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Impact of Folate Intake on Prostate Cancer Recurrence Following Definitive Therapy: Data from CaPSURE™

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Abstract

Purpose—A randomized, placebo controlled clinical trial of folic acid supplementation for the chemoprevention of colorectal adenoma revealed an increased incidence of prostate cancer in the treatment group. Limited data exist on postdiagnostic folate/folic acid intake and the risk of prostate cancer progression. We prospectively examined the association between postdiagnostic folate consumption and the risk of prostate cancer recurrence after radical prostatectomy, external beam radiation therapy and brachytherapy.

Materials and Methods—This study was done in 1,153 men treated with radical prostatectomy, external beam radiation therapy and brachytherapy who had clinical stage T1-T2c prostate adenocarcinoma and participated in the CaPSURE Diet and Lifestyle substudy by completing the semiquantitative Food Frequency Questionnaire in 2004 to 2005. We used Cox proportional hazards regression to analyze the association between folate intake and prostate cancer progression.

Results—Prostate cancer progressed in 101 men (8.76%) during a mean 34-month followup. After multivariate adjustment we observed no evidence of an association of the intake of total folate, dietary folate or dietary folate equivalents with prostate cancer recurrence. On secondary analysis by treatment after radical prostatectomy patients in the lowest decile of dietary folate intake had a 2.6-fold increase in the risk of recurrence (HR 2.56, 95% CI 1.23–5.29, p = 0.01). In patients treated with external beam radiation and brachytherapy we observed no evidence of an association between prostate cancer progression and increased folate intake.

Conclusions—Results suggest that the consumption of foods and multivitamins that contain folate is not associated with prostate cancer progression after definitive treatment.

Keywords

prostate; folic acid; prostatic neoplasms; neoplasm recurrence; local; disease progression

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Study received approval from the institutional review boards of University of California-San Francisco and collaborating institutions.

Prostate cancer remains the most common nondermatological malignancy and the second leading cause of cancer death in men in the United States with an estimated 28,170 prostate cancer deaths in 2012.[1] There is increasing concerns that folic acid supplementation could increase the risk of cancer and promote the progression of existing tumors, primarily due to the observation of an increased incidence of colorectal cancer in individuals with adenoma who were randomized to folate supplementation.[2] Folate (vitamin B9) is essential to sustain the proliferation of all cell types and the disruption of 1-carbon metabolism can promote carcinogenesis by interfering with DNA replication and repair, and the regulation of gene expression through methylation.[3,4] While folate is found naturally in a wide variety of foods, including dark green leafy vegetables, fruits, nuts, beans and grains,[5] the Food and Drug Administration began requiring manufacturers to add folic acid to enriched breads, cereals and flours in 1998. A recent meta-analysis revealed an increased incidence of prostate cancer in men receiving folic acid supplements (average intake 0.4 to 1.0 mg/day).[6] However, to our knowledge the effect of folate supplementation on men with prostate cancer is unknown.

We prospectively analyzed the association between postdiagnostic folate consumption and the risk of prostate cancer recurrence in men with nonmetastatic disease at presentation who participated in the CaPSURE Diet and Lifestyle substudy. Based on the reported dual role of folate intake in carcinogenesis, ie that excess and inadequate folate intake may affect carcinogenesis, we hypothesized that an inadequate or a high level of folate intake from diet and supplements may increase the risk of recurrent prostate cancer after definitive treatment.

MATERIALS AND METHODS

Study Population

This study was done in 1,153 men treated with RP, EBRT and BT for clinical stage T1-T2c prostate adenocarcinoma who participated in the CaPSURE Diet and Lifestyle substudy by completing the semiquantitative FFQ in 2004 to 2005. Briefly, CaPSURE is a longitudinal, observational database registry of men with biopsy proven prostate adenocarcinoma in which patients were enrolled consecutively from 1995 to 2005.[7] A total of 40 urologists/urology clinics, including 34 community based clinics, 3 academic institutions and 3 Veterans Administration hospitals, enrolled men with biopsy verified prostate cancer. CaPSURE participants complete surveys at baseline and every 6 months thereafter. Urologists provide clinical data at baseline and subsequent clinic visits. The institutional review boards of University of California-San Francisco and collaborating institutions approved this study. Participating urologists report complete clinical data at accession and followup visits. Patients are followed until death or study withdrawal. Data completeness and accuracy are ensured by random sample chart review every 6 months. Additional details about the registry were previously reported.[8]

Dietary Assessment

In 2004 to 2005 we administered the FFQ at 1 time point that asked about the usual consumption of 127 foods, beverages and nutritional supplements during the previous year. Men were asked how often on average they consumed a specific portion of each item, eg ½

cup of broccoli. The 9 frequency options ranged from less than once per month to 6 or more times per day. The FFQ delineates the intake of vitamins B2, B6, B12 and methionine, thereby accurately accounting for the intake of supplemental complex B vitamins.

All FFQs were administered after definitive treatment. In this analysis groups of interest containing folate included total folate after 1998, including included supplements and fortified foods, dietary folate without vitamin supplements and DFEs in mcg. The DFE of a food equals the amount contributed by folate naturally in the food plus 1.7 times the amount of added folic acid. The FFQ was based on the well validated Willett FFQ, which has been used to study diet and chronic disease relations in various populations.[9] Notably, folate measurements from the Willett FFQ were validated in a different population than the current study population. The de-attenuated correlation between 2, 1-week diet records and the original FFQ was 0.77 for folate from food and 0.70 for folate from food and supplements.[10]

Clinical Followup

We abstracted clinical data on treatments, biopsy Gleason sum, clinical stage, PSA and metastases from medical records or urologist reports. Self-reported hospitalizations were verified through hospital records. The National Death Index and Bureau of Vital Statistics were checked for mortality data. Death certificates were used to verify the date, cause and location of death.

Prostate cancer progression was defined as prostate cancer death, prostate cancer bone metastasis, biochemical recurrence or the initiation of secondary treatment. Death was attributable to prostate cancer if prostate cancer was listed as the primary, secondary or tertiary cause of death and no other malignancy was listed as a higher order cause. An outcome of bone metastasis was defined as a urologist report of 1) prostate cancer progression to bone, 2) positive bone scan or 3) radiation for metastasis at a bone site. Biochemical recurrence was defined as 2 consecutive PSA values 0.2 ng/ml or greater at least 8 weeks after RP or 3 consecutive PSA increases after EBRT or BT. Secondary treatment was defined as any treatment initiated at least 6 months after primary treatment ended. After primary treatment the initiation of secondary treatment is indicative of biochemical or clinical evidence of disease progression.[11] The date of prostate cancer progression was considered the first of prostate cancer death, diagnosis of bone metastases from prostate cancer, second PSA 0.2 ng/ml or greater in patients with RP midway between the dates of the nadir and the first increasing PSA in patients treated with EBRT or BT, or the initiation of secondary treatment.

Study Inclusion Criteria

The base population for analysis included 2,134 men who completed the FFQ in 2004 to 2005. We excluded 37 men with stage T3b or greater at diagnosis, 160 not treated with RP, EBRT or BT and 51 who reported an implausible energy intake of greater than 800 to 4,200 kcal per day. We also excluded 733 men with a prostate cancer progression event before the FFQ, resulting in 1,153 who were eligible for analysis.

Statistical Methods

We examined the association between postdiagnostic folate intake and the risk of prostate cancer progression using Cox proportional hazards regression. Person-time was calculated from the date of the FFQ until the date of prostate cancer progression, nonprostate cancer death, last contact or end of followup on August 21, 2009, whichever was first. We modeled folate intake quintiles using indicator variables and tested for evidence of linear trends using the median of each quintile as a continuous term. We also examined folate as a binary variable and compared the highest decile to the lowest 9 deciles, and the lowest decile to the remaining 9 deciles to examine whether extreme levels of folate intake increased the risk of prostate cancer progression.

Our multivariate models were adjusted for total energy intake, age at diagnosis, primary treatment type, biopsy Gleason sum and months between diagnosis and the FFQ. We did not adjust for hospital type. We also performed secondary analysis stratified by treatment type to assess whether the association between folate consumption and the risk of prostate cancer progression differed in men treated with varying modalities. Other factors assessed for confounding included body mass index, total caloric intake, methionine, and vitamins B2, B6 and B12 intake, which were not included in the final model because they did not affect the null result. All statistical tests were 2-sided with $p < 0.05$ considered significant. All analysis was done using SAS®, version 9.1.3.

RESULTS

Of the 1,153 men with clinically localized prostate cancer in our study population 840 (73%) were treated with RP, 209 (18%) received BT and 104 (9.0%) underwent EBRT. At diagnosis 533 men (46%) were between 60 and 69 years old, 260 (23%) were between 50 and 59 years old, and 324 (28%) were 70 years old or older. Most participants were overweight (598 or 52%) or obese (224 or 19%) and almost all were white (1,102 or 95%). In addition, 68% of the men had PSA between 4.1 and 10 ng/ml at diagnosis, 54% were diagnosed with clinical stage T1 and 71% had a biopsy Gleason sum of 6.

Prostate cancer progressed in 101 men, including biochemical recurrence in 62%, secondary treatment in 32%, prostate cancer death in 4% and bone metastasis in 2%, during a mean ± SD followup of 34 ± 20 months. Secondary treatments included initiation of luteinizing hormone-releasing hormone agonists in 38% of cases, finasteride in 19%, anti-androgens in 6%, second line medication in 3%, EBRT in 28%, orchiectomy in 3% and cryotherapy in 3%. Median followup from FFQ to censoring was 28 months in the 840 patients with RP, 40 months in the 209 with EBRT and 26 months in the 104 with BT (supplementary table 1, http://jurology.com/).

Mean dietary folate intake was 442 ± 177 mcg and mean DFE intake was 1,058 ± 578 mcg (table 1). The total folate, dietary folate or DFE intake was not associated with prostate cancer recurrence after adjusting for primary treatment, age at diagnosis, Gleason score, energy intake and time from diagnosis to FFQ (table 2 and supplementary table 2, http://jurology.com/).

On secondary analysis stratified by treatment patients in the lowest decile of dietary folate intake (range 123,252 mcg) were at 2.6-fold increase risk of progression after RP (HR 2.56, 95% CI 1.23–5.29, p = 0.01), although total folate or DFE was not associated with risk (table 3). In patients treated with EBRT and BT we observed no evidence of an association between prostate cancer progression and increased intake of total folate (HR 0.3, 95% CI 0.03–2.3, p = 0.24), dietary folate (HR 0.27, 95% CI 0.03–2.12, p = 0.21) or DFE (HR 0.66, 95% CI 0.15–2.94, p = 0.59), although the number of events may have been too small to detect a difference.

DISCUSSION

In what is to our knowledge a novel prospective study we observed no association between post-diagnostic folate consumption, as determined by the FFQ, and prostate cancer progression after definitive treatment. Although a 24% increased risk of incident prostate cancer in men on folic acid supplements (RR 1.24, 95% CI 1.03–1.49) was reported,[6] a recent large meta-analysis of trials of folic acid supplementation revealed no increase or decrease in the incidence of prostate cancer during the first 5 years of treatment.[12,13] However, the relation between excess folate intake after diagnosis and the risk of prostate cancer progression has not been well studied.

Folate is an essential factor in the 1-carbon metabolism pathway, which is responsible for nucleotide synthesis and biological methylation reactions, including DNA, RNA and histone methylation.[14] Dietary deficiency or excess of nutrients involved in the 1-carbon metabolism pathway was hypothesized to increase the prostate cancer risk but evidence is inconsistent.[15–23] Numerous cancers, including prostate cancer, show a general pattern of global DNA hypomethylation and gene specific hypermethylation,[24] suggesting that 1-carbon cycle deficiency or excess may have a role in tumor development or progression. It was hypothesized that folate supplementation before pre-neoplastic lesions develop may prevent tumor by enhancing genomic DNA stability while folate supplementation may increase established cancer growth.[25] However, we observed no increased risk of prostate cancer recurrence in men with high folate intake in this study population.

The recommended daily intake of folate in men is 0.4 mg per day and the intake in our study population ranged from 0.1 to 1.4 mg per day (mean 0.44), comparable to the intake in the general population.[26] Men in the top quintile of folate intake from supplements and fortified foods (DFE) in our study population had an intake level of 1.5 to 3.9 mg per day, above the recommended daily limit of consumption (tolerable upper limit 1 mg per day). Nonetheless, the deleterious effects of folate consumption on prostate cancer progression, if they exist, may not become evident until serum levels are supraphysiological (intake greater than 1 mg per day).

Folate is a water soluble vitamin and, therefore, it is expected to be excreted when in excess. However, 40% of older adults in the United States have unmetabolized serum folic acid, which persists after fasting and of which the presence is not explained by folic acid intake alone.[27] Furthermore, folate intake may not necessarily correlate with serum and prostate tissue folate levels. In patients with prostate cancer greater than 40-fold variability can occur

in prostate tissue folate levels.[28] Finally, given the relatively short followup, the observed effect of folate intake may reflect posttreatment prevention rather than its effect on subclinical disease progression.

The current study has several limitations, including the short followup (other studies have included much longer outcomes), the small number of prostate cancer deaths or metastases and the lack of prediagnostic dietary data. A 2.6-fold increased risk of recurrence after RP was observed in patients in the lowest decile of dietary folate intake, although this was a post hoc analysis and the finding may have been due to chance. Residual confounding could exist since the largest group in the current cohort comprised men who underwent RP while men on folic acid supplements may be more likely to undergo PSA testing after treatment. In folic acid deficiency DNA methylation and repair are hampered and the resulting DNA instability increases the risk of cancer.[6] A potential explanation for the observed phenomenon may involve prostate specific membrane antigen, which increases cell folate uptake and proliferation in the presence of limiting levels of folate.[29] In vivo prostate cells are highly susceptible to genetic and epigenetic changes in response to mild folate depletion, indicating a broad effect of folate depletion on epigenetic regulation.[30] Overweight and obese patients, who made up a large part of the current cohort, may require even higher folate intake to impact carcinogenesis, which may partly explain the higher rate of progression after RP. Finally, we did not sample homocysteine levels to correlate measures of folate intake assessed by the FFQ. While plausible mechanistic explanations exist, no effect of low folate intake on progression was observed in patients treated with radiation, which may reflect selection bias in treatment type.

In addition, analysis of an individual nutrient in the 1-carbon metabolism pathway may not account for its synergistic functional interaction with other nutrients while MTHFR genetic variants may modify the association between high folate intake and prostate cancer risk.[15] There may also be unmeasured residual confounding, although we considered several other dietary and lifestyle factors as potential confounders. Finally, self-reported dietary intake may not accurately reflect circulating levels of the nutrient due to variations in absorption and metabolism.

CONCLUSIONS

Folate consumption after prostate cancer diagnosis was not associated with the risk of prostate cancer progression after definitive therapy for clinically localized disease. The observation that severely deficient dietary folate intake may increase the risk of recurrence after RP requires further investigation before providing any dietary guidance to patients newly diagnosed with prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

BT	brachytherapy
DFE	dietary folate equivalent
EBRT	external beam radiation therapy
FFQ	Food Frequency Questionnaire
PSA	prostate specific antigen
RP	radical prostatectomy

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Table 1

Folate intake by source in 1,153 men with prostate cancer from CaPSURE

	Overall	RP	BT	EBRT
No. pts	1,153	840	209	104
Mean ± SD folate (mcg): *				
Total	709 ± 326	714 ± 321	693 ± 331	702 ± 354
Dietary	442 ± 177	444 ± 179	432 ± 173	448 ± 174
DFE	1,058 ± 578	1,067 ± 569	1,033 ± 596	1,039 ± 625

* Total folate includes supplements and fortified foods, dietary folate does not include supplements and DFE of food equals amount contributed by folate naturally plus 1.7 times amount of added folic acid so that DFE can be greater than total folate.

Table 2

Post-diagnostic folate consumption and relative risk of prostate cancer progression after definitive treatment by folate source

Folate (mcg)	No. Pts	Decile	Estimated HR (95% CI)*	p Value
Total:				
126,309	115	Lowest	1.25 (0.64–2.44)	0.50
310,2191	1,038	Remaining	1 (referent)	
Dietary:				
123,252	115	Lowest	1.52 (0.80–2.92)	0.19
253,1414)	1,038	Remaining	1 (referent)	
DFE:				
138,364	114	Lowest	1.48 (0.79–2.76)	0.21
365,3939	1,039	Remaining	1 (referent)	

*Adjusted for total energy intake, age, primary treatment, disease grade and months between diagnosis and FFQ.

Table 3

Post-diagnostic dietary folate intake lowest decile and risk of recurrence by treatment

Folate (decile)	Estimated HR (95% CI)*	p Value
RP (69 progressions/840 pts)		
Total:		
Lowest	1.61 (0.78–3.34)	0.19
Remaining	1 (referent)	
Dietary:		
Lowest	2.56 (1.23–5.29)	0.01
Remaining	1 (referent)	
DFE:		
Lowest	1.89 (0.93–3.83)	0.07
Remaining	1 (referent)	
EBRT or BT (32 progressions/313 pts)		
Total:		
Lowest	0.30 (0.03–2.30)	0.24
Remaining	1 (referent)	
Dietary:		
Lowest	0.27 (0.03–2.12)	0.21
Remaining	1 (referent)	
DFE:		
Lowest	0.66 (0.15–2.94)	0.59
Remaining	1 (referent)	

*Adjusted for total energy intake, age, disease grade and months between diagnosis and FFQ.