observed an inverse association between folate intake and risk of ER+/PR− tumors. This finding was unexpected and may be due to chance.

Four previous prospective studies have examined whether the association between folate and breast cancer varies according to ER and PR status of the breast tumor, and the results are inconclusive. In the Nurses' Health Study, folate intake was inversely associated with the risk of developing ER- but not ER+ tumors (14). In the Iowa Women's Health Study (16), there was no overall relation between folate intake and ER- or ER+ tumors; however, an increased risk of ER- tumors was observed among women who had a low total folate intake and a high alcohol intake. In contrast, in the Women's Health Study, plasma folate concentrations were positively associated with risk of developing ER+ or PR+ breast tumors (15). No association between folate intake and ER- breast cancer was found in the Nurses' Health Study II (17).

This study has several strengths, including the prospective and population-based design, a large sample size, detailed information on diet, and information on hormone receptor status. The prospective design precluded recall bias and the almost complete follow-up of the study population through linkage with computerized population-based registers of cancer and deaths minimizes the concern that our results have been affected by differential loss to follow-up. Another strength is that exposure data were collected from participants at two time points. Repeated assessments of diet were used in our main analyses, which provide a better measure of long-term intake than a single measurement of diet at baseline.

Our study is limited by the fact that dietary intake was assessed with a self-administered FFQ, which will inevitably lead to some error in the measurement of folate intake. Because of the prospective design, any misclassification due to measurement error is likely to be nondifferential and would tend to attenuate the associations. We cannot exclude that the lack of association between folate intake and total breast cancer risk was due to misclassification. However, we have observed previously inverse relations between dietary folate intake and risk of ovarian (28), pancreatic (29), and colorectal (30) cancers in this study cohort, suggesting that our assessment of dietary folate is sufficiently accurate to detect true relationships. Furthermore, by updating and averaging the repeated measurements of diet, we reduced within-person fluctuations and took into account changes over time, which should improve validity. Another limitation is the relatively low folate intake in this study population. Thus, we may have overlooked an association between folate intake and total breast cancer if only relatively high folate intakes are associated with risk of breast cancer. Finally, although we adjusted for major known risk factors for breast cancer, we cannot exclude the possibility of residual confounding from these variables or from other uncontrolled dietary or nondietary factors. Nevertheless, the similar results in the age-adjusted and multivariate-adjusted models argue against residual confounding.

In conclusion, results from this prospective cohort study of Swedish women do not support an association between folate intake and total breast cancer risk but suggest that folate intake may be inversely associated with ER+/PR- tumors. Further studies are needed to elucidate the possible association between folate and hormone receptor-defined breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Kim YI. Folate and DNA methylation: a mechanistic link between folate deficiency and colorectal cancer? Cancer Epidemiol Biomarkers Prev 2004;13:511–9.
2. Choi SW, Mason JB. Folate and carcinogenesis: an integrated scheme. J Nutr 2000;130:129–32.
3. Sanjoaquin MA, Allen N, Couto E, Roddam AW, Key TJ. Folate intake and colorectal cancer risk: a meta-analytical approach. Int J Cancer 2005;113:825–8.
4. Larsson SC, Giovannucci E, Wolk A. Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis. Gastroenterology 2006;131:1271–83.
5. Larsson SC, Giovannucci E, Wolk A. Folate and risk of breast cancer: a meta-analysis. J Natl Cancer Inst 2007;99:64–76.
6. Lewis SJ, Harbord RM, Harris R, Smith GD. Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. J Natl Cancer Inst 2006;98:1607–22.
7. Rohan TE, Jain MG, Howe GR, Miller AB. Dietary folate consumption and breast cancer risk. J Natl Cancer Inst 2000;92:266–9.
8. Zhang S, Hunter DJ, Hankinson SE, et al. A prospective study of folate intake and the risk of breast cancer. JAMA 1999;281:1632–7.
9. Sellers TA, Kushi LH, Cerhan JR, et al. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. Epidemiology 2001;12:420–8.
10. Baglietto L, English DR, Gertig DM, Hopper JL, Giles GG. Does dietary folate intake modify effect of alcohol consumption on breast cancer risk? Prospective cohort study. BMJ 2005;331:807.
11. Tjønneland A, Christensen J, Olsen A, et al. Folate intake, alcohol and risk of breast cancer among postmenopausal women in Denmark. Eur J Clin Nutr 2006;60:280–6.
12. Stolzenberg-Solomon RZ, Chang SC, Leitzmann MF, et al. Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr 2006;83:895–904.
13. Zhu K, Davidson NE, Hunter S, et al. Methyl-group dietary intake and risk of breast cancer among African-American women: a case-control study by methylation status of the estrogen receptor alpha genes. Cancer Causes Control 2003;14:827–36.
14. Zhang SM, Hankinson SE, Hunter DJ, Giovannucci EL, Colditz GA, Willett WC. Folate intake and risk of breast cancer characterized by hormone receptor status. Cancer Epidemiol Biomarkers Prev 2005;14:2004–8.
15. Lin J, Lee IM, Cook NR, et al. Plasma folate, vitamin B-6, vitamin B-12, and risk of breast cancer in women. Am J Clin Nutr 2008;87:734–43.
16. Sellers TA, Vierkant RA, Cerhan JR, et al. Interaction of dietary folate intake, alcohol, and risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002;11:1104–7.
17. Cho E, Holmes M, Hankinson SE, Willett WC. Nutrients involved in one-carbon metabolism and risk of breast cancer among premenopausal women. Cancer Epidemiol Biomarkers Prev 2007;16:2787–90.
18. Food standards. Amendment of standards of identity for enriched grain products to require addition of folic acid. Fed Regist 1996;61:8781–97.
19. Bergström L, Kylberg E, Hagman U, Erikson H, Bruce Å. The food

composition database KOST: the National Food Administration's Information System for nutritive values of food. Vår Fö da 1991;43:439–47.
20. Messerer M, Johansson SE, Wolk A. The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men. J Nutr 2004;134:1800–5.
21. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984;23:305–13.
22. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
23. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–40.
24. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall; 1984.
25. Ericson U, Sonestedt E, Gullberg B, Olsson H, Wirfalt E. High folate intake is associated with lower breast cancer incidence in postmenopausal women in the Malmo Diet and Cancer cohort. Am J Clin Nutr 2007;86:434–43.
26. Lapidus RG, Nass SJ, Butash KA, et al. Mapping of ER gene CpG island methylation-specific polymerase chain reaction. Cancer Res 1998;58:2515–9.
27. Ferguson AT, Lapidus RG, Baylin SB, Davidson NE. Demethylation of the estrogen receptor gene in estrogen receptor-negative breast cancer cells can reactivate estrogen receptor gene expression. Cancer Res 1995;55:2279–83.
28. Larsson SC, Giovannucci E, Wolk A. Dietary folate intake and incidence of ovarian cancer: the Swedish Mammography Cohort. J Natl Cancer Inst 2004;96:396–402.
29. Larsson SC, Håkansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. J Natl Cancer Inst 2006;98:407–13.
30. Larsson SC, Giovannucci E, Wolk A. A prospective study of dietary folate intake and risk of colorectal cancer: modification by caffeine intake and cigarette smoking. Cancer Epidemiol Biomarkers Prev 2005;14:740–3.