Short Communication

Folate Intake and Stomach Cancer Incidence in a Prospective Cohort of Swedish Women

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Abstract

Background: **Experimental and epidemiologic evidence suggests that folate may play a role in the development of some cancers. Case-control studies and one prospective cohort study on folate intake in relation to stomach cancer risk have yielded inconsistent results.**
Methods: **We prospectively investigated the relation between folate intake and the incidence of stomach cancer among 61,433 women in the Swedish Mammography Cohort. Participants completed a food frequency questionnaire at baseline (1987-1990) and again in 1997. During follow-up through December 2004, 156 incident stomach cancer cases were diagnosed. Cox proportional hazards models were used to calculate multivariate-adjusted hazard ratios.**
Results: **There was no association between dietary folate intake (i.e., folate from food sources) and the risk of stomach cancer. The multivariate hazard ratio for the highest compared with the lowest category of updated average dietary folate intake was 1.04 (95% confidence interval, 0.61-1.86; P_{trend} = 0.91). The relation between dietary folate intake and stomach cancer did not vary significantly by intake of alcohol, methionine, or caffeine.**
Conclusion: **Results from this prospective study do not support an association between dietary folate intake and risk of stomach cancer.** (Cancer Epidemiol Biomarkers Prev 2006;15(7):1409–12)

Introduction

Dietary factors are supposed to play an important role in the etiology of stomach cancer (1). The most abundant evidence for an effect of diet on stomach cancer incidence has been related to a lower risk with greater consumption of fruits and vegetables (1, 2). Fruits and vegetables are major sources of folate, which has been inversely associated with risk of various cancers (3-12). Folate is a methyl group donor involved in both methylation and DNA synthesis pathways, and aberrations in either of these pathways may lead to cancer (13-15).

Epidemiologic studies concerning folate intake and risk of stomach cancer have yielded inconsistent results. Although some case-control studies have found a statistically significant inverse association between folate intake and stomach cancer risk (16-18), other case-control studies failed to show such an association (19-23). Only one previous prospective cohort study has reported on the association of folate intake with stomach cancer risk, and that study showed no association (24). To our knowledge, no previous study have examined whether the relation between folate and stomach cancer risk is modified by consumption of alcohol, which impairs folate metabolism (25, 26) and has been reported to modify the association between folate and risk of colon (27), breast (5, 6), and ovarian cancer (7).

In the present study, we sought to evaluate prospectively the association of folate intake, using repeated measures of diet, with risk of stomach cancer in the Swedish Mammography Cohort, a population-based prospective study with 18 years of follow-up. We also examined whether this relation was modified by intake of alcohol, methionine, or caffeine.

Materials and Methods

Study Population. The Swedish Mammography Cohort was established between 1987 and 1990, when all 90,303 women who were born between 1914 and 1948 and residing in two counties (Västmanland and Uppsala counties) in central Sweden received a mailed questionnaire concerning diet, weight, height, and education (28); 66,651 women responded to the questionnaire (74% response rate). A follow-up questionnaire was sent to all 56,030 participants who were still alive and living in the study area in the autumn of 1997 to update dietary data and to collect information on other lifestyle factors; 39,227 women returned a completed questionnaire (70% response rate). This study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Dietary Assessment. A food frequency questionnaire with 67 and 96 food items was sent to women at baseline and in 1997, respectively, to assess usual dietary intake. Women were asked how often, on average, they had consumed each type of food during the previous year. Nutrient intakes were computed by multiplying the consumption frequency of each food by the nutrient content of age-specific portion sizes, using composition values obtained from the Swedish Food Administration Database (29). The 1997 questionnaire also asked for information on the use of multivitamins and folic acid supplements. Total folate intake was calculated by summing intake of folate from foods and supplements. All nutrients

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were adjusted for total energy intake by using the residual method (30). In a random subsample of 129 women from the study population, the correlation coefficient for correlations between dietary folate intakes recorded on the baseline food frequency questionnaire compared with four 1-week weighed diet records was 0.50.

Case Ascertainment and Follow-up. We ascertained incident stomach cancer cases (International Classification of Diseases, Ninth Revision code 151) by computerized linkage of the study cohort with the national and regional Swedish Cancer registers. The Swedish cancer registers provide close to 100% complete case coverage (31, 32). Dates of death and migration were obtained by computerized linkage to the Swedish Death and Population registers at Statistics Sweden.

Analytic Cohort. For these analyses, we excluded from the baseline cohort women who were outside the age range of 40 through 76 years (n = 165), those with missing (n = 707) or incorrect identification numbers (n = 413), and those lacking date on the questionnaire (n = 608), date of moving out of the study area (n = 79), or date of death (n = 16). After further exclusion of women with implausible values for energy intake (i.e., 3 SDs from the mean value for $\log_e$-transformed energy, n = 793) and those with a cancer diagnosis (other than nonmelanoma skin cancer) before baseline (n = 2,437), the analytic cohort for the primary analyses consisted of 61,433 women. Of the 39,227 women who completed the 1997 questionnaire, 36,664 women were cancer-free as of December 1997 and had adequately completed the 1997 food frequency questionnaire.

Statistical Analysis. Women were categorized into quartiles according to their dietary folate intake at baseline. In our primary analyses, we calculated cumulative averaged dietary folate intake using both the baseline and 1997 dietary data to better reflect long-term intake and to reduce random within-person variation (33). Specifically, dietary data from the baseline questionnaire was used to predict stomach cancers diagnosed from baseline through 1997, and the average of the baseline and 1997 intake was used to predict outcomes from 1998 through 2004. If data from the 1997 questionnaire was not available, dietary data from the baseline questionnaire was used for the entire follow-up. In a secondary analysis, we used data from the baseline questionnaire only (without updating and averaging diet). In a subanalysis including women who completed the 1997 questionnaire, total folate intake (categorized into tertiles) in 1997 was used to predict stomach cancers diagnosed from 1998 through 2004.

For each participant, follow-up time accrued from the date of enrollment (for analyses of dietary folate intake) or January 1, 1998 (for analyses of total folate intake) and ended at the date of diagnosis of stomach cancer, death, migration, or December 31, 2004, whichever came first. We used Cox proportional hazards models (34) to estimate hazard ratios with 95% confidence intervals. Age in months and year of enrollment were used as stratification variables within each Cox model. In multivariate models, we controlled for age, education, and intakes of total energy, alcohol, vitamin C, β-carotene, coffee, and tea. Variables examined but not included in the final model because they did not alter the association between folate intake and stomach cancer risk were body mass index, cigarette smoking, and consumption of fruits, vegetables, red meat, processed meat, and white meat. Tests based on the log likelihood ratio test and graphical methods showed no evidence that the proportional hazards assumption was violated for any analysis.

Tests for trend across quartiles of folate intake were conducted by modeling the median values of each quartile as a continuous variable. We did an additional analysis excluding the first 3 years of follow-up to remove early cases in whom the association between dietary folate intake and stomach cancer risk may have been biased because of changes in diet due to preclinical symptoms. We conducted analyses stratified by potential effect modifiers, including alcohol, methionine, and caffeine intake (the median intake of these dietary factors was used as a cutoff point). The likelihood ratio test was used to assess the significance of the interactions. Analyses were conducted with SAS statistical software (version 9.1; SAS Institute, Inc., Cary, NC). All Ps were two sided.

Results

Table 1 shows the baseline characteristics of the study population according to dietary folate intake at baseline. The median daily dietary folate intake at baseline and in 1997 was 230 μg (interquartile range, 203-260 μg) and 270 μg (interquartile range, 228-319 μg), respectively. Compared with women in the lowest quartile of dietary folate intake, those with higher intakes were older and more likely to have a post-secondary education but were less likely to be nondrinkers of alcohol. Higher dietary folate was associated with greater intakes of vitamin C, β-carotene, and tea, and with lower consumption of coffee and alcohol (among drinkers).

Among 61,433 women followed-up for a total of 903,586 person-years, from 1987 through 2004, we ascertained 156

Table 1. Age-standardized baseline characteristics according to quartiles of energy-adjusted dietary folate intake at baseline, the Swedish Mammography Cohort (1987-1990)

Characteristic	Dietary folate intake (μg/d)*			
	<203 (n = 15,705)	203-229 (n = 15,077)	230-259 (n = 15,206)	≥260 (n = 15,445)
Median dietary folate intake*	184	216	244	285
Mean age (y)	53.2	53.3	53.7	54.6
Mean body mass index (kg/m^2)	24.7	24.7	24.7	24.8
Post-secondary education (%)	9.2	11.5	13.7	16.4
Regular multivitamin use (%)†	13.7	18.7	20.7	25.7
Folic acid supplement use (%)†	0.8	0.7	1.0	1.5
Nondrinkers of alcohol (%)‡	37.3	31.7	30.1	31.4
Alcohol (g/wk)§	28.5	26.7	25.6	24.3
Median vitamin C intake (mg/d)*	44.5	60.9	75.9	103
Median β-carotene intake (mg/d)*	1.4	2.2	2.6	4.2
Coffee (cups/d)	2.6	2.4	2.3	2.2
Tea (cups/d)	0.3	0.5	0.7	0.9

*Energy-adjusted to 1,700 kcal/d by using the residual method (30).
†Information from the 1997 questionnaire.
‡The proportion of nondrinkers in the whole study population was 33%.
§Alcohol intake among drinkers.

Table 2. Age- and multivariate-adjusted hazard ratios and 95% confidence intervals of stomach cancer according to dietary folate intake based on baseline and updated average intakes in the Swedish Mammography Cohort (1987-2004)

	Dietary folate intake (μg/d)				P_{trend}
	<203	203-229	230-259	≥260	
Baseline intake					
Cases	42	44	29	41	
Person-years of follow-up	229,872	222,902	224,672	226,140	
Age-adjusted HR (95% CI)*	1.00 (reference)	1.14 (0.74-1.76)	0.69 (0.43-1.13)	0.88 (0.57-1.38)	0.30
Multivariate HR (95% CI)†	1.00 (reference)	1.13 (0.71-1.79)	0.74 (0.43-1.28)	1.05 (0.60-1.87)	0.87
Updated average intake‡					
Cases	36	39	31	50	
Person-years of follow-up	202,613	204,503	222,873	273,597	
Age-adjusted HR (95% CI)*	1.00 (reference)	1.09 (0.69-1.73)	0.78 (0.48-1.27)	0.94 (0.60-1.46)	0.57
Multivariate HR (95% CI)†	1.00 (reference)	1.14 (0.71-1.83)	0.75 (0.44-1.30)	1.04 (0.61-1.86)	0.91

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

*Hazard ratios from Cox proportional hazards models that were stratified by age in months and year of enrollment.

†Multivariate hazard ratios from Cox proportional hazards models that were stratified by age in months and year of enrollment and adjusted for education (less than high school, high school graduate, or more than high school) and intakes of total energy (continuous), alcohol (0, 0.1-14.9, 15.0-29.9, or ≥30 g/wk), vitamin C (quartiles), β-carotene (quartiles), coffee (≤1, 2-3, or ≥4 cups/d), and tea (never/seldom, <1 cup/d, or ≥1 cup/d).

‡Stomach cancer incidence from 1987 through 1997 was related to folate intake at baseline, and the incidence from 1998 through 2004 was related to the average folate intake at baseline and in 1997.

incident cases of stomach cancer (76 cases were diagnosed from baseline through 1997, and 80 cases were diagnosed from 1998 through 2004). There was no association between baseline or updated average dietary folate intake and the risk of stomach cancer in age-adjusted or multivariate analyses (Table 2). In a multivariate analysis of updated average dietary folate intake, the hazard ratio comparing the highest with the lowest quartile of intake was 1.04 (95% confidence interval, 0.61-1.86). Excluding the first 3 years of follow-up did not change the results materially (multivariate hazard ratio, 1.01; 95% confidence interval, 0.55-1.91). The association between dietary folate intake and stomach cancer was not significantly modified by intake of alcohol ($P_{interaction}$ = 0.17), methionine ($P_{interaction}$ = 0.83), or caffeine ($P_{interaction}$ = 0.98).

In a subanalysis using data from the 1997 questionnaire, we found no significant association between total folate intake (i.e., folate from foods and dietary supplements) and stomach cancer risk. The multivariate hazard ratios (adjusted for the same variables as in Table 2) for the highest versus the lowest tertile of total folate intake was 0.88 (95% confidence interval, 0.40-1.93).

Discussion

In this population-based prospective cohort of Swedish women with 18 years of follow-up and repeated measures of diet, we observed no association between dietary folate intake and risk of stomach cancer. This relation was not modified by intake of alcohol, methionine, or caffeine.

Results from previous epidemiologic studies concerning the relation between folate intake and risk of stomach cancer have been inconsistent. Our overall null findings are consistent with results from the only other prospective cohort study of folate intake and risk of stomach cancer (24). In the Netherlands Cohort Study with 6.3 years of follow-up, the multivariate relative risk for the top versus the bottom quintile of baseline folate intake was 1.0 (24). Five case-control studies also observed no significant association between folate intake and stomach cancer risk (19-23). However, three other case-control studies carried out in the United States (17, 18) and Spain (16) reported a statistically significant 30% to 50% reduction in stomach cancer risk for the highest versus the lowest category of folate intake. A high folate intake was associated with a nonsignificant lower risk of stomach cancer in an Italian case-control study of subjects with a family history of gastric cancer (35).

The major strengths of our study include its population-based and prospective design, the availability of dietary exposure information collected from participants at two time points, and the virtually complete follow-up of the cohort through linkage with computerized population-based registers of cancer and deaths. The prospective collection of information eliminates the possibility of biased recall of diet, and the practically complete cohort follow-up minimizes the likelihood of bias caused by differential loss-to-follow-up. Repeated assessments of diet were used in our primary analyses, which provide a better measure of long-term intake than does our baseline diet although associations with stomach cancer risk were not different for baseline and updated diet. Limitations of this study include an inability to examine the association between folate intake and stomach cancer risk by anatomic or histologic subtype, or by *Helicobacter pylori* infection status. Because diet was assessed with a self-administered food frequency questionnaire, and because information on dietary supplement use was not collected at baseline, some degree of misclassification of folate intake was inevitable, which would tend to attenuate any true association of folate intake with risk of stomach cancer. Although we found no significant relationship between total folate intake and risk of stomach cancer in a subanalysis using data from the 1997 questionnaire (which inquired about supplement use), we cannot rule out that we missed a weak association due to lack of statistical power.

In summary, the findings from this population-based prospective cohort of women do not support an association between folate intake and risk of stomach cancer. Future studies should examine whether this relation varies by anatomic subsite, histologic subtype, and possibly by *H. pylori* infection status.

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