

# Supplemental and Dietary Vitamin E Intakes and Risk of Prostate Cancer in a Large Prospective Study

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## Abstract

Supplemental vitamin E ( $\alpha$ -tocopherol) has been linked to lower prostate cancer incidence in one randomized trial and several, although not all, observational studies. The evidence regarding dietary intake of individual vitamin E isoforms and prostate cancer is limited and inconclusive, however. We prospectively examined the relations of supplemental vitamin E and dietary intakes of  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols to prostate cancer risk among 295,344 men, ages 50 to 71 years and cancer-free at enrollment in 1995 to 1996, in the NIH-AARP Diet and Health Study. At baseline, participants completed a questionnaire that captured information on diet, supplement use, and other factors. Proportional hazards models were used to estimate relative risks (RR) and 95% confidence intervals (95% CI) of prostate cancer. During 5 years of follow-up, 10,241 incident prostate cancers were

identified. Supplemental vitamin E intake was not related to prostate cancer risk (for >0-99, 100-199, 200-399, 400-799, and  $\geq$ 800 IU/d versus never use: RR, 0.97, 0.89, 1.03, 0.99, and 0.97 (95% CI, 0.87-1.07) respectively;  $P_{\text{trend}} = 0.90$ ). However, dietary  $\gamma$ -tocopherol, the most commonly consumed form of vitamin E in the United States, was significantly inversely related to the risk of advanced prostate cancer (for highest versus lowest quintile: RR, 0.68; 95% CI, 0.56-0.84;  $P_{\text{trend}} = 0.001$ ). These results suggest that supplemental vitamin E does not protect against prostate cancer, but that increased consumption of  $\gamma$ -tocopherol from foods is associated with a reduced risk of clinically relevant disease. The potential benefit of  $\gamma$ -tocopherol for prostate cancer prevention deserves further attention. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1128-35)

## Introduction

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a large trial conducted in Finnish male smokers, showed significant reductions in prostate cancer incidence and mortality among subjects randomized to receive 50 mg (equivalent to 50 IU) vitamin E (DL- $\alpha$ -tocopheryl acetate) daily for 5 to 8 years (1). Several, although not all, observational studies have also shown a protective effect of supplemental vitamin E use on prostate cancer, particularly in smokers (2-4). These cumulative findings, especially those from the ATBC Study, helped give rise to the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a large nutritional intervention trial designed to examine whether daily supplementation with

vitamin E (400 IU DL- $\alpha$ -tocopheryl acetate) and/or selenium (200  $\mu$ g L-selenomethionine) reduces the incidence of prostate cancer among 32,400 men in the United States (5).

There is substantial data regarding the association between total dietary vitamin E and prostate cancer, with most studies showing equivocal or modest inverse associations between the two (6). Few studies, however, have evaluated whether consumption of specific vitamin E isoforms, including  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols, are related to prostate cancer.  $\alpha$ -Tocopherol is generally considered the most bioactive form of vitamin E because it is preferentially retained in the bloodstream by the hepatic  $\alpha$ -tocopherol transfer protein (7).  $\gamma$ -Tocopherol, however, is the most commonly consumed form of vitamin E in the United States (8) and has several anticarcinogenic properties that are distinct from those of  $\alpha$ -tocopherol. For example,  $\gamma$ -tocopherol and its primary metabolite 2,7,8-trimethyl-2-( $\beta$ -carboxyethyl)-6-hydroxychroman, but not  $\alpha$ -tocopherol, exhibit anti-inflammatory activities via inhibition of cyclooxygenase-2 activity (9). Therefore, in epidemiologic studies, it may be more informative to evaluate the relationships of individual vitamin E isoforms, rather than total dietary vitamin E, with prostate cancer risk.

We prospectively examined whether supplemental vitamin E and dietary tocopherol intakes were related to prostate cancer in the National Institutes of Health (NIH) AARP Diet and Health Study. With over 10,000 incident prostate cancer cases available for analysis, including 1,476 advanced cases, this is the largest prospective study to date to examine hypotheses related to vitamin E and prostate cancer prevention.

## Materials and Methods

**Study Population.** The NIH-AARP Diet and Health Study was initiated in 1995 to 1996, when an extensive baseline

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**Note:** Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry.

The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health (DOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or DOH. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

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**Table 1. Baseline characteristics (means and proportions) by categories of supplemental vitamin E use and dietary  $\alpha$ - and  $\gamma$ -tocopherol intakes in the NIH-AARP Diet and Health Study**

	Supplemental vitamin E (IU/d)*				Quintiles of dietary $\alpha$ -tocopherol (mg/d)			Quintiles of dietary $\gamma$ -tocopherol (mg/d)		
	0	>0-399	400-799	$\geq$ 800	1 (<5.5)	3 (6.5-7.5)	5 (>8.8)	1 (<9.7)	3 (12.4-14.9)	5 (>18.2)
Participants, no.	115,788	110,460	53,852	15,244	58,898	58,898	58,898	59,002	59,002	59,002
Age, y	62.1	61.9	62.7	62.4	61.9	62.1	62.5	62.2	62.0	62.3
Body mass index, kg/m <sup>2</sup>	27.6	27.1	27.0	27.2	27.2	27.4	27.2	26.8	27.3	27.6
Physical activity, times per week <sup>†</sup>	2.39	2.59	2.92	2.96	2.25	2.62	2.85	2.74	2.60	2.44
Race, %										
White	93.4	93.1	94.9	95.5	92.2	94.4	93.4	92.1	94.2	94.0
Black	3.1	2.9	1.7	1.8	3.6	2.3	2.7	2.9	2.5	3.1
Other <sup>‡</sup>	3.5	4.0	3.3	2.8	4.2	3.3	3.9	5.1	3.4	2.9
Smoking status, %										
Never	29.0	30.2	29.7	28.1	25.3	30.4	31.8	29.6	29.6	28.9
Former	59.2	59.1	62.7	62.8	59.0	60.3	60.7	59.9	60.1	59.9
Current	11.9	10.7	7.6	9.1	15.8	9.3	7.5	10.5	10.3	11.3
Education, % $\geq$ college degree	42.7	49.2	51.3	51.5	41.0	48.3	50.4	49.4	48.1	43.1
Family history of prostate cancer, % yes	8.1	8.5	8.5	8.3	7.7	8.5	8.6	7.8	8.4	8.7
Personal history of diabetes, % yes	11.1	9.4	9.7	10.8	7.9	9.9	12.8	8.6	9.7	12.8
Screening history, % yes <sup>§</sup>										
PSA <sup>  </sup>	67.9	71.5	77.5	76.2	66.9	72.6	73.6	71.1	72.2	70.4
DRE <sup>¶</sup>	83.9	86.5	89.5	88.3	82.6	87.1	87.6	85.5	86.5	85.7
Multivitamin use, % yes	0	91.7	74.9	72.6	48.9	52.1	53.6	53.5	52.5	48.4
Daily dietary intake**										
Total energy, kcal	2,022	2,016	1,990	2,022	1,935	2,015	2,095	1,983	2,006	2,069
Red meat, g	76.2	70.6	63.4	62.0	67.2	75.7	63.9	52.1	75.3	80.2
Fish, g	19.5	20.7	22.3	23.4	13.8	21.3	25.7	17.7	20.9	23.0
Tomatoes, pyramid servings	0.60	0.63	0.68	0.72	0.42	0.64	0.82	0.60	0.65	0.62
$\alpha$ -Linolenic acid, g	1.32	1.30	1.29	1.28	0.95	1.34	1.56	0.90	1.32	1.68
Calcium, mg <sup>††</sup>	757	956	1,088	1,171	810	929	977	975	928	823
Vitamin C, mg <sup>††</sup>	180	450	831	1,128	372	450	522	519	450	378
$\beta$ -Carotene, $\mu$ g <sup>††</sup>	3,566	4,695	5,913	6,595	2,827	4,470	6,473	4,709	4,591	4,425
Selenium, $\mu$ g <sup>††</sup>	96	111	113	113	91	110	111	97	109	107

\*Includes vitamin E obtained from multivitamins and single supplements: 1 IU = 0.45 mg  $\alpha$ -tocopherol equivalents.

<sup>†</sup>Defined as physical activity for at least 20 min that caused increases in breathing or heart rate, or worked up a sweat.

<sup>‡</sup>Includes Hispanics, Asians, Pacific Islanders, and American Indians/Alaskan natives.

<sup>§</sup>Available for individuals ( $n = 176,876$ ) who completed the supplemental questionnaire that inquired about screening history.

<sup>||</sup>PSA blood test within 3 y before baseline.

<sup>¶</sup>DRE within 3 y before baseline.

\*\*Adjusted for total energy intake.

<sup>††</sup>Includes intakes from diet and supplements.

questionnaire was mailed to 3.5 million AARP members ages 50 to 71 years residing in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two metropolitan areas (Atlanta, Georgia and Detroit, Michigan; ref. 10). This questionnaire ascertained information on usual dietary intake, use of individual and multivitamin supplements, and other risk factors. A total of 617,119 individuals returned the baseline questionnaire, with 567,169 determined to be satisfactorily completed. In late 1996, a second questionnaire was mailed to participants who had successfully completed the baseline questionnaire. There were specific questions regarding prostate-specific antigen (PSA) testing and digital rectal examination (DRE) during the 3 years before baseline. A total of 334,910 persons responded to the second questionnaire.

Among the 567,169 individuals who returned the baseline questionnaire, we excluded those with duplicate questionnaires ( $n = 179$ ), persons who had died or moved out of the study area before baseline ( $n = 582$ ), a withdrawal from the study ( $n = 1$ ), individuals who had questionnaires completed by proxy respondents ( $n = 15,760$ ), women ( $n = 225,471$ ), men who had been previously diagnosed with cancer, except for non-melanoma skin cancer ( $n = 27,245$ ), and men who reported extreme values for total energy intake (beyond twice the interquartile range of Box-Cox log-transformed intake, which corresponds to  $<415$  and  $>6,144$  kcal/d;  $n = 2,587$ ). After these exclusions, 295,344 men were available for analysis, of whom 176,876 had available information from the more detailed second questionnaire. We also excluded subjects with extreme

values for individual dietary tocopherol intakes in those specific analyses ( $n = 854, 647, 332,$  and  $159$  for  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols, respectively).

The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

**Assessment of Vitamin E Intake.** The dietary component of the baseline questionnaire asked about the frequency of consumption and corresponding portion sizes of 124 food items during the past 12 months. There were specific questions on the consumption of nuts and seeds, salad dressing, butter, margarine, fats, and oils, which are major dietary sources of vitamin E. In addition, those who reported regularly using oil to fry or sauté vegetables, eggs, or meat were asked about the kinds of oils used, including corn, olive, safflower, sunflower, and canola. Daily dietary intakes of  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols were estimated using the method by Subar et al. (11), linking food codes from the U.S. Department of Agriculture's 1994 to 1996 Continuing Survey of Food Intake by Individuals (CSFII) to those from the Nutrition Data Systems for Research (NDS-R, University of Minnesota<sup>5</sup>). This database, unlike that from 1994 to 1996 CSFII, contains values for individual tocopherols for an extensive number of foods and brand name products. Addition of tocopherols to the Diet and Health Study food-frequency questionnaire database was

<sup>5</sup> <http://www.ncc.umn.edu/>

accomplished in the same manner as for carotenoids (12). The food-frequency questionnaire was validated using two 24-h recalls in a subset of the cohort (13). The top five contributors to each individual tocopherol among men in our cohort were as follows:  $\alpha$ -tocopherol (ready-to-eat cereals, salad dressings, margarine and butter, nuts and seeds, and potato/corn/other chips),  $\beta$ -tocopherol (ready-to-eat cereals, breads and rolls, salad dressings, fried potatoes, and beans),  $\gamma$ -tocopherol (margarine and butter, salad dressings, fried potatoes, oils (predominantly corn), and cookies and brownies),  $\delta$ -tocopherol (margarine and butter, crackers, cookies and brownies, macaroni and cheese, and breads and rolls).

Estimates of nutrient intakes from supplements were calculated separately from those for food. The baseline questionnaire asked about the frequency of use of three types of multivitamins (Stress-tabs type, Therapeutic or Theragran-type, and One-a-day type) and five single nutrient supplements, including vitamin E. There were five possible response categories (never, <1 time per week, 1-3 times per week, 4-6 times per week, or every day), and the following frequencies were assigned to each: 0, 1 per week, 2 per week, 5 per week, and 1 per day. The total daily amount of each single nutrient supplement was also ascertained. For vitamin E, the possible response categories were < 100, 100 to 250, 300 to 500,  $\geq 600$  IU, or unknown, and the following doses were assigned to each corresponding category: 100, 200, 400, and 800 IU (individuals who reported vitamin E supplement use but did not provide dose information were assigned a default value of 400 IU). Dosage was not queried for multivitamins. Daily supplemental vitamin E intake was calculated for each subject by adding the amount obtained from individual vitamin E supplements (daily frequency of use  $\times$  dose) plus the amount from multivitamin pills (daily frequency of use  $\times$  30 IU, the standard amount of vitamin E assigned to multivitamins based on nationally representative data from the Third National Health and Nutrition Examination Survey; ref. 14). Information on duration of supplement use was not available.

We did not combine dietary  $\alpha$ -tocopherol with supplemental vitamin E as a measure of total vitamin E intake, as the amounts obtained from supplements greatly exceeded the amounts obtained from food [i.e., average daily dietary intake of  $\alpha$ -tocopherol = 7.7 mg and average daily supplemental vitamin E intake among users = 111 mg  $\alpha$ -tocopherol equivalents (247 IU)].

#### Ascertainment and Classification of Prostate Cancer Cases.

Incident, first primary prostate cancer cases (*International Classification of Disease, 9th version*, rubric 185 or *International Classification of Disease, 10th version*, rubric C61) were identified through December 31, 2000 via probabilistic linkage

of the NIH-AARP cohort database to those of the state cancer registries. In a validation study, we estimated that 90% of all cancer cases in our cohort were validly identified via linkage to state cancer registries compared with self-reports and medical records (15). We defined localized (organ confined) prostate cancer cases as those with a clinical or pathologic stage of T1a-T2b and N0M0 according to the American Joint Committee on Cancer 1997 Tumor-Node-Metastasis classification system (16). Cases with clinical or pathologic stage T3, T4 or N1 or M1 as well as individuals who died of prostate cancer during 1995 to 2000, were considered to have advanced tumors. Six hundred and twenty-two cases (7%) had no information on stage and were assumed to be organ confined. Exclusion of stage T<sub>1a</sub> tumors ( $n = 92$ ) and stage T<sub>3a</sub> tumors ( $n = 222$ ) from the localized and advanced case groups, respectively, did not materially alter the results; these cases were retained in all analyses. Information on Gleason grade was unavailable.

**Statistical Analysis.** Follow-up time for each participant accrued from the date of return of the baseline questionnaire to the date of prostate cancer diagnosis, death, or end of the study period. Cox proportional hazards models with age as the underlying time metric were used to estimate relative risks (RR) and 95% confidence intervals (95% CI) of prostate cancer. Tests for trend were conducted using the median value of each exposure category modeled as a continuous variable. The proportional hazards assumption was tested and upheld in all analyses. Covariates selected for evaluation as confounders included those consistently associated with prostate cancer risk in the literature or those representing significant predictors of total prostate cancer in our data set. In addition to age, all multivariate models were adjusted for body mass index (<25, 25-29.9, 30-34.9, 35-39.9, and  $\geq 40$  kg/m<sup>2</sup>), race (White, Black, other races combined), smoking status (never, former, current), educational attainment (<12 years, 12 years or high school equivalent, some college, college graduate, or postgraduate), personal history of diabetes (yes, no), and family history of prostate cancer (yes, no). Quintiles of daily dietary intakes of red meat,  $\alpha$ -linolenic acid, vitamin C (including supplements), and  $\beta$ -carotene (including supplements) were also included in all multivariate models as they altered the vitamin E-prostate cancer risk estimates by >10%. Dietary tocopherols were adjusted for energy intake using the residual method (17). Height, physical activity, and dietary intakes of fish, tomatoes, alcohol, calcium, and selenium did not confound the observed associations; these variables were not retained in our models.

Effect modification was evaluated in stratified analyses and statistically tested by adding multiplicative interaction terms to

**Table 2. RR and 95% CI for prostate cancer according to categories of supplemental vitamin E use in the NIH-AARP Diet and Health Study**

Supplemental vitamin E*	Supplemental vitamin E (IU/d)*						<i>P</i> <sub>trend</sub>
	0	>0-99	100-199	200-399	400-799	$\geq 800$	
Median, IU	0	31.4	133.9	257.7	429.3	826.7	
Person-years	499,529	351,855	51,863	73,221	231,808	65,443	
All cases, no.	4,023	2,743	380	622	1,950	523	
Age-adjusted RR (95% CI)	1.00 (reference)	0.99 (0.94-1.04)	0.91 (0.82-1.02)	1.06 (0.97-1.15)	1.00 (0.94-1.05)	0.97 (0.89-1.06)	0.84
Multivariate RR <sup>†</sup> (95% CI)	1.00 (reference)	0.97 (0.92-1.03)	0.89 (0.80-0.99)	1.03 (0.94-1.13)	0.99 (0.92-1.06)	0.97 (0.87-1.07)	0.90
Localized cases, no.	3,459	2,330	319	527	1,680	450	
Age-adjusted RR (95% CI)	1.00 (reference)	0.98 (0.93-1.03)	0.89 (0.80-1.00)	1.04 (0.95-1.14)	1.00 (0.94-1.06)	0.97 (0.88-1.07)	0.94
Multivariate RR <sup>†</sup> (95% CI)	1.00 (reference)	0.97 (0.91-1.03)	0.88 (0.78-0.99)	1.03 (0.93-1.14)	1.00 (0.93-1.08)	0.99 (0.88-1.10)	0.61
Advanced cases, no.	564	413	61	95	270	73	
Age-adjusted RR (95% CI)	1.00 (reference)	1.05 (0.92-1.19)	1.04 (0.80-1.36)	1.15 (0.92-1.43)	1.00 (0.87-1.16)	0.97 (0.76-1.24)	0.73
Multivariate RR <sup>†</sup> (95% CI)	1.00 (reference)	1.00 (0.87-1.16)	0.94 (0.71-1.25)	1.02 (0.80-1.29)	0.89 (0.74-1.07)	0.86 (0.65-1.13)	0.11

\* Includes vitamin E obtained from multivitamins and single supplements: 1 IU = 0.45 mg  $\alpha$ -tocopherol equivalents.

<sup>†</sup> Adjusted for age, race, smoking status, education, personal history of diabetes, family history of prostate cancer, body mass index, and dietary intakes of red meat,  $\alpha$ -linolenic acid, vitamin C (including supplements), and  $\beta$ -carotene (including supplements).

**Table 3. RR and 95% CI for prostate cancer according to quintiles of dietary tocopherols in the NIH-AARP Diet and Health Study**

	Quintile of intake					<i>P</i> <sub>trend</sub>
	1	2	3	4	5	
<b>α-Tocopherol</b>						
Median (range), mg/d	4.8 (0.44-5.5)	6.1 (5.5-6.5)	7.0 (6.5-7.5)	8.0 (7.5-8.8)	10.0 (8.8-33.7)	
All cases, no.	1,956	2,050	2,058	2,095	2,047	
Age-adjusted RR (95% CI)	1.00 (reference)	1.03 (0.97-1.10)	1.03 (0.97-1.09)	1.03 (0.97-1.10)	0.99 (0.93-1.06)	0.68
Multivariate RR* (95% CI)	1.00 (reference)	1.02 (0.95-1.09)	1.00 (0.94-1.08)	1.01 (0.94-1.08)	0.97 (0.90-1.05)	0.29
Localized cases, no.	1,682	1,751	1,737	1,814	1,751	
Age-adjusted RR (95% CI)	1.00 (reference)	1.02 (0.96-1.10)	1.01 (0.94-1.08)	1.04 (0.97-1.11)	0.98 (0.92-1.05)	0.62
Multivariate RR* (95% CI)	1.00 (reference)	1.01 (0.94-1.09)	0.99 (0.92-1.07)	1.03 (0.95-1.11)	0.98 (0.90-1.06)	0.53
Advanced cases, no.	274	299	321	281	296	
Age-adjusted RR (95% CI)	1.00 (reference)	1.08 (0.92-1.27)	1.16 (0.98-1.36)	1.00 (0.85-1.19)	1.05 (0.89-1.24)	0.90
Multivariate RR* (95% CI)	1.00 (reference)	1.03 (0.86-1.22)	1.06 (0.88-1.27)	0.89 (0.73-1.08)	0.93 (0.76-1.13)	0.21
<b>β-Tocopherol</b>						
Median (range), mg/d	0.18 (0.007-0.22)	0.25 (0.22-0.28)	0.30 (0.28-0.33)	0.36 (0.33-0.40)	0.45 (0.40-1.36)	
All cases, no.	1,984	2,012	2,069	2,062	2,084	
Age-adjusted RR (95% CI)	1.00 (reference)	1.00 (0.94-1.07)	1.03 (0.97-1.09)	1.02 (0.96-1.08)	1.02 (0.96-1.08)	0.52
Multivariate RR* (95% CI)	1.00 (reference)	0.99 (0.93-1.05)	1.01 (0.95-1.08)	1.00 (0.93-1.06)	1.00 (0.93-1.07)	0.98
Localized cases, no.	1,701	1,718	1,773	1,771	1,776	
Age-adjusted RR (95% CI)	1.00 (reference)	1.00 (0.93-1.07)	1.03 (0.96-1.10)	1.02 (0.95-1.09)	1.01 (0.95-1.08)	0.68
Multivariate RR* (95% CI)	1.00 (reference)	0.99 (0.92-1.06)	1.01 (0.95-1.09)	1.00 (0.93-1.08)	1.00 (0.93-1.07)	0.93
Advanced cases, no.	283	294	296	291	308	
Age-adjusted RR (95% CI)	1.00 (reference)	1.04 (0.88-1.22)	1.04 (0.89-1.23)	1.02 (0.86-1.20)	1.07 (0.91-1.26)	0.49
Multivariate RR* (95% CI)	1.00 (reference)	1.00 (0.84-1.18)	0.99 (0.83-1.17)	0.96 (0.80-1.14)	1.00 (0.84-1.19)	0.90
<b>γ-Tocopherol</b>						
Median (range), mg/d	7.8 (0.53-9.7)	11.1 (9.7-12.4)	13.6 (12.4-14.9)	16.4 (14.9-18.2)	20.8 (18.2-57.5)	
All cases, no.	2,102	2,036	1,979	2,077	2,037	
Age-adjusted RR (95% CI)	1.00 (reference)	0.97 (0.92-1.03)	0.95 (0.89-1.01)	1.00 (0.94-1.06)	0.97 (0.91-1.03)	0.49
Multivariate RR* (95% CI)	1.00 (reference)	0.95 (0.89-1.01)	0.92 (0.86-0.99)	0.96 (0.89-1.03)	0.93 (0.86-1.00)	0.14
Localized cases, no.	1,769	1,757	1,678	1,790	1,762	
Age-adjusted RR (95% CI)	1.00 (reference)	1.00 (0.93-1.07)	0.96 (0.90-1.03)	1.02 (0.96-1.09)	0.99 (0.93-1.06)	0.96
Multivariate RR* (95% CI)	1.00 (reference)	0.98 (0.92-1.06)	0.94 (0.87-1.02)	1.00 (0.93-1.08)	0.97 (0.90-1.06)	0.78
Advanced cases, no.	333	279	301	287	275	
Age-adjusted RR (95% CI)	1.00 (reference)	0.84 (0.72-0.98)	0.91 (0.72-1.06)	0.87 (0.74-1.01)	0.83 (0.71-0.97)	0.05
Multivariate RR* (95% CI)	1.00 (reference)	0.77 (0.65-0.92)	0.80 (0.67-0.96)	0.74 (0.61-0.89)	0.68 (0.56-0.84)	0.001
<b>δ-Tocopherol</b>						
Median (range), mg/d	1.1 (0.04-1.4)	1.7 (1.4-1.9)	2.2 (1.9-2.5)	2.9 (2.5-3.3)	4.0 (3.3-13.8)	
All cases, no.	2,025	2,051	1,945	2,080	2,135	
Age-adjusted RR (95% CI)	1.00 (reference)	1.01 (0.95-1.08)	0.95 (0.90-1.01)	1.00 (0.94-1.07)	0.99 (0.93-1.06)	0.82
Multivariate RR* (95% CI)	1.00 (reference)	1.00 (0.94-1.07)	0.95 (0.89-1.01)	0.99 (0.93-1.06)	0.99 (0.93-1.06)	0.82
Localized cases, no.	1,707	1,740	1,669	1,785	1,859	
Age-adjusted RR (95% CI)	1.00 (reference)	1.02 (0.95-1.09)	0.97 (0.91-1.04)	1.02 (0.95-1.09)	1.02 (0.96-1.09)	0.52
Multivariate RR* (95% CI)	1.00 (reference)	1.01 (0.95-1.09)	0.97 (0.90-1.04)	1.02 (0.95-1.09)	1.02 (0.95-1.10)	0.45
Advanced cases, no.	318	311	276	295	276	
Age-adjusted RR (95% CI)	1.00 (reference)	0.98 (0.84-1.14)	0.86 (0.73-1.01)	0.91 (0.78-1.07)	0.84 (0.72-0.99)	0.03
Multivariate RR* (95% CI)	1.00 (reference)	0.95 (0.81-1.12)	0.84 (0.71-0.99)	0.88 (0.74-1.04)	0.80 (0.67-0.96)	0.01

\*Adjusted for age, race, smoking status, education, personal history of diabetes, family history of prostate cancer, body mass index, and dietary intakes of red meat, α-linolenic acid, vitamin C (including supplements), β-carotene (including supplements), and total energy.

the appropriate multivariate model. We examined whether the associations between supplemental and dietary vitamin E and prostate cancer risk varied according to subgroups defined by race, smoking status, family history of prostate cancer, PSA and DRE screening history, and intakes of selenium and vitamin C. To conserve statistical power, supplemental vitamin E use was collapsed into four (rather than six) categories and dietary tocopherols were divided into tertiles (rather than quintiles) in all stratified analyses.

For all comparisons, *P* values were two sided, and  $\alpha < 0.05$  indicated statistical significance.

## Results

During up to 5 years of follow-up (1995-2000), 10,241 incident prostate cancer cases were identified. Of these, 8,765 were localized (organ confined), and 1,476 were advanced. Over 60% of men reported consuming supplemental vitamin E, either in multivitamins or as single supplements.

Baseline characteristics according to categories of supplemental vitamin E and dietary α- and γ-tocopherol intakes are shown in Table 1. Use of supplemental vitamin E was

associated with elements of a healthier lifestyle. Men who consumed higher daily doses of supplemental vitamin E were leaner, more physically active, less likely to currently smoke, and more likely to have had a PSA or DRE screening test compared with never users. Increasing use of supplemental vitamin E was positively associated with intakes of fish, tomatoes, calcium, vitamin C, β-carotene, and selenium and inversely related to red meat consumption. Similar associations were noted across categories of dietary α-tocopherol, with the exception of family history of prostate cancer, personal history of diabetes, and consumption of α-linolenic acid, all of which were positively related to intake of this specific tocopherol. Higher dietary intakes of γ-tocopherol, tended to be related to unhealthy lifestyle characteristics and behaviors. For example, men in higher quintiles of dietary γ-tocopherol had higher body mass indexes, were less physically active, and were more likely to report a family history of prostate cancer at baseline than men in the lowest quintile. Energy intake and consumption of red meat, fish, α-linolenic acid, and selenium were each positively associated, whereas calcium, vitamin C, and β-carotene intakes were inversely related, to dietary γ-tocopherol.

There was no relation between vitamin E supplement use and total or localized prostate cancer and a suggestive inverse association for advanced disease, although the latter association was not statistically significant (for  $\geq 800$  IU/d versus never use: RR, 0.86; 95% CI, 0.65-1.13;  $P_{\text{trend}} = 0.11$ ; Table 2). When multivitamin users were excluded from the analysis ( $n = 152,710$ ), an inverse association was observed for total prostate cancer among men consuming  $\geq 800$  IU of vitamin E per day from single nutrient supplements compared with never users (for  $\geq 800$  IU/d versus never use: RR, 0.78; 95% CI, 0.64-0.96;  $P_{\text{trend}} = 0.03$ ). This was driven largely by the association with localized cancers, which comprised over 85% of cases (for  $\geq 800$  IU/d versus never use: RR, 0.79; 95% CI, 0.64-0.98;  $P_{\text{trend}} = 0.05$ ).

Higher intake of  $\gamma$ -tocopherol was associated with significant reduction in the risk of advanced prostate cancer in a dose-dependent manner, with adjustment for several confounding factors strengthening the observed associations (Table 3). A similar pattern was noted for  $\delta$ -tocopherol (perhaps owing to the strong correlation between  $\gamma$ - and  $\delta$ -tocopherol intakes:  $r = 0.88$ ), although the magnitude of the point estimate was not as great as that for  $\gamma$ -tocopherol.  $\alpha$ - and  $\beta$ -tocopherols were unrelated to prostate cancer.

Exclusion of men diagnosed within the first year of follow-up did not alter the vitamin E-prostate cancer associations, suggesting that altered vitamin supplement regimens and/or dietary habits due to the presence of asymptomatic disease at baseline did not bias the results (for total prostate cancer,  $\geq 800$  IU/d versus never use of supplemental vitamin E: RR, 0.94; 95% CI, 0.83-1.05; for advanced disease, highest versus lowest quintile of dietary  $\gamma$ -tocopherol: RR, 0.65; 95% CI, 0.51-0.82). Adjustment for self-reported PSA and DRE screening practices in the full cohort, which was carried out by assigning men who did not complete the supplementary questionnaire on screening practices to a missing category, did not alter the vitamin E-prostate cancer associations (for total prostate cancer, 0, >0-99, 100-199, 200-399, 400-799, and  $\geq 800$  IU/d of supplemental vitamin E: RR, 1.0, 0.97, 0.89, 1.02, 0.97, and 0.96 (95% CI, 0.87-1.06) respectively;  $P_{\text{trend}} = 0.67$ ; for advanced disease, increasing quintiles of dietary  $\gamma$ -tocopherol: RR, 1.0, 0.77, 0.80, 0.74, and 0.68 (95% CI, 0.56-0.83), respectively;  $P_{\text{trend}} = 0.0009$ ). These results were very similar to those obtained from the subset of men who completed the second questionnaire, in which we adjusted for PSA and DRE (data not shown).

The association between supplemental vitamin E and prostate cancer risk did not vary according to smoking status (Table 4). Because previous studies found that use of supplemental vitamin E was protective against prostate cancer

in combined groups of current and recent smokers (i.e., quit within the past 10 years; refs. 2, 3), we also examined potential interactions using this alternative categorization. We found no interaction in the cohort as a whole, but when multivitamin users were excluded from the analysis, there was a significant inverse association between use of high-dose supplemental vitamin E and localized prostate cancer among current/recent smokers (for  $\geq 800$  IU/d versus never use: RR, 0.52; 95% CI, 0.29-0.94;  $P_{\text{trend}} = 0.06$ ). This was not observed in nonsmokers (RR, 0.86; 95% CI, 0.59-1.24;  $P_{\text{trend}} = 0.52$ ) or those who smoked in the distant past (quit  $\geq 10$  years ago: RR, 0.83; 95% CI, 0.61-1.12;  $P_{\text{trend}} = 0.26$ ,  $P_{\text{interaction}} = 0.10$ ).

Although the interaction between dietary  $\gamma$ -tocopherol and smoking status was not statistically significant, dietary  $\gamma$ -tocopherol was most protective against advanced prostate cancer in nonsmokers and former smokers, with virtually no association apparent in current smokers (Table 5). There was a statistically significant interaction between  $\gamma$ -tocopherol and total selenium intake, with an inverse association noted between  $\gamma$ -tocopherol and advanced prostate cancer among men in the lowest tertile of total selenium intake but not among subjects in higher selenium categories (Table 5). A similar interaction was noted between dietary  $\alpha$ -tocopherol and selenium for advanced disease ( $P_{\text{interaction}} = 0.003$ ). Family history of prostate cancer, race, prostate cancer screening practices, and vitamin C intake did not modify any of the vitamin E-prostate cancer associations (data not shown). Associations for  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols were similar in the subgroup of men that did not consume supplemental vitamin E (either from multivitamins or single nutrient supplements) compared with overall. In this subgroup, however, a suggestive inverse association between dietary  $\alpha$ -tocopherol and advanced prostate cancer emerged (for highest versus lowest quintile: RR, 0.74; 95% CI, 0.54-1.02;  $P_{\text{trend}} = 0.02$ ).

## Discussion

In this large prospective study, supplemental vitamin E intake was not related to prostate cancer risk overall, although a modest inverse association was noted in the subgroup of men who did not consume multivitamins. Dietary  $\gamma$ -tocopherol was significantly inversely related to advanced disease. This inverse association was particularly evident among men with low selenium intake.

The most convincing evidence for a protective effect of vitamin E on prostate cancer comes from the ATBC Study, in which statistically significant reductions in prostate cancer incidence (32%) and mortality (41%) were observed among male smokers

**Table 4. RR and 95% CI for prostate cancer according to categories of supplemental vitamin E intake, stratified by smoking status, in the NIH-AARP Diet and Health Study**

	Total no.	Supplemental vitamin E (IU/d)*, RR <sup>†</sup> (95% CI)				$P_{\text{trend}}$
		0	>0-399	400-799	$\geq 800$	
<b>Nonsmoker</b>						
All cases	3,244	1.00 (reference)	1.03 (0.94-1.12)	1.03 (0.91-1.16)	1.04 (0.86-1.25)	0.82
Localized cases	2,794	1.00 (reference)	1.02 (0.93-1.13)	1.05 (0.92-1.19)	1.10 (0.91-1.34)	0.33
Advanced cases	450	1.00 (reference)	1.06 (0.83-1.35)	0.88 (0.64-1.23)	0.66 (0.38-1.17)	0.07
<b>Former smoker</b>						
All cases	6,119	1.00 (reference)	0.95 (0.89-1.01)	0.97 (0.89-1.06)	0.91 (0.80-1.04)	0.56
Localized cases	5,231	1.00 (reference)	0.95 (0.88-1.02)	0.99 (0.90-1.08)	0.91 (0.79-1.05)	0.77
Advanced cases	888	1.00 (reference)	0.96 (0.80-1.14)	0.89 (0.71-1.12)	0.90 (0.64-1.26)	0.41
<b>Current smoker</b>						
All cases	878	1.00 (reference)	0.95 (0.80-1.13)	0.90 (0.70-1.16)	1.15 (0.81-1.63)	0.68
Localized cases	740	1.00 (reference)	0.93 (0.77-1.12)	0.90 (0.68-1.18)	1.14 (0.78-1.67)	0.62
Advanced cases	138	1.00 (reference)	1.12 (0.72-1.73)	0.93 (0.48-1.79)	1.18 (0.49-2.89)	0.92

NOTE: All  $P_{\text{interaction}} > 0.05$ .

\* Includes vitamin E obtained from multivitamins and single supplements: 1 IU = 0.45 mg  $\alpha$ -tocopherol equivalents.

† Adjusted for age, race, education, personal history of diabetes, family history of prostate cancer, body mass index, and daily dietary intakes of red meat,  $\alpha$ -linolenic acid, vitamin C (including supplements), and  $\beta$ -carotene (including supplements).

**Table 5. RR and 95% CI for prostate cancer according to tertiles of dietary  $\gamma$ -tocopherol, stratified by smoking status and total selenium intake, in the NIH-AARP Diet and Health Study**

	Total no.	Tertiles of dietary $\gamma$ -tocopherol (mg/d), RR* (95% CI)			<i>P</i> <sub>trend</sub>
		1 (<11.5)	2 (11.6-15.9)	3 (>15.9)	
<b>Nonsmoker</b>					
All cases	3,237	1.00 (reference)	0.99 (0.90-1.09)	0.97 (0.87-1.08)	0.54
Localized cases	2,788	1.00 (reference)	1.02 (0.92-1.13)	1.01 (0.90-1.13)	0.96
Advanced cases	449	1.00 (reference)	0.86 (0.67-1.11)	0.77 (0.58-1.02)	0.07
<b>Former smoker</b>					
All cases	6,116	1.00 (reference)	0.93 (0.87-0.99)	0.95 (0.88-1.02)	0.23
Localized cases	5,228	1.00 (reference)	0.94 (0.87-1.01)	0.97 (0.89-1.06)	0.59
Advanced cases	888	1.00 (reference)	0.86 (0.72-1.03)	0.82 (0.67-1.00)	0.06
<b>Current smoker</b>					
All cases	878	1.00 (reference)	1.09 (0.91-1.31)	1.17 (0.96-1.43)	0.12
Localized cases	740	1.00 (reference)	1.08 (0.89-1.33)	1.19 (0.96-1.47)	0.12
Advanced cases	138	1.00 (reference)	1.13 (0.72-1.78)	1.08 (0.66-1.79)	0.79
<b>Low selenium intake (&lt;94.5 <math>\mu</math>g/d)<sup>†</sup></b>					
All cases	3,481	1.00 (reference)	1.00 (0.91-1.09)	0.94 (0.85-1.04)	0.24
Localized cases	2,980	1.00 (reference)	1.02 (0.92-1.12)	0.99 (0.89-1.11)	0.91
Advanced cases	501	1.00 (reference)	0.89 (0.71-1.11)	0.67 (0.51-0.88)	0.005
<b>Moderate selenium intake (94.5-116 <math>\mu</math>g/d)<sup>†</sup></b>					
All cases	3,325	1.00 (reference)	0.99 (0.90-1.09)	1.00 (0.90-1.11)	0.93
Localized cases	2,859	1.00 (reference)	1.01 (0.91-1.12)	1.03 (0.92-1.15)	0.62
Advanced cases	466	1.00 (reference)	0.85 (0.66-1.10)	0.85 (0.64-1.12)	0.29
<b>High selenium intake (&gt;116 <math>\mu</math>g/d)<sup>†</sup></b>					
All cases	3,425	1.00 (reference)	0.90 (0.82-0.99)	0.96 (0.86-1.06)	0.64
Localized cases	2,917	1.00 (reference)	0.90 (0.81-0.99)	0.96 (0.86-1.08)	0.73
Advanced cases	508	1.00 (reference)	0.92 (0.72-1.18)	0.93 (0.71-1.23)	0.70

NOTE: All *P*<sub>interaction</sub> > 0.05, with the exception of selenium intake and advanced prostate cancer (*P* = 0.007).

\* Adjusted for age, race, smoking status (except in models stratified by smoking), education, personal history of diabetes, family history of prostate cancer, body mass index, and daily dietary intakes of red meat,  $\alpha$ -linolenic acid, vitamin C (including supplements),  $\beta$ -carotene (including supplements), and total energy.

<sup>†</sup> Includes selenium intakes from diet and supplements.

randomized to receive 50 mg DL- $\alpha$ -tocopheryl acetate supplements daily for 5 to 8 years (1). Reductions in incident prostate cancer were limited to clinically significant disease. The SUPPLEMENTATION EN VITAMINES ET MINÉRAUX ANTIOXIDANTS (SU.VI.MAX) Study also showed a significant reduction in the rate of prostate cancer among men receiving a multivitamin/multimineral supplement containing 30 mg vitamin E, although that finding was restricted to those with a normal baseline PSA level (<3  $\mu$ g/L), and the protective effect could not be attributed to any specific micronutrient (18). In contrast, both the Heart Outcomes Prevention Evaluation (HOPE) trial and the Heart Protection Study showed no effect of daily vitamin E supplementation, either alone (19) or in combination with vitamin C and  $\beta$ -carotene (20), on the incidence of prostate cancer in men at high risk for coronary heart disease. Two ongoing trials (SELECT and Physician's Health Study II) are testing a priori whether supplemental vitamin E reduces the risk of prostate cancer in healthy men (5, 21).

Five prospective cohort studies and one case-control investigation have evaluated the association between supplemental vitamin E intake and incident prostate cancer. There was no association for vitamin E supplement use versus non-use in the Leisure World Study (22), nonsignificant protective relationships for use versus nonuse in the Netherlands Cohort Study (23) and for those using vitamin E daily in a case-control study conducted in the United States (24), and a suggestive, although nonsignificant, inverse association for regular ( $\geq 4$  times per week) and higher-dose ( $\geq 400$  IU/d) vitamin E supplement use among current smokers in the Cancer Prevention Study II Nutrition Cohort (4). Two prospective studies found significant reductions in the risk of advanced (3) or metastatic/fatal (2) prostate cancer with increasing dose [ $>400$  IU/d in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (3) and  $>15$  IU/d in the Health Professional's Follow-up Study (2)] and duration [ $>10$  years in the PLCO Trial (3)] of vitamin E supplement use, but only among the combination of current smokers and recent quitters, which corroborate the ATBC Study findings (1).

Two previous reports found no difference in the association between supplemental vitamin E use and prostate cancer risk when men taking multivitamins were excluded from the analysis (3, 4). In contrast, we observed no relation in the overall cohort but did see a modest inverse association between vitamin E supplement use and localized prostate cancer among men who did not consume multivitamins. The most likely explanations for this subgroup finding are that multivitamin use increases the risk of prostate cancer, that multivitamins block any protective effects of large doses of vitamin E obtained from single supplements, or chance. We are currently addressing the relation of multivitamin use to prostate cancer risk in a separate publication (25).

Three prospective studies reported that dietary vitamin E (a term that encompasses eight structurally related isoforms: four tocopherols and four tocotrienols), either alone or combined with supplemental vitamin E, was unrelated to prostate cancer risk (2, 23, 26), and one study showed a suggestive protective association with increasing total vitamin E intake, although it was limited to men receiving the trial vitamin E intervention (27). Only two studies have prospectively evaluated whether individual tocopherols are differentially associated with prostate cancer (3, 27). In the PLCO Cancer Screening Trial, Kirsh et al. reported that dietary intakes of  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols were unrelated to prostate cancer risk (3). Hartman et al. found that dietary  $\gamma$ -tocopherol intake was inversely associated with total prostate cancer in the ATBC Study, but only among men receiving the trial vitamin E intervention (27). Higher circulating concentrations of  $\alpha$ -tocopherol (28-31) and  $\gamma$ -tocopherol (29, 32, 33) have been linked with a significantly lower risk of prostate cancer in several nested case-control studies. In CLUE II, serum  $\gamma$ -tocopherol was strongly inversely associated with aggressive disease (32), which is similar to our results for dietary  $\gamma$ -tocopherol. In the same study,  $\gamma$ -tocopherol was protective when serum selenium levels were also high; this contrasts with our finding in which dietary  $\gamma$ -tocopherol was only protective among men with low selenium intake.

$\alpha$ -Tocopherol is the form of vitamin E found in virtually all dietary supplements, and this isoform functions as the primary fat-soluble antioxidant that protects lipids in cellular membranes from peroxidation (34).  $\gamma$ -Tocopherol is the most widely consumed dietary form of vitamin E in the United States but has only recently begun to receive attention as a possible chemopreventive agent. Similar to  $\alpha$ -tocopherol,  $\gamma$ -tocopherol is a powerful antioxidant nutrient; interestingly, it is a superior scavenger of reactive nitrogen oxide species (35, 36). Unlike  $\alpha$ -tocopherol, however,  $\gamma$ -tocopherol also has the capacity to decrease inflammation through its inhibitory effects on the cyclooxygenase-2 enzyme (9). This nutrient also seems to effectively inhibit proliferation and decrease cell cycle progression via reduction of cyclin levels in prostate carcinoma cell lines (37). These biological mechanisms may underlie the strong inverse associations between  $\gamma$ -tocopherol and aggressive prostate cancer observed in our study.

Strengths of this study include the large number of prostate cancer cases, which afforded ample power to detect modest associations and to evaluate effect modification by several important factors. We were also able to test whether a large number of variables confounded the vitamin E-prostate cancer associations. In addition, the database and methodology used to estimate intake of individual tocopherols from the dietary questionnaire were more comprehensive than in previous studies.

Limitations include the short period of follow-up time; the possibility of undiagnosed prostate cancer at baseline due to slow tumor growth rates; the lack of information on Gleason score, which is an important clinical variable that predicts survival; and our reliance on relatively crude measures of prostate cancer screening practices, which were only available for a subset of the cohort. We had no information on duration of vitamin E supplement use, which might be important given the long induction and latency period for prostate cancer (38). It is also widely known that dietary questionnaires are limited in their ability to quantify vitamin E intake, which is due to the underreporting of vitamin E-rich vegetable fat and oil consumption (39) and the ubiquity of vitamin E in a wide variety of foods, many of which are not included on dietary questionnaires (40). Although the Nutrition Data Systems for Research database is more comprehensive than others, it does not contain values for individual tocopherols for *all* foods and brand name products; given the wide range of brands and potential interchanging of oils in some products, completely accurate quantification of tocopherol intakes may be difficult. We did not collect blood samples from participants and therefore could not use biomarkers to validate our dietary tocopherol estimates.

In summary, we found no overall association between vitamin E supplement use and prostate cancer. However, higher intake of  $\gamma$ -tocopherol was associated with a significant reduction in the risk of advanced prostate cancer, providing support for continued research efforts directed towards this vitamin E isoform.

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