Folate intake, post–folic acid grain fortification, and pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[1–3]

Brietta M Oaks, Kevin W Dodd, Cari L Meinhold, Li Jiao, Timothy R Church, and Rachael Z Stolzenberg-Solomon

ABSTRACT

Background: Folate plays a critical role in DNA methylation, synthesis, and repair. Several epidemiologic studies suggest that higher folate intake is associated with decreased pancreatic cancer risk.

Objective: We investigated the association between dietary folate intake and pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort.

Design: Dietary data were collected with the use of a self-administered food-frequency questionnaire (1998–2005). Among the 51,988 male and 57,187 female participants, aged 55–74 y at enrollment, with complete dietary and multivitamin information, 162 men and 104 women developed pancreatic cancer during follow-up (January 1998 to December 2006; median: 6.5 y). We used Cox proportional hazards regression with age as the time metric to calculate hazard ratios (HRs) and 95% CIs.

Results: The highest compared with the lowest quartile of food folate was associated with a significantly decreased pancreatic cancer risk among women ($\geq$253.3 compared with $\leq$179.1 μg/d; HR = 0.47; 95% CI: 0.23, 0.94; *P* for trend: 0.09) but not among men ($\geq$229.6 compared with $\leq$158.0 μg/d; HR = 1.20; 95% CI: 0.70, 2.04; *P* for trend: 0.67; *P* for interaction by sex: 0.03). There was also a significant inverse trend in risk of pancreatic cancer across increasing quartiles of total folate in women (*P* for trend: 0.04) but not in men (*P* for trend: 0.65). Folic acid supplements were not associated with pancreatic cancer.

Conclusion: These findings support an association between higher food and total folate intakes and decreased risk of pancreatic cancer in women but not in men. *Am J Clin Nutr* 2010;91:449–55.

INTRODUCTION

In 2008, ≈37,680 individuals were diagnosed with pancreatic cancer and 34,290 died as a result, which makes it the fourth-leading cause of cancer-related deaths in the United States (1, 2). With only 5% of cases who survive 5 y after diagnosis (1), dietary studies of pancreatic cancer etiology are particularly challenging because of potential reverse causation and other biases in retrospective case-control analyses for this rapidly fatal gastrointestinal cancer. The most consistently observed risk factors for pancreatic cancer are smoking, obesity, and family history of pancreatic cancer (3).

Folate is a water-soluble B vitamin that plays a critical role in DNA synthesis, methylation, and repair (4). Imbalance in these 3 functions may contribute to carcinogenesis. Folic acid is the synthetic form of folate and has increased bioavailability compared with natural folate. In prospective analyses (5–7), low intake of folate found naturally in food has been associated with a statistically significant increased risk of pancreatic cancer. However, high concentrations of folic acid from supplements and multivitamins have been associated with a nonsignificant increased risk of pancreatic cancer in 2 prospective studies (5, 8), whereas a third prospective study found no association with folic acid (6). Two nested, case-control studies used blood samples to look at serum concentrations of folate. The first study, in male smokers with marginal folate status, found a statistically significant decreased pancreatic cancer risk among men with higher, compared with lower, serum folate status (5). The other study found no association overall; however, nonsignificant inverse associations were observed in subgroup analyses restricted to nonusers of multivitamins (9).

Since the United States started mandatory folic acid grain fortification in 1998, some within the nutrition community have expressed concern that high folic acid intake, either from grain fortification or supplements, may unintentionally increase cancer risk among individuals in the United States (10, 11). These concerns are based on animal studies and clinical trial results (12, 13). The aim of the present study is to examine whether dietary folate is associated with decreased pancreatic cancer risk and whether folic acid from supplements or grain fortification increases pancreatic cancer risk.

[1] From the Nutritional Epidemiology Branch, the Division of Cancer Epidemiology and Genetics (BMO, CLM, LJ, and RZS-S) and the Biometry Research Group, the Division of Cancer Prevention (KWD), National Cancer Institute, National Institutes of Health, Rockville, MD; the University of Minnesota, Minneapolis, MN (TRC); and George Washington University, Washington, DC (BMO).

[2] Supported by the Intramural Research Program of the National Institutes of Health, the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by a Cancer Research Training Award from the National Cancer Institute (BMO).

[3] Address correspondence to BM Oaks or RZ Stolzenberg-Solomon, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Room 3022, Rockville, MD. E-mail: boaks@ucdavis.edu, rs221z@nih.gov.

Received July 23, 2009. Accepted for publication November 18, 2009.

First published online December 9, 2009; doi: 10.3945/ajcn.2009.28433.

SUBJECTS AND METHODS

Study design and population

Participants for this study were from the control and intervention arms of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) conducted by the National Cancer Institute. Details of the study have been described elsewhere (14). Briefly, the trial recruited 78,234 women and 76,704 men, aged 55–74 y, from 10 centers between November 1993 and July 2001. Exclusion criteria included a personal history of prostate, lung, colorectal, or ovarian cancer; a recent history of screening procedures for one of the PLCO cancers; or current treatment of any cancer (except nonmelanoma skin cancer). Eligible subjects randomly assigned to the intervention arm had regular screenings for the 4 PLCO cancers, which included chest X-ray, flexible sigmoidoscopy, prostate-specific antigen screening, digital rectal examination, cancer antigen 125 screening, and transvaginal ultrasound. Eligible subjects randomly assigned to the control arm were instructed to follow their usual medical practice. Of those enrolled in the PLCO, only those with complete dietary and multivitamin information, nonextreme energy intake, and nonextreme body mass index (BMI; in kg/m^2; outliers for BMI and energy intake were defined as above the sum of the 75th percentile and 2 times the interquartile range or below the 25th percentile minus 2 times the interquartile range after transformation to a normal distribution of the BMI) were included in this analysis. After these exclusions, 51,988 men and 57,187 women remained for this current analysis.

Each eligible participant provided written informed consent. The study was approved by the institutional review boards of the National Cancer Institute and each of the centers that participated.

Pancreatic cancer case ascertainment

Pancreatic cancer cases were ascertained through a mailed annual questionnaire in which subjects were asked if they had been diagnosed with cancer by a health care provider. They were then asked to provide information on the type of cancer. Additional sources for identification of pancreatic cases included state registries, death certificates, physician reports, and reports from next of kin (for deceased subjects). These cases were then confirmed by abstraction from medical records. The definition of a pancreatic cancer case was limited to primary pancreatic adenocarcinomas (*International Classification of Diseases for Oncology, Third Edition*, code C250-C259) and excluded endocrine pancreatic tumors (histology type 8150, 8151, 8153, 8155, 8240, 8246, 8502, and 8520). This analysis included 162 men and 104 women (n = 266) with confirmed incident pancreatic cancer ascertained between January 1998 and December 2006.

Assessment of diet, vitamin supplement use, and other baseline characteristics

Baseline characteristics, which included demographic factors, medical history, and health-related behaviors, were collected from all study subjects at the time of randomization, through a self-administered baseline questionnaire. Dietary data were collected with the use of a self-administered food-frequency questionnaire (FFQ), the Diet History Questionnaire, version 1.0 (National Cancer Institute, 2007), which was distributed to the intervention and control arms of the trial between 1998 and 2005 (15). The diet history questionnaire queried frequency and portion size of 124 food items and supplement use during the past year (16). We examined both pre- and postfortification folate intake and pancreatic cancer. Folate intake was analyzed in accordance with the following 5 sources: *1*) natural folate (polyglutamates found naturally in food), *2*) fortified folic acid (folic acid added to food), *3*) food folate (a combination of natural folate and fortified folic acid), *4*) supplemental folic acid (folic acid from vitamin supplements), and *5*) total folate intake (a combination of food folate and supplemental folic acid). Food folate content was assigned based on pre–folic acid fortification (1998) database information from the1994–1996 Continuing Survey of Food Intake by Individuals (17). Post–folic acid grain fortification database information from the Nutrition Data System for Research was used to assess folic acid from fortified food. The Nutrition Data System for Research combines nutrition information from the US Department of Agriculture Nutrient Database for Standard Reference, food manufacturers, scientific literature, and other published food tables (18). Supplemental folic acid use and dose were derived from recent use (current or 2 y ago) of 4 multivitamins: One-a-Day (100% of the Recommended Dietary Allowance; Bayer Corp, Pittsburgh, PA), a therapeutic or high-dose type (>100% of the Recommended Dietary Allowance; eg, Theragran; Bristol-Myers Squibb, New York, NY), Stresstabs (B-complex + vitamin C; Inverness Medical Inc, Waltham, MA), and B-complex. The B-complex multivitamin was assigned a 200-μg folic acid dose, whereas the other multivitamins were assigned a 400-μg folic acid dose.

Statistical analysis methods

Follow-up time was calculated in person-years from the date of dietary questionnaire completion to the date of diagnosis of pancreatic cancer, death from any cause, or the end date of study follow-up, whichever occurred first. For this analysis, follow-up time was from January 1998 to December 2006 (median: 6.5 y), which provides 667,734 person-years of observation.

To test for trend associations of continuous and categorical baseline characteristics of the cohort across sex-specific total folate quartiles, we used generalized linear models and the Cochran-Armitage test. Spearman's ρ was used to estimate correlations between study variables (results not presented). Because of a high correlation between dietary variables and total energy intake, folate and other nutrients were energy adjusted with the use of the nutrient density method [nutrient intake per 1000 calories (19)]. Multivariable Cox proportional hazards regression with age as the underlying time metric was used to calculate hazard ratios (HRs) and 95% CIs. Variables were analyzed as both categorical and continuous. Folate was included in models as both categorical and continuous. For categorical analysis, folate was divided into quartiles based on the sex-specific distribution in the cohort. A score variable based on the median values of each category was calculated for trend tests. For continuous analysis, the folate variable was divided by the difference between the 90th and 10th percentile of the distribution of the folate variable.

Variables were considered confounders if they were associated with both pancreatic cancer and folate (in any form) and changed the unadjusted risk estimate by ≥10%. Variables examined as potential confounders included age, race, education (<8 y, 8–11 y, completed high school, post–high school training other than college, some college, college graduate, postgraduate, or data missing), sex, family history of pancreatic cancer (no, yes, or data missing), self-reported history of diabetes (no, yes, or data missing), BMI (<18.5, 18.5–24.9, 25–29.9, ≥30, or data missing), height, energy intake, energy-adjusted saturated fat, vitamins B-6 and B-12, fruit and vegetable intake, alcohol consumption, physical activity, and smoking history (never, quit ≥15 y ago, quit ≥2 y ago and <15 y ago, current or quit <2 y ago and smokes <20 cigarettes/d, current or quit <2 y ago and smokes >20 cigarettes/d, or data missing). Interactions by alcohol consumption, vitamins B-6 and B-12, sex, BMI, and smoking habits (never, former, or current) were tested with the use of cross-product terms in the multivariable continuous models and were considered significant with a P value ≤0.05. All statistical analyses were performed with the use of SAS software, version 9.1 (SAS Institute Inc, Cary, NC), and all P values were based on 2-sided tests.

RESULTS

Baseline characteristics of this cohort categorized by energy-adjusted total dietary folate intake before fortification are shown in **Table 1**. Overall, men and women with higher concentrations of folate were older, more educated, and more likely to report recent multivitamin use; tended to consume more fruit, vegetables, and vitamins B-6 and B-12; had a lower BMI; were less likely to be African American or to report being a current smoker; and tended to consume less energy, saturated fat, and alcohol than those with lower concentrations of folate. Men in the highest compared with lowest total folate quartile were more likely to report being diabetic, whereas women in the highest compared with lowest quartile were less likely to report being diabetic.

HRs and 95% CIs for pancreatic cancer for natural folate, fortified folic acid, food folate, supplemental folic acid, total folate, and multivitamin use are presented in **Table 2**. A significant interaction was found between total folate intake and sex (P = 0.03), so data are presented stratified by sex.

Women in the highest quartile of food folate intake showed a statistically significant 53% decreased risk of pancreatic cancer (HR = 0.47; 95% CI: 0.23, 0.94; P for trend: 0.09) compared with those in the lowest quartile. Increasing quartiles of total folate showed a significant trend of decreased pancreatic cancer risk in women (P for trend: 0.04). In continuous analyses, food folate and total folate had a nonsignificant decreased risk of pancreatic cancer (HR = 0.56, 95% CI: 0.31, 1.00; and HR = 0.65, 95% CI: 0.37, 1.14 per quartile unit, respectively). No significant association was found between supplemental folic acid use and pancreatic cancer risk (≥400 compared with 0 μg/d; HR = 0.87; 95% CI: 0.55, 1.36; P for trend: 0.58).

Among men, no significant association was found between any of the folate variables and pancreatic cancer risk. Men in the highest quartile of food folate had an HR of 1.20 (95% CI: 0.70, 2.04; P for trend: 0.67) when compared with men in the lowest quartile. Men in the highest quartile of total folate had an HR of 0.95 (95% CI: 0.59, 1.54; P for trend: 0.65) when compared with men in the lowest quartile. In continuous analyses, no significant association was observed between food folate or total folate and risk of pancreatic cancer (HR = 1.27, 95% CI: 0.81, 2.00; and HR = 1.26, 95% CI: 0.78, 2.02 per quartile unit, respectively). No significant association was found between supplemental folic acid use and pancreatic cancer risk (≥400 compared with 0 μg/d (HR = 1.15; 95% CI: 0.81, 1.64; P for trend: 0.45). No significant interactions were observed by smoking, alcohol, vitamin B-6, vitamin B-12, or BMI.

DISCUSSION

In this prospective study, we analyzed the risk of pancreatic cancer in relation to folate intake, in consideration of the mandatory folic acid fortification of grains in the United States that began in 1998. A significant decreased risk of pancreatic cancer was found among women with higher intakes of food folate when compared with women with lower intakes of food folate. No significant association was found among men. Total folate showed a significant decrease in pancreatic cancer risk with increasing intake across quartiles in women, and folic acid from grains or supplements was not associated with pancreatic cancer in either men or women.

The major strength of this study was its prospective design, in which diet and other analyzed variables were obtained before diagnosis of pancreatic cancer, which eliminated recall bias and decreased reverse causation. In addition, unlike previous prospective studies of folate and pancreatic cancer, this study consisted of men and women from the same cohort, which decreased any methodologic bias that might occur when men and women come from different cohorts. We were also able to examine the different components of total dietary folate, particularly folic acid.

Previous studies that examined the relation between pancreatic cancer and folate intake have shown mixed results. The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study cohort of 27,101 male Finnish smokers (n = 157 cases) showed a significant 50% reduction in pancreatic cancer for high compared with low folate intake from foods (5). A combined analysis of women from the Nurses' Health Study and men from the Health Professionals Follow-Up Study, did not report an association with total folate intake in men or women, although a nonsignificant 34% and 35% decrease in pancreatic cancer risk was evident when the highest food folate category was compared with the lowest category in men and women, respectively (8). Women and men from the Swedish Mammography Cohort and the Cohort of Swedish Men showed results similar to this study, with a statistically significant 75% and 67% decreased risk of pancreatic cancer (n = 135 cases) associated with increased intake of dietary and total folate, respectively (6). The Netherlands Cohort Study did not find any statistically significant associations between folate and pancreatic cancer but showed a statistically nonsignificant increased risk of pancreatic cancer with natural folate (20). However, a limitation of this study was that diabetes, a putative risk factor for pancreatic cancer, was not examined as a potential confounder. When compared with these previous prospective studies, the concentration of total folate intake in our PLCO population is in a slightly higher range, particularly among women participants (ie, Quartile 1 < 238.9 μg/d and Quartile 4 > 534.3 μg/d).

TABLE 1
Baseline characteristics of men and women from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial by energy-adjusted total dietary folate intake on the basis of values before folic acid fortification (1998–2005)[1]

	Quartiles of energy-adjusted total folate intake in women (n = 57,187)					Quartiles of energy-adjusted total folate intake in men (n = 51,988)				
	1	2	3	4	P for trend	1	2	3	4	P for trend
n	14,296	14,297	14,297	14,297	—	12,997	12,997	12,997	12,997	—
Total folate intake (μg/d)	≤238.9	239.0–399.0	399.1–534.2	≥534.3	—	≤186.9	187.0–280.6	280.7–413.5	≥413.6	—
Age[2] (y)	62.0	62.2	62.4	63.0	<0.0001	62.0	62.7	62.5	63.2	<0.0001
Race (%)										
Black	4.5	4.6	2.8	2.9	<0.0001	3.0	3.2	2.3	2.3	<0.0001
White	92.1	90.0	93.4	90.4	0.25	93.6	90.1	91.4	89.0	<0.0001
Asian	1.4	3.5	2.4	4.9	<0.0001	1.1	4.0	4.0	6.4	<0.0001
Other	1.9	2.0	1.4	1.8	0.10	2.3	2.7	2.3	2.3	0.52
Postsecondary education (%)	60.6	68.0	70.2	69.8	<0.0001	67.8	75.5	77.9	80.7	<0.0001
Folate intake[3] (μg/d)										
Natural folate[4]	132.4	160.9	159.5	186.0	<0.0001	109.6	141.5	140.3	161.6	<0.0001
Fortified folic acid[5]	61.7	75.2	73.5	87.2	<0.0001	53.8	78.8	77.2	95.5	<0.0001
Food folate[6]	181.6	223.8	220.8	262.3	<0.0001	150.1	204.7	202.7	242.0	<0.0001
Supplemental folic acid[7]	9.1	184.8	378.3	415.5	<0.0001	4.7	64.4	314.5	403.9	<0.0001
Total folate[8]	185.9	316.3	465.6	674.0	<0.0001	151.8	227.5	346.6	541.9	<0.0001
Multivitamin use, recent (%)	13.7	24.6	34.9	34.8	<0.0001	8.3	14.4	29.7	32.9	<0.0001
Height (cm)	163.4	163.4	163.5	162.8	<0.0001	178.1	178.0	178.2	177.4	<0.0001
Current BMI (kg/m^2)	27.5	27.1	26.6	26.3	<0.0001	28.0	27.6	27.4	27.0	<0.0001
Self-reported diabetes (%)	6.3	6.3	4.9	6.0	0.0003	6.8	9.6	8.1	9.6	<0.0001
Family history of pancreatic cancer (%)	2.9	3.1	3.3	2.9	0.69	2.0	2.1	2.1	2.3	0.22
Smoking status (%)										
Never	55.3	56.8	56.4	58.3	<0.0001	33.1	39.5	37.9	39.4	<0.0001
Former	32.6	34.2	36.6	35.2	<0.0001	51.2	51.3	52.8	54.4	<0.0001
Current	12.0	8.9	7.0	6.5	<0.0001	15.7	9.2	9.3	6.2	<0.0001
Daily intakes[3]										
Energy (kcal)	1610.4	1760.0	1585.6	1090.4	<0.0001	2178.9	2073.4	2166.8	1484.1	<0.0001
Alcohol (g)	6.6	5.9	5.4	3.4	<0.0001	21.0	14.4	13.2	7.7	<0.0001
Fruit (servings)	1.0	1.3	1.3	1.5	<0.0001	0.6	1.0	0.9	1.2	<0.0001
Vegetables (servings)	1.1	1.3	1.3	1.5	<0.0001	0.8	1.0	1.0	1.1	<0.0001
Saturated fat (g)	12.2	11.0	10.8	9.5	<0.0001	13.1	11.2	11.5	10.0	<0.0001
Vitamin B-6 (mg)	1.0	1.2	1.2	1.3	<0.0001	0.9	1.1	1.1	1.3	<0.0001
Vitamin B-12 (μg)	2.4	2.5	2.5	2.7	<0.0001	2.6	2.7	2.7	2.8	<0.0001

[1] All values are means. Generalized linear models and the Cochran-Armitage test were used to test for trend associations of continuous and categorical baseline characteristics.
[2] Age at randomization.
[3] All folate variables, nutrients, and foods are energy adjusted except for supplemental folic acid and alcohol.
[4] Polyglutamates found naturally in food.
[5] Folic acid added to food.
[6] Natural folate and fortified folic acid combined.
[7] Folic acid from vitamin supplements.
[8] Food folate and supplemental folic acid combined.

Previous studies that examined folate intake and pancreatic cancer were conducted in populations before or without mandatory folic acid grain fortification. Also, the different FFQs used to assess diet and folate intake could provide different estimates for folate intake across study populations.

With regard to folic acid from supplements, some past studies have found positive associations between supplemental folic acid use and pancreatic cancer risk. In the ATBC Study, a nonsignificant increased risk of pancreatic cancer with supplemental folic acid use was found [relative risk (RR) = 1.60; 95% CI: 0.92, 2.77). Likewise, Skinner et al (8) showed a nonsignificant increased risk (RR = 1.47; 95% CI: 0.98, 2.21) among former users of multivitamins and a significant increased risk (RR = 1.31; 95% CI: 1.02, 1.67) of pancreatic cancer among current users of multivitamins in pooled analyses. Larsson et al (6) compared individuals with ≥300 μg supplemental folic acid/d with those with 0 μg supplemental folic acid/d and did not find an association with pancreatic cancer risk (rate ratio = 1.02; 95% CI: 0.56, 1.88). Similar to Larsson, we did not find an association between folic acid supplements and pancreatic cancer risk.

In contrast to previous prospective studies (5, 6, 8), our study was conducted in the United States after folic acid grain fortification, with our FFQ administered in 1998 and follow-up through 2006. Given the concern from past studies that folic acid supplements might increase the risk of pancreatic cancer (5, 8), our results from the examination of fortified folic acid are of

TABLE 2

Hazard ratios (HRs) for pancreatic cancer according to quartiles of baseline folate intakes for men (n = 51,988) and women (n = 57,187) who participated in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (1998–2006)

	Quartiles						Multivitamin use	
	1	2	3	4	P for trend	Continuous HR	No	Yes
Women								
Natural folate (μg/d)[1]	≤125.6	125.7–151.1	151.2–183.2	≥183.3				
No. of cases	26	25	25	28				
HR (95% CI)[2]	1	0.69 (0.38, 1.25)	0.87 (0.50, 1.51)	0.93 (0.54, 1.60)	0.95			
HR (95% CI)[3]	1	0.62 (0.33, 1.16)	0.81 (0.45, 1.47)	0.72 (0.39, 1.35)	0.51	0.69 (0.40, 1.20)		
Fortified folic acid (μg/d)[4]	≤ 48.3	48.4–65.6	65.7–90.0	≥90.1				
No. of cases	31	22	23	28				
HR (95% CI)[2]	1	0.70 (0.40, 1.23)	0.69 (0.39, 1.21)	0.83 (0.49, 1.40)	0.63			
HR (95% CI)[3]	1	0.63 (0.35, 1.14)	0.69 (0.39, 1.23)	0.72 (0.41, 1.26)	0.39	0.72 (0.42, 1.21)		
Food folate (μg/d)[5]	≤179.1	179.2–213.1	213.2–253.2	≥253.3				
No. of cases	27	18	38	21				
HR (95% CI)[2]	1	0.66 (0.35, 1.23)	1.34 (0.80, 2.26)	0.72 (0.39, 1.31)	0.63			
HR (95% CI)[3]	1	0.58 (0.30, 1.12)	1.06 (0.60, 1.88)	0.47 (0.23, 0.94)	0.09	0.56 (0.31, 1.00)		
Supplemental folic acid (μg/d)[6]	0	<400	≥400					
No. of cases	37	12	55					
HR (95% CI)[2]	1	0.75 (0.39, 1.46)	0.92 (0.60, 1.43)		0.81			
HR (95% CI)[3]	1	0.80 (0.41, 1.56)	0.87 (0.55, 1.36)		0.58			
Total folate (μg/d)[7]	≤238.9	239.0–399.0	399.1–534.2	≥534.3				
No. of cases	29	30	24	21				
HR (95% CI)[2]	1	1.12 (0.66, 1.91)	0.79 (0.44, 1.41)	0.69 (0.38, 1.25)	0.12			
HR (95% CI)[3]	1	1.01 (0.58, 1.76)	0.75 (0.41, 1.36)	0.56 (0.30, 1.06)	0.04	0.65 (0.37, 1.14)		
Multivitamin use								
No. of cases							82	22
HR (95% CI)[2]							1	0.81 (0.49, 1.32)
HR (95% CI)[3]							1	0.82 (0.49, 1.36)
Men								
Natural folate (μg/d)[1]	≤109.7	109.8–131.1	131.2–157.6	≥157.7				
No. of cases	37	35	48	42				
HR (95% CI)[2]	1	0.79 (0.49, 1.27)	1.06 (0.68, 1.65)	0.89 (0.56, 1.41)	0.89			
HR (95% CI)[3]	1	0.83 (0.51, 1.38)	1.11 (0.69, 1.78)	0.91 (0.55, 1.53)	0.92	1.25 (0.79, 1.96)		
Fortified folic acid (μg/d)[4]	≤47.4	47.5–66.8	66.9–94.5	≥94.6				
No. of cases	38	48	25	51				
HR (95% CI)[2]	1	1.26 (0.81, 1.95)	0.66 (0.39, 1.10)	1.04 (0.67, 1.63)	0.70			
HR (95% CI)[3]	1	1.31 (0.84, 2.04)	0.65 (0.38, 1.10)	1.06 (0.66, 1.70)	0.73	0.96 (0.65, 1.41)		
Food folate (μg/d)[5]	≤ 158.0	158.1–190.0	190.1–229.5	≥ 229.6				
No. of cases	34	46	27	55				
HR (95% CI)[2]	1	1.17 (0.73, 1.85)	0.69 (0.41, 1.16)	1.16 (0.73, 1.84)	0.74			
HR (95% CI)[3]	1	1.21 (0.75, 1.96)	0.71 (0.41, 1.24)	1.20 (0.70, 2.04)	0.67	1.27 (0.81, 2.00)		
Supplemental folic acid (μg/d)[6]	0	<400	≥400					
No. of cases	67	25	70					
HR (95% CI)[2]	1	1.25 (0.78, 2.01)	1.07 (0.76, 1.52)		0.73			
HR (95% CI)[3]	1	1.33 (0.82, 2.17)	1.15 (0.81, 1.64)		0.45			

(Continued)

TABLE 2 (*Continued*)

	Quartiles						Multivitamin use	
	1	2	3	4	*P* for trend	Continuous HR	No	Yes
Total folate (μg/d)[7]	≤186.9	187.0–280.6	280.7–413.5	≥413.6				
No. of cases	43	31	38	50				
HR (95% CI)[2]	1	0.65 (0.40, 1.05)	0.85 (0.54, 1.34)	0.89 (0.57, 1.39)	0.87			
HR (95% CI)[3]	1	0.70 (0.43, 1.16)	0.91 (0.57, 1.47)	0.95 (0.59, 1.54)	0.65	1.26 (0.78, 2.02)		
Multivitamin use								
No. of cases							130	32
HR (95% CI)[2]							1	0.95 (0.63, 1.43)
HR (95% CI)[3]							1	0.94 (0.62, 1.42)
Sexes combined[8]								
Natural folate (μg/d)[1]								
HR (95% CI)[3]	1	0.68 (0.27, 1.08)	0.96 (0.58, 1.34)	0.81 (0.41, 1.21)		0.94 (0.58, 1.30)		
Fortified folic acid (μg/d)[4]								
HR (95% CI)[3]	1	0.90 (0.52, 1.27)	0.61 (0.37, 0.84)	0.87 (0.50, 1.24)		0.82 (0.49, 1.15)		
Food folate (μg/d)[5]								
HR (95% CI)[3]	1	0.83 (0.43, 1.24)	0.90 (0.51, 1.30)	0.73 (0.29, 1.17)		0.86 (0.48, 1.23)		
Supplemental folic acid (μg/d)[6]	0	<400	≥400					
HR (95% CI)[3]	1	1.02 (0.61, 1.44)	1.00 (0.71, 1.29)					
Total folate (μg/d)[7]								
HR (95% CI)[3]	1	0.84 (0.47, 1.22)	0.81 (0.43, 1.20)	0.69 (0.28, 1.09)		0.90 (0.53, 1.27)		
Multivitamin use								
HR (95% CI)[3]							1	0.86 (0.53, 1.19)

[1] Polyglutamates found naturally in food.
[2] Cox proportional hazards regression with the use of a univariate model. Adjusted for total energy and should be considered as adjusted for age because age is the time metric.
[3] Cox proportional hazards regression with the use of a multivariable model. Adjusted for total energy, smoking, self-reported diabetes, BMI, and saturated fat intake with age as the time metric.
[4] Folic acid from fortified grain.
[5] Natural folate and fortified folic acid combined.
[6] Folic acid from vitamin supplements.
[7] Food folate and supplemental folic acid combined.
[8] Multivariable analysis of men and women combined used sex-specific cutoffs for folate intakes.

particular interest. Our findings show no association between folic acid added to foods and pancreatic cancer risk. Furthermore, when folic acid from fortified foods was examined in combination with natural food folate (which created the variable food folate), we found a significantly decreased risk of pancreatic cancer in women in the highest quartile. These findings do not support the theory that folic acid grain fortification increases the risk of pancreatic cancer.

Two studies have examined serum folate levels in relation to pancreatic cancer and presented results that support the findings in our analysis. The first study was a nested, case-control study that used subjects from the ATBC Study and found a statistically significant decreased risk of pancreatic cancer with higher concentrations of serum folate, which supports the relation found between total folate intake and pancreatic cancer risk in our analysis (5). The other study, a pooled, nested, case-control study from 4 American cohorts (the Nurses' Health Study, the Health Professionals Follow-Up Study, the Physicians' Health Study, and the Women's Health Initiative) found no association between serum folate and pancreatic cancer except for a nonsignificant decreased risk of pancreatic cancer with increased serum folate in nonusers of multivitamins, which supports the relation we found between food folate intake and pancreatic cancer risk (9).

The limitations of our study should be considered when our results are interpreted. First, although we had a sizable cohort, the number of pancreatic cancer cases was relatively small because of the rarity of the disease, which limited our ability to do stratified analysis among nonusers of multivitamins. We also were not able to evaluate the measurement error of the FFQ within this cohort. Although we evaluated and controlled for putative risk factors for pancreatic cancer in our multivariable models, residual confounding may be present. Finally, with a median follow-up time of 6.5 y, it is not possible to know from this study if the relation between folate and pancreatic cancer risk would change over a longer period of time. However, a lag analysis that excluded cases that occurred during the first 5 y of the study did not yield a substantial difference in risk estimates (ie, total folate in women: Quartile 1, referent; Quartile 2, HR = 0.98; Quartile 3, HR = 0.76; and Quartile 4, HR = 0.52; and in men: Quartile 1, referent; Quartile 2, HR = 0.79; Quartile 3, HR = 0.83; and Quartile 4, HR = 1.02).

The results from the current study differ from previous studies in that we found a significant relation between folate intake and pancreatic cancer risk only in women. Other studies have found men and women to have similar trends. The reason for the sex difference in the results in our study is unclear, although women reported a higher folate intake than men, and it is possible that this contributes to the difference of risk by sex. In addition, men in the highest compared with lowest total folate quartile were more likely to report being diabetic, whereas women in the highest compared with lowest quartile were less likely to report being diabetic. It is possible that these men may have modified their diets because of their diabetes and their reported folate intake does not represent their long-term intake. This could explain the lack of association in men. Although we controlled for diabetes, residual confounding could be present.

In conclusion, our findings support a decreased risk of pancreatic cancer with greater food folate and total folate intakes in women but not in men. Folic acid grain fortification did not appear to adversely influence the risk of pancreatic cancer in our study; however, additional studies conducted in the United States during the post–folic acid grain fortification era are needed before conclusions can be reached.

The authors' responsibilities were as follows—RZS-S: study concept; BMO, RZS-S, CLM, KWD, LJ, and TC: study design and conduct; BMO, RZS-S, and KWD: data analysis, interpretation of results, and writing and revision of manuscript; BMO: manuscript revision; RZS-S: mentoring of first author; RZS-S, CLM, LJ, and TC: critical critique of the manuscript; and CLM, LJ, and TC: editing of manuscript. None of the authors had a conflict of interest.

REFERENCES

1. Homer MJ, Ries LAG, Krapcho M, et al. SEER cancer statistics review, 1975-2006. National Cancer Institute. Available from: http://seer.cancer.gov/csr/1975_2006 (cited 10 May 2009).
2. American Cancer Society. Cancer facts & figures 2008. Atlanta, GA: American Cancer Society, 2008.
3. Hart AR, Kennedy H, Harvey I. Pancreatic cancer: a review of the evidence on causation. Clin Gastroenterol Hepatol 2008;6:275–82.
4. Kim YI. Folate and cancer prevention: a new medical application of folate beyond hyperhomocysteinemia and neural tube defects. Nutr Rev 1999;57:314–21.
5. Stolzenberg-Solomon RZ, Pietinen P, Barrett MJ, Taylor PR, Virtamo J, Albanes D. Dietary and other methyl-group availability factors and pancreatic cancer risk in a cohort of male smokers. Am J Epidemiol 2001;153:680–7.
6. Larsson SC, Hakansson 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.
7. Stolzenberg-Solomon RZ, Albanes D, Nieto FJ, et al. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. J Natl Cancer Inst 1999;91:535–41.
8. Skinner HG, Michaud DS, Giovannucci EL, et al. A prospective study of folate intake and the risk of pancreatic cancer in men and women. Am J Epidemiol 2004;160:248–58.
9. Schernhammer E, Wolpin B, Rifai N, et al. Plasma folate, vitamin B6, vitamin B12, and homocysteine and pancreatic cancer risk in four large cohorts. Cancer Res 2007;67:5553–60.
10. Kim YI. Will mandatory folic acid fortification prevent or promote cancer? Am J Clin Nutr 2004;80:1123–8.
11. Mason JB, Dickstein A, Jacques PF, et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. Cancer Epidemiol Biomarkers Prev 2007;16:1325–9.
12. Song J, Medline A, Mason JB, Gallinger S, Kim YI. Effects of dietary folate on intestinal tumorigenesis in the apcMin mouse. Cancer Res 2000;60:5434–40.
13. Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas. JAMA 2007;297:2351–9.
14. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000;21(suppl):273S–309S.
15. Subar AF, Midthune D, Kulldorff M, et al. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. Am J Epidemiol 2000;152:279–86.
16. Diet history questionnaire. Risk factor monitoring and methods. National Cancer Institute. Version current 04 May 2009. Available from: http://www.riskfactor.cancer.gov/DHQ (cited 10 May 2009).
17. Subar AF, Thompson FE, Smith AF, et al. Improving food frequency questionnaires: a qualitative approach using cognitive interviewing. J Am Diet Assoc 1995;95:781–8.
18. NDSR descriptive overview. University of Minnesota Nutrition Coordinating Center. Version current 09 Mar 2009. Available from: http://www.ncc.umn.edu/products/ndsr.html (cited 10 May 2009).
19. Willet WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(suppl):1220S–8S.
20. Keszei AP, Verhage BA, Heinen MM, Goldbohm RA, van den Brandt PA. Dietary folate and folate vitamers and the risk of pancreatic cancer in the Netherlands cohort study. Cancer Epidemiol Biomarkers Prev 2009;18:1785–91.