

Supplemental and Dietary Vitamin E, β -Carotene, and Vitamin C Intakes and Prostate Cancer Risk

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On behalf of the PLCO Trial

Background: Vitamin E, β -carotene, and vitamin C are micronutrient antioxidants that protect cells from oxidative damage involved in prostate carcinogenesis. In separate trials, supplemental vitamin E was associated with a decreased risk of prostate cancer among smokers and supplemental β -carotene was associated with a decreased risk of prostate cancer among men with low baseline plasma β -carotene levels. **Methods:** We evaluated the association between intake of these micronutrient antioxidants from foods and supplements and the risk of prostate cancer among men in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. At baseline, trial participants completed a 137-item food frequency questionnaire that included detailed questions on 12 individual supplements. Cox proportional hazards models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). All statistical tests were two-sided. **Results:** We identified 1338 cases of prostate cancer among 29361 men during up to 8 years of follow-up. Overall, there was no association between prostate cancer risk and dietary or supplemental intake of vitamin E, β -carotene, or vitamin C. However, among current and recent (i.e., within the previous 10 years) smokers, decreasing risks of advanced prostate cancer (i.e., Gleason score ≥ 7 or stage III or IV) were associated with increasing dose (RR for >400 IU/day versus none = 0.29, 95% CI = 0.12 to 0.68; $P_{\text{trend}} = .01$) and duration (RR for ≥ 10 years of use versus none = 0.30, 95% CI = 0.09 to 0.96; $P_{\text{trend}} = .01$) of supplemental vitamin E use. Supplemental β -carotene intake at a dose level of at least 2000 $\mu\text{g}/\text{day}$ was associated with decreased prostate cancer risk in men with low (below the median of 4129 $\mu\text{g}/\text{day}$) dietary β -carotene intake (RR = 0.52, 95% CI = 0.33 to 0.81). Among smokers, the age-adjusted rate of advanced prostate cancer was 492 per 100 000 person-years in those who did not take supplemental vitamin E, 153 per 100 000 person-years in those who took more than 400 IU/day of supplemental vitamin E, and 157 per 100 000 person-years in those who took supplemental vitamin E for 10 or more years. Among men with low dietary β -carotene intake, the age-adjusted rate of prostate cancer was 1122 per 100 000 person-years in those who did not take supplemental β -carotene, and 623 per 100 000 person-years in those who took at least 2000 $\mu\text{g}/\text{day}$ of supplemental β -carotene. **Conclusions:** Our results do not provide strong support for population-wide implementation of high-dose antioxidant supplementation for the prevention of prostate cancer. However, vitamin E supplementation in male smokers and β -carotene supplementation in men with low dietary β -carotene intakes were associated with reduced risk of this disease. [J Natl Cancer Inst 2006;98:245–54]

Micronutrient antioxidants, including vitamin E, carotenoids, and vitamin C, neutralize free radicals (1), which may play a role in prostate carcinogenesis by causing oxidative damage to DNA, lipid membranes, and proteins (2). Vitamin E, which comprises a mixture of tocopherols, is a lipid-soluble antioxidant that is found in vegetable oils, nuts, whole grains, and other foods (3). Carotenoids are found in a variety of orange or yellow fruits and vegetables as well as in some dark green leafy vegetables, including spinach and Brussels sprouts (4). Vitamin C (ascorbic acid) is a water-soluble antioxidant found mainly in citrus fruits, strawberries, melons, tomatoes, broccoli, and peppers (5).

The most common carotenoids in the human diet include β -carotene, α -carotene, β -cryptoxanthin, lutein and zeaxanthin, and lycopene. Three large randomized trials have reported on the association between β -carotene supplementation and prostate cancer risk. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study found that male smokers who were randomly assigned to receive 20 mg of β -carotene daily experienced a nonsignificant increase in prostate cancer risk compared with those not receiving β -carotene (6). The Physicians' Health Study found that, overall, men who took 50 mg of β -carotene supplements on alternate days did not have a reduced risk of prostate cancer; however, among men with low plasma levels of β -carotene, those who took the supplements had a lower risk of prostate cancer than those who did not take supplements (7). The β -Carotene and Retinol Efficacy Trial (CARET) found no association between β -carotene supplementation and prostate cancer risk (8).

Vitamin E is the collective term for eight tocopherols and tocotrienols, with α , β , γ , and δ vitamers for each. Whereas γ -tocopherol is the most prevalent form of vitamin E in the diet (9), α -tocopherol (the form of vitamin E found in dietary supplements) is the most biologically available form because it is

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See "Notes" following "References."

DOI: 10.1093/jnci/djj050

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preferentially retained in the plasma and transported to tissues (10). Thus, supplemental vitamin E has the potential to make a much larger contribution than dietary vitamin E to the overall vitamin E intake (11).

Two large randomized trials have yielded contradictory findings regarding the association between α -tocopherol supplementation and prostate cancer risk. In addition to the findings regarding β -carotene supplements and risk of prostate cancer, the ATBC study also reported that male smokers who were randomly assigned to receive 50 mg of α -tocopherol daily had a significantly lower incidence of prostate cancer compared with those not receiving α -tocopherol (6). Recent findings from the Heart Outcomes Prevention Evaluation (HOPE) Trial, in which participants were randomly assigned to receive 400 IU of vitamin E daily or placebo, indicate that vitamin E does not reduce the incidence of either prostate cancer (not a primary outcome measure) or total cancer (12). The ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT), a 2×2 factorial randomized controlled chemoprevention trial, examines the effects of supplemental vitamin E (400 IU of α -tocopherol/day) alone and in combination with selenium (200 μ g/day) on prostate cancer incidence among more than 35 000 men (13). Enrollment for SELECT was completed in 2004, and follow-up will continue for up to 12 years.

Findings from the completed trials and from large-scale prospective studies have raised several important issues that require further investigation. First, it is possible that only smokers may benefit from increased vitamin E intake (6,14) and that nonsmokers who use vitamin E supplements might actually be at increased risk, at least with regard to prostate cancer (15). Second, there are questions concerning the appropriate dose and form of vitamin E supplementation; the dose of vitamin E that is being tested in SELECT (400 IU/day) is eightfold higher than the dose that was found to be effective in the ATBC Study (6) (in both studies, vitamin E was provided as DL- α -tocopheryl acetate), and observational studies have not consistently identified an optimal dose for potential primary prevention of prostate cancer. There are similar unresolved questions regarding optimum intakes of β -carotene and vitamin C for prostate cancer prevention, and potential interactions with host or lifestyle factors, such as the suggestion that only those individuals who are somewhat deficient in β -carotene may benefit from β -carotene supplementation (7).

Here we report on the association between prostate cancer incidence and intakes of vitamin E, carotenoids, and vitamin C from foods and from dietary supplements among men who were randomly assigned to the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. The PLCO trial is a randomized two-arm trial designed to evaluate the effect of screening for these cancers on disease-specific mortality by comparing the screened arm with a control arm of men undergoing routine medical care and to support etiologic studies of cancer (16,17). Results of our study in the screening arm of the PLCO trial are unbiased by differential prostate cancer screening, which is difficult to assess in nontrial circumstances.

SUBJECTS AND METHODS

Study Setting

The PLCO Trial is a multicenter, randomized study that enrolled participants from November 1, 1993, to June 30, 2001 (17).

The PLCO Trial is a multicenter, randomized study that enrolled participants from November 1, 1993, to June 30, 2001, and will continue follow-up through 2015. The trial used direct mailings, advertisements, and other means to recruit men and women from the general population. Screening procedures were carried out at centers in Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC. Men aged 55–74 years were eligible for the trial if they had no history of prostate, colon, or lung cancer; were not under treatment for any cancer (excluding nonmelanoma skin cancer); had not had surgical removal of the prostate, one lung, or the colon; had not taken finasteride in the previous 6 months; had not had more than one prostate-specific antigen (PSA) test in the previous 3 years; and were not participating in another screening or cancer prevention trial. Study participants provided written informed consent documents that were approved by the institutional review boards of the U.S. National Cancer Institute and the 10 screening centers.

Men who were randomly assigned to the screening arm of the PLCO trial were screened for prostate cancer with serum PSA testing (at study entry and annually for 5 years) and with digital rectal examinations (DREs; at study entry and annually for 3 years). Men assigned to the screening arm also received flexible sigmoidoscopy and chest x-rays for early detection of colorectal and lung cancers, respectively. Men who had a positive PSA test (i.e., a PSA level > 4 ng/mL) or a DRE that was suspicious for prostate cancer were referred to their medical-care providers for diagnostic evaluations for prostate cancer. Thus, although the screening examinations in the PLCO trial were carried out under a standard research protocol, any diagnostic follow-up was community based. Among men who had a positive PSA test or DRE, the diagnostic biopsy rate within 3 years of the positive test was 64%; this biopsy rate reflects the prevailing clinical practice in the 10 PLCO study regions (18). Trial participants were asked to provide information about recent diagnoses of cancer through annual mailed endpoint follow-up questionnaires.

For participants for whom prostate cancer was suspected, medical and pathology records related to the diagnostic follow-up were obtained from medical care providers by study personnel. For all participants who died, we obtained the death certificates and medical and pathology records relating to death. Data related to cancer diagnosis and death were abstracted by trained medical abstractors who also performed systematic quality-control reviews on data for approximately 100 prostate cancer cases per year. Clinical stage groups were assigned on the basis of clinical (57% of tumors) or clinical and surgical (43% of tumors) assessments of the extent of tumor involvement, using the TNM (tumor–node–metastasis) stage of disease classification (19). Gleason scores were assigned according to the highest summary values reported for biopsy and prostatectomy results.

Study Population

Of the 38 352 men who were randomly assigned to the screening arm of the trial, we excluded men who reported having a history (prior to study entry) of cancer (other than nonmelanoma skin cancer, $n = 1001$); men who did not have an initial PSA test or DRE ($n = 2530$); men who received an initial screening examination but with whom there was no subsequent contact ($n = 1045$); men who did not complete a baseline risk factor

questionnaire (n = 903); and men who did not provide a dietary questionnaire (n = 6604) or intake information for more than seven items on the food frequency part of the questionnaire (n = 250) or who reported having an energy intake in the top or bottom 1% of the reported energy intake distribution (corresponding to >5573 kcal/day and <781 kcal/day, respectively; n = 634). We also excluded men whose initial screening examination upon randomization occurred after October 1, 2001, the censor date for this analysis (n = 155). After these exclusions, the analytic cohort comprised 29 361 men (some participants were included in more than one exclusion category), of whom 90.7% were white, 4.0% were Asian/Pacific Islanders, 3.3% were black, 1.8% were Hispanic, and 0.2% were American Indians/Alaskan Natives.

Data Collection Procedures

At study entry (baseline), participants provided the following information by questionnaire: age, race, education level, height, weight, adult occupation, smoking history, family medical history (including family history of prostate cancer), personal medical history (including use of selected medications), and physical activity level.

Dietary information was collected through a self-administered food frequency questionnaire (available at <http://www3.cancer.gov/prevention/plco/DQX.pdf> [last accessed: January 3, 2006]) that included 137 food items and assessed the participant's usual diet over the previous year, including the usual portion size (small, medium, or large) for 77 items and information on five types of multivitamins (i.e., One-A-Day type, Theragran or other high-dose therapeutic types, Stresstabs, B-complex, other) and seven types of single-nutrient supplements (i.e., vitamin E, β -carotene, and vitamin C, among others). Participants were asked to report whether they had taken the dietary supplement since age 25 years (yes/no) and whether they were taking the supplement currently (yes/no) or were taking it 2 years ago (yes/no) or 5 years ago (yes/no), and to give the duration of use (<1, 1–2, 3–4, 5–9, 10–14, 15–19, \geq 20 years). Participants were also asked to report the frequency of their multivitamin use (<2 pills/week, 2–4 pills/week, 5–6 pills/week, 1 pill/day, \geq 2 pills/day), and the dose per day for single-nutrient supplements (response categories varied by supplement type).

Men who reported using a single-nutrient supplement but did not report the dose were assigned the value that corresponded to the sex-specific mode among users, as appropriate: for vitamin E this value was 400 IU/day; for β -carotene, 2000 μ g/day; and for vitamin C, 500 mg/day. Men who reported using multivitamins but did not report their frequency of use were assigned a value of 1 pill/day, the sex-specific mode among users for each type. The doses of individual vitamins or nutrients in multivitamins were assigned on the basis of the amounts contained in the similarly named, generic multivitamins most frequently taken by men aged 55–74 years as reported in the Third National Health and Nutrition Examination Survey (20): One-A-Day types contribute 30 IU of vitamin E, 750 mg of β -carotene, and 60 mg of vitamin C; Therapeutic or high-dose types contribute 30 IU of vitamin E, 825 μ g of β -carotene, and 120 mg of vitamin C; and Stresstabs contribute 30 IU of vitamin E and 500 mg of vitamin C to the individual vitamin totals of interest. The average dose of multivitamins per day was calculated by dividing the dose by the frequency of intake. Total supplemental intake was the sum of the

amounts contributed from single-nutrient supplements and from multivitamin use.

Nutrient intakes were derived by using frequency and portion-size responses from the food frequency questionnaires, in which nutrient values per portion were multiplied by the daily frequency of intake and summed across all relevant food items. Gram weights per portion size (small, medium, large) were assigned using data from the two 24-hour dietary recalls that were administered as part of the 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII), a nationally representative survey conducted during the period when the food frequency questionnaire was being used (21). Cutpoints between small and medium portions and between medium and large portions correspond to the 25th and 75th percentiles, respectively, for portion sizes reported by male CSFII participants 51 years or older (22). Values for most nutrients were determined from the U.S. Department of Agriculture sources (23); values for individual tocopherols and carotenoids were determined from the University of Minnesota Nutrition Data System for Research (24) using methodology developed by Dixon et al. (25).

Data Analysis

Person-years were calculated from the date of the baseline prostate cancer PSA screen at study entry to the date of the most recently completed endpoint follow-up questionnaire or the date of prostate cancer diagnosis or death, or October 1, 2001, whichever came first. Between enrollment and the censor date, 9% of the cohort died or were lost to follow-up. Absolute rates were standardized to the age distribution of person-years experienced by all study participants, using 5-year age categories. We used Cox proportional hazards regression analysis, with age as the underlying time metric (26), to generate unadjusted and multivariable-adjusted relative risks (RRs) and 95% confidence intervals (CIs). We also evaluated the risks of potentially clinically significant prostate tumors by stratifying results according to advanced versus nonadvanced cancer. We defined advanced cases as those with stage III or IV tumors or with a Gleason score of 7 or higher and nonadvanced cases as those with stage I or II tumors and a Gleason score lower than 7. All *P* values are two-sided and are considered statistically significant if less than .05.

If less than 1% of the data for a variable were missing, the missing values were imputed from the mean (for continuous variables) or mode (for categorical variables) of the known values; if 1% or more of the data were missing, we included an extra category for missing values. The two exceptions to this rule were the participants with missing physical activity information (<1% of total participants), whom we assigned to the “no or low physical activity” category, and the participants with missing diabetes status (2.7% of total participants), whom we assigned to the “no disease” category. Nonresponse to a food item was considered to indicate that the participant did not consume the item. We ran separate models that included or excluded participants with missing information and found that the models gave similar results with respect to the association between the antioxidant micronutrients and prostate cancer risk.

For the analysis of prostate cancer risk, dietary intake was categorized into quintiles of average daily intake. Where feasible, supplemental vitamin use was categorized into roughly equal groups, among users. Multivariable analyses were adjusted for

suspected prostate cancer risk factors, including age (by modeling age as the underlying metric), total energy intake (kilocalories/day; quintiles), race (white, black, Asian/Pacific Islander, other), study center, family history of prostate cancer (yes/no), body mass index (<25 kg/m², 25–<30 kg/m², ≥30 kg/m²), smoking status (never, current, former, pipe–cigar only), physical activity (i.e., hours spent in vigorous activity per week; none, <1, 1, 2, 3, ≥4), total fat intake (grams/day; quintiles), red meat intake (grams/day; quintiles), diabetes (yes/no), aspirin use (never, <1 pill/day, ≥1 pill/day), and total number of prostate cancer screening examinations during the follow-up period (as a time-dependent variable). Dietary values were adjusted for energy intake by using the residual method (27).

For dietary intakes, tests for trends in relative risks were conducted by assigning the median value for each category and treating this variable as continuous, using a Wald chi-square statistic. For supplement intakes, for which the distributions were based on a discrete number of choices, we tested for trends in relative risks by using the actual values rather than the median values. To test the statistical significance of interactions on a multiplicative scale, a cross-product term of the micronutrient intake value (on a continuous scale) and the risk factor variable (e.g., smoking status) were included in multivariable models.

The proportionality assumption was evaluated by inspecting the log–log plots for the exposure variables under study and by testing for evidence of a statistical interaction with time. To specifically study whether the association between the dietary exposure and the risk of prostate cancer differed statistically significantly between the first year of follow-up (which may have included a greater proportion of prevalent cases) and the subsequent years of follow-up, we defined a time-dependent covariate which was the product of time (dichotomized at 1 year after the start of follow-up) and the dietary exposure of interest and tested the statistical significance of the resulting coefficient(s) using a Wald chi-square statistic or a –2-log likelihood statistic, as appropriate. There was no evidence of violation of the proportionality assumption in any of the models.

RESULTS

Among 29 361 men who were monitored for up to 8 years (average follow-up = 4.2 years), 1338 men (4.6%) were diagnosed with prostate cancer (470 men were diagnosed in the first year of follow-up, 516 men were diagnosed between years 1 and 3, and 352 men were diagnosed after year 3). The total case series included 520 men (38.9%) diagnosed with advanced disease (i.e., Gleason score of 7 or higher or stage III or IV).

A total of 16 548 men (56%) reported current or recent (i.e., “2 years ago”) use of multivitamin or single vitamin supplements. Differences in baseline characteristics between supplement users and nonusers were generally small (Table 1); however, men who reported taking supplemental vitamins were less likely than nonusers to be current smokers, were more likely to use aspirin, and had diets that were higher in β-carotene and vitamin C and lower in red meat and total fat than those of nonusers.

Specific supplemental vitamin use (which includes contributions from both single-nutrient supplements and multivitamins) was reported as follows: 15 155 men (52%) used vitamin E, 12 203 men (42%) used β-carotene, and 15 080 men (51%) used vitamin C. Mean dietary and supplement intakes (among users)

Table 1. Baseline characteristics of study participants by use of supplemental vitamins*

Characteristic	Supplemental vitamin use	
	No (n = 12 813)	Yes (n = 16 548)
Mean age at study entry, y (SD)	63.4 (5.3)	63.2 (5.3)
Mean current BMI, kg/m ² (SD)	27.8 (4.1)	27.3 (4.1)
Family history of prostate cancer, %	7.2	7.3
History of diabetes, %	8.8	8.2
Average no. of screens/y†	0.85	0.86
Smoking status, %		
Never	29.4	29.7
Current	12.0	9.8
Former	50.9	52.3
Cigar or pipe only	7.8	8.2
Mean physical activity, h/wk (SD)	2.1 (1.9)	2.4 (1.9)
Race, %		
White	90.5	90.8
Black	3.8	2.9
Asian/Pacific Islander	3.7	4.3
Hispanic/American Indian/Alaskan Native	1.9	1.9
Daily aspirin use, %	24.8	35.0
Mean dietary intake/day (SD)		
Energy, kcal	2333 (861)	2346 (838)
Lycopene, μg	10 577 (6391)	11 153 (6824)
Vitamin E‡, mg	12.0 (7.2)	12.5 (7.5)
β-Carotene, μg	4425 (2308)	4833 (2510)
Vitamin C, mg	159.7 (81.7)	177.8 (90.0)
Red meat, g	99.8 (51.6)	88.6 (50.1)
Total fat, g	76.9 (15.6)	74.0 (15.7)

*Supplemental vitamin use defined as current or recent (i.e., “2 years ago”) supplement use and includes both single supplement use and multivitamin use. All values other than age were directly standardized for age. Dietary vitamin E, β-carotene, and vitamin C intakes and red meat and fat intakes were also standardized for energy intake. SD = standard deviation; BMI = body mass index.

†Average number of prostate cancer screening examinations (prostate-specific antigen test and/or digital rectal examination) during the period of active screening (years 0–5).

‡Measured as milligrams of total α-tocopherol equivalents.

for vitamin E were 12 mg of total α-tocopherol equivalents and 279 IU, respectively; for β-carotene, 4817 μg and 1224 μg, respectively; and for vitamin C, 176 mg and 494 mg, respectively.

Current or recent (i.e., “2 years ago”) supplemental vitamin E intake was not associated with prostate cancer incidence either overall (Table 2) or among men with high (≥median value of 11.3 mg/day) or low (below the median) dietary vitamin E intakes (data not shown). There was no association between the risk of prostate cancer and the level of supplemental β-carotene intake in the full study population (Table 2). However, among men with dietary β-carotene consumption below the median (4129 μg/day), there was an inverse association between high supplemental β-carotene intake and the risk of prostate cancer (RR for ≥2000 μg/day versus none = 0.52, 95% CI = 0.33 to 0.81). In men with low dietary β-carotene intake, the age-adjusted rate of prostate cancer was 1122 per 100 000 person-years among those who did not take supplemental β-carotene, and 623 per 100 000 person-years among those who took at least 2000 μg/day of supplemental β-carotene. Dietary and supplemental vitamin C intakes were not associated with a reduced risk of prostate cancer.

Additional adjustment for dietary micronutrient intake did not alter the associations between supplement use and risk of

Table 2. Relative risks (with 95% confidence intervals) of prostate cancer by supplemental and dietary antioxidant intake*

Antioxidant group	Intake category†					<i>P</i> _{trend‡}
	1	2	3	4	5	
Vitamin E						
Supplemental intake§						
Range, IU/day	0	>0–30	>30–400	>400	N/A	
No. of cases	675	274	175	214		
RR (95% CI)	1.00 (referent)	1.02 (0.89 to 1.18)	0.92 (0.77 to 1.08)	0.97 (0.83 to 1.13)		.81
Dietary intake						
Quintile median, mg/day	8.6	10.2	11.3	12.6	15.8	
No. of cases	263	256	271	258	290	
RR (95% CI)	1.00 (referent)	0.92 (0.77 to 1.09)	0.94 (0.79 to 1.13)	0.87 (0.72 to 1.05)	0.93 (0.78 to 1.12)	.33
β-Carotene						
Supplemental intake						
Range, μg/day	0	>0–<750	750–<1500	1500–<2000	≥2000	
No. of cases	801	57	352	47	81	
RR (95% CI)	1.00 (referent)	0.91 (0.70 to 1.20)	1.00 (0.88 to 1.14)	1.15 (0.85 to 1.54)	0.82 (0.65 to 1.04)	.55
Dietary intake						
Quintile median, μg/day	2180	3191	4119	5338	7744	
No. of cases	227	274	258	288	291	
RR (95% CI)	1.00 (referent)	1.09 (0.91 to 1.30)	0.96 (0.80 to 1.15)	1.01 (0.85 to 1.21)	0.96 (0.80 to 1.15)	.40
Vitamin C						
Supplemental intake						
Range, mg/day	0	>0–60	>60–<560	≥560		
No. of cases	666	206	202	264	N/A	
RR (95% CI)	1.00 (referent)	0.98 (0.83 to 1.14)	0.98 (0.83 to 1.15)	1.01 (0.87 to 1.17)		.98
Dietary intake						
Quintile median, mg/day	77	119	155	195	268	
No. of cases	229	231	291	283	304	
RR (95% CI)	1.00 (referent)	0.88 (0.73 to 1.06)	1.03 (0.86 to 1.24)	0.95 (0.79 to 1.15)	1.00 (0.83 to 1.22)	.65

*Supplemental vitamin use defined as average daily current or recent (2 years ago) use and includes both single supplement use and multivitamin use. Relative risks adjusted for age, total energy, race, study center, family history of prostate cancer, body mass index, smoking status, physical activity, total fat intake, red meat intake, history of diabetes, aspirin use, and number of screening examinations during the follow-up period. IU = international units; N/A = not applicable; RR = relative risk; CI = confidence interval.

†Dietary intake was categorized by quintiles of intake.

‡Two-sided, based on the chi-square test for trend.

§A common form of α-tocopherol in supplements is the DL-α-tocopheryl acetate (a synthetic form, also known as *all rac* α-tocopheryl acetate); for this form, 1 mg = 1 IU.

||Measured as milligrams of total α-tocopherol equivalents.

prostate cancer. Although the overall results were similar when multivitamin users were excluded, the number of men who used single-nutrient supplements alone was too small to justify analysis of the various dose ranges within this subgroup.

We found no association between the risk of prostate cancer and dietary intakes of α-, β-, δ-, or γ-tocopherol (Table 3). There was no association between prostate cancer risk and dietary intake of any the common carotenoids (i.e., α-carotene, β-cryptoxanthin, lutein and zeaxanthin, or lycopene).

There was no statistically significant association between the risk of prostate cancer and the duration of use of supplemental vitamin E, β-carotene, or vitamin C, although a slightly reduced risk was suggested for the longest duration of vitamin E use (Table 4). High-dose supplemental vitamin E intake was associated with a reduced risk of advanced prostate cancer in current and recent smokers (RR for >400 IU/day versus none = 0.29, 95% CI = 0.12 to 0.68; *P*_{trend} = .01) (Table 5). These associations were similar when advanced stage (stage III–IV: RR for >400 IU versus none = 0.21, 95% CI = 0.05 to 0.94; *P*_{trend} = .18) and grade (Gleason score ≥7: RR for >400 IU versus none = 0.22, 95% CI = 0.08 to 0.61; *P*_{trend} = .01) were considered separately. Increasing dose of supplemental vitamin E appeared to be associated with a reduced risk of advanced prostate cancer in current and recent smokers but not in nonsmokers (*P*_{interaction} = .05, for current and recent versus never-smokers). The risk of

nonadvanced cancer tended, however, to increase with increasing supplemental vitamin E intake among current and recent smokers (*P*_{trend} = .03). The risk estimates for supplemental and dietary β-carotene and vitamin C did not vary by smoking status or by disease status (advanced versus nonadvanced) (data not shown).

In current and recent smokers, greater duration of supplemental vitamin E use was associated with a reduced risk of advanced prostate cancer (RR for ≥10 years of use versus none = 0.30, 95% CI = 0.09 to 0.96; *P*_{trend} = .01) but with an increasing risk of nonadvanced disease (*P*_{trend} = .02) (Table 6). There were no statistically significant trends regarding duration of vitamin E supplement use and prostate cancer risk in any of the other tobacco-use strata.

Among smokers, the age-adjusted rate of advanced prostate cancer was 492 per 100 000 person-years in those who did not take supplemental vitamin E, 153 per 100 000 person-years in those who took more than 400 IU/day of supplemental vitamin E, and 157 per 100 000 person-years in those who took supplemental vitamin E for 10 or more years.

DISCUSSION

Overall, our analysis of more than 1300 prostate cancer patients in the screening arm of the PLCO Trial showed no

Table 3. Relative risks (with 95% confidence intervals) of prostate cancer according to dietary intake of specific carotenoids and forms of vitamin E*

Antioxidant group	Quintile of intake					<i>P</i> _{trend} †
	1	2	3	4	5	
Dietary vitamin E						
α-Tocopherol						
Quintile median, mg/day	6.1	7.4	8.4	9.5	12.6	
No. of cases	260	248	266	275	289	
RR (95% CI)	1.00 (referent)	0.89 (0.75 to 1.06)	0.93 (0.78 to 1.11)	0.91 (0.76 to 1.09)	0.92 (0.77 to 1.10)	.63
β-Tocopherol						
Quintile median, mg/day	0.26	0.33	0.38	0.45	0.58	
No. of cases	257	263	261	285	272	
RR (95% CI)	1.00 (referent)	0.98 (0.82 to 1.16)	0.93 (0.78 to 1.11)	0.96 (0.81 to 1.14)	0.87 (0.73 to 1.04)	.12
γ-Tocopherol						
Quintile median, mg/day	10.5	13.3	15.5	17.6	21.1	
No. of cases	294	259	276	263	246	
RR (95% CI)	1.00 (referent)	0.86 (0.72 to 1.03)	0.93 (0.77 to 1.12)	0.88 (0.72 to 1.08)	0.87 (0.70 to 1.09)	.34
δ-Tocopherol						
Quintile median, mg/day	1.7	2.3	2.7	3.1	3.9	
No. of cases	282	232	276	270	278	
RR (95% CI)	1.00 (referent)	0.81 (0.67 to 0.96)	0.95 (0.80 to 1.14)	0.95 (0.79 to 1.14)	0.96 (0.79 to 1.16)	.71
Dietary carotenoids‡						
α-Carotene						
Quintile median, μg/day	472	784	1081	1476	2317	
No. of cases	249	270	266	277	276	
RR (95% CI)	1.00 (referent)	1.01 (0.85 to 1.21)	0.95 (0.80 to 1.14)	0.96 (0.81 to 1.15)	0.92 (0.76 to 1.10)	.25
β-Cryptoxanthin						
Quintile median, μg/day	65	122	178	241	359	
No. of cases	225	256	264	301	292	
RR (95% CI)	1.00 (referent)	1.04 (0.87 to 1.25)	0.99 (0.83 to 1.19)	1.11 (0.92 to 1.32)	1.05 (0.87 to 1.27)	.57
Lutein and zeaxanthin						
Quintile median, μg/day	1437	1995	2501	3138	4428	
No. of cases	217	256	275	303	287	
RR (95% CI)	1.00 (referent)	1.04 (0.86 to 1.25)	1.06 (0.89 to 1.28)	1.09 (0.91 to 1.30)	0.95 (0.78 to 1.14)	.43
Lycopene						
Quintile median, μg/day	5052	7555	9650	12 271	17 593	
No. of cases	269	287	268	271	243	
RR (95% CI)	1.00 (referent)	1.10 (0.93 to 1.30)	1.06 (0.89 to 1.25)	1.07 (0.90 to 1.27)	0.95 (0.79 to 1.13)	.33

*Relative risks adjusted for age, total energy, race, study center, family history of prostate cancer, body mass index, smoking status, physical activity, total fat intake, red meat intake, history of diabetes, aspirin use, and number of screening examinations during the follow-up period. RR = relative risk; CI = confidence interval.

†Two-sided, based on the chi-square test for trend.

‡Relative risks for dietary β-carotene intake are presented in Table 2.

association between prostate cancer risk and dietary intake or dietary supplementation with three antioxidant vitamins—vitamin E, β-carotene, and vitamin C. Among current and recent smokers, however, high-dose (>400 IU/day) and long-duration (≥10 years) vitamin E supplementation were related to decreased risk for advanced prostate cancer and possibly to increased risk for nonadvanced disease. Also, among men who reported having a relatively low dietary β-carotene intake, high-dose β-carotene supplementation was associated with a reduced risk of prostate cancer. Our cohort findings, although based on relatively short follow-up, do not provide strong support for population-wide implementation of high-dose antioxidant supplementation for the prevention of prostate cancer. They do suggest, however, that in certain population subgroups there was an association between supplement intake and reduced risks of prostate cancer.

Several prospective cohort studies (14,15,28–30) and a randomized controlled trial (6,31) have reported reduced risks of prostate cancer among smokers who use vitamin E supplements (6,15,30) or who have high serum levels of α-tocopherol (14,28,29,31); no prospective studies have reported any statistically significant associations between vitamin E supplement use or serum α-tocopherol levels and prostate cancer risk in non-smokers. Similar to our study, the ATBC Study, which included only smokers, found that the protective effect associated with

supplemental vitamin E intake was limited to more aggressive disease (stage II–IV) (6), and the Health Professionals Follow-up Study (HPFS) noted a decreased risk of metastatic or fatal prostate cancer among smokers and an increased risk among never-smokers (15).

The role of tobacco in the association between vitamin E and prostate cancer is not clear. Smokers may have increased vitamin E requirements (32). However, tobacco use itself was only weakly associated with prostate cancer in this study (data not shown) and in most other investigations (33). If smoking is in fact associated with an increased risk of prostate cancer, as some studies that analyzed the long-term detailed histories of participants have reported (34,35), then vitamin E might mitigate smoking-induced genetic or hormonal changes that increase risk of advanced prostate cancer (15). Thus, future studies to evaluate the role of vitamin E in prostate cancer prevention should be adequately powered to take into account the potential role of tobacco use (36). A further consideration in evaluating vitamin E in prostate cancer prevention is that supplementation with vitamin E at the levels associated with the reduced risk of prostate cancer among the smokers in our study (>400 IU/day) has been associated in some studies with other health risks: a meta-analysis showed dose-dependent increases in overall mortality in nine of 11 studies (37), and the HOPE

Table 4. Relative risks (with 95% confidence intervals) of prostate cancer by duration of supplement use*

Supplement	Duration of supplement use (y)					<i>P</i> _{trend} †
	0	>0–2	3–4	5–9	≥10	
Supplemental vitamin E						
No. of cases‡	642	128	64	62	118	
Median dose, IU/day	0	400	413	430	430	
RR (95% CI)	1.00 (referent)	0.92 (0.76 to 1.12)	0.97 (0.75 to 1.26)	0.87 (0.67 to 1.13)	0.84 (0.69 to 1.02)	.06
Supplemental β-carotene						
No. of cases‡	781	55	22	23	29	
Median dose, μg/day	0	2000	2619	2500	2750	
RR (95% CI)	1.00 (referent)	0.89 (0.68 to 1.18)	0.84 (0.54 to 1.27)	1.05 (0.69 to 1.60)	1.08 (0.74 to 1.57)	.98
Supplemental vitamin C						
No. of cases‡	600	83	65	71	200	
Median dose, mg/day	0	500	560	560	560	
RR (95% CI)	1.00 (referent)	0.85 (0.67 to 1.07)	1.23 (0.95 to 1.60)	1.03 (0.80 to 1.32)	0.90 (0.76 to 1.06)	.41

*Supplemental vitamin use among current or recent (2 years ago) users, assessed at baseline, includes both single supplement use and multivitamin use. Relative risks adjusted for age, total energy, race, study center, family history of prostate cancer, body mass index, smoking status, physical activity, total fat intake, red meat intake, history of diabetes, aspirin use, and number of screening examinations during the follow-up period. IU = international units; RR = relative risk; CI = confidence interval.

†Two-sided, based on the chi-square test for trend.

‡The total number of cases across all duration categories for each supplement does not add up to the total number of supplement users due to missing data for duration of supplement use.

Trial found an increased risk of heart failure in at-risk subjects (12). However, other studies show no health risk [reviewed in Hathcock et al. (38)].

A role for β-carotene supplementation in prostate cancer prevention is also unproven. Our finding, that a decreased risk of prostate cancer was associated with high-dose β-carotene supplementation in men who had relatively low β-carotene dietary intakes, is consistent with results from one randomized trial that reported a lower risk of prostate cancer among β-carotene supplement users who had low baseline plasma β-carotene levels (7); however, other β-carotene supplementation trials show either possible excess prostate cancer risks (6) or no effect (8). Observational studies have, in general, shown no association between β-carotene blood concentrations (14,29,39–41) and the risk of

prostate cancer [with one exception (42)], whereas some dietary studies had reported inverse associations (43–46) and others have reported no association (47–53). There are some concerns regarding very high levels of β-carotene supplementation; for example, smokers who were randomly assigned to receive 20 or 30 mg of β-carotene in the ATBC Study (6) and CARET (8), respectively, were at increased risk of lung cancer, heart disease, and death from all causes, risks that have persisted years after the interventions ceased (54–56).

Antioxidants are considered as potential chemoprotective agents primarily because of their ability to limit cellular exposure to reactive oxygen species, which can promote cancer and other degenerative diseases (57). However, excess antioxidants may also interfere with certain protective functions of reactive oxygen

Table 5. Relative risks (with 95% confidence intervals) of total, advanced, and nonadvanced prostate cancer by supplemental vitamin E use and smoking history*

Case type†	Supplemental vitamin E, IU/day				<i>P</i> _{trend} ‡
	0	>0–30	>30–400	>400	
All cases (n = 1338)	1.00 (referent)	1.02 (0.89 to 1.18)	0.92 (0.77 to 1.08)	0.97 (0.83 to 1.13)	.81
Never smokers (n = 437)	1.00 (referent)	1.09 (0.85 to 1.40)	0.92 (0.69 to 1.24)	1.05 (0.79 to 1.38)	.99
Current smoker/quit within past 10 y (n = 239)	1.00 (referent)	1.13 (0.82 to 1.55)	0.97 (0.65 to 1.45)	0.78 (0.52 to 1.17)	.98
Quit ≥10 y ago (n = 551)	1.00 (referent)	0.90 (0.71 to 1.13)	0.93 (0.72 to 1.21)	0.93 (0.73 to 1.18)	.61
Advanced cases (n = 520)	1.00 (referent)	0.85 (0.67 to 1.07)	0.94 (0.73 to 1.23)	0.91 (0.71 to 1.18)	.61
Never smokers (n = 176)	1.00 (referent)	1.34 (0.91 to 1.96)	1.16 (0.74 to 1.81)	1.29 (0.84 to 1.98)	.44
Current smoker/quit within past 10 y (n = 91)	1.00 (referent)	0.67 (0.38 to 1.17)	0.72 (0.37 to 1.38)	0.29 (0.12 to 0.68)	.01
Quit ≥10 y ago (n = 211)	1.00 (referent)	0.63 (0.41 to 0.95)	1.03 (0.69 to 1.54)	0.95 (0.65 to 1.40)	.96
Nonadvanced cases (n = 714)	1.00 (referent)	1.18 (0.97 to 1.42)	1.00 (0.80 to 1.26)	1.08 (0.88 to 1.35)	.47
Never smokers (n = 231)	1.00 (referent)	0.96 (0.67 to 1.37)	0.92 (0.62 to 1.36)	1.09 (0.75 to 1.59)	.70
Current smoker/quit within past 10 y (n = 125)	1.00 (referent)	1.67 (1.07 to 2.59)	1.46 (0.85 to 2.49)	1.47 (0.87 to 2.47)	.03
Quit ≥10 y ago (n = 297)	1.00 (referent)	1.05 (0.78 to 1.40)	0.89 (0.62 to 1.29)	0.90 (0.64 to 1.25)	.42

*Supplemental vitamin E use among current or recent (2 years ago) users, assessed at baseline, includes both single supplement use and multivitamin use. Relative risks adjusted for age, total energy, race, study center, family history of prostate cancer, body mass index, physical activity, total fat intake, red meat intake, history of diabetes, aspirin use, and number of screening examinations during the follow-up period. IU = international units.

†Advanced cases defined as those with a Gleason score of 7 or greater or stage III or IV. Nonadvanced cases defined as those with a Gleason score lower than 7 and stage I or II. Case numbers do not sum to total because advanced/nonadvanced status was not determined for 104 cases and because subjects who never smoked cigarettes but smoked a pipe or cigar are excluded (includes 111 cases).

‡Two-sided, based on the chi-square test for trend.

Table 6. Relative risks (with 95% confidence intervals) of total, advanced, and nonadvanced prostate cancer by duration of supplemental vitamin E use and smoking history*

Case type†	Duration of supplement use (y)					P _{trend‡}
	0	>0-2	3-4	5-9	≥10	
All cases (n = 1014)	1.00 (referent)	0.92 (0.76 to 1.12)	0.97 (0.75 to 1.26)	0.87 (0.67 to 1.13)	0.84 (0.68 to 1.02)	.06
Never smokers (n = 333)	1.00 (referent)	1.06 (0.77 to 1.46)	0.92 (0.57 to 1.47)	0.62 (0.36 to 1.05)	0.87 (0.62 to 1.23)	.17
Current smoker/quit within past 10 y (n = 177)	1.00 (referent)	0.88 (0.54 to 1.43)	0.86 (0.44 to 1.65)	1.14 (0.64 to 2.04)	0.85 (0.51 to 1.41)	.66
Quit ≥10 y ago (n = 419)	1.00 (referent)	0.78 (0.56 to 1.08)	1.02 (0.69 to 1.51)	1.02 (0.70 to 1.50)	0.85 (0.63 to 1.15)	.43
Advanced cases (n = 400)	1.00 (referent)	0.91 (0.67 to 1.23)	0.88 (0.57 to 1.35)	0.85 (0.56 to 1.29)	0.82 (0.60 to 1.13)	.15
Never smokers (n = 127)	1.00 (referent)	1.14 (0.68 to 1.91)	0.97 (0.44 to 2.12)	0.97 (0.46 to 2.03)	1.11 (0.66 to 1.88)	.78
Current smoker/quit within past 10 y (n = 71)	1.00 (referent)	0.69 (0.32 to 1.47)	0.71 (0.25 to 1.99)	0.17 (0.02 to 1.21)	0.30 (0.09 to 0.96)	.01
Quit ≥10 y ago (n = 167)	1.00 (referent)	0.85 (0.51 to 1.42)	0.91 (0.47 to 1.76)	1.17 (0.65 to 2.10)	0.93 (0.58 to 1.49)	.93
Nonadvanced cases (n = 535)	1.00 (referent)	1.02 (0.79 to 1.32)	1.20 (0.86 to 1.67)	0.89 (0.62 to 1.29)	0.90 (0.69 to 1.19)	.52
Never smokers (n = 183)	1.00 (referent)	1.19 (0.78 to 1.79)	1.07 (0.59 to 1.96)	0.52 (0.24 to 1.13)	0.87 (0.54 to 1.40)	.28
Current smoker/quit within past 10 y (n = 90)	1.00 (referent)	1.21 (0.62 to 2.35)	1.08 (0.42 to 2.75)	2.19 (1.09 to 4.41)	1.73 (0.95 to 3.15)	.02
Quit ≥10 y ago (n = 219)	1.00 (referent)	0.72 (0.45 to 1.13)	1.25 (0.77 to 2.03)	0.82 (0.46 to 1.46)	0.73 (0.47 to 1.14)	.22

*Supplemental vitamin E use among current or recent (2 years ago) users, assessed at baseline, includes both single supplement use and multivitamin use. Relative risks adjusted for age, total energy, race, study center, family history of prostate cancer, body mass index, physical activity, total fat intake, red meat intake, history of diabetes, aspirin use, and number of screening examinations during the follow-up period. RR = relative risk; CI = confidence interval.

†Advanced cases defined as those with a Gleason score of 7 or greater or stage III or IV. Nonadvanced cases defined as those with a Gleason score lower than 7 and stage I or II. Case numbers do not sum to total because advanced/nonadvanced status was not determined for 104 cases, subjects who never smoked cigarettes but smoked a pipe or cigar were excluded (including 111 cases), and there were missing data for duration of supplement use (including 372 cases).

‡Two-sided, based on the chi-square test for trend.

species (57). Results of two meta-analyses (37,58) have suggested that administration of certain antioxidants at high pharmacologic doses is associated with an increase in all-cause mortality, particularly among individuals with preexisting health conditions. Also, heritable factors are important determinants of prostate cancer risk (59) and as yet unidentified genetic factors may be involved in the association between vitamin E intake and prostate cancer risk in smokers. Some genetic differences that have been identified between smokers and nonsmokers are largely related to tobacco dependency (60); however, these differences probably do not account for the associations we observed because they are unlikely to be related to vitamin E absorption or metabolism as well.

Data on tocopherols from dietary interviews and serum analyses provide complementary information; however, they can yield discrepant results. Results from questionnaire-based studies on dietary tocopherol intake are inconsistent, with most showing no association between intake and prostate cancer risk (47-49,61,62) and some (50,63,64) noting an inverse association. In one study (39,65), higher levels of serum γ -tocopherol (the form often more common in the diet) were found to be associated with lower prostate cancer risk than were greater levels of α -tocopherol (the form used in vitamin E supplements). The ATBC Study (31) reported prostate cancer risk reductions of similar magnitude for higher serum levels of γ - and α -tocopherol. We, however, did not find statistically significant associations between prostate cancer risk and the dietary intake of either of these forms of vitamin E or for dietary β - or δ -tocopherol intakes. These differences may reflect the limitations inherent in studies that use a food frequency questionnaire to collect data. For example, our study was limited because the food frequency questionnaire collected dietary information relevant to a restricted period and generally did not capture nut intake or the types of vegetable oil consumed, both of which are major sources of vitamin E. Also, the nutrient databases used in food

frequency questionnaire-based analyses such as ours have limited ability to quantify intake of individual tocopherols (11). Another limitation of our study is that our analysis was based on a detailed dietary and supplemental assessment at baseline; multiple assessments over the entire period of prostate cancer development may have resulted in more precise exposure estimates. Uncontrolled, unknown confounders could have biased our findings; however, results of this study and of several others (6,15,30) suggest that supplemental vitamin E is associated with a decreased risk of prostate cancer in smokers.

The strengths of the our study include its prospective design, our collection of detailed information on supplement use, the fact that the analyses were adjusted for many potential confounders, and the fact that all participants were recruited from the screening arm of a randomized trial, which reduced the likelihood that differential screening practices were related to micronutrient antioxidant intakes. Also, the large number of prostate cancer cases allowed us to stratify the analyses by aggressiveness of disease and by smoking status.

In summary, overall risks for prostate cancer were unaffected by supplemental dietary antioxidant use among participants in the PLCO Trial; however, vitamin E supplementation in smokers and β -carotene supplementation in men with low dietary β -carotene were associated with reduced risks of this disease.

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NOTES

PLCO Cancer Screening Trial is funded by the National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. This research was supported by the Intramural Research Program of the NIH, National Cancer Institute. The leading and corresponding authors, as well as several coauthors, were/are employed by the study sponsor and were primarily responsible for the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Manuscript received June 23, 2005; revised December 7, 2005; accepted December 20, 2005.