

Short Communication

The Association between Baseline Vitamin E, Selenium, and Prostate Cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study¹

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Abstract

The association between prostate cancer and baseline vitamin E and selenium was evaluated in the trial-based cohort of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study ($n = 29,133$). During up to 9 years of follow-up, 317 men developed incident prostate cancer. Multivariate Cox proportional hazards models that adjusted for intervention group, benign prostatic hyperplasia, age, smoking, and urban residence were used to evaluate associations between prostate cancer and exposures of interest. There were no significant associations between baseline serum α -tocopherol, dietary vitamin E, or selenium and prostate cancer overall. The associations between prostate cancer and vitamin E and some of the baseline dietary tocopherols differed significantly by α -tocopherol intervention status, with the suggestion of a protective effect for total vitamin E among those who received the α -tocopherol intervention (relative risk was 1.00, 0.68, 0.80, and 0.52 for increasing quartiles; $P = 0.07$).

Introduction

Vitamin E is the major lipid-soluble antioxidant in cell membranes and may play a role in reducing cancer incidence. Vitamin E, a free-radical scavenger, inhibits lipid peroxidation (1, 2) and has been reported to suppress chemically initiated tumors in some (3), but not all, animal studies (4, 5). In addition, vitamin E acts to block the *in vivo* formation of *N*-nitroso compounds that have been related to certain cancers (6). Vitamin E is a generic descriptor for tocopherol and tocotrienol derivatives that exhibit the biological activity of α -tocopherol. Although α -tocopherol seems to be most important, at least eight tocopherols and tocotrienols have vitamin E

activity, but little is known of any association they might have with cancer.

Selenium, an essential component of the enzyme glutathione peroxidase, plays a role in the stabilization of hydrogen and lipid peroxides. Selenium may also protect against cancer through other mechanisms including inhibition of cell proliferation and stimulation of the immune system (7). Selenium and vitamin E have each been reported to compensate for deficiency of the other and to synergistically act to inhibit carcinogenesis (8, 9).

Supplementation with α -tocopherol (50 mg daily) resulted in a 34% reduction in the incidence of prostate cancer in the ATBC Study³ (10). Another recent report found that persons who received selenium supplementation (200 μ g daily) had significantly lower prostate cancer incidence compared with those receiving a placebo (11). These encouraging results prompted us to evaluate whether pretrial vitamin E or selenium status in the ATBC Study cohort, as measured by baseline serum and/or dietary intake measures and independent of the trial supplementation, was associated with risk for prostate cancer. A secondary objective was to assess whether other tocopherols and tocotrienols showed similar associations with prostate cancer.

Subjects and Methods

Sample Population. The ATBC Study was conducted in Finland between 1985 and 1993 as a joint project between the National Public Health Institute of Finland and the United States National Cancer Institute. The overall design, rationale, and objectives of this study have been published (12). Briefly, the ATBC Study was a randomized, double-blind, placebo-controlled, primary prevention trial conducted to determine whether daily supplementation with α -tocopherol, β -carotene, or both would reduce the incidence of lung or other cancers. A total of 29,133 male smokers between the ages of 50 and 69 years were recruited from southwestern Finland and randomly assigned to 1 of 4 groups: (a) 50 mg/day α -tocopherol (as *dl*- α -tocopheryl acetate); (b) 20 mg/day β -carotene; (c) both α -tocopherol and β -carotene; or (d) placebo. Recruitment took place between 1985 and 1988, and follow-up continued for 5–8 years until death or trial closure (April 30, 1993). Median follow-up was 6.1 years. Men continue to be followed postintervention. Men who: (a) were alcoholics; (b) had cirrhosis of the liver, severe angina with exertion, or chronic renal insufficiency; or (c) had been previously diagnosed with cancer were excluded. Those taking supplements of vitamins E or A or β -carotene in excess of defined amounts or receiving antio-

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³ The abbreviations used are: ATBC Study, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BPH, benign prostatic hyperplasia; RR, relative risk; CI, confidence interval; BMI, body mass index.

agulant therapy were also excluded (12). The ATBC Study was approved by the institutional review boards of both the National Public Health Institute of Finland and the United States National Cancer Institute, and written informed consent was obtained from each participant before randomization.

Case Identification. For this analysis, cohort cases were defined as incident cases of prostate cancer (International Classification of Diseases 9, code 185) diagnosed by April 30, 1994 ($n = 317$). These cancers were identified through the Finnish Cancer Registry and the Register of Causes of Death. Medical records were reviewed centrally by study physicians, including oncologists, to confirm diagnoses. Cases with histology or cytology available (98%) were also reviewed by pathologists.

Data Collection. At baseline, study subjects completed a demographic and general medical history questionnaire and a food frequency (use) questionnaire and provided a fasting blood sample. Serum α -tocopherol was determined by high-performance liquid chromatography (13) at one laboratory. The between-run coefficient of variation was 2.2%. The ATBC Study food use questionnaire consisted of a modified diet history including both portion size and frequency of consumption for 203 food items and 73 mixed dishes (14). This instrument was intended to measure usual consumption over the previous 12 months. Dietary intake was estimated through the use of food composition data available from the National Public Health Institute of Finland. Finland began fortification of agricultural fertilizers with selenium in the fall of 1984 (15). As a result, average selenium intake increased 2–3-fold in the next 5 years, stabilizing at 125 $\mu\text{g}/\text{day}$, until it was lowered in 1993 to approximately 80 $\mu\text{g}/\text{day}$ (16). The selenium content of foods used to calculate selenium intake during the ATBC Study were analyzed in 1986. This seems to be a good estimate for the whole trial period, because the Spearman correlation between calculated selenium intakes based on the 1986 selenium database and the 1984 database was 0.87. Also, the correlation between the calculated intakes based on the prefortification time and the 1986 calculations was 0.83. Thus, the 1986 selenium intakes also seem to rank the men very well for the pretrial time, when the selenium intake levels were quite low. Previous research has shown that for dietary vitamin E and selenium, the food use questionnaire had intraclass correlation coefficients of 0.70 and 0.63, respectively for reproducibility, and Pearson correlation coefficients, after energy adjustment were 0.69 and 0.53, respectively, for validity (14).

Statistical Analysis. Statistical analyses were performed using SAS Institute, Inc. software (17, 18). Cox regression methods were used to estimate the associations between serum vitamin E, dietary tocopherol and tocotrienols, and dietary selenium and the incidence of prostate cancer (19). Our analysis used follow-up time as the underlying time metric and adjusted for age at randomization as a continuous variable. Dietary variables were log-transformed to meet the assumptions of regression and to minimize the effects of outliers and were adjusted for calories. Serum α -tocopherol was adjusted for serum cholesterol and was log-transformed for analysis. Dietary and serum variables were entered into models both as continuous predictors and as indicator variables defined by the second through fourth quartiles of intake among the entire cohort, with the lowest quartile as the reference group. An ordinal score variable was also created (*i.e.*, 1, 2, 3, and 4) to test for dose-response relationships across levels of dietary and serum variables. Supplemental intake of vitamin E and selenium and other vitamins and minerals of interest was either added to dietary intake or coded as an indicator variable of any use/no use. Intervention

Table 1 Selected baseline characteristics for prostate cancer cases and noncases^a

Characteristic	Prostate cancer ($n = 317$)	No prostate cancer ($n = 28,816$)	<i>P</i>
Age (yr)	60.9 \pm 5.1	57.2 \pm 5.1	<0.001
BMI (kg/m^2)	26.4 \pm 3.6	26.3 \pm 3.8	0.47
Smoking (cigarettes/day)	18.8 \pm 5.0	20.4 \pm 8.8	<0.001
Serum α -tocopherol (mg/l)	11.8 \pm 3.2	11.9 \pm 3.6	0.66
Total energy intake (kcal/day)	2737 \pm 824	2816 \pm 787	0.04
Vitamin E intake (mg/day)			
Total	13.7 \pm 11.5	14.5 \pm 15.9	0.21
Dietary	11.7 \pm 5.5	12.1 \pm 5.7	0.18
Supplemental (for users) ^b	20.9 \pm 36.4	24.2 \pm 41.4	0.60
Selenium intake ($\mu\text{g}/\text{day}$)			
Total	93.9 \pm 40.2	95.9 \pm 36.5	0.06
Dietary	86.6 \pm 28.1	89.8 \pm 28.0	0.03
Supplemental (for users) ^b	56.5 \pm 38.9	68.9 \pm 45.3	0.08
Supplements (% used any)	27.2	21.2	0.009
Marital status (% married)	77.9	80.2	0.30
Living in urban area (% yes)	51.1	42.3	0.002
Education (% > elementary)	23.0	21.0	0.38
Family history (% positive)	18.0	14.2	0.11
BPH (%)	8.8	3.9	0.001

^a Mean \pm SD, Wilcoxon test for continuous variables; %, χ^2 test for categorical variables.

^b Mean \pm SD for those using this supplement.

group assignment was included in all models, coded as three indicator variables for α -tocopherol, β -carotene, and both α -tocopherol and β -carotene supplementation, using the placebo group as a reference.

Multivariate models were developed from a basic model that included trial intervention group and age at randomization. Other variables that produced significant changes in log likelihoods ($P < 0.05$) or produced a material (>10%) change in the coefficient for another covariate were retained in the models. The associations between serum α -tocopherol, dietary tocopherols, tocotrienols, and selenium and prostate cancer were evaluated within models that added prior history of BPH (yes/no), urban residence (yes/no), and either total energy (dietary measures) or serum cholesterol (serum α -tocopherol). Results are reported as multivariate adjusted RRs of prostate cancer incidence with 95% CIs. Effect modification was assessed by including factors and their cross-product terms in the model and through stratified analyses by intervention group or within low and high categories of factors (based on median splits). We checked the validity of the proportional hazards assumption by examining the cross-product term of follow-up time and the covariate of interest. There were no departures from proportional hazards assumptions for any covariate included in the final models.

Results

There were 317 incident cases of prostate cancer ascertained over approximately 9 years of follow-up. Median follow-up was 7 years. Selected baseline characteristics for prostate cancer cases and noncases are presented in Table 1. Those who developed prostate cancer were, on average, 3.7 years older than those not developing prostate cancer, smoked fewer cigarettes/day, and were more likely to have a history of BPH and to live in an urban area. Dietary information was available for 302 prostate cases. Both groups had similar intake of both dietary and supplemental vitamin E. Dietary intake of specific subfractions of vitamin E (tocopherols and tocotrienols) did not

differ significantly between the two groups (data not shown). Prostate cancer cases tended to have lower intakes of total energy and both dietary and supplemental selenium and were also more likely to have used any vitamin/mineral supplement. Overall, micronutrient supplement use in this population was 21.2%, with only 8.8% reporting that they used a supplement containing selenium, and 10.1% reporting that they used a supplement containing vitamin E (only 6.2% were taking both). BMI, serum α -tocopherol, and marital status did not differ significantly between cases and noncases.

There were no significant protective or harmful associations between prostate cancer and any of the measures of vitamin E or selenium for the data as a whole (data not shown). Our analyses evaluated dietary and supplemental vitamin E and selenium, specific tocopherol and tocotrienols, and serum α -tocopherol. Furthermore, there was no significant synergistic effect of vitamin E and selenium intake. The RR estimates and 95% CIs for low selenium/high vitamin E, high selenium/low vitamin E, and high selenium/high vitamin E intake as compared to low selenium/low vitamin E intake (based on median splits) were 0.92 (0.65–1.31), 0.86 (0.58–1.28), and 1.04 (0.75–1.45), respectively.

We did not observe any meaningful effect modification for any of these associations by energy, total fat, antioxidant vitamin intake, BMI, age, number of cigarettes smoked daily, BPH, or length of follow-up. There was, however, significant effect modification by the α -tocopherol intervention for two of the dietary associations (total vitamin E intake and γ -tocopherol intake, both $P = 0.01$), and there was marginal effect modification for another (dietary α -tocopherol, $P = 0.06$). Therefore, in Table 2, we present the RR of prostate cancer for the quartiles of dietary intake or serum concentration according to the trial α -tocopherol supplementation group. In the group that received the α -tocopherol intervention, there was a suggestion of a protective association with increasing total vitamin E intake. The effect was limited to the highest quartile, however, and the effect was limited within that quartile to those with the very highest intakes. This finding was not supported by the serum α -tocopherol analyses. There was also a suggestion of a similar association for dietary γ -tocopherol intake. In the non- α -tocopherol group, there was the suggestion of slightly increased risk for vitamin E intake (and for some of its fractions), but not for serum α -tocopherol (Table 2). When cases diagnosed during the first 2 years were excluded, the results were essentially unchanged.

In assessing prestudy supplement use, we observed a marginally significant positive association between prostate cancer and supplemental selenium (RR, 1.36; 95% CI, 0.98–1.90) and a positive association for use of any vitamin supplement (RR, 1.32; 95% CI, 1.03–1.68). Selenium supplement use was highly correlated with the use of other supplements, including copper, zinc, vitamin A, vitamin E, folate, and iron; therefore, these findings should be regarded as preliminary and require further exploration. Baseline vitamin E supplementation was not associated with prostate cancer risk (RR, 1.12; 95% CI, 0.80–1.57). We did not observe any effect modification of these associations by other factors (listed above), and the RR estimates did not change appreciably with the exclusion of prostate cancer cases diagnosed during the first 2 years of follow-up.

Discussion

In this trial-based cohort of older male smokers, prestudy dietary vitamin E, selenium, and serum vitamin E (α -tocopherol) were not associated with the incidence of prostate cancer in the

group as a whole. In addition, specific tocopherols and tocotrienols from dietary sources, as well as pretrial use of vitamin E supplements, were unrelated to prostate cancer risk. For some of the dietary associations, the results were altered by α -tocopherol supplementation during the intervention. For both total vitamin E intake and γ -tocopherol intake, there was a trend for increasing intake to be protective among those receiving α -tocopherol supplementation during the trial. These effects, however, were not supported by the serum α -tocopherol results. The Spearman correlation coefficient between total vitamin E intake and γ -tocopherol is 0.76 in this data; therefore, it is difficult to determine whether the result for total vitamin E is independent of that for γ -tocopherol. Among those not receiving α -tocopherol supplementation, there was a significant positive association between δ -tocopherol intake and prostate cancer risk. There is no support in the literature for a positive association between δ -tocopherol and prostate cancer. Therefore, we regard this finding as preliminary and suggest that, despite its nominal statistical significance, it may be due to chance.

The lack of an inverse association between total vitamin E intake and prostate cancer among men who did not receive α -tocopherol supplementation is, at first glance, not consistent with our trial finding of a substantial protective effect on prostate cancer incidence from α -tocopherol supplementation (10). However, before the trial, in comparison to the trial period, the percentage of men taking supplemental α -tocopherol was low (10.1%), the mean dose among supplement users was substantially lower, and supplement use was likely to be more irregular.

Two recent controlled trials evaluated the preventive effects of vitamin E or selenium supplementation on prostate cancer. In the randomized trial results reported for the ATBC Study, α -tocopherol supplementation (50 mg/daily) for 5–8 years led to a 34% reduction in prostate cancer incidence in older smokers (10). The other trial, which was conducted in the United States and included men and women, smokers and nonsmokers, showed that total cancer incidence and mortality were reduced, including 57% fewer prostate cancers among persons who received 200 μ g of supplemental selenium daily for approximately 5 years (11). In both trials, the supplemental dosages greatly exceeded the average prestudy intake reported here: only 2% of the ATBC Study population had pretrial daily intakes of at least 50 mg of α -tocopherol or 200 μ g of selenium. Therefore, the disparity in intake levels might account for the present findings not corroborating with the results of the two trials.

Observational studies are inconsistent with regard to a beneficial association between vitamin E or selenium and prostate cancer, but they offer little in the way of supportive data. Of the few cohort studies having a sufficient number of prostate cancers for analysis, one failed to demonstrate a protective association between serum vitamin E and prostate cancer, although such an association was observed for lung cancer (20). Contrary results were obtained in another study showing an inverse association between serum vitamin E and prostate cancer (21). In two separate reports from another Finnish cohort, no association was found between serum α -tocopherol (22) or serum selenium (23) and prostate cancer. A large population-based case-control study in Sweden found that dietary vitamin E was not significantly associated with prostate cancer (24). Dietary selenium and prostate cancer risk were unrelated in one large case-control study in Utah (25). Several other observational studies included prostate cancers as a component of "all cancers" in their examination of the relationship between vita-

Table 2 RR of prostate cancer according to quartiles of vitamin E or selenium by α -tocopherol supplementation group^a

Nutrient intake ^b	Non-AT ^c (n = 190)			AT (n = 127)		
	RR	95% CI	P	RR	95% CI	P
Vitamin E (including supplements)						
Q1 <8.40	1.00			1.00		
Q2 8.41-11.25	0.87	0.56-1.36	0.28	0.68	0.41-1.15	0.07
Q3 11.26-15.96	1.09	0.70-1.69		0.80	0.48-1.34	
Q4 >15.96	1.19	0.76-1.86		0.52	0.29-0.95	
Vitamin E						
Q1 <8.17	1.00			1.00		
Q2 8.17-10.70	0.81	0.52-1.27	0.17	0.66	0.39-1.11	0.21
Q3 10.71-14.44	1.07	0.69-1.67		0.74	0.43-1.26	
Q4 >14.44	1.26	0.80-2.00		0.65	0.36-1.18	
α -Tocopherol						
Q1 <7.03	1.00			1.00		
Q2 7.03-9.21	1.01	0.66-1.55	0.28	0.72	0.43-2.10	0.29
Q3 9.22-12.43	0.98	0.62-1.56		0.76	0.43-1.20	
Q4 >12.43	1.30	0.82-2.07		0.70	0.44-1.31	
β -Tocopherol						
Q1 <0.54	1.00			1.00		
Q2 0.54-0.77	1.02	0.66-1.57	0.13	0.84	0.51-1.39	0.41
Q3 0.78-1.09	1.07	0.69-1.67		0.76	0.44-1.29	
Q4 >1.09	1.42	0.90-2.25		0.81	0.46-1.44	
δ -Tocopherol						
Q1 < 0.36	1.00			1.00		
Q2 0.36-0.71	0.93	0.60-1.45	0.02	1.28	0.78-2.11	0.36
Q3 0.72-2.32	1.29	0.85-1.96		1.37	0.83-2.26	
Q4 >2.32	1.48	0.99-2.22		0.70	0.38-1.26	
γ -Tocopherol						
Q1 <3.00	1.00			1.00		
Q2 3.00-5.75	0.94	0.62-1.44	0.12	0.82	0.51-1.34	0.08
Q3 5.76-11.02	1.13	0.74-1.71		0.91	0.56-1.48	
Q4 >11.02	1.33	0.88-1.99		0.56	0.32-0.98	
α -Tocotrienol						
Q1 <1.30	1.00			1.00		
Q2 1.30-1.84	1.10	0.73-1.66	0.66	1.32	0.79-2.20	0.86
Q3 1.85-2.53	0.98	0.63-1.51		1.30	0.76-2.22	
Q4 >2.53	0.93	0.57-1.52		1.04	0.56-1.95	
β -Tocotrienol						
Q1 <1.77	1.00			1.00		
Q2 1.77-2.41	0.79	0.51-1.22	0.58	0.95	0.5-1.57	0.87
Q3 2.42-3.19	1.03	0.66-1.60		0.75	0.42-1.34	
Q4 >3.19	1.08	0.64-1.80		1.04	0.55-1.97	
δ -Tocotrienol						
Q1 <0.02	1.00			1.00		
Q2 0.02-0.05	0.97	0.66-1.44	0.63	1.23	0.74-1.95	0.39
Q3 0.06-0.11	0.81	0.53-1.26		1.28	0.75-2.03	
Q4 >0.11	1.17	0.78-1.77		0.72	0.40-1.21	
γ -Tocotrienol						
Q1 <0.12	1.00			1.00		
Q2 0.12-0.20	0.88	0.58-1.33	0.43	0.83	0.50-1.34	0.50
Q3 0.21-0.13	0.93	0.61-1.42		1.06	0.65-1.73	
Q4 >0.31	1.17	0.77-1.77		0.74	0.42-1.29	
Selenium (including supplements)						
Q1 <71.52	1.00			1.00		
Q2 71.52-89.12	1.09	0.71-1.68	0.49	0.80	0.47-1.35	0.64
Q3 89.13-111.05	0.97	0.59-1.60		0.78	0.43-1.44	
Q4 >111.05	1.27	0.70-2.20		0.84	0.43-1.67	
Selenium						
Q1 <70.11	1.00			1.00		
Q2 70.11-85.63	1.08	0.70-1.68	0.50	0.63	0.36-1.09	0.50
Q3 85.64-105.63	1.02	0.61-1.70		0.76	0.41-1.39	
Q4 >105.64	1.32	0.70-2.47		0.72	0.33-1.55	
Serum α -tocopherol						
Q1 <9.78	1.00			1.00		
Q2 9.78-11.47	1.04	0.69-1.56	0.80	0.86	0.52-1.44	0.37
Q3 11.48-13.60	0.91	0.58-1.42		0.82	0.48-1.39	
Q4 >13.60	0.98	0.60-1.60		0.76	0.42-1.37	

^a Models adjusted for age, BPH, living in an urban area, β -carotene intervention, and total energy (dietary factors) or serum cholesterol (serum α -tocopherol).

^b Q, quartile. Units for nutrients are: Vitamin E, tocopherols and tocotrienols, mg/day; selenium, μ g/day; and serum α -tocopherol, mg/l.

^c AT, α -tocopherol supplementation group.

min E, selenium, or both and cancer. Each of these studies had fewer than 60 prostate cancer cases. Of these, two do not support the hypothesis that higher serum vitamin E is related to lower overall risk of cancer (26, 27), and four observed an inverse association between serum selenium and cancer (28–31). None of these six studies reported risk of prostate cancer as a separate site; however, one (27) reported that serum vitamin E values were not significantly different for prostate cases (compared to controls), and one (30) reported that serum selenium values were lower in prostate cancer cases, but not significantly so.

In this study, there was a marginally positive association between selenium supplement use and prostate cancer, which we would interpret cautiously. Vitamin supplement users are known to differ from nonusers with respect to various characteristics including, for example, being better educated, being less overweight, and being more physically active (32, 33). It is reasonable to speculate that they might also be more inclined to have regular examinations by a physician and to have their prostate-specific antigen determined, either of which could lead to the discovery of prostate cancer. Furthermore, supplement use might result from the perception of declining health or the diagnosis of cancer, rather than being its cause. Although we were able to exclude confounding by BPH or other factors as the reason behind the finding, and removal from the analysis of early cases did not alter the result, the possibility also remains that selenium supplement use is a marker for some unknown or unmeasured risk factor for prostate cancer.

One of the important strengths of this investigation is that the assessment of exposures took place at study entry for men without known cancer. Another strength was the relatively large number of prostate cancer cases in this population, which allowed for more stable RR estimates and, in addition, permitted us to examine in detail associations of interest and several important covariates to rule out confounding and effect modification. We also had access to both dietary and biochemical measurements with which to assess vitamin E status. Dietary intake has been shown to be a significant predictor of serum α -tocopherol, and in this population, serum and dietary α -tocopherol did not demonstrate seasonal variability (34). Serum α -tocopherol is thought to be representative of long-term intake, and degradation over time when stored at -70 degrees is minimal (20). In addition, we used a validated instrument with good reproducibility to evaluate dietary consumption with nutrient intake quantified through a Finnish nutrient database.

There are also some limitations to this study. The generalizability of these results may be somewhat restricted, because the study included only older smokers who participated in a clinical trial. At the end of 9 years of follow-up, the men ranged in age from 58–77 years, a period during which the majority of prostate cancers are diagnosed. Finally, the intake of vitamin E and selenium at baseline were largely from dietary sources, with only a small percentage of men using vitamin E supplements at entry; thus, few had intakes in the range achieved with supplementation during the trial.

In summary, we found no significant associations between baseline serum α -tocopherol or dietary selenium and prostate cancer. The relationship between baseline dietary vitamin E and prostate cancer differed by α -tocopherol intervention status, with an inverse association being observed only among those who received the α -tocopherol intervention, particularly for total vitamin E, dietary vitamin E, and γ -tocopherol, and with no association evident in the non- α -tocopherol-supplemented group.

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