

Higher baseline serum concentrations of vitamin E are associated with lower total and cause-specific mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study¹⁻³

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ABSTRACT

Background: A meta-analysis of 19 trials suggested a small increase in the risk of all-cause mortality with high-dose vitamin E supplementation. Little is known, however, about the relation between mortality and circulating concentrations of vitamin E resulting from dietary intake, low-dose supplementation, or both.

Objective: We examined whether baseline serum α -tocopherol concentrations are associated with total and cause-specific mortality.

Design: A prospective cohort study of 29 092 Finnish male smokers aged 50–69 y who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was carried out. Fasting serum α -tocopherol was measured at baseline by using HPLC. Only 10% of participants reported vitamin E supplement use at baseline, and thus serum concentrations of vitamin E mainly reflected dietary intake and other host factors. Risks of total and cause-specific mortality were estimated by using proportional hazards models.

Results: During up to 19 y of follow-up, 13 380 deaths (including 4518 and 5776 due to cancer and cardiovascular disease, respectively) were identified. Men in the higher quintiles of serum α -tocopherol had significantly lower risks of total and cause-specific mortality than did those in the lowest quintile [relative risk (RR) = 0.82 (95% CI: 0.78, 0.86) for total mortality and 0.79 (0.72, 0.86), 0.81 (0.75, 0.88), and 0.70 (0.63, 0.79) for deaths due to cancer, cardiovascular disease, and other causes, respectively; *P* for trend for all < 0.0001]. Cubic regression spline analysis of continuous serum α -tocopherol values indicated greater risk reductions with increasing concentrations up to \approx 13–14 mg/L, after which no further benefit was noted.

Conclusion: Higher circulating concentrations of α -tocopherol within the normal range are associated with significantly lower total and cause-specific mortality in older male smokers. *Am J Clin Nutr* 2006;84:1200–7.

KEY WORDS Antioxidants, α -tocopherol, cancer, cardiovascular disease, cohort study, mortality, smokers

INTRODUCTION

The term *vitamin E* collectively refers to 8 structurally related isomers, of which α -tocopherol is the most biologically active and the predominant form in blood (1). As the primary fat-soluble antioxidant that protects lipids from peroxidation, α -tocopherol is able to scavenge mutagenic free radicals and inhibit the oxidation of LDL cholesterol, and these abilities have important

implications for the prevention of carcinogenesis and atherosclerosis (2). α -Tocopherol also has several important functions that are independent of its antioxidant activity, including inhibition of protein kinase C (PKC) activity, modulation of gene expression, inhibition of cellular proliferation, enhancement of immune responses, interference with sex-steroid signaling, and suppression of tumor angiogenesis (3–6).

Inverse associations between dietary and supplemental vitamin E intakes and the incidence of several common chronic diseases have been noted in many observational studies, whereas results from studies using blood concentrations of vitamin E have been more limited and inconsistent (7, 8). The relation between vitamin E status and overall mortality—which reflects both incidence and survival—has been less thoroughly investigated and remains controversial. Serologic studies to date have yielded null results, although many were based on small numbers of endpoints (9–21). Randomized trials of supplemental vitamin E have not shown substantial beneficial effects on mortality endpoints (7, 22). In fact, a recent meta-analysis of 19 such trials suggested a small increase in the risk of all-cause mortality with high-dose vitamin E supplementation (23), although aspects of this analysis have been challenged (24). Given the range of findings, it is important to know how variations in vitamin E concentrations achieved primarily through diet rather than supplementation affect mortality in free-living populations.

We evaluated the prospective association between circulating concentrations of α -tocopherol and total and cause-specific mortality in a cohort of male smokers. With > 13 000 deaths available for analysis, this is the largest serologic study of vitamin E

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² Supported by US Public Health Service contracts no. N01-CN-45165, N01-RC-45035, and N01-RC-37004 from the Intramural Research Program of the National Institutes of Health and the National Cancer Institute.

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Received April 6, 2006.

Accepted for publication May 26, 2006.

and mortality to date and the first to be conducted entirely within a population of smokers.

SUBJECTS AND METHODS

Study population

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a randomized, double-blind, placebo-controlled, 2 × 2 factorial design, primary chemoprevention trial that tested whether daily supplementation with vitamin E or β -carotene reduced the incidence of lung and other cancers. Details regarding study design, methods, participant characteristics, and compliance were reported previously, as were the main trial findings and postintervention follow-up results (25–27). Briefly, 29 133 participants meeting all eligibility criteria (male residents of southwestern Finland aged 50–69 y who smoked ≥ 5 cigarettes/d) were randomly assigned to receive supplements (50 mg *all-rac*- α -tocopheryl acetate, 20 mg β -carotene, or both) or placebo between 1985 and 1988. Reasons for exclusion included proven malignancy (other than non-melanoma skin cancer or carcinoma in situ), severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, other diseases or conditions that might limit participation in a long-term intervention trial, current anticoagulant therapy, or refusal to discontinue the use of vitamin E, vitamin A, or β -carotene supplements in excess of previously defined amounts (ie, >20 mg vitamin E, >20 000 IU vitamin A, and >6 mg β -carotene). The trial ended on 30 April 1993, and ascertainment of morbidity and mortality endpoints continued thereafter.

Written informed consent was obtained from each participant before randomization. The institutional review boards of both the National Public Health Institute of Finland and the US National Cancer Institute approved the study.

Baseline data collection

Before randomization, all subjects were asked to provide detailed demographic, smoking, and occupational information; to give a history of medical examinations and physician-confirmed diseases; and to complete a 276-item dietary questionnaire. Height, weight, blood pressure, and heart rate were measured by specially trained Registered Nurses. An overnight fasting blood sample was collected from each participant, protected from light, divided into aliquots, and stored at -70 °C until it was analyzed. Serum concentrations of α -tocopherol, β -carotene, and retinol were measured by using HPLC (28), whereas total and HDL-cholesterol concentrations were measured by using an enzymatic assay (CHOD-PAP method; Boehringer Mannheim, Mannheim, Germany). The between-run CV for serum α -tocopherol was 2.2%. Serum α -tocopherol and cholesterol measurements were available for 29 092 participants (99.9%).

Ascertainment of deaths

All deaths from baseline through the end of the follow-up period (31 December 2003) were identified through the Finnish National Register of Causes of Death. Specific causes of death were derived from the official underlying cause of death and were available for 99.4% of all deaths. Mutually exclusive cause-of-death categories were constructed by using the following codes from the 8th, 9th, and 10th revisions of the *International Classification of Diseases* (ICD-8, -9, and -10, respectively):

ICD-8 and ICD-9 140–239 and ICD-10 C00–D48 for cancer; ICD-8 390–458, ICD-9 390–459, and ICD-10 I00–I99 for cardiovascular disease (CVD); and ICD-8 and ICD-9 000–136, 240–389, and 460–E999 and ICD-10 A00–B99, D50–H95, and J00–Y98 for all other causes combined.

During up to 19 y of follow-up (median: 15.7 y), 13 409 deaths occurred. Of these subjects, 13 380 (99.8%) had baseline measurements of serum α -tocopherol and cholesterol. There were 4518 cancer deaths (including 2221, 351, 302, and 223 due to lung, prostate, pancreatic, and colorectal cancer, respectively), 5776 CVD deaths (including 3901, 474, and 348 due to coronary heart disease (CHD), ischemic stroke, and hemorrhagic stroke, respectively), and 3002 deaths due to other causes combined (including 1102 due to respiratory diseases).

Statistical analysis

Person-years of observation were calculated from the date of randomization to the date of death or the end of follow-up (31 December 2003), whichever came first. Serum α -tocopherol concentrations were adjusted for serum total cholesterol concentrations by using the residual method (29) (all values in the text and tables reflect this standardization) and were categorized into quintiles. RRs of death and 95% CIs for serum α -tocopherol quintiles compared with the reference category (quintile 1) were estimated with the use of Cox proportional hazards models, and tests for linear trend were carried out by taking the median value of each quintile and modeling it as a continuous variable. In cause-specific models, deaths other than the endpoint of interest were censored at the time when the event occurred. All multivariate models were adjusted for age, number of cigarettes smoked/d, number of years of smoking, trial intervention group (α -tocopherol or no α -tocopherol and β -carotene or no β -carotene), and serum total cholesterol. CVD models were also adjusted for serum HDL-cholesterol concentrations and history of CVD, whereas models of deaths due to other causes were further adjusted for serum HDL-cholesterol concentrations, because each of these variables independently altered main effects risk estimates by $\geq 10\%$. The addition to these models of other potentially confounding factors, including systolic and diastolic blood pressure, body mass index (BMI; in kg/m^2), education, physical activity, baseline vitamin E supplement use, history of diabetes, alcohol consumption, calorie intake, and energy-adjusted daily dietary intakes of fruit and vegetables, red meat, and fat, did not alter the primary serologic associations, and these factors were not included in the final multivariate models.

Kaplan-Meier survival curves were generated, and the log-rank test statistic was used to test for differences in overall and cause-specific survival across quintiles of serum α -tocopherol. Adjusted RRs and 95% CIs for total and cause-specific mortality were estimated for continuous values of serum α -tocopherol in proportional hazards models that included terms for a 4-knot cubic spline (30). Knots were located at the 5th, 25th, 75th, and 95th percentiles of the serum α -tocopherol distribution. The reference value for these curves (RR = 1.00) was set at the midpoint of the lowest quintile (9.1 mg/L). To minimize the influence of extreme outliers, subjects with serum α -tocopherol values in the top or bottom percentile of the distribution (≤ 6.7 or ≥ 20.7 mg/L) were excluded ($n = 602$).

Interactions between serum α -tocopherol and age (<57 or ≥ 57 y), smoking dose (<20 or ≥ 20 cigarettes/d) and duration (<36 or ≥ 36 y), BMI (<25 or ≥ 25), alcohol consumption



TABLE 1

Baseline characteristics by quintile of cholesterol-adjusted serum α -tocopherol¹

	Quintile of serum α -tocopherol (mg/L) ²					<i>P</i> ³
	<10.0 (<i>n</i> = 5975)	10.0–11.0 (<i>n</i> = 5474)	11.1–12.1 (<i>n</i> = 5853)	12.2–13.5 (<i>n</i> = 5872)	>13.5 (<i>n</i> = 5918)	
Serum α -tocopherol (mg/L)	8.8 ± 1.0 ⁴	10.5 ± 0.3	11.6 ± 0.3	12.8 ± 0.4	15.7 ± 3.3	<0.0001
Age (y)	57.7 ± 5.1	57.3 ± 5.2	57.1 ± 5.0	57.0 ± 5.0	57.0 ± 5.0	<0.0001
Cigarettes/d	21.4 ± 8.9	20.6 ± 8.7	20.1 ± 8.6	20.0 ± 8.8	20.0 ± 9.0	<0.0001
Years smoked (y)	37.0 ± 8.2	36.3 ± 8.3	35.6 ± 8.6	35.3 ± 8.7	35.5 ± 8.4	<0.0001
Systolic blood pressure (mm Hg)	143 ± 19	142 ± 20	141 ± 19	141 ± 19	143 ± 20	<0.0001
Diastolic blood pressure (mm Hg)	88.0 ± 11	87.2 ± 10.9	87.1 ± 10.9	87.2 ± 10.6	88.5 ± 10.8	<0.0001
Serum total cholesterol (mmol/L)	6.59 ± 1.21	6.19 ± 1.08	6.06 ± 1.08	6.02 ± 1.11	6.31 ± 1.24	<0.0001
Serum HDL cholesterol (mmol/L)	1.30 ± 0.34	1.25 ± 0.31	1.21 ± 0.30	1.16 ± 0.29	1.06 ± 0.29	<0.0001
Serum β -carotene (μ g/L)	182 ± 140	206 ± 150	218 ± 171	224 ± 186	229 ± 247	<0.0001
BMI (kg/m ²)	25.6 ± 3.8	25.9 ± 3.8	26.1 ± 3.7	26.5 ± 3.6	27.3 ± 3.8	<0.0001
Education beyond primary school (%)	23.5	28.2	33.6	40.5	47.1	<0.0001
Active in leisure time (%) ⁵	51.0	56.6	60.1	62.0	61.2	<0.0001
Active at work (%) ⁶	56.3	50.6	45.1	39.8	33.5	<0.0001
History of CVD (%) ⁷	38.0	36.9	38.4	42.9	50.7	<0.0001
History of diabetes mellitus (%)	2.9	2.5	3.7	4.5	7.6	<0.0001
Vitamin E supplement use (%)	3.6	5.5	8.1	12.4	20.6	<0.0001
Daily dietary intake ⁸						
Energy (kcal)	2824 ± 809	2870 ± 810	2832 ± 769	2797 ± 768	2759 ± 775	<0.0001
Alcohol (g ethanol)	21.2 ± 24.9	17.7 ± 21.2	16.7 ± 20.3	16.8 ± 19.8	17.5 ± 20.9	<0.0001
Fruit and vegetables (g)	192 ± 118	215 ± 125	234 ± 131	252 ± 135	270 ± 143	<0.0001
Red meat (g)	147 ± 63	148 ± 63	145 ± 61	146 ± 57	146 ± 60	0.10
Fat (g triacylglycerol)	108 ± 17	106 ± 16	106 ± 16	104 ± 16	104 ± 16	<0.0001
Vitamin E (mg)	9.4 ± 2.6	10.5 ± 3.6	11.8 ± 4.3	13.3 ± 5.0	15.2 ± 5.6	<0.0001

¹ CVD, cardiovascular disease.² To convert cholesterol-adjusted serum α -tocopherol values from mg/L to μ mol/L, multiply by 2.322.³ Based on ANOVA for differences in means for continuous variables and chi-square tests for differences in percentiles for categorical variables.⁴ \bar{x} ± SD (all such values).⁵ Moderate or heavy leisure-time physical activity.⁶ Moderate or heavy occupational physical activity in men who were employed (*n* = 16 784).⁷ Includes a history of deep vein thrombosis, superficial venous thrombosis, lung infarction or embolus, hypertension, arterial obstruction, stroke, arrhythmia, enlarged heart, valvular heart disease, myocardial infarction, coronary heart disease, and heart failure.⁸ Based on a subset of subjects with complete dietary information (*n* = 27 074). All foods and nutrients except alcohol are adjusted for energy intake.

(<11 or \geq 11 g/d), serum β -carotene concentration (<170 or \geq 170 μ g/L), daily dietary intakes of vitamin C (<90 or \geq 90 mg) and total carotenoids (<4486 or \geq 4486 μ g), and trial intervention groups (α -tocopherol or no α -tocopherol and β -carotene or no β -carotene) were statistically tested by the addition of the relevant cross-product term to main effects models and were further evaluated in stratified analyses. We also evaluated whether the relation of serum α -tocopherol to CVD mortality varied according to selected risk factors for heart disease—categorized according to the clinical practice guidelines of the National Heart, Lung, and Blood Institute (31)—including blood pressure (<140/90 or \geq 140/90 mm Hg), serum total cholesterol (<200, 200–239, or \geq 240 mg/dL), and serum HDL cholesterol (<40, 40–59, or \geq 60 mg/dL).

The proportional hazards assumption was satisfied. All analyses were conducted with the use of SAS software (version 8.2; SAS Institute Inc, Cary, NC), and statistical tests were 2-tailed with significance levels set at *P* < 0.05.

RESULTS

The mean serum α -tocopherol concentration in the cohort was 11.9 mg/L. Because only 10% of the participants reported vitamin E supplement use at baseline, serum concentrations in this

cohort reflected dietary intake of vitamin E, as well as demographic characteristics, lifestyle behaviors, and hereditary predisposition related to vitamin E transport and metabolism (32, 33). The men in the higher quintiles of serum α -tocopherol were somewhat younger, smoked less, and had lower serum concentrations of HDL cholesterol, higher circulating concentrations of β -carotene, and a higher BMI than did the men in the lowest quintile (Table 1). In addition, these subjects were more likely to be better educated; to be more physically active during leisure time; to have a history of CVD, diabetes, or both; and to consume pretrial vitamin supplements containing vitamin E. With respect to diet, serum α -tocopherol concentrations were inversely associated with alcohol consumption and caloric intake and positively associated with fruit and vegetable and vitamin E intakes.

In proportional hazards models, subjects in the higher quintiles of serum α -tocopherol experienced significantly lower overall mortality and deaths due to cancer, CVD, and other causes combined than did those in the lowest quintile, and a threshold effect was apparent (Table 2). Serum α -tocopherol was not predictive of deaths due to accidental causes (data not shown). Kaplan-Meier survival curves show that the men in the bottom quintile of serum α -tocopherol had significantly lower overall survival than did those in the higher quintiles and that

TABLE 2

Relative risks (RRs) and 95% CIs for total and cause-specific mortality by quintile of cholesterol-adjusted serum α -tocopherol¹

	Quintile of serum α -tocopherol (mg/L) ²					<i>P</i> for trend
	<10.0	10.0–11.0	11.1–12.1	12.2–13.5	>13.5	
Total mortality						
Deaths (<i>n</i>)	3238	2570	2495	2459	2618	
Death rate ³	42.34	34.89	31.21	30.38	32.49	
Age-adjusted RR (95% CI)	1.00	0.84 (0.80, 0.89)	0.76 (0.73, 0.81)	0.74 (0.70, 0.78)	0.80 (0.76, 0.84)	<0.0001
Multivariate RR (95% CI) ⁴	1.00	0.84 (0.80, 0.88)	0.77 (0.73, 0.82)	0.75 (0.72, 0.80)	0.82 (0.78, 0.86)	<0.0001
Cancer mortality						
Deaths (<i>n</i>)	1084	857	856	871	850	
Death rate ³	14.17	11.63	10.71	10.76	10.55	
Age-adjusted RR (95% CI)	1.00	0.84 (0.77, 0.92)	0.78 (0.71, 0.85)	0.78 (0.72, 0.86)	0.77 (0.71, 0.85)	<0.0001
Multivariate RR (95% CI) ⁴	1.00	0.83 (0.75, 0.90)	0.78 (0.71, 0.86)	0.79 (0.72, 0.86)	0.79 (0.72, 0.86)	<0.0001
CVD mortality						
Deaths (<i>n</i>)	1324	1096	1063	1065	1228	
Death rate ³	17.31	14.88	13.30	13.16	15.24	
Age-adjusted RR (95% CI)	1.00	0.88 (0.81, 0.96)	0.80 (0.74, 0.87)	0.79 (0.73, 0.86)	0.92 (0.85, 1.00)	0.02
Multivariate RR (95% CI) ⁵	1.00	0.91 (0.84, 0.99)	0.82 (0.75, 0.89)	0.78 (0.72, 0.85)	0.81 (0.75, 0.88)	<0.0001
Mortality from other causes						
Deaths (<i>n</i>)	814	596	564	504	524	
Death rate ³	10.64	8.09	7.05	6.23	6.50	
Age-adjusted RR (95% CI)	1.00	0.78 (0.70, 0.86)	0.68 (0.61, 0.76)	0.60 (0.54, 0.67)	0.63 (0.57, 0.71)	<0.0001
Multivariate RR (95% CI) ⁶	1.00	0.74 (0.67, 0.83)	0.67 (0.60, 0.75)	0.60 (0.54, 0.67)	0.70 (0.63, 0.79)	<0.0001

¹ Cause of death was not known for 84 subjects. CVD, cardiovascular disease.² To convert cholesterol-adjusted serum α -tocopherol from mg/L to μ mol/L, multiply by 2.322.³ Crude death rate per 1000 subjects.⁴ Adjusted for age, cigarettes smoked/d, years smoked, intervention assignment, and serum total cholesterol.⁵ Adjusted for age, cigarettes smoked/d, years smoked, intervention assignment, serum total cholesterol, serum HDL cholesterol, and history of CVD.⁶ Adjusted for age, cigarettes smoked/d, years smoked, intervention assignment, serum total cholesterol, and serum HDL cholesterol.

these differences appeared within 5 y of study entry and lasted throughout follow-up (Figure 1A). Similar patterns were noted for mortality from cancer (Figure 1B), CVD (Figure 1C), and other causes combined (Figure 1D). All log-rank *P* values were highly significant (*P* < 0.0001).

To further characterize the dose-response relations, we tested serum α -tocopherol as a continuous variable in a restricted 4-knot cubic spline regression analysis (Figure 2). Overall mortality increased as serum α -tocopherol concentrations decreased below the reference value of 9.1 mg/L, the median of the first quintile. In contrast, significant reductions in risk were noted as serum α -tocopherol values increased from 9.1 to \approx 13 mg/L, after which relative mortality drifted toward unity. Similar patterns in risk were observed for cancer mortality, whereas the lowest relative mortality due to CVD and other causes combined occurred at serum α -tocopherol concentrations of \approx 14 mg/L (data not shown).

We also evaluated the association between serum α -tocopherol and the major contributors to each cause-specific category. Subjects in the highest quintile of serum concentrations of α -tocopherol had significantly lower mortality due to lung cancer (RR = 0.79; 95% CI: 0.70, 0.90; *P* for trend = 0.002), prostate cancer (RR = 0.68; 95% CI: 0.48, 0.95, *P* for trend = 0.02), CHD (RR = 0.84; 95% CI: 0.76, 0.92; *P* for trend = 0.0002), ischemic stroke (RR = 0.63; 95% CI: 0.47, 0.84; *P* for trend = 0.001), hemorrhagic stroke (RR = 0.65; 95% CI: 0.45, 0.92; *P* for trend = 0.009), and respiratory disease (RR = 0.58; 95% CI: 0.47, 0.70; *P* for trend < 0.0001) than did subjects in the lowest quintile. Nonsignificant protective associations were noted for death due to pancreatic cancer (RR = 0.83; 95% CI: 0.59, 1.18; *P* for trend = 0.17) and colorectal cancer (RR = 0.77; 95% CI: 0.51, 1.17; *P* for trend = 0.25).

Higher serum α -tocopherol concentrations were more strongly associated with lower overall mortality in younger and leaner men, in lighter smokers and those who had smoked for fewer years, and in heavier drinkers (Table 3, all *P* values for interaction < 0.05). Risks did not vary according to trial supplementation group (Table 3, *P* value for interaction > 0.05) or across categories of serum β -carotene, dietary vitamin C, or total carotenoid intake (data not shown), and similar patterns were observed for each cause-specific category. We also examined whether the relation between serum α -tocopherol and CVD mortality varied according to specific risk factors for heart disease. The strongest inverse α -tocopherol–CVD mortality associations were noted in the men with normal serum total cholesterol (<200 mg/dL; RR = 0.58; 95% CI: 0.46, 0.72 for the highest versus the lowest serum α -tocopherol quintile; *P* for interaction = 0.01) and in those with high serum HDL cholesterol (\geq 60 mg/dL; RR = 0.66; 95% CI: 0.49, 0.89 for the highest versus the lowest serum α -tocopherol quintile; *P* for interaction < 0.0001).

Our findings were not materially altered when the first 5 y of follow-up were excluded from the analysis (for total mortality, RR = 0.82; 95% CI: 0.77, 0.86 for the highest versus the lowest serum α -tocopherol quintile; *P* for trend < 0.0001). Similarly, the removal of subjects who used, before the trial, supplements that contained vitamin E (*n* = 2928) did not change the results (RR = 0.82; 95% CI: 0.78, 0.87 for the highest versus the lowest quintile of serum α -tocopherol; *P* for trend < 0.0001) or alter the distribution of serum α -tocopherol values in the cohort. The spline curves were also unaffected. Exclusion of the 12 482 men who reported a history of CVD, diabetes, or both at baseline

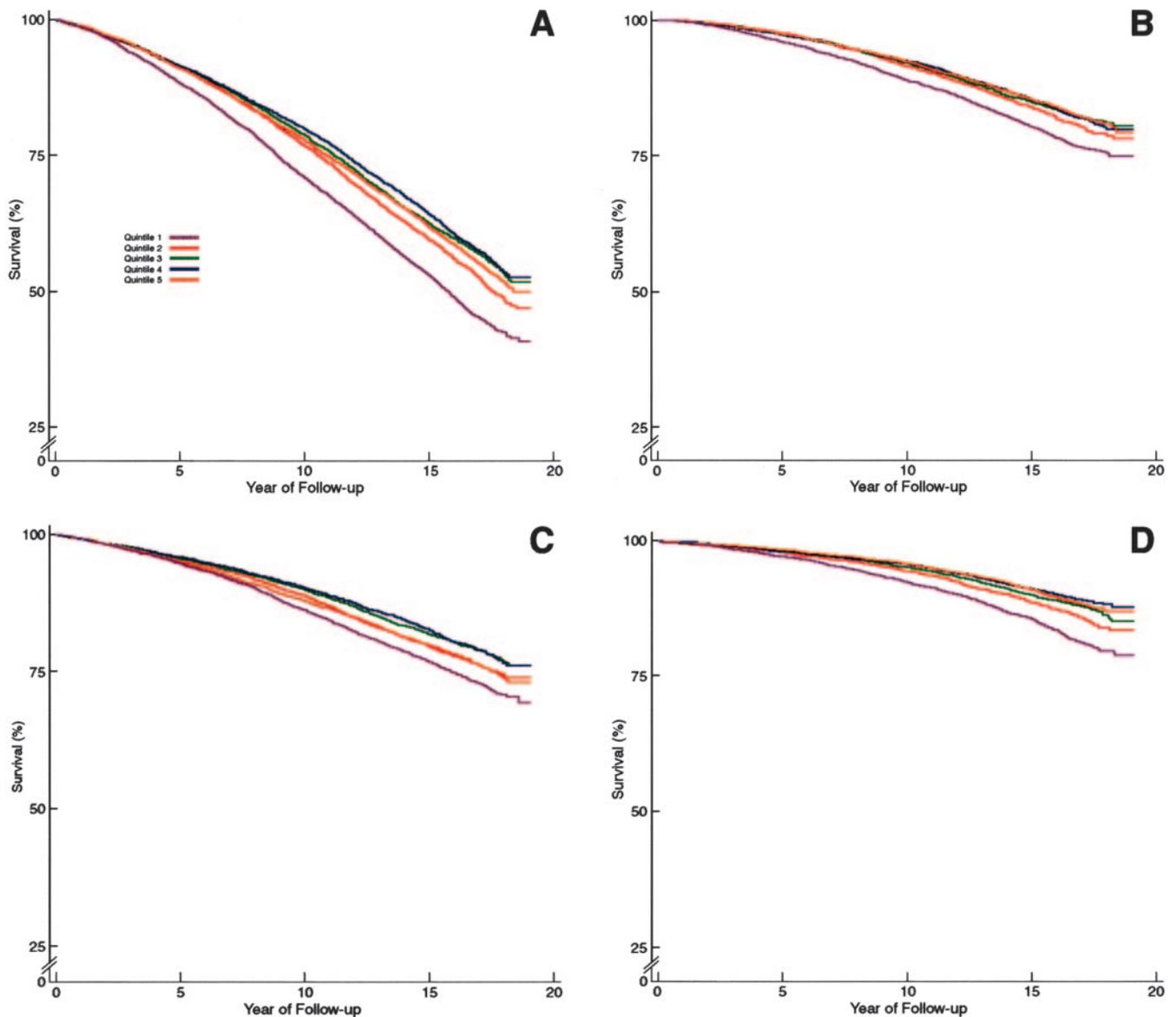


FIGURE 1. Kaplan-Meier survival curves for total (A) and cause-specific (cancer, B; cardiovascular disease, C; other causes, D) mortality according to quintiles of cholesterol-adjusted serum α -tocopherol.

strengthened the association between serum α -tocopherol and each mortality endpoint except cancer. This was particularly evident for CVD deaths [RR = 1.00 (referent); 0.89 (95% CI: 0.79, 1.01), 0.79 (0.70, 0.90), 0.74 (0.65, 0.84), and 0.74 (0.64, 0.84) for increasing serum α -tocopherol quintiles; P for trend < 0.0001].

DISCUSSION

We found a significant inverse relation between baseline serum α -tocopherol concentrations and both overall and cause-specific mortality in this large cohort of older male smokers. Cubic regression spline analysis indicated that the optimum relative reduction in mortality occurred at α -tocopherol values of 13–14 mg/L. The observed associations were somewhat stronger in the younger and leaner men, in those who smoked less, and in the heavier drinkers and, for CVD mortality, in the men with normal total and high HDL-cholesterol concentrations.

One of the primary biological functions of α -tocopherol is that of a chain-breaking antioxidant nutrient; as such, it protects lipids in membranes and lipoproteins from free radical damage, thereby limiting DNA mutation and oxidative modification of lipoproteins (4). α -Tocopherol may also affect human health through the inhibition of protein kinase C activity, which plays an important role in cell proliferation, adhesion, immune responses, and gene expression (4), or through the direct modulation of genes involved in growth, apoptosis, and inflammation (34). Because these processes contribute to both carcinogenesis and atherogenesis, the lower mortality from cancer and CVD in men with higher α -tocopherol concentrations is biologically plausible and is made more specific and convincing by the absence of a similar association with accidental causes of death.

Our findings support a more robust role for circulating α -tocopherol in overall, cancer, and CVD mortality than was suggested by previous studies (9–21). None of those reports



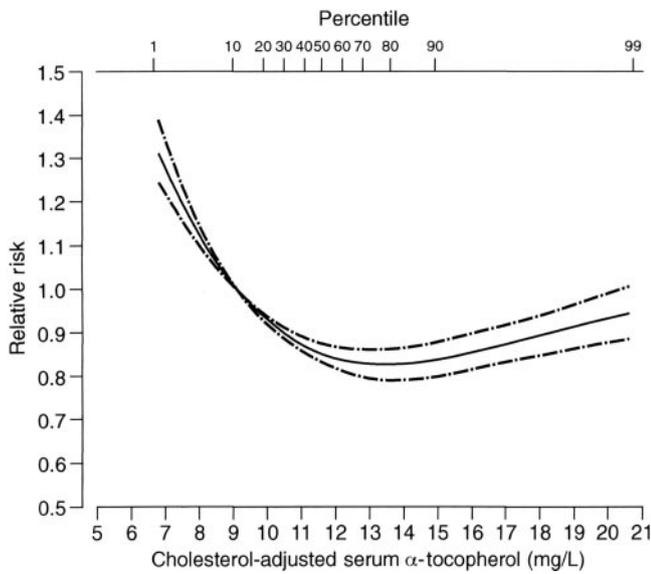


FIGURE 2. Cubic spline regression for total mortality according to cholesterol-adjusted serum α -tocopherol concentrations. —, Predicted relative risks; - - -, 95% CI. The reference value (9.1 mg/L; relative risk = 1.00) corresponds to the median value of the first quintile of serum α -tocopherol concentrations. To convert cholesterol-adjusted serum α -tocopherol concentrations from mg/L to μ mol/L, multiply by 2.322.

showed significant benefit or harm with increasing α -tocopherol concentrations after adjustment for important risk factors, although nonsignificant protective associations with total (11) and

cause-specific (9, 12, 13, 17, 20) mortality were apparent in several cohorts. With the large number of events resulting from a higher baseline risk factor profile and sustained, long-term follow-up, our study provided ample power to detect a modest relation between serum α -tocopherol and mortality. The largest previously published investigation included only 630 deaths (16); other studies reported fewer than 300 deaths overall. Although smokers made up a large proportion of subjects in several studies, none of the studies was conducted exclusively in that group. Three studies, however, performed subgroup analyses based on smoking status—one found that higher plasma α -tocopherol concentrations were marginally associated with increased risk of total mortality in continuous smokers (19), another ascertained that prostate cancer mortality was higher in smokers with low plasma vitamin E concentrations (12), which is consistent with our findings, and the third found no interaction between smoking status and blood concentrations of vitamin E with respect to all-cause mortality (11).

Our results also contrast with findings from clinical trials that showed little or no effect of supplemental vitamin E on various mortality endpoints, including deaths due to cancer and vascular disease (7, 22). For example, the ATBC Study, within which the current study is based, found that daily supplementation with 50 mg synthetic *all-rac*- α -tocopheryl acetate had no effect on total mortality, although more deaths from hemorrhagic (but not thromboembolic) stroke were observed in the α -tocopherol-supplemented group (26, 35, 36). Recent findings from the Women’s Health Study (WHS; 37) and the Supplementation en

TABLE 3
Relative risks (RRs) and 95% CIs for total mortality by quintile of cholesterol-adjusted serum α -tocopherol, stratified by selected factors¹

	Quintile of serum α -tocopherol (mg/L) ²										P for trend
	<10.0		10.0–11.0		11.1–12.1		12.2–13.5		>13.5		
	Deaths	RR ³	Deaths	RR (95% CI) ³	Deaths	RR (95% CI) ³	Deaths	RR (95% CI) ³	Deaths	RR (95% CI) ³	
	<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>		
Age											
<57 y	1086	1.0	892	0.79 (0.72, 0.86)	835	0.67 (0.61, 0.74)	828	0.67 (0.61, 0.73)	927	0.74 (0.68, 0.81)	<0.0001
≥57 y	2152	1.0	1678	0.86 (0.81, 0.92)	1660	0.83 (0.78, 0.88)	1631	0.80 (0.75, 0.86)	1691	0.86 (0.80, 0.91)	<0.0001
Cigarettes smoked/d											
<20	1013	1.0	882	0.85 (0.77, 0.93)	884	0.76 (0.69, 0.83)	921	0.73 (0.66, 0.79)	948	0.76 (0.69, 0.83)	<0.0001
≥20	2225	1.0	1688	0.83 (0.78, 0.89)	1611	0.78 (0.73, 0.83)	1538	0.77 (0.72, 0.83)	1670	0.85 (0.80, 0.91)	<0.0001
Years smoked											
<36 y	985	1.0	839	0.82 (0.75, 0.90)	834	0.70 (0.64, 0.77)	825	0.68 (0.62, 0.75)	879	0.75 (0.68, 0.82)	<0.0001
≥36 y	2253	1.0	1731	0.85 (0.79, 0.90)	1661	0.81 (0.76, 0.87)	1634	0.79 (0.74, 0.84)	1739	0.85 (0.80, 0.91)	<0.0001
Daily alcohol consumption											
<11 g	1294	1.0	1178	0.88 (0.81, 0.95)	1140	0.81 (0.75, 0.88)	1211	0.85 (0.78, 0.92)	1281	0.91 (0.84, 0.99)	0.07
≥11 g	1649	1.0	1180	0.81 (0.75, 0.87)	1136	0.75 (0.69, 0.80)	1043	0.66 (0.61, 0.72)	1144	0.74 (0.69, 0.80)	<0.0001
BMI (kg/m ²)											
< 25	1576	1.0	1202	0.85 (0.78, 0.91)	1033	0.73 (0.67, 0.79)	889	0.69 (0.63, 0.75)	710	0.71 (0.65, 0.78)	<0.0001
≥ 25	1660	1.0	1366	0.84 (0.78, 0.90)	1458	0.82 (0.76, 0.88)	1568	0.81 (0.75, 0.87)	1908	0.88 (0.83, 0.94)	0.005
Trial intervention group											
α -Tocopherol	1628	1.0	1291	0.84 (0.78, 0.90)	1256	0.77 (0.72, 0.83)	1223	0.74 (0.69, 0.80)	1311	0.81 (0.75, 0.87)	<0.0001
No α -tocopherol	1610	1.0	1279	0.84 (0.78, 0.91)	1239	0.77 (0.72, 0.83)	1236	0.77 (0.71, 0.83)	1307	0.82 (0.77, 0.89)	<0.0001
β -Carotene	1606	1.0	1292	0.86 (0.80, 0.93)	1312	0.83 (0.77, 0.89)	1265	0.79 (0.73, 0.85)	1343	0.83 (0.78, 0.90)	<0.0001
No β -carotene	1632	1.0	1278	0.84 (0.78, 0.90)	1183	0.74 (0.69, 0.80)	1194	0.75 (0.69, 0.81)	1275	0.82 (0.76, 0.88)	<0.0001

¹ All P values for interaction < 0.05 except trial intervention groups.

² To convert cholesterol-adjusted serum α -tocopherol from mg/L to μ mol/L, multiply by 2.322.

³ Adjusted for age, cigarettes smoked/d, years smoked, intervention assignment, and serum total cholesterol.

Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (38)—randomized trials conducted in apparently healthy populations—also found no overall mortality benefit for vitamin E supplementation, either alone or in combination with other vitamins and minerals, although a significant reduction in CVD deaths was noted in the WHS, and a lower risk of all-cause mortality was observed among men in the SU.VI.MAX study. In contrast, a meta-analysis of 19 mostly null trials (23) indicated a small but significant increase in all-cause mortality with high-dose vitamin E supplementation (ie, ≥ 400 IU/d), but these data have been challenged (24).

Discrepancies between our findings and results of previous trials of vitamin E and mortality could be due to several factors (39, 40). Serum antioxidants and other micronutrients, including α -tocopherol, may be highly correlated with each other because of their simultaneous ingestion in foods. In our cohort, for example, α - and γ -tocopherol concentrations were highly correlated [$r = 0.51$; data were available for a small subset of the cohort (41)]; γ -tocopherol is a powerful scavenger of reactive nitrogen oxide species (42, 43) and an inhibitor of the cyclooxygenase-2 enzyme (44). Supplements contain higher doses of single nutrients and are therefore consumed without the added benefit of potentially important cofactors. In fact, high doses of α -tocopherol have been shown to antagonize vitamin K (45) and to reduce the plasma concentrations of γ - and δ -tocopherols (46). Furthermore, pharmacologic doses of vitamin E may modulate different biological pathways than do concentrations achieved through dietary means. These differences have been shown for β -carotene, which acts as an antioxidant at low concentrations and interferes with normal retinoid signaling at higher concentrations in smokers (47), but have not been adequately explored with respect to vitamin E. Finally, our results could be due to uncontrolled confounding arising from unknown or unmeasured factors, including lifestyle, whereas randomized controlled trials are free of this bias.

Notable strengths of our study include the large number of events, the ample power to detect modest associations between serum α -tocopherol and mortality (as well as interactions with potentially important modifiers of risk), and the use of a biochemical measurement (rather than self-reported dietary intake) of α -tocopherol, which was available for almost all study participants. The use of a biochemical measure of α -tocopherol provided a more precise measure of internal dose and avoided errors in quantifying dietary intake that result from the underreporting of intakes of vitamin E–rich vegetable fats and oils (48) and the ubiquity of vitamin E in a wide variety of foods, many of which are not included on dietary questionnaires (1). An additional strength of this study is the relative homogeneity of the cohort, which limits potential confounding by socioeconomic and lifestyle factors. Accordingly, education, physical activity, BMI, blood pressure, and alcohol and energy intakes did not confound the observed associations.

The use of a single measure of serum α -tocopherol, which provides a snapshot of nutrient status at one point in time but may not reflect usual concentrations, may have been a limitation. However, the correlation coefficient between serum α -tocopherol at baseline and 3 y after randomization in those who did not receive the α -tocopherol supplement was 0.71, which indicates relative stability of serum α -tocopherol over a period of several years. We were able to carefully control for

several important and potentially confounding variables, including smoking dose and duration, serum cholesterol, and medical history. Although smokers may have higher vitamin E requirements due to enhanced antioxidant depletion rates, their plasma α -tocopherol concentrations do not generally differ from those in nonsmokers (49), which limits the possibility that our results are explained by residual confounding due to this important predictor of mortality. Nevertheless, it is imperative that future studies address the effect of serum vitamin E on mortality in racially and ethnically diverse populations, in women, and in nonsmokers, because our findings may not be generalizable to those groups.

In summary, the current study suggests that higher serum concentrations of α -tocopherol (up to 13–14 mg/L, which is within the normal range) are associated with moderately lower total and cause-specific mortality in older male smokers, independent of several important predictors of mortality. Because supplemental vitamin E has not been shown to reduce mortality in randomized trials, efforts to improve vitamin E status through dietary means (eg, through increased consumption of foods rich in vitamin E, including nuts, seeds, whole grains, and dark-green leafy vegetables) may be warranted, particularly if future prospective studies show similar serum α -tocopherol–mortality associations in diverse populations, including nonsmokers. 

We thank Barry Graubard for his assistance with the spline regression analysis.

MEW performed the data analysis and wrote the manuscript; KAL, SJW, and DA assisted with data interpretation. PP, PRT, JV, and DA contributed to the study design and to data collection for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and the ongoing follow-up study, and provided critical review of the manuscript. None of the authors had any personal or financial conflict of interest.

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