REPORTS

Serum α-Tocopherol and Subsequent Risk of Lung Cancer Among Male Smokers

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Background: Higher blood levels of α-tocopherol, the predominant form of vitamin E, have been associated in some studies with a reduced risk of lung cancer, but other studies have yielded conflicting results. To clarify this association, we examined the relationship between prospectively collected serum α-tocopherol and lung cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort. *Methods:* The ATBC Study was a randomized, clinical trial of 29 133 white male smokers from Finland who were 50–69 years old and who had received α-tocopherol (50 mg), β-carotene (20 mg), both, or neither daily for 5–8 years. Data regarding medical histories, smoking, and dietary factors were obtained at study entry, as was a serum specimen for baseline α-tocopherol determination. α-Tocopherol measurements were available for 29 102 of the men, among whom 1144 incident cases of lung cancer were diagnosed during a median observation period of 7.7 years. The association between α-tocopherol and lung cancer was evaluated with the use of multivariate proportional hazards regression. *Results:* A 19% reduction in lung cancer incidence was observed in the highest versus lowest quintile of serum α-tocopherol (relative risk = 0.81; 95% confidence interval = 0.67–0.97). There was a stronger inverse association among younger men (<60 years), among men with less cumulative tobacco exposure (<40 years of smoking), and possibly among men receiving α-tocopherol supplementation. *Conclusions:* In the ATBC Study cohort, higher serum α-tocopherol status is associated with lower lung cancer risk; this relationship appears stronger among younger persons and among those with less cumulative smoke exposure. These findings suggest that high levels of α-tocopherol, if present during the early critical stages of tumorigenesis, may inhibit lung cancer development. [J Natl Cancer Inst 1999;91: 1738–43]

Many carcinogens create free radicals that damage DNA and other cellular structures, both initiating and promoting tumor development (1). Antioxidants can neutralize free radicals, thereby preventing this cell damage and subsequent malignant transformation. α-Tocopherol (the predominant and most active form of vitamin E in humans) is the major chain-breaking antioxidant in lipid phases, such as within the hydrophobic regions of cellular membranes or low-density lipoproteins (2), and it is thought to inhibit carcinogenesis primarily through its antioxidant activity (3). In addition to its antioxidant role, α-tocopherol may also inhibit carcinogenesis through various alternative mechanisms, including inhibition of cell proliferation (4), induction of apoptosis (i.e., programmed cell death) (4), inhibition of angiogenesis (5), and enhancement of immune function (6).

Observational studies in humans of the association between α-tocopherol and lung cancer have yielded inconsistent results. Prediagnostic serum levels have been shown to be inversely associated with lung cancer in some (7–9) but not all (10–12) cohort investigations, and case–control studies [reviewed in (13)] are generally supportive of reduced lung cancer risk among persons having higher blood levels of α-tocopherol.

We investigated the relationship between prospectively collected serum α-tocopherol and lung cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Although this controlled trial did not provide evidence of lung cancer prevention from α-tocopherol supplementation overall (14), it was important in this setting to evaluate whether prerandomization serum α-tocopherol concentrations, reflecting usual dietary intake, absorption, and other aspects of the vitamin's metabolism, were predictive of the subsequent development of lung cancer. The study's size and number of events provided sufficient power to tightly control for confounding and to carefully evaluate effect modification by several relevant study factors. Underlying our investigation was the hypothesis that, because the ATBC Study was made up of older, chronic cigarette smokers, baseline serum levels might better reflect their long-term exposure to antioxidants during earlier, critical periods of tumorigenesis.

SUBJECTS AND METHODS

Sample population. The sample population consisted of 29 133 white male smokers aged 50–69 years participating in the ATBC Study conducted in Finland. The ATBC Study was a randomized, placebo-controlled trial designed to determine whether α-tocopherol (50 mg/day), β-carotene (20 mg/day), or both substances would reduce the incidence of lung and other cancers. The overall design, rationale, and objectives of this study have been published (15). Recruited during the period from 1985 through 1988, participants were followed during the active trial period until death or April 30, 1993 (median follow-up, 6.1 years). The trial results showed a 16% increase in lung cancer incidence among men who received β-carotene supplementation and no effect for vitamin E (14). Men continue to be followed after intervention. Excluded from the study were men who were alcoholics, who had cirrhosis of the liver, who had severe angina with exertion, who were diagnosed with chronic renal insufficiency, who were previously diagnosed with cancer, or who were taking vitamin A or E or β-carotene beyond specified doses (14). The ATBC Study was approved by the institutional review boards of the National Cancer Institute (U.S.) and the National Public Health Institute of Finland, and written informed consent was obtained from each participant prior to random assignment.

Identification of lung cancer case patients. Participants in the trial who were diagnosed with incident primary cancer of the lung or bronchus [International Classification of Diseases, 9th revision, code No. 162 (15)] up to December 31, 1994, were identified through the Finnish Cancer Registry and the Register of Causes of Death, which provided close to 100% case ascertainment nationwide (16). The medical records of the case patients diagnosed during the intervention period (up to April 30, 1993;

n = 874) were centrally reviewed independently by two study physicians, and those of the cases patients who were identified after intervention (up to December 31, 1994; n = 270) were reviewed by one study physician. Histologic or cytologic confirmation, with the use of the classification of the International Classification of Diseases for Oncology (17), was made for 93% of the cases. Histologic subtype information for the trial period case patients was obtained from central review of histopathologic and cytologic specimens by two pathologists and pulmonary cytologists, respectively. Thirty-four percent of the cases were of the squamous cell type, 18% were of the small-cell type, 13% were adenocarcinomas, and 35% were of other and indeterminant cell types. Locally reviewed pathology reports on postintervention cases were available but were not included in the histologic subtype analyses.

Data collection. General medical history, diet, smoking, and other background data—along with a fasting blood sample—were obtained from all subjects at baseline. Blood samples were protected from light, divided into aliquots, and frozen and were analyzed soon after collection (within 2 years), thus minimizing the risk of α-tocopherol degradation. Serum concentrations of α-tocopherol were determined by high-performance liquid chromatography at one laboratory (18), and the between-run coefficients of variability were 2.2%. α-Tocopherol was successfully measured for 29 102 (99.9%) participants. The dietary information was gathered with the use of a validated, self-administered food-use questionnaire given to all participants before the randomization process (19). Using a color picture booklet as an aid, participants were asked to report their usual frequency of consumption and portion sizes during the previous year for more than 270 common food items and beverages. Of the entire cohort, 27 111 (93.1%) men completed the questionnaire. Dietary nutrient intake (including α-tocopherol and all vitamin E compounds) was estimated through the use of food composition data available from the National Public Health Institute of Finland. Because higher dose vitamin E supplementation was one of the exclusion criteria of the main trial, we had only 2928 men reporting taking some form of supplemental vitamin E at baseline, with the usual daily dose being 6.7 mg. A separate variable was created that combined baseline dietary intake and self-reported supplemental intake of vitamin E.

Statistical analyses. Statistical analyses were performed with the use of software developed by the SAS Institute, Inc. (Cary, NC). Cox regression models were used to estimate the association between serum and dietary α-tocopherol and the incidence of lung cancer. All correlations were Spearman correlation coefficients. Dietary and serum variables were log-transformed and evaluated both as continuous predictors and as indicator variables defined by quintiles on the basis of their distribution among the entire cohort, with the lowest quintile serving as the reference group. Dietary α-tocopherol and vitamin E (four tocopherols and four tocotrienols, combined) were evaluated separately. An ordinal score value based on the median value within each quintile was used to test for trend or dose–response relationship across quintiles. Serum α-tocopherol was adjusted for serum cholesterol, and dietary α-tocopherol and vitamin E were adjusted for calories. Calorie adjustment for the dietary factors was performed by two

separate methods: 1) the residual method described by Willett (20) and 2) the inclusion of total energy intake as a continuous covariate in the hazard models. Multivariate models were developed by including serum α-tocopherol in a model for lung cancer as previously described (14). This model included age at random assignment, body mass index (BMI) defined as the weight in kilograms divided by the square of the height in meters, years of cigarette smoking, number of cigarettes smoked daily, and intervention group. Other study factors were assessed as confounders by evaluating whether their inclusion into the multivariate model changed the risk estimates by more than 15%. Intervention group assignment was evaluated with indicator variables for supplementation with α-tocopherol, β-carotene, both, or none (reference). Effect modification was assessed by inclusion of factors and their cross-product terms in the model and by stratified analysis of study factors by tertile or median split categories based on their distribution among the entire cohort. The validity of the proportional hazards assumption was tested by evaluating the cross-product term of log of follow-up time and the covariate of interest. All reported *P* values (including tests for trend and interaction) are two-sided and were considered statistically significant if less than .05.

RESULTS

The analytical cohort comprised 29 102 men, including 1144 men diagnosed with incident cases of lung cancer ascertained during up to 10 years of follow-up (median, 7.7 years). Serum α-tocopherol levels, after adjustment for serum cholesterol levels, ranged from 1.4 to 110.6 mg/L, with the median value being 11.6 mg/L. α-Tocopherol concentrations were statistically significantly correlated with dietary α-tocopherol intake (*r* = .36) but not with age, years of cigarette smoking, number of cigarettes smoked daily, alcohol consumption, or serum β-carotene or retinol concentrations (range of *r* values, –0.07 to 0.09). The demographic and smoking characteristics, serum vitamins, and dietary intakes at baseline for lung cancer case patients and noncase subjects are shown in Table 1. Compared with noncase subjects, patients were—on average—older; had smoked for a longer time; had lower serum α-tocopherol, β-carotene, and retinol concentrations; and consumed a diet lower in calories, vitamins, and other micronutrients. Twelve percent of the case patients and 10% of the noncase subjects reported using vitamin E supplements prior to random assignment to an intervention.

Baseline serum α-tocopherol, dietary α-tocopherol, and dietary vitamin E were inversely associated with lung cancer risk (Table 2). We observed reductions in estimated relative risk of 19% (95% confi-

dence interval [CI] = 3%–33%), 20% (95% CI = 3%–34%), and 23% (95% CI = 7%–36%) for the fifth compared with the first quintile of serum α-tocopherol, dietary α-tocopherol, and dietary vitamin E, respectively. The risk estimates remained unchanged when intakes of α-tocopherol and vitamin E were evaluated by combining baseline dietary and supplemental sources (data not shown). The associations between serum α-tocopherol and lung cancer mortality, based on 883 deaths, were essentially the same as for cancer risk (data not shown). To avoid potential bias from the influence of preclinical cancer on baseline serum levels or dietary intake, we did separate analyses that excluded case patients diagnosed early during follow-up (i.e., within the first, second, or third years) and observed no changes in the risk estimates (data not shown).

We evaluated the association between serum α-tocopherol and lung cancer according to histologic subtypes (Table 3). We observed only modest differences. Only the more smoking-related cancers (21)—i.e., squamous cell and small-cell carcinomas—exhibited inverse associations with α-tocopherol; only for squamous cell carcinoma did the test for trend approach statistical significance (*P* = .09).

We evaluated modification of the association between baseline serum α-tocopherol and lung cancer by age, education, number of cigarettes smoked daily, years of smoking, alcohol consumption, dietary vitamin C intake, serum β-carotene, serum retinol, and intervention assignment. We observed material interactions only with age, years of smoking, and possibly α-tocopherol intervention assignment (Table 4, A). There were statistically significant trends for men younger than 60 years and men who had smoked fewer than 40 years at study entry. The risk estimates regarding the fifth compared with the first quintile of serum α-tocopherol were reduced by 40% (among men <60 years old) and 50% among lighter smokers who smoked for fewer than 40 years. An inverse association was also stronger and statistically significant among men who were in the α-tocopherol supplementation arm of the trial. The tests for interaction were statistically significant only for age and for years of smoking. It should be borne in mind that, in this population of older smokers, age and years of smoking are highly correlated

Table 1. Median and interquartile range for baseline demographic characteristics, daily nutrient and alcohol intake, and cigarette smoking for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of Finnish male smokers with and without lung cancer

Characteristic	Case subjects* (n = 1144)	Control subjects* (n = 27 958)
Age, y	60 (56–63)	56 (53–61)
Age started smoking, y	18 (16–20)	19 (17–21)
No. of years of smoking	41 (37–45)	36 (31–41)
Cigarettes/day	20 (17–25)	20 (15–25)
Body mass index, kg/m²†	25.3 (22.9–27.7)	26.0 (23.7–28.5)
Serum nutrients		
α-Tocopherol,‡ mg/L	11.4 (9.8–12.8)	11.6 (10.3–13.2)
β-Carotene, μg/L	162 (99–246)	172 (111–263)
Retinol, μg/L	556 (481–635)	578 (502–662)
Alcohol, g/day	10.2 (1.7–24.8)	11.0 (2.6–25.6)
Energy intake, kcal	2635 (2159–3187)	2724 (2259–3264)
Dietary antioxidants§		
Total vitamin A, μg	1678 (1059–2736)	1746 (1131–2866)
Vitamin C, mg	80.0 (58.5–108.2)	88.3 (64.6–118.9)
Vitamin E, all forms, mg	9.9 (7.4–13.4)	10.8 (8.2–14.5)
α-Tocopherol, mg¶	8.5 (6.5–11.6)	9.2 (7.0–12.5)
γ-Tocopherol, mg¶	4.7 (2.5–9.5)	5.8 (3.0–11.1)

*Median (interquartile range).

†Body mass index is defined as the weight in kilograms divided by the square of the height in meters.

‡Serum α-tocopherol adjusted for cholesterol.

§Complete dietary information was available for only 27 111 participants in the cohort.

¶α- and γ-tocopherol fractions account for approximately 93% of total vitamin E intake.

(r = .66): The younger age and lower smoke-years categories represent some of the same men (e.g., 47% of men <55 years old smoked for <32 years).

On the basis of these findings, we hypothesized that older subjects and/or those with a longer history of smoking probably had a greater cumulative carcinogenic exposure that required higher levels of α-tocopherol for protection against lung cancer. Therefore, we explored whether the trial α-tocopherol supplementation influenced the effect of age and years of smoking on the relationship between baseline serum α-tocopherol and lung cancer (Table 4, B). An inverse association was apparent among the younger subjects given supplements of α-tocopherol but not among older subjects. The test for interaction between the α-tocopherol supplementation group and serum concentrations, however, was only suggestive among men younger than 60 years, and the three-way interaction (group × serum level × age) was not significant (P = .30).

Similar effect modification by α-tocopherol supplementation group was apparent for years of smoking, with an inverse association for baseline serum α-tocopherol being observed only among the shorter term smokers (i.e., <40 years) who received the trial α-tocopherol

supplementation (Table 4, B). The baseline serum α-tocopherol concentration was not significantly related to lung cancer risk among either the longer term smokers who received α-tocopherol and men not given supplements of α-tocopherol (regardless of years of smoking). The interaction between α-tocopherol group and serum α-tocopherol was significant among the men who smoked for fewer than 40 years, while the three-way interaction was not (P = .35)

DISCUSSION

We found serum α-tocopherol to be inversely associated with lung cancer risk in a trial-based cohort of 29 102 male smokers in Finland. Similar inverse associations were observed for dietary α-tocopherol and vitamin E intake. These relationships persisted after we controlled for several potential confounders, including age, smoking, alcohol consumption, other dietary factors, and β-carotene and α-tocopherol supplementation group. The inverse association between serum α-tocopherol and lung cancer was apparent only in younger men, in men with less cumulative tobacco exposure, and possibly in men who had received α-tocopherol supplementation during the trial.

Table 2. Adjusted relative risks (RRs)* and 95% confidence intervals (CIs) of lung cancer by quintile of baseline serum α-tocopherol, dietary α-tocopherol, and all forms of dietary vitamin E, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of Finnish male smokers

Quintile†	No. of case patients	Person-years	RR (95% CI)	P for trend‡
Serum α-tocopherol, mg/L§				
Q1: <10.0	301	42 670	1.00 (referent)	
Q2: 10.0–11.0	201	39 581	0.79 (0.66–0.93)	
Q3: 11.1–12.1	225	42 154	0.88 (0.73–1.05)	
Q4: 12.2–13.5	221	42 435	0.88 (0.74–0.81)	
Q5: >13.5	196	42 922	0.81 (0.67–0.97)	.09
Dietary α-tocopherol, mg¶				
Q1: <9.34	280	38 113	1.00 (referent)	
Q2: 9.34–10.8	222	38 973	0.90 (0.75–1.07)	
Q3: 10.9–12.2	189	39 312	0.79 (0.66–0.95)	
Q4: 12.3–14.2	189	39 633	0.85 (0.71–1.03)	
Q5: >14.2	175	39 852	0.80 (0.66–0.97)	.02
Dietary vitamin E, all forms, mg¶				
Q1: <7.63	292	38 104	1.00 (referent)	
Q2: 7.63–9.64	212	39 004	0.83 (0.69–0.99)	
Q3: 9.65–11.9	182	39 390	0.73 (0.61–0.88)	
Q4: 12.0–15.7	194	39 532	0.84 (0.70–1.01)	
Q5: >15.7	175	39 850	0.77 (0.64–0.93)	.01

*RR after adjustment for age, body mass index, years of smoking, cigarettes per day, energy (for dietary α-tocopherol and all vitamin E forms), and intervention assignment.

†Quintile (Q) cut points are based on the distribution of log-transformed values of serum α-tocopherol, dietary α-tocopherol, and total vitamin E in the entire cohort.

‡P for trends are based on the statistical significance of the coefficient of the scored quintile variable (median value within each quintile). All P values are two-sided and are considered to be statistically significant if <.05.

§Serum α-tocopherol adjusted for cholesterol.

¶Complete dietary information was available for only 27 111 participants in the cohort.

Table 3. Adjusted relative risks (RRs)* and 95% confidence intervals (CIs) of lung cancer by quintile of baseline serum α-tocopherol according to tumor histology, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of Finnish male smokers

Histotype (No. of case patients)	RR (95% CI) by quintiles of baseline serum α-tocopherol,† mg/L					P for trend‡
	1.4–9.9	10.0–11.0	11.1–12.1	12.2–13.5	>13.5	
Squamous cell carcinoma (388)§	1.00 (referent)	0.84 (0.62–1.13)	0.92 (0.69–1.23)	0.81 (0.59–1.20)	0.76 (0.55–1.04)	.09
Small-cell carcinoma (213)§	1.00 (referent)	0.59 (0.38–0.90)	0.70 (0.47–1.06)	0.93 (0.63–1.36)	0.69 (0.45–1.05)	.28
Adenocarcinoma (145)	1.00 (referent)	0.96 (0.58–1.58)	0.79 (0.46–1.34)	1.06 (0.64–1.73)	0.98 (0.59–1.63)	.97

*RR after adjustment for age, body mass index, years of smoking, cigarettes per day, and intervention assignment.

†Adjusted for cholesterol.

‡P for trends are based on the statistical significance of the coefficient of the scored quintile variable (median value within each quintile). All P values are two-sided and are considered to be statistically significant if <.05.

§Differences in the distribution of histologic subtypes (smoking-related—i.e., squamous and small-cell—versus non-smoking-related—i.e., adenocarcinoma) among serum α-tocopherol quintiles tested by chi-squared, χ^2_p = .5.

Table 4. Adjusted relative risks (RRs)* and 95% confidence intervals (CIs) of lung cancer by quintile of baseline serum α-tocopherol, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of Finnish male smokers

	RR (95% CI) by quintiles of baseline serum α-tocopherol,† mg/L					P for trend‡	P interaction§
	1.4–9.9	10.0–11.0	11.1–12.1	12.2–13.5	>13.5		
A) Stratified according to age, number of years of smoking, and intervention assigment							
Age at baseline, y							
<55	1.00 (referent)	0.66 (0.42–1.04)	0.74 (0.48–1.14)	0.71 (0.46–0.97)	0.61 (0.38–0.97)	.06	.006
55–59	1.00 (referent)	0.81 (0.59–1.11)	0.73 (0.53–1.01)	0.85 (0.62–1.16)	0.61 (0.43–0.87)	.01	
≥60	1.00 (referent)	0.84 (0.67–1.07)	1.05 (0.79–1.28)	1.01 (0.79–1.28)	1.03 (0.81–1.31)	.53	
No. of years of smoking							
<32	1.00 (referent)	0.50 (0.27–0.94)	0.62 (0.35–1.10)	0.46 (0.25–0.85)	0.48 (0.25–0.89)	.01	.004
32–40	1.00 (referent)	0.71 (0.53–0.95)	0.75 (0.57–1.00)	0.79 (0.60–1.04)	0.72 (0.54–0.96)	.05	
>40	1.00 (referent)	0.92 (0.72–1.18)	1.08 (0.85–1.37)	1.11 (0.87–1.41)	0.97 (0.75–1.25)	.74	
α-Tocopherol supplementation with β-carotene							
Yes	1.00 (referent)	0.72 (0.56–0.93)	0.76 (0.59–0.97)	0.77 (0.60–0.99)	0.71 (0.55–0.92)	.02	.15
No	1.00 (referent)	0.87 (0.68–1.12)	1.06 (0.83–1.35)	1.06 (0.83–1.20)	0.93 (0.72–1.20)	.99	
α-Tocopherol supplementation without β-carotene							
Yes	1.00 (referent)	0.83 (0.58–1.20)	0.91 (0.64–1.30)	0.78 (0.54–1.14)	0.63 (0.42–0.94)	.03	.12
No	1.00 (referent)	0.85 (0.59–1.21)	0.83 (0.57–1.21)	1.05 (0.73–1.50)	1.05 (0.73–1.51)	.48	
β-Carotene supplementation							
Yes	1.00 (referent)	0.75 (0.58–0.96)	0.91 (0.72–1.15)	0.90 (0.71–1.15)	0.81 (0.63–1.04)	.25	.99
No	1.00 (referent)	0.84 (0.65–1.09)	0.87 (0.67–1.13)	0.91 (0.70–1.17)	0.82 (0.63–1.07)	.21	
B) Stratified by age at baseline and number of years of smoking according to α-tocopherol supplementation							
Age at baseline, y, AT¶							
<60							
Yes	1.00 (referent)	0.68 (0.48–0.98)	0.61 (0.48–0.88)	0.67 (0.47–0.96)	0.47 (0.32–0.71)	.001	.09
No	1.00 (referent)	0.84 (0.57–1.22)	0.89 (0.62–1.29)	0.96 (0.66–1.39)	0.79 (0.53–1.18)	.42	
≥60							
Yes	1.00 (referent)	0.77 (0.54–1.10)	0.91 (0.65–1.28)	0.87 (0.61–1.24)	1.00 (0.71–1.41)	.93	.75
No	1.00 (referent)	0.91 (0.64–1.28)	1.20 (0.87–1.66)	1.15 (0.82–1.61)	1.06 (0.76–1.40)	.43	
Years smoked, AT¶							
<40							
Yes	1.00 (referent)	0.54 (0.35–0.86)	0.68 (0.45–1.02)	0.59 (0.38–0.90)	0.44 (0.28–0.71)	.001	.02
No	1.00 (referent)	0.73 (0.46–1.16)	0.83 (0.54–1.29)	0.70 (0.44–1.10)	0.89 (0.57–1.39)	.54	
≥40							
Yes	1.00 (referent)	0.83 (0.61–1.13)	0.80 (0.58–1.09)	0.88 (0.65–1.20)	0.84 (0.63–1.12)	.48	.63
No	1.00 (referent)	0.95 (0.70–1.28)	1.17 (0.87–1.56)	1.27 (0.95–1.70)	0.94 (0.69–1.29)	.65	

*RR after adjustment for age, body mass index, years of smoking, cigarettes per day, and intervention assignment.

†Adjustment for cholesterol.

‡P for trends are based on the statistical significance of the coefficient of the score quintile variable (median value within each quintile). All P values are two-sided and are considered to be statistically significant if <.05.

§P for interaction based on the statistical significance of the cross-product term added to multivariate models.

¶AT refers to α-tocopherol supplement group.

Relatively few studies have examined the association between dietary intake or blood levels of α-tocopherol and lung cancer. In general, null or weak inverse associations have been observed. Of six prospective studies evaluating serum levels of this substance *(7–12)*, only three *(7–9)* showed statistically significant inverse associations. Case–control studies have generally reported lower α-tocopherol levels among case patients than among control subjects [reviewed in *(13)*]. Data regarding modification of this effect by smoking history are inconsistent. Comstock et al. *(7)* observed no differences in lung cancer risk associated with serum α-tocopherol concentrations across smoking categories (i.e., nonsmokers, former smokers, or current smokers). Consistent with our findings, Knekt et al. *(10,22)* found in another Finnish cohort that a higher serum α-tocopherol concentration was more protective among male nonsmokers and younger subjects.

Our investigation is unique among these reports and is strengthened by having both biochemical and dietary measurements of α-tocopherol collected prospectively and evaluated for nearly the entire cohort of more than 29 000 men. Although we observed similar results for both indicators, it is not clear whether dietary and serum α-tocopherol values are interchangeable. Serum assessment is generally considered more accurate and biologically meaningful than dietary estimates of the vitamin, in that it reflects the aggregate effects of intake (from both diet and supplemental sources), absorption, utilization, and other aspects of metabolism, including depletion of serum and tissue sources by oxidative stressors such as cigarette smoking *(23)*. Furthermore, our use of prospectively collected samples minimized the possibility that differences in α-tocopherol concentrations were an artifactual consequence of cancer. On the other hand, given the one-time measurement of serum concentration and possible diurnal—but not seasonal *(24)*—variation, dietary estimate provides an alternative indicator of chronic exposure to the vitamin.

We did not observe a sequential dose–response association of serum α-tocopherol; instead, a threshold was seen between the first and second quintile, suggesting that serum α-tocopherol concentrations greater than 10 mg/L were sufficient for reducing lung cancer risk by about 20%. These results could be explained by the relatively narrow range of serum α-tocopherol in our population, which might be accounted for, in part, by the propensity of cigarette smoke to reduce α-tocopherol concentrations in blood, presumably because of the high uptake and turnover of antioxidants in smokers *(23)*. Unfortunately, the serum values are not directly comparable to those from other similar cohort studies because the methods of biochemical analysis, duration of storage, and adjustment for serum cholesterol all varied substantially between studies.

α-Tocopherol has been shown experimentally to inhibit carcinogen-induced DNA damage *(25)*, to modulate the redox potential of the cell *(26)*, and to alter expression of metabolic enzymes such as glutathione-*S*-transferase *(27)*. Aside from its antioxidant role in the prevention of cancer, there is a growing body of evidence suggesting that α-tocopherol exerts other effects. α-Tocopherol has been shown to regulate cell growth and differentiation, probably through its influence on several interconnected pathways. For example, α-tocopherol is thought to block prostaglandin and arachidonic acid metabolism *(28)*, it inhibits protein kinase C activity *(29)*, and it may affect expression of hormones and growth factors *(30,31)*. The multiple functions of α-tocopherol may allow it to inhibit tumorigenesis at various stages, from initiation and promotion to progression and tumor growth.

The stronger inverse association observed among younger men and men who smoked for fewer years—presumably subgroups with less cumulative exposure to tobacco carcinogens—is intriguing. Higher α-tocopherol status might be protective only in such a lower risk setting. It is also possible that high α-tocopherol levels slowed the progression or growth of subclinical tumors among these subgroups, such that their clinical manifestation and diagnosis were delayed beyond the period of observation. Alternatively, the interaction with age could be explained by age-related changes in metabolism and transport of α-tocopherol; e.g., activity of lipoprotein lipase, an enzyme that during lipolysis releases α-tocopherol from the chylomicrons and transfers it to tissues, has been shown to decrease with age *(32–34)*. The limited age range of our population (50–69 years old), however, and the possibly stronger association for the tumors with more smoking-related histology make a compelling argument for smoking-related effects. These findings also highlight the need for further studies to evaluate broader populations that include nonsmokers and younger and older adults and test whether similar associations exist among women.

Our study is unique in its ability to evaluate prospectively *within the same cohort* the potential impact of both chronic vitamin E status, as assessed by serum α-tocopherol, dietary α-tocopherol, and vitamin E, and a randomized, placebo-controlled test of daily α-tocopherol supplementation. We have previously reported *(14)* that the latter demonstrated no effect on lung cancer incidence overall, although secondary analyses suggested that participants having longer exposure to α-tocopherol supplementation may have accrued some marginal benefit (i.e., a 10%–15% reduction in incidence). The present findings reinforce the importance of adequate vitamin E status to lung cancer risk, particularly among smokers. The fact that this beneficial relationship for higher pretrial α-tocopherol status was observed primarily among those given supplements of α-tocopherol (50 mg daily) suggests synergism between usual intake and the controlled intervention. Such a finding could be explained by higher pretrial levels representing those subjects with more efficient absorption, metabolism, and ultimate bioavailability of α-tocopherol. Alternatively, in the presence of higher background vitamin E status, supplementation may have provided the higher dosages possibly required for inhibition of carcinogenesis. While it is tempting, based on the present data, to speculate that the administration of greater quantities of α-tocopherol (i.e., >50 mg daily) might have produced a substantial reduction in lung cancer incidence in the ATBC Study, only future studies, and controlled trials in particular, can shed light on this question.

Our data are compatible with a beneficial influence of higher vitamin E status on lung cancer development and indicate a possibly stronger effect among persons who have accumulated lower levels of lung carcinogens from chronic cigarette smoking. Additional prospective studies of vitamin E status and lung cancer that include women and nonsmokers and that assess the association across a spectrum of lung cancer risk (e.g., especially age and smoking exposures) will be particularly informative.

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