

Vitamin E Supplements and Risk of Prostate Cancer in U.S. Men

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Abstract

Supplementation with α -tocopherol (a form of vitamin E) was associated with decreased risk of prostate cancer in a randomized trial among Finnish smokers. We examined the association between vitamin E supplement use and prostate cancer incidence in the Cancer Prevention Study II Nutrition Cohort. Participants in the study completed a detailed questionnaire at enrollment in 1992–1993. Historical information was also available from a questionnaire completed in 1982 at enrollment in a previous cohort. Through August 31, 1999, we documented 4,281 cases of incident prostate cancer among 72,704 men. Multivariate-adjusted rate ratios (RRs) were calculated using Cox Proportional

Hazards models. Regular vitamin E supplement use (≥ 4 times per week) was not associated with overall risk of prostate cancer or with risk of advanced prostate cancer at diagnosis. No trend was seen with increasing dose of vitamin E. Men who reported regular vitamin E use in both 1982 and in 1992–1993 were not at lower risk of prostate cancer. Among current smokers, there was a suggestion of slightly reduced risk with regular vitamin E supplement use [RR = 0.87, 95% confidence interval (CI) = 0.67–1.11]. Our results do not support an important role for vitamin E supplements in prostate cancer prevention. (Cancer Epidemiol Biomarkers Prev 2004;13(3):378–382)

Introduction

Prostate cancer incidence and mortality were reduced among male smokers, men receiving 50 IU of vitamin E (as α -tocopherol), for up to 8 years in the Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study (ATBC Study) (1). The reduction in prostate cancer incidence and mortality was unexpected and prompted the Selenium and Vitamin E Cancer Prevention Trial (SELECT) sponsored by the National Cancer Institute (2). The ongoing SELECT trial will examine the independent and joint effects of selenium and vitamin E (α -tocopherol) supplementation in 32,000 men over more than 12 years. However, results from the SELECT trial will not be available for many years.

Vitamin E is a potent antioxidant and has been hypothesized to decrease cancer risk (3). In diet, vitamin E occurs in several different forms, including both α -tocopherol and γ -tocopherol (4). Although α -tocopherol plasma levels were associated with reduced prostate cancer risk in two prospective studies (5, 6), results from two population-based prospective studies raised the possibility that only plasma γ -tocopherol is associated with prostate cancer risk (7, 8). Because the high doses of α -tocopherol present in vitamin E supplements can reduce γ -tocopherol concentrations in plasma (9), it has been hypothesized that vitamin E supplement use could

actually increase prostate cancer risk (10). This hypothesis is supported by the significantly increased risk of prostate cancer associated with vitamin E supplement use observed among never smokers in a recent cohort study (11).

We examined the association between vitamin E supplement use and prostate cancer incidence in a large prospective cohort of elderly men.

Materials and Methods

Study Population. Men in this study were selected from the 86,404 male participants in the Cancer Prevention Study II (CPS-II) Nutrition Cohort (hereafter referred to simply as the Nutrition Cohort), a prospective study of cancer incidence and mortality among 184,192 U.S. men and women. The Nutrition Cohort, as described in detail elsewhere (12), is a subgroup of the approximately 1.2 million participants in the CPS-II.

Participants were 50–74 years of age at enrollment in 1992 or 1993, when they completed a self-given mailed questionnaire. Follow-up questionnaires were sent in September 1997 and 1999 to ascertain newly diagnosed cancers. For living cohort members, the response rate was close to 91% for both questionnaires.

We excluded from this analysis men who were lost to follow-up from enrollment through August 31, 1999, who reported any prevalent cancer (except non-melanoma skin cancer) at enrollment or whose self-report of prostate cancer could not be confirmed, and men with incomplete information on vitamin E use ($N = 13,700$). The analytic cohort consisted of 72,704 men.

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Identification of Cases of Prostate Cancer. We identified and verified 4,281 incident cases of fatal or non-fatal prostate cancer that occurred between enrollment and August 31, 1999. Prostate cancer cases were identified through a self-report of cancer on the two follow-up questionnaires ($N = 4,154$) and verified by medical records ($N = 3,304$), from linkage with state cancer registries ($N = 850$), or identified if recorded as the underlying cause of death on a death certificate during follow-up through August 31, 1999 ($N = 127$). Deaths were ascertained among cohort members through linkage with the National Death Index (13).

For analysis of advanced prostate cancer, we included prostate cancer cases verified by medical records as stages C and D according to the Whitmore-Jewett staging system, those classified as regional or distant by a state cancer registry, and prostate cancer deaths. A total of 668 advanced cases was included in the analysis of advanced cases.

Supplemental Vitamin E Intake Assessment. Supplemental vitamin E intake at enrollment in 1992–1993 was ascertained using a semiquantitative 68-item food frequency questionnaire (FFQ). The FFQ, a modification of the brief "Health Habits and History Questionnaire" (HHHQ) (14, 15), asked to report the number of vitamin E tablets taken per week during the last year. Response categories were 1–3 per week, 4–6 per week, 1 per day, 2 per day, 3 per day, 4 per day, or 5 or more per day. Information about dose was also collected for vitamin E tablets in IUs (100 IU, 200 IU, 400 IU, 1000 IU, don't know). A total of 1,073 men out of the 12,099 reporting individual vitamin E supplement use did not report dose and were assigned a dose of 400 IU, the most common individual vitamin E supplement dose reported. Total supplemental vitamin E intake includes contributions from both individual vitamin E supplements and multivitamin pills. Daily vitamin E supplement dose was estimated from the FFQ using the Diet Analysis System version 3.8a (15), which estimates the vitamin E content of multivitamins as 31 IU per pill. Dietary intake of α -tocopherol in the U.S. is considerably lower, averaging about 15 IU per day (4).

Long-term vitamin E supplement use was assessed through historical information obtained in the 1982 CPS-II questionnaire. This questionnaire included a section asking about current use of four supplements (multivitamins, vitamin A, vitamin C, and vitamin E). For each supplement, participants were asked to report the number of times used in the last month and the number of years of use.

Supplemental vitamin E intake at baseline was examined by frequency and dose based on responses to the 1992–1993 questionnaire. We classified men by frequency of use as never vitamin E supplement users, occasional users (men who reported taking one to three multivitamin pills or vitamin E tablets per week), or regular users (men who reported taking four or more multivitamin pills or vitamin E tablets per week). Among regular users, daily supplement use was common, with 83% of men reporting daily use of vitamin E supplements (from multivitamin or individual supplements).

Daily dose of vitamin E from supplements (individual supplements and multivitamins combined) was categorized into four categories of IUs (None, 31 IU, 32 to <400

IU, ≥ 400 IU). The category of 31 IU per day represents predominantly men who use multivitamins but not individual vitamin E supplements. An intake of 400 or more IU represents at least daily use of an individual vitamin E supplement at the most commonly reported dose (400 IU). Long-term vitamin E supplement use was examined by combining information from the 1982 and 1992 questionnaires. For these analyses, men who in 1982 reported multivitamin or individual vitamin E use 16 or more times per month (roughly equivalent to 4 times per week) and regular use of vitamin E supplements in 1992 were categorized as regular users; those who reported no use of vitamin E supplements in either 1982 or 1992 were classified as never users, and those who reported unquantified "occasional" use, or intake 1–15 times per month in 1982 and/or in 1992 were categorized as occasional users. We repeated all the analyses both including and excluding men who reported multivitamin use.

Statistical Analysis. We used Cox proportional hazards modeling to examine the association of supplemental vitamin E intake with prostate cancer incidence while adjusting for other potential risk factors. All Cox models were adjusted for age (single year of age at enrollment) and race (white, black, other) by stratification within the model (16). Multivariate models also included variables adjusting for education, family history of prostate cancer in a brother and/or father, smoking, body mass index (BMI) (kg/m^2), and quintiles of total energy intake, energy adjusted total fat intake, lycopene, and total (dietary plus supplements) calcium intake. All covariates except age, were modeled as dummy variables using categories shown in Table 1.

We examined whether the association between supplemental vitamin E intake and prostate cancer incidence varied by other examined risk factors. Because the ATBC trial (1) observed a reduction in prostate cancer incidence among smokers that have taken α -tocopherol supplement, we examined the association between both regular vitamin E intake and vitamin E dose (none, 1–31, ≥ 32 IU) and prostate cancer incidence stratified by smoking status (never, current, and former smoker). All interaction P values presented are two-sided P values for heterogeneity of rate ratios (RRs) calculated using the likelihood ratio statistic (17).

Results

More than one-third (38%) ($N = 27,736$) of men included in the analysis reported taking vitamin E as individual supplements or multivitamins at baseline. Approximately 17% ($N = 12,099$) reported taking individual vitamin E supplements; an additional 21% ($N = 15,637$) reported taking multivitamins. The age-adjusted percentage distribution of potential prostate cancer risk factors varied with vitamin E supplement use (Table 1). Men taking vitamin E supplements regularly were older, more likely to be highly educated, former smokers, thinner, have had PSA screening before study entry, and consume a diet higher in calcium and lycopene, and lower in total calories and fat.

We found no evidence of reduced risk of prostate cancer among men taking vitamin E supplements

Table 1. Age-adjusted percentages and means^{a,b} of demographic characteristics by vitamin E dose in 1992, CPS-II Nutrition Cohort, 1992–1999

	Vitamin E dose/day in IUs							
	None (n = 44,968)		1–31 (n = 14,745)		32 to <400 (n = 5,164)		≥400 (n = 7,827)	
	No.	% or mean	No.	% or mean	No.	% or mean	No.	% or mean
Age group								
<60	11,910	26.5	3,649	24.8	1,267	24.5	1,534	19.6
60–69	26,229	58.3	8,613	58.4	2,856	55.3	4,410	56.3
70–79	6,554	14.6	2,379	16.1	987	19.1	1,793	22.9
≥80	275	0.6	104	0.7	54	1.1	90	1.2
Race								
White	43,803	97.4	14,383	97.5	5,019	97.2	7,638	97.6
Black	589	1.3	143	1.0	66	1.3	72	1.0
Smoking status in 1992								
Never	14,395	32.0	4,680	31.8	1,763	34.1	2,525	32.2
Current	4,420	9.7	1,240	8.4	426	8.4	536	7.2
Former, <10 yrs	3,916	8.7	1,392	9.5	498	9.7	734	9.7
Former, >10 yrs	21,269	47.4	7,160	48.5	2,357	45.6	3,893	49.2
Former, Unk yrs	548	1.2	142	1.0	66	1.3	71	0.9
BMI								
<25	14,829	33.2	5,848	39.6	2,063	39.5	3,149	39.3
25 to <30	22,483	49.9	6,878	46.7	2,460	47.9	3,663	47.3
≥30	6,991	15.4	1,822	12.4	589	11.6	913	12.1
Education								
<High School	4,107	9.2	1,005	6.8	352	6.7	513	6.3
High School Grad	9,389	20.9	2,495	16.9	773	15.0	1,208	15.2
Some College	11,516	25.7	3,862	26.2	1,318	25.3	2,045	25.8
College Grad	9,259	20.5	3,373	22.9	1,211	23.5	1,762	22.7
Graduate School	10,385	23.0	3,926	26.7	1,480	28.9	2,245	29.3
Family history of PrCa								
No	40,156	89.3	13,131	89.1	4,547	88.0	6,983	89.2
Yes	4,812	10.7	1,614	10.9	617	12.0	844	10.8
History of PSA testing								
Never/After 1992	24,569	54.5	7,827	53.1	2,735	53.2	3,975	51.2
Before 1992	8,611	19.2	3,316	22.5	1,142	22.1	1,936	24.6
Calcium intake (mg/day)								
mean		806.7		977.6	–	1,036.3	–	1,116.3
Total fat intake (g/day)								
mean	–	69.0	–	66.1	–	65.1	–	63.1
Lycopene intake (μg/day)								
mean	–	4,577.5	–	4,760.3	–	5,061.1	–	5,376.5
Total calorie intake								
mean	–	1,810.3	–	1,793.2	–	1,804.2	–	1,772.3
Dietary vitamin E intake (g)								
mean	–	8.9	–	8.8	–	9.0	–	9.0

^aPercentages may not sum to 100 due to missing data.

^bPercentages and means are directly adjusted to the age distribution of the entire study population.

(from multivitamins or individual vitamin E supplements) regularly in 1992–1993 [RR = 1.00, 95% confidence interval (CI) = 0.93–1.07]. Similarly, no reduced risk was seen for prostate cancer cases that were advanced at diagnosis (RR = 0.98, 95% CI = 0.83–1.16) (Table 2). No dose-response with increasing vitamin E supplement intake was observed (Table 2). Results were similar when men taking multivitamins were excluded (data not shown). Long-term vitamin E supplement use was not associated with risk of overall incident prostate cancer or with risk of advanced prostate cancer (Table 2). In addition, no association was seen when men taking multivitamins were excluded (data not shown).

Current smokers who used vitamin E supplements regularly had slightly lower risk of prostate cancer than men who did not use vitamin E supplements (Table 3). This decreased risk was seen among all vitamin E users (RR = 0.87, 95% CI = 0.67–1.11) and also among those with long-term use (RR=0.87, 95% CI = 0.60–1.26). No association was seen between advanced prostate cancer and vitamin E use among current smokers (RR = 1.05, 95% CI = 0.59–1.87 for regular *versus* never vitamin E use, based on 19 prostate cancer cases).

Risk estimates associated with vitamin E supplement use were similar when we stratified by use of PSA testing before 1992. No significant interactions were observed

Table 2. RRs and 95% CIs for prostate cancer incidence associated with vitamin E supplement intake, CPS-II Nutrition Cohort, 1992–1999

	All prostate cancer				Advanced prostate cancer			
	Cases	Person-Years	RR (95% CI) ^a	RR (95% CI) ^b	Cases	Person-Years	RR (95% CI) ^a	RR (95% CI) ^b
Vitamin E use in 1992								
None	2,588	271,727	1.0	1.0	413	264,199	1.0	1.0
Occasional	190	19,158	1.07 (0.92–1.24)	1.03 (0.89–1.19)	35	18,618	1.21 (0.86–1.71)	1.24 (0.88–1.76)
Regular	1,503	146,633	1.05 (0.98–1.12)	1.00 (0.93–1.07)	220	142,220	0.97 (0.82–1.14)	0.98 (0.83–1.16)
Long-term vitamin E use								
None	2,078	220,584	1.0	1.0	335	214,551	1.0	1.0
Occasional	1,549	155,986	1.04 (0.98–1.11)	1.01 (0.94–1.08)	235	151,394	0.98 (0.83–1.16)	1.00 (0.84–1.18)
Regular use ^c	654	60,948	1.09 (1.00–1.19)	1.03 (0.94–1.12)	98	59,091	1.03 (0.82–1.29)	1.03 (0.81–1.30)
Vitamin E dose/day								
None	2,588	271,727	1.0	1.0	413	264,199	1.0	1.0
1–31 IU	883	88,946	1.03 (0.96–1.11)	0.99 (0.92–1.07)	125	86,275	0.92 (0.75–1.13)	0.94 (0.76–1.15)
32 to <400 IU	328	30,659	1.11 (0.99–1.25)	1.06 (0.95–1.19)	61	29,811	1.27 (0.97–1.66)	1.29 (0.98–1.70)
≥400 IU	482	46,185	1.04 (0.94–1.15)	0.98 (0.89–1.08)	69	44,752	0.96 (0.74–1.24)	0.97 (0.74–1.26)
			<i>P trend</i> = 0.32	<i>P trend</i> = 0.83			<i>P trend</i> = 0.95	<i>P trend</i> = 0.90

^aAdjusted for age and race.^bAdjusted for age, race, smoking status, BMI, education, energy adjusted calcium, total fat, lycopene intake, total calorie intake, family history of prostate cancer, and PSA history.^cRegular user (≥4 times per week) in 1992–1993 and in 1982.

between vitamin E supplement use and any of the other potential risk factors included in this analysis.

Discussion

In this large prospective study, recent intake of vitamin E supplements was not associated with either total or advanced incident prostate cancer. No association between vitamin E use and prostate cancer risk was seen among men with daily doses of vitamin E (greater than 400 IU) or among long-term vitamin E users.

Previous observational studies have not shown consistently a lower risk of prostate cancer with vitamin E use (18). Vitamin E supplementation of at least 100 IU/day was not associated with the overall risk of prostate cancer in a prospective study of the Health Professionals cohort (11). Consistent with the Finnish ATBC trial, however, vitamin E supplement use was associated with decreased risk of metastatic or fatal prostate cancer among current smokers or recent (≤10 years) quitters (11). One case-control study reported significantly lower risk among men in the highest tertile of total vitamin E intake (diet plus supplements) (19); a second case-control study (20)

Table 3. RRs and 95% CIs for prostate cancer incidence associated with vitamin E supplement intake by smoking status, CPS-II Nutrition Cohort, 1992–1999

	Never smokers			Current smokers			Former smokers		
	Cases	Person-Years	RR (95% CI) ^a	Cases	Person-Years	RR (95% CI) ^a	Cases	Person-Years	RR (95% CI) ^a
Vitamin E use									
None	875	88,263	1.0	220	25,865	1.0	1,471	155,125	1.0
Regular	513	47,574	1.01 (0.90–1.14)	93	11,047	0.87 (0.67–1.11)	890	86,677	1.01 (0.92–1.10)
Long-term vitamin E use									
None	701	71,883	1.0	175	21,098	1.0	1,186	125,629	1.0
Occasional	532	50,194	1.05 (0.94–1.18)	117	13,385	0.96 (0.76–1.23)	1,092	90,856	0.99 (0.91–1.09)
Regular use ^b	223	20,541	1.02 (0.87–1.19)	35	4,122	0.87 (0.60–1.26)	395	35,849	1.06 (0.94–1.19)
Vitamin E dose/day									
None	875	88,263	1.0	220	25,865	1.0	1,471	155,124	1.0
1–31 IU	314	28,584	1.07 (0.94–1.22)	60	7,229	0.90 (0.67–1.21)	504	52,346	0.97 (0.87–1.07)
32 to <400 IU	106	10,649	0.98 (0.80–1.20)	20	2,437	0.87 (0.54–1.38)	199	17,264	1.15 (0.99–1.34)
≥400 IU	161	15,122	0.95 (0.80–1.13)	27	3,074	0.87 (0.58–1.31)	293	27,559	1.02 (0.90–1.16)
			<i>P trend</i> = 0.43			<i>P trend</i> = 0.48			<i>P trend</i> = 0.52

^aAdjusted for age, race, BMI, education, energy adjusted calcium, total fat, lycopene intake, total calorie intake, family history of prostate cancer, and PSA history.^bRegular user (≥4 times per week) in 1992–1993 and in 1982.

found slightly lower risk among men taking vitamin E supplements daily, although this association was not statistically significant.

Observational studies of plasma levels of vitamin E and risk of prostate cancer have also produced conflicting results (5, 6, 8, 21–25). Four studies reported no association between α -tocopherol and prostate cancer (22–25), one found plasma levels of α -tocopherol inversely associated with risk of prostate cancer mortality among smokers (21), and two studies found lower levels of α -tocopherol associated with prostate cancer among smokers (5, 21). High plasma levels of γ -tocopherol were associated with a decreased risk of developing prostate cancer in two population-based cohort studies while no associations with plasma levels of α -tocopherol were observed (7, 8).

Our results may be compatible with a small reduction in risk of prostate cancer among smokers who regularly use vitamin E (RR = 0.87, 95% CI = 0.67–1.11). Our study lacks the statistical power to examine the association between vitamin E use and advanced prostate cancer among smokers. Such a selective effect on advanced cancer among smokers is supported by results from the ATBC trial (1), conducted among smokers, where reduced risk with α -tocopherol supplementation was limited to prostate cancers stages II to IV.

In summary, results from this study do not support a strong role of vitamin E in prostate cancer prevention, although a modest protective effect among smokers cannot be ruled out.

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