Null Results in Brief

Null Association between Prostate Cancer and Serum Folate, Vitamin B_6, Vitamin B_{12}, and Homocysteine

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Introduction

Folate is necessary for DNA synthesis, repair, and methylation, and biological reactions involving folate require vitamins B_6 and B_{12} as cofactors. Low concentrations of these vitamins can impair one-carbon metabolism pathways (1), leading to homocysteine accumulation, insufficient methyl groups for DNA methylation, or depletion of DNA synthesis and repair precursors, thus, potentially promoting carcinogenesis (2). These nutrients have been implicated with respect to several malignancies, including colorectum, lung, and cervix (3), and may impact prostate cancer (4). Both hyper- and hypomethylated DNA have been found in prostate tumors (4), and the activation of estrogen receptors in prostate cancer cell lines and tissues is regulated through promoter region methylation (5). We examined whether high serum folate, vitamin B_6, or vitamin B_{12} or low serum homocysteine was associated with decreased prostate cancer risk.

Materials and Methods

The ATBC[6] Study (6) included 29,133 male smokers, ages 50–69 years, recruited from southwestern Finland from 1985 to 1988. Subjects were provided α-tocopherol and/or β-carotene supplements or placebo for 5–8 years, with postintervention follow-up continuing through the Finnish Cancer Registry. The study was approved by the institutional review boards of the National Cancer Institute and the National Public Health Institute of Finland. Cases were defined as incident prostate cancers diagnosed through 1994 with available serum ($n = 232$). Two controls were matched to each case based on clinic, intervention group, date of baseline blood draw ($\pm$45 days), age ($\pm$5 years), and serum availability ($n = 464$). At baseline, participants completed detailed dietary questionnaires and provided fasting serum samples (stored at -70°C), which were analyzed as described (7). Cases and matched controls were assayed consecutively within batches. Coefficients of variation, calculated from masked quality-control samples, were 9% (folate), 6% (B_{12}), and 15% (B_6 and homocysteine). ORs and 95% CIs were estimated using conditional logistic regression models, adjusted for BPH at baseline (with no other confounders identified). Effect modification was assessed through a cross-product term and stratification. We had 88% power to detect an OR of $\geq$2.0 for the highest *versus* lowest quartile ($\alpha = 0.05$).

Results

Prostate cancer cases reported greater use of vitamin/mineral supplements than did controls, but cases did not differ with respect to other demographic, dietary, and serum factors examined. Many subjects had inadequate serum vitamin status (92% for folate, with 24% deficient; 55% for B_6; and 1% for B_{12}), and 19% had mildly elevated homocysteine. Correlations between nutrient intakes and serum concentrations were modest; for folate, B_6, and B_{12}, Spearman r values were 0.20, 0.33, and 0.13, respectively. Homocysteine was inversely correlated with folate, B_6, and B_{12} (r values: -0.40, -0.12, and -0.19, respectively).

Serum folate, B_6, B_{12}, and homocysteine were not associated with prostate cancer risk (Table 1). There was no evidence of effect modification by age, intervention group, smoking, body mass index, BPH, or intake of folate, B_6, B_{12}, or methionine; however, the association between homocysteine and prostate cancer risk was modified significantly by alcohol intake (p interaction = 0.04), with a positive association observed among those who consumed more alcohol (OR = 1.71 and 95% CI = 0.76–3.83 for highest *versus* lowest quartile) and a modest inverse association among those who consumed less alcohol. Consistent with this, an opposite pattern was observed for serum folate (interaction not significant). We observed no material differences in the associations based on disease stage.

Discussion

We observed no association between serum factors related to one-carbon metabolism and prostate cancer risk, although these relationships may be modified by alcohol intake. Smoking has been inversely associated with folate status, and all enrollees in the ATBC Study smoked $\geq$5 cigarettes/day at baseline; however, other investigations from this cohort showed inverse associations for these one-carbon factors (*e.g.*, pancreas and lung cancers). Whether smokers

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[6] The abbreviations used are: ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention; OR, odds ratio; CI, confidence interval; BPH, benign prostatic hyperplasia.

Table 1 Adjusted ORs and 95% CIs of prostate cancer by baseline serum nutrient quartiles (ATBC Study, 1985–1994)

Serum nutrients	Cases (n = 224)[a]	Controls (n = 454)	OR[b]	95% CI
Folate (nM)				
1 (≤6.87)	56	118	1.00	
2 (6.88–8.69)	55	109	1.10	0.69–1.75
3 (8.70–10.79)	52	114	1.04	0.64–1.67
4 (>10.79)	61	113	1.20	0.74–1.94
			p trend = 0.52	
Vitamin B_6 (nM)				
1 (≤19.31)	57	114	1.00	
2 (19.32–27.88)	58	113	1.03	0.67–1.60
3 (27.89–41.08)	45	114	0.76	0.46–1.24
4 (>41.08)	64	113	1.11	0.71–1.75
			p trend = 0.64	
Vitamin B_{12} (pM)				
1 (≤280.91)	53	114	1.00	
2 (280.92–345.57)	61	113	1.19	0.76–1.86
3 (345.58–414.91)	52	114	1.00	0.62–1.60
4 (>414.91)	58	113	1.12	0.70–1.78
			p trend = 0.81	
Homocysteine (μM)				
1 (≤10.08)	53	114	1.00	
2 (10.09–11.79)	51	113	0.94	0.58–1.52
3 (11.80–14.20)	62	115	1.15	0.71–1.86
4 (>14.20)	58	112	1.05	0.64–1.73
			p trend = 0.68	

[a] Eight cases and 10 controls were lost due to cracked vials.
[b] ORs are adjusted for BPH. Controls were matched to cases on age, clinic, intervention group, and date of baseline blood draw.

may benefit from these nutrients for only selected cancers, and whether individuals with high alcohol intakes have increased requirements for folate and one-carbon metabolism cofactors, should be pursued in other studies.

The prospective study design is an important strength that minimized the possibility of disease or treatment effects on serum, and we examined several key serum factors related to one-carbon metabolism. The study included only older male smokers who participated in the original prevention trial, limiting the generalizability of the present study. Furthermore, study subjects had relatively low concentrations of folate and B_6, a strength when compared with studies not capturing well the low serum range, but a potential limitation if higher concentrations are essential for cancer risk reduction. In conclusion, although one-carbon metabolism factors may be associated with the risk of several malignancies (3), the factors do not seem to be related to prostate cancer in this study.

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