Dietary factors of one-carbon metabolism and prostate cancer risk

Stephanie J Weinstein, Rachael Stolzenberg-Solomon, Pirjo Pietinen, Philip R Taylor, Jarmo Virtamo, and Demetrius Albanes

ABSTRACT

Background: Folate is hypothesized to be inversely associated with the risk of several cancers, but such a potential association has not been well studied for prostate cancer. Vitamin B-6, vitamin B-12, methionine, and alcohol can influence folate-related metabolism.

Objective: The objective was to investigate the associations between dietary factors of one-carbon metabolism and prostate cancer risk within the α-Tocopherol, β-Carotene Cancer Prevention Study.

Design: Of the cohort’s 27,111 Finnish male smokers aged 50–69 y who had complete dietary data, 1,270 had a diagnosis of incident prostate cancer between 1985 and 2002. Folate, vitamin B-6, vitamin B-12, methionine, and alcohol intakes were estimated from a 276-item modified dietary history questionnaire. Cox proportional hazard models, adjusted for age and vitamin supplement use, estimated relative risks (RR) and 95% CIs.

Results: Vitamin B-6 intake was inversely associated with prostate cancer risk (RR for highest versus lowest quintile: 0.88; 95% CI: 0.72, 1.07; \textit{P} for trend = 0.045), whereas vitamin B-12 intake was associated with significantly increased risk (RR = 1.36; 95% CI: 1.14, 1.96; \textit{P} for trend = 0.01). No association between folate or alcohol intake and prostate cancer risk was observed. No differences were found in the above associations according to stage of disease or subgroups of several potential effect modifiers.

Conclusions: We found no convincing evidence for a protective role of one-carbon metabolism against prostate cancer, although these observations can be generalized only to smokers. The possible modest protective association with vitamin B-6 and the significantly elevated risk with vitamin B-12 intake warrant further investigation.


KEY WORDS Prostatic neoplasms, folic acid, vitamin B-6, vitamin B-12, methionine, alcohol

INTRODUCTION

Prostate cancer is the most common nonskin cancer in men in the United States: an estimated 234,460 new cases and 27,350 deaths will occur in 2006 (1). This malignancy is the most common cancer in men in Finland, where the age-adjusted incidence rate in 2003 was 95.3 per 100,000 (2). Incidence and mortality rates for prostate cancer vary internationally (3–5). The only established risk factors for prostate cancer are age, ethnicity (ie, being African American), and family history. Results of migrant studies suggest that environmental factors such as diet could play an important role in modifying prostate cancer risk (6).

Folate has long been hypothesized to be related to cancer risk (7, 8). Biological reactions requiring folate, known as one-carbon metabolism reactions, include purine and pyrimidine synthesis and the conversion of methionine to S-adenosylmethionine (SAM), the molecule primarily responsible for the methylation of DNA. Vitamins B-6 and B-12 also play a role in one-carbon metabolism as enzyme cofactors (9). In addition, alcohol intake can negatively influence folate status and metabolism (10). Therefore, low intakes of vitamin B-6, vitamin B-12, folate, or methionine or high intakes of alcohol may lead to insufficient availability of methyl groups for DNA methylation, to the depletion of precursors needed for DNA synthesis and repair, or both, and thus they potentially could promote carcinogenesis (8, 9). Both hypermethylated and hypomethylated DNA have been found in prostate tumors (11–13). These dietary factors related to one-carbon metabolism have been implicated in the development of several malignancies, including colon (14–16), breast (17), pancreatic (18), lung (19), and cervical (20) cancers, and they may also affect the development of prostate cancer (21, 22). In addition to one study of serum one-carbon factors in the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study cohort (23), 3 prospective studies (24–26) and one case-control study (27) reported on one-carbon nutrients and prostate cancer, and 2 other case-control studies included some one-carbon nutrients in a broad examination of dietary factors (28, 29). The results of these studies have been mixed.

To test the hypothesis that dietary factors related to one-carbon metabolism may influence prostate cancer risk, we examined those factors in a large cohort of male Finnish smokers. Whereas folic acid fortification of enriched grain products was mandated in the United States in 1998 (30), no such fortification program...
SUBJECTS AND METHODS

Study cohort

The ATBC Study was conducted in Finland as a joint project between the Finnish National Public Health Institute and the US National Cancer Institute. The overall design, rationale, and objectives of this study were reported previously (31). Briefly, the ATBC Study was a randomized, double-blind, placebo-controlled, primary prevention trial to determine whether daily supplementation with \( \alpha \)-tocopherol, \( \beta \)-carotene, or both would reduce the incidence of lung or other cancers in male smokers. A total of 29,133 men aged 50–69 y who smoked \( \geq 5 \) cigarettes/d were recruited from southwestern Finland between 1985 and 1988 and randomly assigned to 1 of 4 groups on the basis of a 2 \( \times \) 2 factorial design. Men who had prior cancer or serious illness or who reported current use of vitamin E (\( > 20 \) mg/d), vitamin A (\( > 20,000 \) IU/d), or \( \beta \)-carotene (\( > 6 \) mg/d) were ineligible. Participants received either \( \alpha \)-tocopherol (50 mg/d) as dl-\( \alpha \)-tocopheryl acetate, \( \beta \)-carotene (20 mg/d) as all-trans-\( \beta \)-carotene, both supplements, or placebo capsules for 5–8 y (median: 6.1 y); administration ceased at the subject’s death or at trial closure (30 April 1993). Postintervention follow-up continued through the Finnish Cancer Registry.

Written informed consent was obtained from each participant before randomization. This study was approved by the institutional review boards of the National Cancer Institute (United States) and the National Public Health Institute (Finland).

Data collection

At baseline, height and weight were measured, and participants completed a general risk factor and medical history questionnaire, including vitamin supplement use. They also completed a food-frequency questionnaire (FFQ), which consisted of a modified diet history, including frequency of consumption for 203 food items and 73 mixed dishes; a picture booklet was used to aid in portion size estimation. This instrument was intended to measure usual consumption over the previous 2 mo and was reviewed with each participant by study nurses at baseline. The questionnaires were satisfactorily completed by 93% of the subjects, and the other 7% of subjects were not used in these or other dietary analyses (31, 32). The reproducibility and validity of this FFQ were reported previously (32). In the validity study, subjects completed the dietary instrument at the beginning and end of a 6-mo period, and they kept food-consumption records for 24 d in the interim period. Correlations between the 2 types of measures ranged from 0.40 for selenium to 0.80 for alcohol, and that for folate was 0.54. For the reproducibility study, subjects completed the instrument 3 times at 3-mo intervals and intraclass correlations varied from 0.56 for vitamin A to 0.88 for alcohol; most fell between 0.60 and 0.70, and that for folate was 0.70 (14, 32). Nutrient intake was estimated on the basis of food-composition data from the National Public Health Institute. Data on supplement use were obtained from open-ended questions regarding the use of any vitamin or trace element preparation in the past 2 wk, the name of the preparation, and the daily dose. The total intakes of specific vitamins or minerals reflect the consumption of individual and multivitamin supplements.

Case identification

Cases were defined as incident prostate cancers (International Classification of Diseases 9, code 185) diagnosed by 30 April 2002. During follow-up (\( \leq 17 \) y), 1,347 cases were identified, and 1,270 with complete baseline dietary information are included in this analysis. These cancers were identified through the Finnish Cancer Registry and the Register of Causes of Death. For cases diagnosed through April 1999, the medical records were reviewed centrally by 2 study oncologists for diagnostic confirmation and staging, and cases with histologic or cytologic slides available were also reviewed and confirmed by pathologists. Information on prostate cancer cases diagnosed since May 1999 were derived only from the Finnish Cancer Registry, which provides almost 100% case ascertainment (33). Advanced cases (\( n = 347 \)) included the 303 cases diagnosed through April 1999 with stage III or IV tumors according to the tumor-node-metastasis staging system of the American Joint Committee on Cancer (34) and the 44 cases diagnosed after April 1999 with regional or distant metastases. Because Finland has not adopted population-based prostate-specific antigen (PSA) screening programs, nearly all prostate cancer cases in the cohort were diagnosed clinically, and very few were initially identified by a finding of an elevated PSA.

Statistical analysis

Follow-up time for each participant was calculated as the time between the date of randomization to diagnosis of prostate cancer, death, or 30 April 2002, whichever came first, for a total of 336,502 person-years of observation. Only subjects with complete dietary information (\( n = 27,111 \)) were included in the analyses. Case and noncase characteristics were compared statistically by using the general linear models procedure in SAS after adjustment for age at randomization. Supplemental intakes of vitamins were added to dietary intakes, and these total nutrient intake variables were log transformed and adjusted for energy intake by using the residual method (35). Models excluding supplemental intake gave similar results (data not shown). Cox proportional hazard models were used to determine relative risks (RR) and 95% CIs for the association between prostate cancer and dietary nutrients. Quintile categories of the nutrients were created on the basis of the distribution of the cohort and entered into the models as indicator variables with the lowest quintile as the referent category. Tests for linear trend were obtained by assigning to each nutrient quintile the median value and treating that value as a continuous variable. The multivariate models were adjusted for age at randomization and vitamin supplement use. Intervention group, benign prostatic hyperplasia, physical activity (light and moderate activity at work and at least moderate activity at leisure), urban residence, education, marital status, body mass index (BMI; in kg/m\(^2\)), height, smoking (number of cigarettes/d, number of years smoked, and pack-years), total...
energy, and alcohol consumption were not confounders in our sample (ie, when added to the model, each variable produced <10% change in any of the nutrient coefficients). Effect modification was assessed in stratified analyses and was statistically evaluated by including the cross-product term of the nutrient variables (quintiles) by the effect modifier (split at the median). The assumption of constant risk for proportional hazards models, tested by examining the cross-product term of follow-up time and the variable of interest, was met for all the nutrients. Statistical analyses were performed with SAS software (version 8.02; SAS Institute Inc, Cary, NC), and all P values were 2-sided.

**RESULTS**

A comparison of baseline characteristics of cases and noncases, adjusted for age, are shown in Table 1. Cases were significantly older, taller, and more likely to live in an urban area, have more than an elementary school education, and have a history of benign prostatic hyperplasia or a family history of prostate cancer than were noncases. Cases smoked significantly fewer cigarettes per day for a shorter period of time and had significantly higher vitamin B-12 intake than did noncases. Of the entire cohort, 21.0% reported the use of any supplement, whereas 5.9%, 12.9%, and 7.4% reported the use of single or multivitamin supplements containing folate, vitamin B-6, and vitamin B-12, respectively. Other reported supplement items included selenium-based products, other mineral-only supplements, other single vitamin supplements, and herbal supplements. In the small number of subjects who consumed folate, vitamin B-6, and vitamin B-12 supplements, supplemental intakes accounted for 26%, 27%, and 57% of the total nutrient intake, respectively.

When baseline characteristics of the cohort were examined by quintile of total folate intake, men with greater intakes tended to be younger, taller, have a higher BMI, be more physically active, live outside an urban area, be married, have more than an elementary school education, and have smoked for fewer years (data not shown) than did men with lower intake. The men with higher intakes also had significantly higher intakes of total energy, vitamin B-6, vitamin B-12, and methionine; significantly lower intakes of alcohol; and significantly greater use of vitamin supplements. These relations held after adjustment for age and total energy intake and did not differ when the cohort was evaluated by quintile of total folate intake. The men with higher intake, respectively.

The correlations between nutrient intakes and serum concentrations of folate, vitamin B-6, and vitamin B-12 were modest (Spearman’s r = 0.20, 0.33, and 0.13, respectively, based on 646 subjects) (23) and appeared to be altered by smoking status for folate (r = 0.17 and 0.25 for heavier and lighter smokers, respectively) and vitamin B-6 (r = 0.31 and 0.35 for heavier and lighter smokers, respectively). Correlations were stronger in
cases for vitamins B-6 and B-12, in controls for folate, and in higher alcohol drinkers for vitamin B-6.

Vitamin B-6 had a significant inverse relation with prostate cancer risk, but the RR for the highest quintile was not significant. Vitamin B-12 was associated with a significantly greater risk of prostate cancer (Table 2). The inverse association with vitamin B-6 became stronger when vitamin supplement use was added to the model, but this variable did not affect the RRs for the other nutrients. We observed no association between folate or alcohol intake and prostate cancer in this cohort. When nutrient values were not adjusted for energy by the residual method, only the results for methionine were attenuated (RR = 1.09; 95% CI: 0.92, 1.30 for highest versus lowest quintile). Individual and simultaneous adjustments for intakes of folate, vitamin B-6, methionine, iron, beef, poultry, pork, total protein, protein from animal sources, total fat, fat from animal sources, and total energy did not attenuate the vitamin B-12 association (RR = 1.45; 95% CI: 1.18, 1.78 for highest versus lowest quintile). Control for other correlates of vitamin B-12 intake—specifically, fish, organ meats, sausages, cholesterol, and various fatty acids and various minerals—also did not attenuate the vitamin B-12 association, nor were these or any of the above factors directly related to prostate cancer risk. Finally, the inclusion of the nondietary variables found in Table 1 did not attenuate the vitamin B-12 association.

Vitamin B-6 was inversely associated with prostate cancer risk in the heavier smokers (RR for highest versus lowest quintile = 0.74; 95% CI: 0.56, 0.96; P for trend = 0.01 for ≥ 20 cigarettes/d; RR for highest versus lowest quintile = 0.75; 95% CI: 0.58, 0.98; P for trend = 0.01 for ≥ 37 y of smoking), and no association was found in the lighter smokers (RR for highest versus lowest quintile = 1.09; 95% CI: 0.80, 1.42 for highest versus lowest quintile). The inverse association with alcohol intake was greater than the median (11.0 g/d) and slightly above the null when alcohol intake was greater than the median (11.0 g/d) and slightly above the null when alcohol intake was below the median; however, neither these findings nor their interaction (P = 0.44) was significant. No other evidence was found for effect modification between the intake of the one-carbon nutrients and age, BMI, total energy, smoking, alcohol intake, or study intervention group.

### Table 2

Relative risks (RRs) (95% CIs) of prostate cancer by quintile of baseline dietary intake

<table>
<thead>
<tr>
<th>Dietary nutrient intakes</th>
<th>Cases (n = 1270)</th>
<th>Person-years of follow-up</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Folate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (≤283 µg/d)</td>
<td>256</td>
<td>64 753</td>
<td>1.00</td>
</tr>
<tr>
<td>2 (&gt;283 and ≤313 µg/d)</td>
<td>242</td>
<td>67 514</td>
<td>0.91 (0.77, 1.09)</td>
</tr>
<tr>
<td>3 (&gt;313 and ≤341 µg/d)</td>
<td>263</td>
<td>67 891</td>
<td>1.00 (0.84, 1.19)</td>
</tr>
<tr>
<td>4 (&gt;341 and ≤378 µg/d)</td>
<td>250</td>
<td>68 146</td>
<td>0.95 (0.80, 1.13)</td>
</tr>
<tr>
<td>5 (&gt;378 µg/d)</td>
<td>259</td>
<td>68 199</td>
<td>0.96 (0.81, 1.15)</td>
</tr>
<tr>
<td>P for trend</td>
<td>—</td>
<td>—</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Vitamin B-6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (≤2.1 mg/d)</td>
<td>256</td>
<td>65 041</td>
<td>1.00</td>
</tr>
<tr>
<td>2 (&gt;2.1 and ≤2.4 mg/d)</td>
<td>279</td>
<td>67 026</td>
<td>1.07 (0.90, 1.27)</td>
</tr>
<tr>
<td>3 (&gt;2.4 and ≤2.6 mg/d)</td>
<td>271</td>
<td>68 068</td>
<td>1.05 (0.89, 1.25)</td>
</tr>
<tr>
<td>4 (&gt;2.6 and ≤3.0 mg/d)</td>
<td>220</td>
<td>69 364</td>
<td>0.86 (0.71, 1.03)</td>
</tr>
<tr>
<td>5 (&gt;3.0 mg/d)</td>
<td>244</td>
<td>67 004</td>
<td>0.88 (0.72, 1.07)</td>
</tr>
<tr>
<td>P for trend</td>
<td>—</td>
<td>—</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>Vitamin B-12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (≤7.7 µg/d)</td>
<td>222</td>
<td>68 080</td>
<td>1.00</td>
</tr>
<tr>
<td>2 (&gt;7.7 and ≤9.4 µg/d)</td>
<td>259</td>
<td>67 012</td>
<td>1.18 (0.99, 1.42)</td>
</tr>
<tr>
<td>3 (&gt;9.4 and ≤11.2 µg/d)</td>
<td>269</td>
<td>66 957</td>
<td>1.25 (1.05, 1.49)</td>
</tr>
<tr>
<td>4 (&gt;11.2 and ≤14.0 µg/d)</td>
<td>232</td>
<td>67 505</td>
<td>1.07 (0.89, 1.29)</td>
</tr>
<tr>
<td>5 (&gt;14.0 µg/d)</td>
<td>288</td>
<td>66 948</td>
<td>1.36 (1.14, 1.62)</td>
</tr>
<tr>
<td>P for trend</td>
<td>—</td>
<td>—</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Methionine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (≤1726 mg/d)</td>
<td>236</td>
<td>67 166</td>
<td>1.00</td>
</tr>
<tr>
<td>2 (&gt;1726 and ≤1901 mg/d)</td>
<td>283</td>
<td>67 278</td>
<td>1.19 (1.00, 1.41)</td>
</tr>
<tr>
<td>3 (&gt;1901 and ≤2057 mg/d)</td>
<td>248</td>
<td>67 668</td>
<td>1.07 (0.89, 1.28)</td>
</tr>
<tr>
<td>4 (&gt;2057 and ≤2251 mg/d)</td>
<td>232</td>
<td>68 025</td>
<td>0.98 (0.82, 1.17)</td>
</tr>
<tr>
<td>5 (&gt;2251 mg/d)</td>
<td>271</td>
<td>66 366</td>
<td>1.22 (1.03, 1.46)</td>
</tr>
<tr>
<td>P for trend</td>
<td>—</td>
<td>—</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinkers</td>
<td>151</td>
<td>35 972</td>
<td>1.00</td>
</tr>
<tr>
<td>1 (≤3.7 g/d)</td>
<td>255</td>
<td>59 989</td>
<td>0.98 (0.80, 1.20)</td>
</tr>
<tr>
<td>2 (&gt;3.7 and ≤10.0 g/d)</td>
<td>234</td>
<td>60 543</td>
<td>0.96 (0.78, 1.17)</td>
</tr>
<tr>
<td>3 (&gt;10.0 and ≤18.7 g/d)</td>
<td>236</td>
<td>60 234</td>
<td>1.03 (0.84, 1.26)</td>
</tr>
<tr>
<td>4 (&gt;18.7 and ≤32.2 g/d)</td>
<td>202</td>
<td>60 640</td>
<td>0.90 (0.73, 1.11)</td>
</tr>
<tr>
<td>5 (&gt;32.2 g/d)</td>
<td>192</td>
<td>59 125</td>
<td>0.94 (0.76, 1.16)</td>
</tr>
<tr>
<td>P for trend</td>
<td>—</td>
<td>—</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Note: All dietary nutrients except alcohol were log transformed and adjusted for energy intake by using the residual method. Supplemental intakes of folate and vitamins B-6 and B-12 were added to dietary intakes. Models were adjusted for age at randomization and vitamin supplement use.
We observed no differences between findings for the one-carbon nutrients in early or advanced disease. For example, for the highest versus lowest quintiles, RR = 0.85 (95% CI: 0.64, 1.11) for vitamin B-6 in early-stage disease, whereas RR = 0.77 (95% CI: 0.52, 1.12) in advanced disease. Similarly, RR = 1.35 (95% CI: 1.06, 1.71) for vitamin B-12 in early-stage disease, whereas RR = 1.44 (95% CI: 1.02, 2.03) in advanced disease.

DISCUSSION

Dietary folate and alcohol intakes were not associated with prostate cancer risk in our study, whereas the intakes of vitamins B-6 and B-12 were weakly inversely and directly associated with risk, respectively. In the current study, we found no association between folate intake and prostate cancer risk, and we previously found no association between serum folate and prostate cancer risk in a study nested within the ATBC Study cohort (23). Most other studies examining folate intake or status in relation to prostate cancer have been null (24, 26, 28, 29), although one suggested that folate intake may be inversely associated with the risk of advanced prostate cancer (26). One case-control study reported a significant inverse association with folate intake (27), and a recent prospective study reported significant inverse associations with serum folate and prostate cancer incidence and mortality, and the patterns for red blood cell folate were similarly but nonsignificantly inverse (25). The associations between folate intake and prostate or other cancers (14, 16, 17, 27) have been shown to be modified by alcohol intake. We previously found an inverse association for serum folate in those who consumed higher, but not lower, amounts of alcohol, although the interaction was not significant (23). In the current study, we noted a similar pattern for dietary folate, but the inverse RRs for higher folate intakes in the higher consumers of alcohol were weak and not significant. The association between folate and prostate cancer risk was also not modified by alcohol intake in another study (26). Whereas alcohol intake can interfere with folate intake, absorption, transport, and metabolism (10), our data do not suggest that the relation between one-carbon factors and prostate cancer risk is modified by alcohol intake.

Smoking has been inversely associated with folate status, possibly because of decreased folate intake or inactivation of folate and vitamin B-12 cofactors by oxidizing compounds in tobacco smoke (36, 37). Smoking also may cause localized folate deficiencies in particular tissues (37, 38). All of the men enrolled in the ATBC Study smoked ≥5 cigarettes/d at baseline, but no differences were found in the folate risks when stratified by smoking dose or duration. Other investigations in this cohort of smokers showed inverse associations of folate intake and cancers at other organ sites (14, 18). It therefore may be that, for protection against prostate cancer, smokers require folate intakes higher than the intake in the current study.

Vitamin B-6 intake was weakly associated with lower prostate cancer risk in this cohort, although we previously found no association with serum vitamin B-6 (23). Two case-control studies (with 101 and 328 cases, respectively) reported nonsignificantly reduced risks of prostate cancer with higher vitamin B-6 intake (28, 29) and risks in a range similar to that seen in the current study, whereas another study found no association (27). In the current study, risks appeared to be greater in those who smoked more heavily and longer, although the interaction was not significant. In addition to its role in one-carbon metabolism, vitamin B-6 is a co-enzyme in other reactions. In particular, it has been shown that vitamin B-6 binds to the steroid hormone–receptor complex, terminating hormone action (39). Therefore, an insufficiency in vitamin B-6 may cause greater exposure to steroid hormones, such as testosterone (39), which is thought to play a role in prostate cancer development (40).

We found that high vitamin B-12 intake was significantly associated with increased prostate cancer risk. We considered whether this unexpected finding was due to confounding by other nutrients or by other factors that co-occur in foods high in vitamin B-12, such as meats, fats, and protein, but such adjustment did not attenuate the RRs, and none of these factors was directly associated with risk. In addition, the association was not altered by adjustment for other factors, such as smoking, physical activity, education, and disease history. One potential unmeasured confounder is heterocyclic amines, which are present in meats cooked at high temperatures, and one of which has been associated with prostate cancer risk in one study (41). We do not have detailed information on meat-cooking methods in the current study and therefore cannot assess this factor in our cohort. As the current study also found, one case-control study in Yugoslavia (28) reported a positive association for vitamin B-12 intake (odds ratio = 2.07; 95% CI: 1.08, 3.97 for highest versus lowest tertile), and a prospective cohort study in Sweden (24) reported a significantly higher risk with higher plasma vitamin B-12 (odds ratio = 2.96; 95% CI: 1.58, 5.55 for highest versus lowest quartile). We previously found no relation between serum vitamin B-12 and prostate cancer risk in a sample nested within the ATBC cohort, however (23). The correlation between vitamin B-12 intake and serum concentration in the current study was relatively low, which may be explained by the lower vitamin B-12 absorption that is common in older persons (42). In the ATBC Study, lung cancer risk was nonsignificantly elevated in men with high serum concentrations of vitamin B-12 (43), and vitamin B-12 intake was associated with a greater risk of esophageal and gastric cancers in a US case-control study (44). Experimental evidence from both animal and human studies supports opposing findings: in some studies, diets deficient in vitamin B-12 are cocarcinogenic, and in other studies, diets with high vitamin B-12 enhance tumor growth (8). The current findings for vitamin B-12 should be further evaluated in other studies. Although other studies have found stronger inverse associations for dietary factors in advanced prostate cancers than in earlier stage tumors (45–47), none of the one-carbon factors we examined differed by stage of disease.

The prospective design of this study is an important strength that minimizes the potential for recall bias in the dietary assessment. We used a validated dietary instrument with good reproducibility to evaluate dietary consumption (32), and nutrient intake was quantified by using a Finnish nutrient database. The large number of items in our dietary questionnaire is a strength compared with shorter instruments, which may miss important sources of particular nutrients (48). As with all dietary assessment instruments, the potential for measurement error in an FFQ can attenuate true associations (49), although energy adjustment may improve this situation (49). The nutrient intakes in the current study were adjusted for energy, but it is possible that true associations were missed in the study. Measurement error, however, is unlikely to explain the significantly greater risk observed with a higher vitamin B-12 intake. Instead, this greater risk could be due to confounding by other, unmeasured factors, although...
adjustment for numerous potential confounders did not affect the risk estimates at all. The correlations between dietary intake and status for the nutrients we examined were modest. Modest correlations are not unexpected for vitamin B-12 (42, 50). Our correlation estimates for folate and vitamin B-6 are in line with others in the literature (50–56), and we believe that the metabolic effects of smoking (36, 57) are reducing the correlations between dietary intakes and serum concentrations of folate and vitamin B-6. This possibility is supported in part by our observation of differing correlations by smoking intensity level and by a recent study showing significantly lower plasma folate, vitamin B-6, and vitamin B-12 in smokers than in nonsmokers (38). That study reported that smoking was such a large determinant of folate status that it rendered dietary folate nonpredictive of plasma folate concentrations (38). We simultaneously examined several key dietary factors related to one-carbon metabolism and so were able to examine these hypotheses thoroughly, and we conducted analyses that were stratified by potentially important effect modifiers, including disease stage. Because population-based PSA screening programs have not been adopted in Finland and no national folic acid fortification program is in place there, our findings are not affected by these influences. Finally, the current study included only male smokers who participated in the original prevention trial, which limited the study’s generalizability. Factors related to one-carbon metabolism have been hypothesized to be important in the development of prostate cancer (21, 22); however, that possibility has not been examined thoroughly. We found no convincing evidence for a protective role for one-carbon metabolism against the development of prostate cancer in a cohort of smokers. Specifically, no association with folate intake was found, and only a weakly protective association with vitamin B-6 was found. Vitamin B-12 intake was associated with a higher, not a lower, risk, and that finding warrants further investigation into both vitamin B-12 intakes and correlates of vitamin B-12 intake.

PP, PRT, JV, and DA contributed to the collection and quality control of the data; SJW conducted the data analyses; RS assisted with data analysis; SJW wrote the manuscript; DA reviewed the statistical analysis and manuscript preparation; and all authors critically reviewed the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES