

Supplemental Vitamin E Intake and Prostate Cancer Risk in a Large Cohort of Men in the United States¹

June M. Chan,² Meir J. Stampfer, Jing Ma, Eric B. Rimm, Walter C. Willett, and Edward L. Giovannucci

Departments of Epidemiology [J. M. C., M. J. S., E. B. R., W. C. W., E. L. G.] and Nutrition [J. M. C., M. J. S., E. B. R., W. C. W., E. L. G.], Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School [M. J. S., J. M., E. B. R., W. C. W., E. L. G.], Boston, Massachusetts 02115

Abstract

A clinical trial of vitamin E and β -carotene supplementation for lung cancer prevention among male smokers in Finland recently reported an unexpected, strong protective effect of vitamin E against prostate cancer incidence and mortality. Our objective was to prospectively examine supplemental vitamin E intake and prostate cancer risk in a distinct U.S. population. In 1986, we identified 47,780 U.S. male health professionals, free from diagnosed cancer, who completed a dietary and lifestyle questionnaire; supplemental vitamin E and prostate cancer incidence were updated biennially through 1996. We estimated relative risks (RRs) from multivariate pooled logistic regression models.

There were 1896 total (non-stage A1), 522 extraprostatic, and 232 metastatic or fatal incident prostate cancer cases diagnosed between 1986–1996. Men consuming at least 100 IU of supplemental vitamin E daily had multivariate RRs of 1.07 (95% confidence interval [CI], 0.95–1.20) for total and 1.14 (95% CI, 0.82–1.59) for metastatic or fatal prostate cancer compared with those consuming none. Current use, dosage, and total duration of use of specific vitamin E supplements or multivitamins were not associated with risk. However, among current smokers and recent quitters, those who consumed at least 100 IU of supplemental vitamin E per day had a RR of 0.44 (95% CI, 0.18–1.07) for metastatic or fatal prostate cancer compared with nonusers.

Thus, supplemental vitamin E was not associated with prostate cancer risk generally, but a suggestive inverse association between supplemental vitamin E and risk of metastatic or fatal prostate cancer among current smokers and recent quitters was consistent with the

Finnish trial among smokers and warrants further investigation.

Introduction

Vitamin E (α -tocopherol) is the major lipid-soluble chain-breaking antioxidant that protects cell membranes and DNA from free radical damage that may lead to malignant transformation (1). *In vitro* (2, 3) and *in vivo* (1, 4) experiments have shown that in some models vitamin E can decrease prostate cancer growth, whereas vitamin E deficiency can lead to reduced cell number in lymphoid tissue and functional abnormalities in cell-mediated immune response (1, 4). Two prospective studies found an increased risk of prostate cancer mortality (5) or aggressive prostate cancer (6) among smokers when comparing low *versus* high serum vitamin E levels. Two case-control studies observed a significant inverse association between dietary vitamin E and prostate cancer risk (7, 8).

In the ATBC³ trial in Finland, 29,133 male smokers, age 50–69 years, were randomly assigned to 50 mg of α -tocopherol (equivalent to 50 IU), β -carotene, both, or placebo for 5–8 (median, 6.1) years to examine these nutrients for lung cancer prevention. Unexpectedly, there was a significant 40% decrease in the cumulative incidence of clinically apparent (stage II–IV) prostate cancer ($n = 192$ cases), and a significant 41% reduction in prostate cancer mortality in the α -tocopherol group ($n = 62$ deaths from prostate cancer). Occurrence of stage 0 or I tumors was unaffected. Additionally, at baseline, significant inverse associations were observed between serum vitamin E and serum androstenedione, dihydrotestosterone, sex hormone-binding globulin, and estrone and a marginal inverse association with testosterone (9). Serum levels and dietary vitamin E at baseline, however, were not associated with subsequent prostate cancer risk (10).

These results in Finnish men led us to examine the impact of supplemental vitamin E in the HPFS.

Materials and Methods

Study Population. The HPFS is an ongoing prospective cohort study of cancer and heart disease among 51,529 U.S. male health professionals. The men are dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians who were age 40–75 years at baseline in 1986. They responded to a mailed baseline questionnaire in 1986, which asked about demographics, anthropometry, family history of disease, medications, disease history, physical activity, and diet. Details on the assessment and validation of body weight (11) and dietary measurements can be found elsewhere (12, 13). We excluded

Received 2/19/99; revised 7/8/99; accepted 7/26/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ Supported by NIH Research Grants CA 58684-04, CA42182-11, HL 35464, CA 55075, CA 72036, and T32-CA-09001 and the Association for the Cure of Cancer of the Prostate Young Investigator Award (to J.C.).

² To whom requests for reprints should be addressed, at Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.

³ The abbreviations used are: ATBC, α -tocopherol β -carotene; HPFS, Health Professionals Follow-up Study; RR, relative risk; CI, confidence interval; PSA, prostate-specific antigen.

men with a history of cancer (other than nonmelanoma skin cancer) at baseline or who did not adequately complete the 1986 dietary questionnaire (3% of total), leaving 47,780 men for follow-up. We mailed follow-up questionnaires biennially to update exposure and disease status, including diagnoses of prostate cancer. Follow-up of the 47,780 men through 1996 was 93% (based on questionnaire returns and deaths). Deaths were reported by family members in response to follow-up questionnaires or were discovered by the postal system or the National Death Index, a highly sensitive method used to identify deaths among nonrespondents. More than 98% of all deaths are ascertained by these methods (14).

Assessment of Supplemental Vitamin E Intake. Supplemental vitamin E intake was assessed every 2 years. In addition, a detailed self-administered semiquantitative food frequency questionnaire was administered in 1986 and 1990. Total supplemental vitamin E intake was the sum of vitamin E from specific supplements and from multivitamins containing vitamin E.

In 1986, we asked about current and past use of vitamin E supplements; current users were asked about their daily dosage (<100, 100–250, 300–500, and \geq 600 IU) and duration of use (0–1, 2–4, 5–9, and \geq 10 years). Based on the most common level within the reported range, the following dose amounts were assigned to correspond to the above dose categories: 50, 200, 400, and 800 IU, respectively; we assigned 1, 3, 7, and 11 years for the duration categories. In subsequent questionnaires, we asked about use of vitamin E supplements (yes or no) and dosage (same categories as above). Men who reported current use of separate vitamin E supplements but did not report the dose (\sim 11% in 1986) were assigned a dosage of 400 IU/day, the mode dose among users.

Men were also asked biennially about current use of multivitamins; in 1986 information on total duration of use, frequency of use, and brand name was solicited. Brand and frequency of use were also assessed in 1990. Using this information, we computed daily intake of vitamin E from multivitamins for each 2-year interval, assuming that the brand reported in 1986 was the same one used in 1988 and that the brand reported in 1990 was the same one used in 1992 and 1994. More than 90% of the self-reported multivitamin brands contained vitamin E; users received an average of 21 IU/day in 1986 and 25 IU/day in 1990 from multivitamins.

For both multivitamin and specific vitamin E supplement use and dose, if a man did not return one of the postbaseline questionnaires, then he was assigned the exposure level from his most recent questionnaire. Of men who answered the 1994 questionnaire, 80% of those who took vitamin E supplements in 1986 also did so in 1994. The parallel proportion for multivitamin use was 72%.

Additionally, men reported in 1986 how often, during the past year, they consumed each of 131 commonly consumed foods and beverages. The questionnaire also asked about consumption of other nutrient supplements and included an open-ended section for reporting unlisted commonly eaten foods. Nutrient intakes were the product of the frequency of intake and the nutrient composition (15) of the specified portion size. When analyzing other nutrients as potential confounders of the vitamin E and prostate cancer relationship, we used the energy-adjusted 1986 nutrient intakes based on residuals from the regression of the nutrient intake on total caloric intake (16).

Details of validation and reproducibility studies of the semiquantitative food frequency questionnaire have been published previously (12). The intraclass correlation between total

vitamin E intake (including supplements) measured by two administrations of the food frequency questionnaire at a 1-year interval to 127 health professionals was 0.72 (12). The Pearson correlation coefficient between total vitamin E (including supplements) measured by the food frequency questionnaire and the average vitamin E intake from two 1-week diet records (spaced 6 months apart) was 0.86 (12). Total vitamin E intake measured by the food frequency questionnaire was also predictive of plasma tocopherol levels (Pearson correlation coefficient = 0.51; $n = 110$) (17).

We calculated vitamin E intake from diet but did not include this in the main analysis, because our focus was on supplemental vitamin E. The mean intake of vitamin E from food only was 11 IU in both 1986 and 1990, whereas the age-adjusted mean intake of supplemental vitamin E among users was 191 IU in 1986. Thus, only vitamin E from supplements provided a level of intake comparable with that given in the ATBC trial.

Case Assessment. On each biennial questionnaire, we asked men to report any recent diagnosis of prostate cancer. All self-reports of prostate cancer were followed up with a request to obtain hospital records and pathology reports. Next of kin were contacted for deceased men. Medical reports were reviewed by a study physician who also classified stage of disease based on initial work-up, prostatectomy reports, and bone scan results. From 1986 to the end of this study period (January 31, 1996), 1949 cases were confirmed by medical records.

Data Analysis. Each of the 47,780 eligible men in the study population contributed follow-up time from the date of return of the baseline questionnaire until the month of diagnosis of prostate cancer (for the cases), until the month of death from other causes, or until the end of the study period, January 31, 1996 (for noncases). By the end of follow-up, we had confirmed 1,896 total (non-stage A1), 522 extraprostatic (stage C or D), and 232 metastatic or fatal cases. We did not include the 53 men diagnosed with stage A1 tumors in the analyses, because A1 tumors are relatively innocuous and asymptomatic, and the ATBC trial found no effect of vitamin E on clinically inapparent tumors. We were also interested in examining the more aggressive tumors separately, because vitamin E supplementation has been linked to reductions in prostate cancer mortality, which is often predicted by stage at diagnosis.

Incidence rates of prostate cancer within categories of vitamin E were calculated as the total number of new cases divided by total person years within that category. RRs were estimated by comparing incidence rates among users and non-users of vitamin E. We used the Mantel-Haenszel summary estimator to adjust for age using 14 2.5-year categories. To adjust for the potential confounding effects of additional dietary and lifestyle characteristics, we used pooled logistic regression models, which computed an estimate summarizing over the five 2-year intervals (18).

The following covariates were considered potential confounders of the vitamin E-prostate cancer association in the main multivariate models: age (in 14 2.5-year categories), period (1986–1987, 1988–1989, 1990–1991, 1992–1993, and 1994–1995), family history of prostate cancer (father or brother), smoking (never, past and quit \geq 10 years ago, past and quit within the last 10 years, current, and missing), current body mass index (kg/m^2), body mass index at age 21 years, physical activity (metabolic equivalents [metabolic hours per week]), vasectomy status (ever and never through 1994), and quintiles of total calories, calcium, lycopene, fructose, and fat intake in 1986.

Table 1 Age-standardized baseline characteristics of 47,780 men in the HPFS by use of supplemental vitamin E in 1986

	User of supplemental vitamin E in 1986 (n = 20,828)	Nonuser of supplemental vitamin E in 1986 (n = 26,952)
Means^a		
Age (yr)	53.8	55.3
BMI (kg/m ²)	24.7	25.1
BMI at age 21 (kg/m ²)	21.9	22.0
Physical activity (MET-h/wk)	24.4	23.3
Supplemental vitamin E (IU/day)	191	0
Dietary vitamin E (IU/day)	11.5	11.1
Total years taking vitamin E before 1986	3.2	0.4
Energy (kcal/day)	1,985	1,986
Calcium (mg/day)	1,013	809
Fructose (g/day)	50	49
Lycopene (ug/day)	10,445	10,319
Fat (g/day)	70	72
Percent^a		
Users of supplemental vitamin E in 1990 ^b	77.1	16.3
Users of supplemental vitamin E in 1994 ^c	85.7	38.6
Never-smokers	48.4	48.6
Distant past smokers	30.0	29.0
Current smokers/recent quitters	21.6	22.4
Family history of prostate cancer (father or brother) reported in 1990	5.7	5.4
Vasectomy (ever/never)	24.9	24.1

^a Means and percents are age standardized across 11 categories of age. BMI, body mass index; MET, h/wk, metabolic equivalents.

^b Computed among the men who returned a 1990 questionnaire.

^c Computed among the men who returned a 1994 questionnaire.

The ATBC trial, which showed a protective effect of vitamin E on prostate cancer, comprised smokers entirely. To examine potential interaction associations between smoking and vitamin E with prostate cancer risk, we stratified on smoking status in 1986 (combining the approximate 8% with missing smoking data in the “never” category). We categorized past smoking into distant past (quit ≥ 10 years ago) and recent past (quit within the last 10 years) and combined the latter group with current smokers, because it had previously been observed that only recent smoking, within the prior 10 years, was associated with metastatic or fatal prostate cancer in this cohort (19).

Additionally, we evaluated supplemental vitamin E intake stratified by median dietary vitamin E intake in 1986 (≤ 10 and > 10 IU) and median dietary lycopene intake in 1986 (< 8686 and ≥ 8686 μg) to examine possible interactions.

In the ATBC trial, a protective effect of vitamin E was observed by the second year of supplementation. To account for this potential lag between initiation of vitamin E supplementation and reduced prostate cancer risk, in a secondary analysis, we considered only vitamin E use of > 2 years at the start of each interval.

Results

Table 1 presents mean baseline age-standardized characteristics by intake of supplemental vitamin E. The absolute difference between means is small for most characteristics, except total calcium, reflecting the presence of calcium in most multivita-

Table 2 Supplemental vitamin E intake and the relative risk of prostate cancer, HPFS, 1986–1996

	Supplemental vitamin E intake (IU/day)			
	0	0.1–15.0	15.1–99.9	≥ 100.0
Person yr	238,779	49,284	64,374	88,645
Total non-A1, cases	926	219	275	476
Age-adjusted RR	1.00	1.07	0.97	1.05
95% CI		0.92–1.24	0.85–1.11	0.99–1.17
Multivariate RR ^a	1.00	1.09	0.95	1.07
95% CI		0.94–1.26	0.83–1.09	0.95–1.20
Extraprostatic, cases	242	61	85	134
Multivariate RR ^a	1.00	1.12	1.16	1.22
95% CI		0.84–1.49	0.90–1.49	0.98–1.52
Metastatic or fatal, cases	110	33	34	55
Multivariate RR ^a	1.00	1.26	1.03	1.14
95% CI		0.85–1.87	0.70–1.52	0.82–1.59

^a Multivariate relative risks (RRs) adjusted for period (1986–1987, 1988–1989, 1990–1991, 1992–1993, and 1994–1995), age (14 2.5-year categories), family history of prostate cancer (father or brother), vasectomy status (ever or never through 1994), smoking (never, past and quit ≥ 10 years ago, past and quit within 10 years, current), quintiles of current body mass index, body mass index at age 21 years and physical activity in 1986 (metabolic hours/week), and quintiles of total calories, calcium, lycopene, fructose, and fat intake per day in 1986.

mins and the tendency for men taking vitamin E supplements to also take calcium supplements. In 1986, $\sim 44\%$ of the men consumed some form of supplemental vitamin E; 42% of the cohort reported taking multivitamins, and 19% reported taking specific vitamin E supplements.

Supplemental vitamin E was not significantly associated with prostate cancer incidence (Table 2). The age-adjusted and multivariate RRs were similar, suggesting minimal confounding by other known prostate cancer risk factors. Men who consumed ≥ 100 IU of supplemental vitamin E per day had multivariate RRs of 1.07 (95% CI, 0.95–1.20) for total prostate cancer, 1.22 (95% CI, 0.98–1.52) for extraprostatic, and 1.14 (95% CI, 0.82–1.59) for metastatic or fatal prostate cancer compared to with those who consumed none. The corresponding RRs for men who consumed 15.1–99.9 IU (range comparable with the 50-IU dose given in the ATBC trial) were 0.95 (95% CI, 0.83–1.09), 1.16 (95% CI, 0.90–1.49), and 1.03 (95% CI, 0.70–1.52), respectively. Current use, dose, and total years of taking specific vitamin E supplements and current use of multivitamins were also not related to prostate cancer risk both in age-adjusted and multivariate models.

We examined the association between supplemental vitamin E and prostate cancer risk within groups of high and low daily lycopene intake and high and low dietary vitamin E consumption at baseline (cut points were medians: 8686 for lycopene and 10 IU for dietary vitamin E). The RRs within each strata were virtually unchanged from the unstratified results in Table 2 (data not shown).

We considered the impact of the imputed data on vitamin E dose by conducting an alternative analysis limited to men with complete data. The results for men with complete information were essentially the same as those in Table 2, with RRs of 1.11 (95% CI, 0.98–1.26) for total, 1.29 (95% CI, 1.02–1.63) for extraprostatic, and 1.08 (95% CI, 0.75–1.57) for metastatic or fatal prostate cancer among men consuming at least 100 IU of vitamin E daily *versus* none.

We also considered the potential for a 2-year lag between consumption of supplemental vitamin E and effect on prostate cancer risk. For total, extraprostatic, and metastatic or fatal

Table 3 Supplemental vitamin E and the multivariate RR^a of total, extraprostatic, and metastatic or fatal prostate cancer by smoking habits in 1986

	Supplemental vitamin E (IU/day) ^b			
	0	0.1–15.0	15.1–99.9	≥100.0
Total non-A1 cases (n = 1896)				
Never-smokers (n = 819)	1.00	1.05 (0.83–1.32)	0.93 (0.75–1.15)	1.02 (0.86–1.21)
Quit ≥10 years ago (n = 708)	1.00	1.07 (0.83–1.37)	0.97 (0.78–1.22)	1.04 (0.86–1.26)
Current smoker/quit within past 10 years (n = 369)	1.00	1.23 (0.88–1.70)	0.97 (0.72–1.32)	1.27 (0.97–1.66)
Extraprostatic cases (n = 522) ^c				
Never-smokers (n = 213)	1.00	1.02 (0.63–1.64)	1.21 (0.81–1.81)	1.45 (1.05–2.02)
Quit ≥10 years ago (n = 193)	1.00	1.57 (1.03–2.40)	1.34 (0.89–2.00)	1.15 (0.80–1.68)
Current smoker/quit within past 10 years (n = 110)	1.00	0.72 (0.37–1.40)	0.76 (0.43–1.34)	1.00 (0.61–1.64)
Metastatic/fatal cases (n = 232) ^c				
Never-smokers (n = 97)	1.00	0.91 (0.44–1.88)	1.29 (0.72–2.29)	1.42 (0.87–2.32)
Quit ≥10 years ago (n = 78)	1.00	2.43 (1.32–4.47)	1.33 (0.67–2.64)	1.49 (0.82–2.69)
Current smoker/quit within past 10 years (n = 55)	1.00	0.78 (0.34–1.77)	0.51 (0.21–1.21)	0.44 (0.18–1.07)

^a Multivariate relative risks (RRs) adjusted for period (1986–1987, 1988–1989, 1990–1991, 1992–1993, and 1994–1995), age (nine 2.5-year categories), family history of prostate cancer (father or brother), vasectomy status (ever or never through 1994), quintiles of current body mass index, body mass index at age 21 years and physical activity in 1986 (metabolic hours/week), and quintiles of total calories, calcium, lycopene, fructose, and fat intake per day in 1986.

^b Numbers in parentheses are 95% CIs.

^c Case totals do not sum because six cases of extraprostatic and two cases of metastatic or fatal prostate cancer were dropped during analysis due to missing data on one of the covariates.

prostate cancer, the multivariate RRs associated with consumption of ≥100 IU daily for at least 2 years *versus* none (men who consumed supplemental vitamin E for <2 years were in the reference group) were 1.05 (95% CI, 0.93–1.18), 1.22 (95% CI, 0.98–1.53), and 1.15 (95% CI, 0.82–1.62), respectively.

In this cohort, men who reported in 1994 that they took multivitamins or specific vitamin E supplements were more likely to have had a serum PSA test (58% of users *versus* 50% of nonusers of multivitamins and 64% of users *versus* 50% of nonusers of vitamin E supplements had had a PSA test by 1994). When we limited the main analyses to men who reported ever having had a PSA test, the results were very similar to those in Table 2 (RRs for taking at least 100 IU per day *versus* none were 1.02, 1.13, and 1.06 for total, extraprostatic, and metastatic or fatal prostate cancer, respectively).

There was no association between baseline total vitamin E (from foods and supplements) in a previous investigation of this cohort (20). With additional years of follow-up and a doubling in case size, we reexamined this relation and observed no consistent association between total vitamin E on risk of total non-A1, extraprostatic, or fatal or metastatic prostate cancer (RRs for comparison of extreme quintiles were 1.00 [95% CI, 0.86–1.17], 0.96 [95% CI, 0.72–1.27], and 0.89 [95% CI, 0.58–1.36], respectively).

Because the ATBC trial was conducted among smokers, we examined the association of supplemental vitamin E consumption within strata of smoking status in 1986 (Table 3). There was no association between supplemental vitamin E and total prostate cancer risk among never-smokers, distant past smokers (quit ≥10 years ago), and current and recent past smokers (quit within the past 10 years). In contrast, among current and recent past smokers, the multivariate RRs for metastatic or fatal prostate cancer associated with increasing consumption levels of supplemental vitamin E were 0.78 (95% CI,

0.34–1.77), 0.51 (95% CI, 0.21–1.21), and 0.44 (95% CI, 0.18–1.07), respectively. When we combined the highest two categories of supplemental vitamin E intake, the multivariate RR of metastatic or fatal prostate cancer among current and recent past smokers consuming >15 IU of supplemental vitamin E was 0.47 (95% CI, 0.24–0.92) compared with those consuming none (data not shown in tables). When we allowed for a 2-year lag between vitamin E supplementation and effect on prostate cancer risk within the smoking-stratified models, we observed results similar to those presented in Table 3.

We previously observed in this population that men with a recent smoking history (current smokers or recent quitters) had a greater risk of metastatic or fatal prostate cancer than men who never smoked (19). However, when we classified categories of supplemental vitamin E intake jointly with smoking habits, men with a recent smoking history who also took >15 IU of supplemental vitamin E per day were not at elevated risk of metastatic or fatal prostate cancer relative to never-smokers (RR, 0.88; 95% CI, 0.45–1.71).

Discussion

We observed no significant overall protective association between supplemental vitamin E intake and prostate cancer risk. However, stratification by smoking yielded divergent results. Among past smokers who had quit for ≥10 years, low but not high dosage of supplemental vitamin E was associated with an increased risk of extraprostatic and metastatic or fatal prostate cancer. Such an association is contrary to most hypotheses on vitamin E. Other than chance, we have no compelling explanation for this surprising result and urge further investigation.

More strikingly, among current smokers or recent quitters in 1986, increasing doses of supplemental vitamin E appeared potentially protective against metastatic or fatal prostate cancer

risk, although the result was statistically significant only when we combined the highest two dosage categories. Current smokers and recent quitters were at higher risk for metastatic or fatal prostate cancer (19), but in the current investigation, those who took >15 IU of supplemental vitamin E had a level of risk of metastatic or fatal prostate cancer comparable with that of men who never smoked.

We were particularly interested in examining the effect of vitamin E on prostate cancer risk among smokers, because the ATBC trial was conducted among men who smoked for a median of 36 years. Also, two prospective studies observed inverse associations between plasma α -tocopherol and incidence of advanced prostate cancer or prostate cancer mortality among smokers (5, 6). Among current smokers and recent quitters, we observed a statistically significant 53% reduction in risk of metastatic or fatal prostate cancer in men consuming >15 IU of supplemental vitamin E per day (the ATBC trial used 50 IU supplements) *versus* none; this was consistent with the 40% reduction in stage II-IV tumors observed in the ATBC trial. Because the prevalence of PSA screening (54% in 1994) in our population of U.S. health professionals was higher than in the ATBC trial (only one case detected by routine screening), it is likely that many of stage II-IV cancers in the ATBC study population were comparable in degree of progression with the extraprostatic and metastatic or fatal cancers diagnosed in our study.

The mechanisms by which vitamin E might reduce prostate cancer development and aggressivity among smokers remain unknown. Smoking itself appears to be more of a risk factor for prostate cancer mortality (19, 21–23) than for prostate cancer incidence (24–30). A dose-response relationship between tobacco and prostate cancer mortality was observed in a large study of U.S. veterans (22). In the current study population, distant past smoking was not related to prostate cancer risk, but men who had smoked within the past 10 years had approximately double the risk of metastatic and fatal prostate cancer relative to nonsmokers (19). Smoking has also been positively related to worse tumor grade and stage at diagnosis (31, 32). Hussain *et al.* (32) observed that among 670 men with prostate cancer, smokers were more likely to have stage D (68 *versus* 53%; $P = 0.01$) and poorly differentiated tumors (58 *versus* 18%; $P < 0.00005$) than nonsmokers. One explanation may be that smokers tend to delay diagnosis and treatment compared with nonsmokers. However, evidence from at least one study suggests that men with a smoking history are as likely if not more so to have digital rectal exams and PSA screening compared with nonsmokers (19).

Alternatively, tobacco may also directly increase the virulence of prostate cancers. Cigarette smoking may induce mutations in oncogenes or tumor suppressor genes related to prostate cancer progression and aggressiveness (for example, in the p53 tumor suppressor gene; Refs. 33–37). Cigarette smoking could also increase plasma testosterone and dihydrotestosterone, which have been associated with increased risk of prostate cancer, especially advanced tumors (38). If so, then one might speculate that vitamin E may help stem the progression of prostate cancer from a localized to distant metastatic or fatal stage, which could perhaps explain why the influence of vitamin E appeared limited to metastatic and fatal cases (Table 3). To further understand the potential interaction between smoking and vitamin E on prostate cancer risk (particularly advanced disease or mortality), it would be useful to study this association in a large population with a balanced proportion of smokers and nonsmokers.

In the ATBC trial, the investigators observed an effect of

vitamin E on prostate cancer incidence and mortality by the second year, and the effect persisted throughout follow-up. To adjust for this time lag, we considered only supplemental vitamin E used for >2 years but still observed no overall association with prostate cancer in our cohort.

The prospective design, large sample size and number of cases, long follow-up, and repeated assessment of vitamin E and multivitamin use reduce the likelihood that bias and misclassification are responsible for these results. Additionally, in the multivariate models we were able to consider the potential confounding effects of several risk factors for prostate cancer.

Men who take supplemental vitamin E might practice other health-seeking behaviors, such as prostate cancer screening with a PSA test. Thus, they might be more likely to have their prostate cancer diagnosed than men who do not take supplements, which could bias the results toward an increased risk among vitamin E users. This could potentially account for the slight increased risk of prostate cancer among users of supplemental vitamin E; however, it is unlikely to be responsible for the overall null effect, because we observed similar RRs when we restricted the analysis to only men who reported having a serum PSA test as of 1994.

Random misclassification of supplemental vitamin E use is unlikely to account for the null results, because results were unchanged when we limited our analysis to men who had complete updated exposure data at all intervals. Additional support for the validity of our vitamin E data are that vitamin E intake predicts plasma tocopherol level (17) and reduced risk of coronary heart disease in this cohort (39).

We considered the possibility that vitamin E supplementation offers protection against prostate cancer, dependent on the level of intake of other nutrients. However, baseline mean plasma α -tocopherol levels in a sample of men in the current study ($27.1 \mu\text{M} = 11.7 \text{ mg/liter}$; Ref. 17) and the ATBC trial (11.9 mg/liter ; Ref. 40) were similar, and any difference is unlikely to account for any discrepancy in the results. High levels of selenium may protect against prostate cancer (41), and men with low serum levels of selenium may have greater risk of cancer (42), especially if they also have low levels of α -tocopherol (42). Thus, vitamin E supplementation might be protective against prostate cancer in populations with low selenium levels but may only have a marginal influence in populations with high selenium levels. Total mean selenium intake in the ATBC trial was $95.9 \mu\text{g/day}$ based on a food questionnaire and food composition information; Finland began fortification of fertilizers with selenium in 1984. In our study, selenium intake was estimated from toenail specimens among 33,737 men who provided toenail specimens in 1987 (41, 43). Median selenium intake among men in the lowest and highest quintiles of toenail selenium was estimated to be 86 and 159 $\mu\text{g/day}$, respectively (41). Thus, the overall median selenium intake of the trial was close to our lowest quintile median, and one may speculate that vitamin E supplementation had greater impact in the Finnish trial due to overall lower selenium status in that population.

There are limited epidemiological data on the association between vitamin E and prostate cancer. Two case-control studies, one from Greece (8) and one from Serbia (7), reported significant reductions in prostate cancer risk associated with intake of vitamin E. Total vitamin E intake (from food and supplements) had been studied previously in the HPFS, and no association with prostate cancer was observed (20); with additional follow-up and cases, we still observed no association between total vitamin E and prostate cancer risk in this U.S. population.

A small prospective study from Switzerland found a statistically significantly increased risk of prostate cancer mortality among smokers with low plasma vitamin E levels (RR, 8.3; 95% CI, 1.0–68.7) comparing the lowest *versus* the highest eighths of the serum vitamin E distribution (5) and an elevated but not statistically significant risk among nonsmokers; there were only 30 cases of prostate cancer death among the 2974 men followed for 17 years (5). A similar association was observed in the prospective Physicians' Health Study in the United States, which had 259 incident cases of aggressive prostate cancer diagnosed during 13 years of follow-up. In this study, smokers in the highest quintile of plasma α -tocopherol had a significant 49% reduction in risk of aggressive prostate cancer; there was no significant association among nonsmokers (6). Two other prospective studies of serum α -tocopherol levels and prostate cancer risk, conducted among residents of Washington County ($n = 103$; Ref. 44) and Japanese-Americans in Hawaii ($n = 142$; Ref. 45), found no association between serum vitamin E and subsequent overall prostate cancer incidence; however, they did not examine the subgroups of smokers with advanced disease.

Our results do not support a general protective effect of supplemental vitamin E against prostate cancer in this U.S. population. However, results from four distinct populations, this U.S. study, the Finnish ATBC trial (40), and the Swiss and U.S. serum investigations (5, 6), suggest that vitamin E may provide particular benefits against advanced prostate cancer or prostate cancer mortality among men with a recent smoking history. Vitamin E supplementation is unlikely to have a major impact on prostate cancer occurrence or progression among nonsmokers. However, additional study is warranted of its possible benefits among smokers, particularly for advanced or fatal disease.

Acknowledgments

We thank LinLin Chen and Rachel Adams for their assistance on this project.

References

- Packer, L. Protective role of vitamin E in biological systems. *Am. J. Clin. Nutr.*, 53: 1050S–1055S, 1991.
- Israel, K., Sanders, B. G., and Kline, K. RRR- α -tocopheryl succinate inhibits the proliferation of human prostatic tumor cells with defective cell cycle/differentiation pathways. *Nutr. Cancer*, 24: 161–169, 1995.
- Sigounas, G., Anagnostou, A., and Steiner, M. DL- α -tocopherol induces apoptosis in erythroleukemia, prostate, and breast cancer cells. *Nutr. Cancer*, 28: 30–35, 1997.
- Grimble, R. F. Effect of antioxidative vitamins on immune function with clinical applications. *Int. J. Vitam. Nutr. Res.*, 67: 312–320, 1997.
- Eichholzer, M., Stahelin, H. B., Gey, K. F., Ludin, E., and Bernasconi, F. Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. *Int. J. Cancer*, 66: 145–150, 1996.
- Gann, P. H., Ma, J., Giovannucci, E., Willett, W., Sacks, F. M., Hennekens, C. H., and Stampfer, M. J. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res.*, 59: 1225–1230, 1999.
- Vlajinac, H. D., Marinkovic, J. M., Ilic, M. D., and Kocov, N. I. Diet and prostate cancer: a case-control study. *Eur. J. Cancer*, 33: 101–107, 1997.
- Tzonou, A., Signorello, L. B., Lagiou, P., Wu, J., Trichopoulos, D., and Trichopoulos, A. Diet and cancer of the prostate: a case-control study in Greece. *Int. J. Cancer*, 80: 704–708, 1999.
- Hartman, T., Dorgan, J., Taylor, P. R., Heinonen, O. P., Chandler, D. W., Galmarini, M., Tangrea, J., Virtamo, J., and Albanes, D. Serum vitamin E as a predictor of serum androgens and estrogens in older men. *Am. J. Epidemiol.*, 147 (Suppl.): S52, 1998.
- Hartman, T., Albanes, D., Pietinen, P., Hartman, A. M., Rautalahti, M., Tangrea, J. A., and Taylor, P. R. The association between baseline vitamin E, selenium, and prostate cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Cancer Epidemiol., Biomarkers & Prev.*, 7: 335–340, 1998.
- Rimm, E. B., Stampfer, M. J., Colditz, G. A., Chute, C. G., Litin, L. B., and Willett, W. C. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology*, 1: 466–473, 1990.
- Rimm, E. B., Giovannucci, E. L., Stampfer, M. J., Colditz, G. A., Litin, L. B., and Willett, W. C. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am. J. Epidemiol.*, 135: 1114–1126, 1992.
- Giovannucci, E., Rimm, E. B., Colditz, G. A., Stampfer, M. J., Ascherio, A., Chute, C. C., and Willett, W. C. A prospective study of dietary fat and risk of prostate cancer. *J. Natl. Cancer Inst.*, 85: 1571–1579, 1993.
- Stampfer, M. J., Willett, W. C., Speizer, F. E., Dysert, D. C., Lipnick, R., Rosner, B., and Hennekens, C. H. Test of the National Death Index. *Am. J. Epidemiol.*, 119: 837–839, 1984.
- U. S. Department of Agriculture. Composition of foods—raw, processed, and prepared, 1963–1988. Agricultural Handbook No. 8 Series. Washington, DC: Department of Agriculture, Government Printing Office, 1989.
- Willett, W. C. Nutritional Epidemiology. New York: Oxford University Press, 1990.
- Ascherio, A., Stampfer, M. J., Colditz, G. A., Rimm, E. B., Litin, L., and Willett, W. C. Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. *J. Nutr.*, 122: 1792–1801, 1992.
- D'Agostino, R. B., Lee, M. L. T., Belanger, A. J., Cupples, L. A., Anderson, K., and Kannel, W. B. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat. Med.*, 9: 1501–1515, 1990.
- Giovannucci, E., Rimm, E. B., Ascherio, A., Colditz, G. A., Spiegelman, D., Stampfer, M. J., and Willett, W. C. Smoking and risk of total and fatal prostate cancer in United States health professionals. *Cancer Epidemiol., Biomarkers & Prev.*, 8: 277–282, 1999.
- Giovannucci, E., Ascherio, A., Rimm, E. B., Stampfer, M. J., Colditz, G. A., and Willett, W. C. Intake of carotenoids and retinol in relation to risk of prostate cancer. *J. Natl. Cancer Inst.*, 87: 1767–1776, 1995.
- Hsing, A. W., McLaughlin, J. K., Schuman, L. M., Bjelke, E., Gridley, G., Wacholder, S., Chien, H. T., and Blot, W. J. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. *Cancer Res.*, 50: 6836–6840, 1990.
- Hsing, A. W., McLaughlin, J. K., Hrubec, Z., Blot, W. J., and Fraumeni, J. F. Tobacco use and prostate cancer: 26-year follow-up of US veterans. *Am. J. Epidemiol.*, 133: 437–441, 1991.
- Coughlin, S. S., Neaton, J. D., and Sengupta, A. Cigarette smoking as a predictor of death from prostate cancer in 348,874 men screened for the Multiple Risk Factor Intervention Trial. *Am. J. Epidemiol.*, 143: 1002–1006, 1996.
- Nomura, A. M., and Kolonel, L. N. Prostate cancer: a current perspective. *Epidemiol. Rev.*, 13: 200–227, 1991.
- Pienta, K. J., and Esper, P. S. Risk factors for prostate cancer. *Ann. Intern. Med.*, 118: 793–803, 1993.
- Engeland, A., Andersen, A., Haldorsen, T., and Tretli, S. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. *Cancer Causes & Control*, 7: 497–506, 1996.
- Slattery, M. L., and West, D. W. Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States). *Cancer Causes & Control*, 4: 559–563, 1993.
- Talamini, R., Franceschi, S., La Vecchia, C., Guarneri, S., and Negri, E. Smoking habits and prostate cancer: a case-control study in northern Italy. *Prev. Med.*, 22: 400–408, 1993.
- Siemiatycki, J., Krewski, D., Franco, E., and Kaiserman, M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *Int. J. Epidemiol.*, 24: 504–514, 1995.
- Adami, H.-O., Bergström, R., Engholm, G., Nyrén, O., Wolk, A., Ekblom, A., Englund, A., and Baron, J. A prospective study of smoking and risk of prostate cancer. *Int. J. Cancer*, 67: 764–768, 1996.
- Daniell, H. W. A worse prognosis for smokers with prostate cancer. *J. Urol.*, 154: 153–157, 1995.
- Hussain, F., Aziz, H., Macchia, R., Avitable, M., and Rotman, M. High grade adenocarcinoma of prostate in smokers of ethnic minority groups and Caribbean island immigrants. *Int. J. Radiat. Oncol. Biol. Phys.*, 24: 451–461, 1992.
- Smith, E. R., and Hagopian, M. Uptake and secretion of carcinogenic chemicals by the dog and rat prostate. In: G. P. Murphy, A. A. Sandberg, and J. P. Karr (eds.), *The Prostate Cell: Structure and Function Part B*, pp. 131–163. New York: Alan R. Liss, 1981.
- Navone, N. M., Troncoso, P., Pisters, L. L., Goodrow, T. L., Palmer, J. L., Nichols, W. W., von Eschenbach, A. C., and Conti, C. J. p53 protein accumu-

- lation and gene mutation in the progression of human prostate carcinoma. *J. Natl. Cancer Inst.*, *85*: 1657–1669, 1993.
35. Brookstein, R., MacGrogan, D., Hilsenbeck, S. G., Sharkey, R., and Allred, D. C. p53 is mutated in a subset of advanced-stage prostate cancers. *Cancer Res.*, *53*: 3369–3373, 1993.
36. Visakorpi, T., Kallioniemi, P. O., Heikkinen, A., Koivula, T., and Isola, J. Small subgroup of aggressive, highly proliferative prostatic carcinomas defined by p53 accumulation. *J. Natl. Cancer Inst.*, *84*: 883–887, 1992.
37. Chi, S-G., De Vere White, R. W., Meyers, F. J., Siders, D. B., Lee, F., and Gumerlock, P. H. p53 mutations in prostate cancer: frequent expressed transition mutations. *J. Natl. Cancer Inst.*, *86*: 926–933, 1994.
38. Gann, P. H., Hennekens, C. H., Ma, J., Longcope, C., and Stampfer, M. J. A prospective study of sex hormone levels and risk of prostate cancer. *J. Natl. Cancer Inst.*, *88*: 1118–1126, 1996.
39. Rimm, E. B., Stampfer, M. J., Ascherio, A., Giovannucci, E., Colditz, G. A., and Willett, W. C. Vitamin E consumption and the risk of coronary heart disease in men. *N. Engl. J. Med.*, *328*: 1450–1456, 1993.
40. Heinonen, O. P., Albanes, D., Virtamo, J., Taylor, P. R., Huttunen, J. K., Harman, A. M., Haapakoski, J., Malila, N., Rautalahti, M., Ripatti, S., Maenpaa, H., Teerenhovi, L., Koss, L., Virolainen, M., and Edwards, B. K. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J. Natl. Cancer Inst.*, *90*: 440–446, 1998.
41. Yoshizawa, K., Willett, W. C., Morris, S. J., Stampfer, M. J., Spiegelman, D., Rimm, E., and Gionavannucci, E. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J. Natl. Cancer Inst.*, *90*: 1219–1224, 1998.
42. Willett, W. C., Polk, B. F., Morris, J. S., Stampfer, M. J., Pressel, S., Rosner, B., Taylor, J. O., Schneider, K., and Hames, C. G. Prediagnostic serum selenium and risk of cancer. *Lancet*, *2*: 130–134, 1983.
43. Longnecker, M. P., Stram, D. O., Taylor, P. R., Levander, O. A., Howe, M., Veillon, C., McAdam, P. A., Patterson, K. Y., Holden, J. M., Morris, J. S., Swanson, C. A., and Willett, W. C. Use of selenium concentration in whole blood, serum, toenails, or urine as a surrogate measure of selenium intake. *Epidemiology*, *7*: 384–390, 1996.
44. Hsing, A. W., Comstock, G. W., Abbey, H., and Polk, B. F. Serologic precursors of cancer. Retinol, carotenoids, and tocopherol and risk of prostate cancer. *J. Natl. Cancer Inst.*, *82*: 941–946, 1990.
45. Nomura, A. M., Stemmermann, G. N., Lee, J., and Craft, N. E. Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. *Cancer Epidemiol., Biomarkers & Prev.*, *6*: 487–491, 1997.