Vitamin E intake, α-tocopherol status, and pancreatic cancer in a cohort of male smokers[1–3]

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ABSTRACT

Background: Evidence indicates that vitamin E has anticarcinogenic properties for gastrointestinal cancers; however, few studies have examined this with respect to exocrine pancreatic cancer.

Objective: The objective was to examine whether vitamin E intake and serum α-tocopherol concentrations were prospectively associated with exocrine pancreatic cancer.

Design: We conducted a cohort analysis of prediagnostic vitamin E intake (4 tocopherols, 4 tocotrienols), serum α-tocopherol concentrations, and pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of male Finnish smokers aged 50–69 y at baseline. During follow-up from 1985 to 2004 (maximum: 19.4 y; median: 16 y), 318 incident cases were diagnosed among cohort participants with complete serum samples (n = 29,092); 306 cases had complete dietary data (n = 27,111). Cox proportional hazards models adjusted for age, smoking history, history of diabetes mellitus, and/or serum cholesterol were used to calculate hazard ratios (HRs) and 95% CIs.

Results: Higher α-tocopherol concentrations were associated with lower pancreatic cancer risk (highest compared with lowest quintile, HR: 0.52; 95% CI: 0.34, 0.80; P for trend = 0.03; continuous HR: 0.91; 95% CI: 0.84, 0.99). Polyunsaturated fat, a putative prooxidant nutrient, modified the association such that the inverse α-tocopherol association was most pronounced in subjects with a high polyunsaturated fat intake (ie, >9.9 g/d; highest compared with lowest quintile, HR: 0.38; 95% CI: 0.20, 0.70; P for trend = 0.03; continuous HR: 0.86; 95% CI: 0.75, 0.97; P for interaction = 0.05 and 0.02, respectively). No associations were observed for dietary tocopherols and tocotrienols.

Conclusion: Our results support the hypothesis that higher α-tocopherol concentrations may play a protective role in pancreatic carcinogenesis in male smokers. *Am J Clin Nutr* 2009;89: 584–91.

INTRODUCTION

Exocrine pancreatic cancer is the third and fourth leading cause of cancer mortality among men and women in Finland (1) and the United States (2), respectively. Because there are no effective screening methods for detecting this malignancy, it is typically diagnosed at advanced stages, which contributes to its high mortality rate (3). Cigarette smoking, history of diabetes, and obesity are among the few consistent risk factors for pancreatic cancer (3).

Vitamin E is a fat-soluble vitamin that refers to a group of 8 structurally related naturally occurring tocopherol and tocotrienol derivatives (4). The major dietary sources of vitamin E are vegetable and seed oils (4). α-Tocopherol (AT) is considered the most biologically active and plentiful form of vitamin E in the plasma and in most tissues of humans (4). Its primary antioxidant function is to prevent cellular damage by scavenging free radicals formed from polyunsaturated fatty acids reacting with oxygen in lipid membranes throughout the body (5)—a function that may be important for cancer prevention. Vitamin E also blocks the endogenous formation of *N*-nitroso-compounds (6), which are suspected carcinogens for some cancers including pancreatic cancer (7). Other nonantioxidant properties of vitamin E that may have implications for prevention of carcinogenesis include inhibition of protein kinase C (PKC) activity and cell division, interference with hormone signaling, enhancement of immune response, regulation of gene expression, and suppression of tumor angiogenesis (5). These latter pathways appear to be dependent on the oxidative stress within specific cells or tissues and may not be explicitly regulated AT alone (5).

Vitamin E has been shown to inhibit pancreatic cancer cell line growth in some (8, 9), but not all (10), studies. Evaluation of the effect of AT on pancreatic carcinogenesis in rodent models has

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reported beneficial (11–13) and null (14, 15) results. Epidemiologic studies that have examined dietary vitamin E (16, 17), serum AT (18–21), or AT supplement interventions (22–25) and pancreatic cancer risk show inconsistent results. Most, including randomized trials that have examined pancreatic cancer as a secondary outcome (22–25), have limited power to detect associations (18–25).

Cigarette smoke, impaired glucose tolerance, and diabetes, which are consistent risk factors for pancreatic cancer, are also sources of oxidative stress in humans (26, 27). Cigarette smoke has been shown to alter vitamin E utilization and increase turnover of blood AT concentrations (5, 26). Therefore, smokers may be more susceptible to the consequences of inadequate vitamin E status than nonsmokers. We conducted a prospective cohort analysis of the association between dietary vitamin E and circulating concentrations of AT and incident pancreatic cancer in Finnish male smokers. Our study is the largest prospective study to evaluate these associations because all cohort members had AT measured in baseline serum and 318 incident pancreatic cancer cases occurred during $\leq$19 y of follow-up.

SUBJECTS AND METHODS

Study population

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a randomized, double-blind, placebo-controlled study that used a 2 $\times$ 2 factorial design to determine whether AT and β-carotene (BC) supplementation would reduce the incidence of lung and other cancers in male Finnish smokers. The cohort consisted of 29,133 male Finnish smokers ($\geq$5 cigarettes/d) between 50 and 69 y of age. Subjects were eligible if they were not alcoholics; did not have cirrhosis of the liver, severe angina with exertion, or a history of malignancy other than nonmelanoma skin cancer or carcinoma in situ; were not taking anticoagulant therapy; or had no other medical conditions that would limit participation in the study for 6 y (28). Subjects were excluded if they were taking supplements of vitamin E (>20 mg/d), vitamin A (>20,000 IU/d), or β-carotene (>6 mg/d) at baseline (28). Between 1985 and 1988, eligible participants were randomly assigned to receive supplements of AT (50 mg/d), β-carotene (20 mg/d), AT+BT, or placebo (28). The trial ended 30 April 1993. For this analysis, follow-up of all subjects began at the date of randomization and ended at the date of pancreatic cancer diagnosis, death, or 30 April 2004, whichever came first. Follow-up was up to 19.4 y (median: 16.0 y). Informed consent from each participant was obtained before randomization, and the study was approved by both the Institutional Review Boards of the National Public Health Institute of Finland and the US National Cancer Institute. For this analysis we used 29,092 subjects with complete serum AT and serum cholesterol data or 27,111 subjects with complete dietary data.

Identification of pancreatic cancer cases

The Finnish Cancer Registry was used to identify pancreatic cancer cases (29), who received their information from short forms from the hospitals, physicians, dentists, death certificates from Statistics Finland, and pathologic, cytologic, and hematologic laboratories. The Finnish Cancer Registry provides nearly 100% case ascertainment in Finland and accurately reports 89% of primary pancreatic cancer cases (29). We included incident primary malignant neoplasm of the exocrine pancreas [*International Classification of Diseases, Ninth Revision*, diagnosis code 157 (ICD9-157)] and excluded endocrine tumors (ICD9-157.4) for this analysis. The pancreatic cancer diagnosis was confirmed through central review of all relevant hospital records for cases diagnosed from baseline through April 1999, whereas cases diagnosed after April 1999 were based solely on Finnish Cancer Registry data. Between baseline and 30 April 2004, 318 incident exocrine pancreatic cancer cases were diagnosed among 29,092 cohort participants with complete serum AT and serum cholesterol data. Of the 27,111 cohort participants with complete dietary data, 306 cases were diagnosed with pancreatic cancer.

Data collection

At the prerandomized baseline visit, study participants completed self-administered questionnaires that queried questions about medical and smoking habits (28). A blood sample was also obtained from the study participants after they fasted overnight, and serum was stored at –70°C (28). Diet was assessed with a validated self-administered dietary-history questionnaire, which determined the frequency of consumption and usual portion size of 276 food items during the past year by using a color picture booklet as a guide for portion size (30). The questionnaires were reviewed together with a study nurse. Data from the dietary questionnaire were linked to the National Public Health Institute's food consumption database. The contents of the 8 tocopherols and tocotrienols in Finnish foods were computed (31). Serum AT and total cholesterol were measured in the frozen prerandomization baseline serum samples within 2 y of blood collection. Serum AT was measured by HPLC in 29,102 subjects (28) with a between-run CV of 2.2%. Total cholesterol was measured enzymatically (CHOD-PAP method; Boehringer Mannheim, Mannheim, Germany) from the same baseline blood samples (n = 29,097 subjects) (28).

Statistical analysis

All statistical analyses were performed by using SAS software (version 9.1; SAS Institute, Inc, Cary, NC) software. For the serum analyses, we included 29,092 subjects with complete serum AT and cholesterol concentrations. Within and across quintiles of serum AT (**Table 1**), we calculated means for the continuous population characteristic variables and frequency proportions for categorical variables. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% CIs. Serum AT and dietary tocopherol (α, β, γ, δ) and tocotrienol (α, β, γ, δ) variables were examined in models as both continuous and categorical variables. Continuous variables were standardized to the average size of the 2 central quartiles. Quintile cutoffs for serum AT and tocopherol and tocotrienol intake were based on the distribution in the cohort. Trend tests across the categorical variables used the P value for the continuous risk estimate. All dietary variables were energy adjusted by using the residual method (32). Potential confounders were evaluated by using both forward and backward modeling by individually adding variables to the models. Variables were kept in the model

TABLE 1
Means and proportions of selected characteristics by quintile (Q) of baseline serum α-tocopherol in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort, Finland (n = 29,092; 1985–1988)

	Serum α-tocopherol quintile (mg/L)[1]				
Baseline characteristic	Q1 (<9.3)	Q2 (≥9.3 to <10.8)	Q3 (≥10.8 to <12.2)	Q4 (≥12.2 to <14.2)	Q5 (≥14.2)
Serum α-tocopherol (mg/L)	7.99	10.11	11.50	13.11	16.91
Age (y)	57.78	57.32	57.00	57.06	56.90
Height (cm)	173.30	173.54	173.86	173.56	173.67
BMI (kg/m^2)	25.56	25.97	26.24	26.49	27.13
Total cigarettes smoked (no./d)	21.2	20.6	20.3	20.1	20.0
Total time smoked (y)	36.8	36.3	35.5	35.5	35.6
Education ≥ primary school (%)	15.64	17.94	20.68	23.14	27.76
Medical history, self-report (%)					
Diabetes mellitus	4.15	3.36	3.61	3.71	6.41
Pancreatitis	2.51	1.18	1.19	1.04	1.31
Bronchial asthma	4.27	3.41	2.95	2.37	2.42
Dietary intake[2]					
Energy (kcal/d)	2826	2840	2839	2803	2768
Total fat (g/d)	100.80	101.44	101.17	101.05	100.56
Saturated fat (g/d)	55.60	54.29	52.78	51.30	49.00
Polyunsaturated fat (g/d)	9.82	11.03	11.98	13.06	14.68
Tocopherols					
α-Tocopherol (μg)	8.69	9.59	10.28	11.03	12.24
β-Tocopherol (μg)	0.75	0.82	0.86	0.91	0.98
δ-Tocopherol (μg)	1.05	1.42	1.70	2.06	2.52
γ-Tocopherol (μg)	5.74	7.11	8.15	9.31	10.79
Tocotrienols					
α-Tocotrienol (μg)	1.93	2.00	2.02	2.03	2.03
β-Tocotrienol (μg)	2.41	2.54	2.59	2.63	2.68
δ-Tocotrienol (μg)	0.05	0.07	0.08	0.09	0.11
γ-Tocotrienol (μg)	0.17	0.20	0.22	0.24	0.27
Folate (μg)	326.9	336.4	342.3	346.0	351.4

[1] P values for trends for the selected characteristics across quintiles of serum α-tocopherol were significant ($P < 0.05$), except for height, cigarettes smoked per day, and total fat intake.

[2] Dietary information was available for only 27,074 of the subjects with serum α-tocopherol concentrations. Dietary variables were adjusted for energy intake by using the residual method.

if they were associated with both the disease risk and exposure and changed the risk estimate by 10% or considered putative pancreatic cancer risk factors and associated with pancreatic cancer in the ATBC cohort. Variables that were examined for potential confounding included the following: study intervention; age at randomization; height; weight; body mass index (BMI; in kg/m^2); number of years smoked; cigarettes smoked per day; education level; serum cholesterol; history of pancreatitis, diabetes mellitus, peptic ulcer disease, gallstones, and bronchial asthma; ATBC intervention; and energy, folate, and total, saturated, and polyunsaturated fat intakes. Age at randomization was the only confounder identified. Our final models included baseline age, smoking history (years smoked and number of cigarettes smoked per day), and history of diabetes mellitus. BMI was not associated with pancreatic cancer in the ATBC cohort, so it was not included in the final model (33). The serum AT models were additionally adjusted for serum cholesterol, because both biomarkers were correlated ($r = 0.62$, $P < 0.0001$). A score variable for serum AT based on the median values of each category was created to test for interactions. Effect modification of the serum AT association by age, intervention, polyunsaturated fat intake, alcohol consumption, history of diabetes, and smoking (cigarettes smoked per day, years smoked, and cumulative smoking dose) was evaluated by including cross product terms of the serum AT trend score or continuous variables and the effect modifier (with median split cutoffs) in multivariable models and stratified analyses. We chose a priori to examine whether polyunsaturated fat, a putative prooxidant nutrient, modified the association between serum AT and pancreatic cancer. The assumption of proportional hazards and effect modification by length of follow-up was tested by using a time-dependent interaction term (<10 and ≥10 y), and the analyses were stratified by follow-up time. The P values for all statistical tests were 2-sided, and an α level of 0.05 used to determine statistical significance.

RESULTS

The means and proportions of selected cohort characteristics according to quintiles of serum AT are shown in Table 1. As serum AT increased, BMI, education, the proportion of subjects reporting a history of diabetes, and dietary intake of all the tocopherols and tocotrienols, polyunsaturated fat, and folate increased ($P < 0.05$). In contrast, baseline age, years smoked, the proportion of subjects reporting a history of pancreatitis or bronchial asthma, and dietary intake of energy

TABLE 2
Hazards ratios (HRs) and 95% CIs for pancreatic cancer by quintile (Q) of baseline serum α-tocopherol and dietary vitamin E (tocopherols and tocotrienols) intakes in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, Finland

	Quintiles						
	Q1	Q2	Q3	Q4	Q5	*P* for trend	Continuous HR[1]
Serum α-tocopherol							
Range (mg/L)	<9.3	≥9.3 to <10.8	≥10.8 to <12.2	≥12.2 to <14.2	≥14.2	—	—
Cases/person-years	82/74,098	59/79,946	44/80,899	79/81,158	54/80,517	—	318/396,617
Crude HR (95% CI)	1.00	0.66 (0.47, 0.92)	0.48 (0.33, 0.69)	0.86 (0.63, 1.17)	0.59 (0.42, 0.83)	0.06	0.93 (0.88, 1.00)
Adjusted HR (95% CI)[2]	1.00	0.65 (0.46, 0.91)	0.47 (0.32, 0.69)	0.81 (0.57, 1.14)	0.52 (0.34, 0.80)	0.04	0.91 (0.84, 0.99)
Tocopherol intake							
α-Tocopherol							
Range (μg)	<7.2	≥7.2 to <8.4	≥8.4 to <10.0	≥10.0 to <13.2	≥13.2	—	—
Cases/person-years	60/72,079	64/73,120	67/74,893	60/75,673	55/75,897	—	306/371,663
Crude HR (95% CI)	1.00	1.05 (0.74, 1.49)	1.06 (0.75, 1.50)	0.94 (0.66, 1.34)	0.86 (0.59, 1.23)	0.93	1.00 (0.94, 1.06)
Adjusted HR (95% CI)[3]	1.00	1.03 (0.72, 1.47)	1.07 (0.75, 1.54)	0.96 (0.67, 1.39)	0.87 (0.60, 1.26)	0.94	1.00 (0.95, 1.06)
β-Tocopherol							
Range (μg)	<0.6	≥0.6 to <0.7	≥0.7 to <0.9	≥0.9 to <1.1	≥1.1	—	—
Cases/person-years	60/72,986	59/73,595	60/74,654	65/74,664	62/75,764	—	306/371,663
Crude HR (95% CI)	1.00	0.97 (0.68, 1.40)	0.97 (0.68, 1.39)	1.05 (0.74, 1.49)	0.99 (0.69, 1.41)	1.00	1.00 (0.94, 1.07)
Adjusted HR (95% CI)[3]	1.00	0.95 (0.66, 1.37)	0.95 (0.66, 1.37)	1.03 (0.72, 1.48)	0.98 (0.68, 1.40)	0.99	1.00 (0.94, 1.07)
δ-Tocopherol							
Range (μg)	<0.3	≥0.3 to <0.6	≥0.6 to <1.0	≥1.0 to <3.2	≥3.2	—	—
Cases/person-years	53/73,444	67/72,812	65/74,840	68/75,718	53/74,849	—	306/371,663
Crude HR (95% CI)	1.00	1.28 (0.89, 1.83)	1.20 (0.83, 1.72)	1.23 (0.86, 1.77)	0.97 (0.66, 1.42)	0.73	0.99 (0.94, 1.04)
Adjusted HR (95% CI)[3]	1.00	1.26 (0.86, 1.85)	1.24 (0.83, 1.87)	1.30 (0.87, 1.93)	1.01 (0.68, 1.50)	0.89	1.00 (0.95, 1.05)
γ-Tocopherol							
Range (μg)	<2.8	≥2.8 to <4.9	≥4.9 to <7.5	≥7.5 to <13.1	≥13.1	—	—
Cases/person-years	53/72,116	71/72,744	68/75,228	62/76,150	52/75,424	—	306/371,663
Crude HR (95% CI)	1.00	1.32 (0.93, 1.89)	1.22 (0.85, 1.74)	1.09 (0.75, 1.57)	0.92 (0.63, 1.36)	0.52	0.99 (0.98, 1.01)
Adjusted HR (95% CI)[3]	1.00	1.32 (0.91, 1.92)	1.30 (0.89, 1.89)	1.18 (0.80, 1.72)	0.98 (0.67, 1.45)	0.79	0.99 (0.93, 1.06)
Tocotrienol intake							
α-Tocotrienol							
Range (μg)	<1.3	≥1.3 to <1.7	≥1.7 to <2.1	≥2.1 to <2.6	≥2.6	—	—
Cases/person-years	69/73,784	60/73,895	62/74,636	55/75,019	60/74,330	—	306/371,663
Crude HR (95% CI)	1.00	0.87 (0.61, 1.23)	0.89 (0.63, 1.25)	0.78 (0.55, 1.11)	0.86 (0.61, 1.22)	0.23	0.96 (0.89, 1.02)
Adjusted HR (95% CI)[3]	1.00	0.82 (0.58, 1.16)	0.82 (0.58, 1.16)	0.72 (0.50, 1.03)	0.80 (0.57, 1.14)	0.13	0.94 (0.88, 1.02)
β-Tocotrienol							
Range (μg)	<1.9	≥1.9 to <2.3	≥2.3 to <2.7	≥2.7 to <3.2	≥3.2	—	—
Cases/person-years	62/72,253	51/73,831	70/74,464	70/75,154	53/75,960	—	306/371,663
Crude HR (95% CI)	1.00	0.80 (0.55, 1.16)	1.09 (0.77, 1.53)	1.07 (0.76, 1.51)	0.80 (0.56, 1.16)	0.84	0.99 (0.93, 1.06)
Adjusted HR (95% CI)[3]	1.00	0.77 (0.53, 1.12)	1.04 (0.74, 1.48)	1.03 (0.73, 1.47)	0.79 (0.55, 1.15)	0.81	0.99 (0.92, 1.06)
δ-Tocotrienol							
Range (μg)	<0.02	≥0.02 to <0.04	≥0.04 to <0.06	≥0.06 to <0.13	≥0.13	—	—
Cases/person-years	60/72,462	59/71,831	68/74,426	66/76,941	53/76,002	—	306/371,663
Crude HR (95% CI)	1.00	0.99 (0.69, 1.42)	1.09 (0.77, 1.55)	1.02 (0.72, 1.45)	0.83 (0.57, 1.20)	0.46	0.98 (0.93, 1.03)
Adjusted HR (95% CI)[3]	1.00	0.93 (0.64, 1.36)	1.11 (0.77, 1.61)	1.12 (0.77, 1.62)	0.88 (0.60, 1.29)	0.82	0.99 (0.94, 1.05)
γ-Tocotrienol							
Range (μg)	<0.10	≥0.10 to <0.15	≥0.15 to <0.22	≥0.22 to <0.33	≥0.33	—	—
Cases/person-years	61/72,782	73/71,934	54/74,610	64/76,135	54/76,202	—	306/371,663
Crude HR (95% CI)	1.00	1.21 (0.86, 1.70)	0.86 (0.59, 1.24)	0.99 (0.70, 1.40)	0.83 (0.58, 1.20)	0.48	0.98 (0.91, 1.04)
Adjusted HR (95% CI)[3]	1.00	1.15 (0.81, 1.62)	0.83 (0.57, 1.21)	0.99 (0.69, 1.43)	0.85 (0.58, 1.23)	0.63	0.98 (0.92, 1.05)

[1] Continuous variables were standardized to the average size of the 2 central quartiles. Therefore, this is the HR associated with a 25% change in serum concentrations relative to the cohort distribution. The *P* for trend is based on the *P* value of the continuous risk estimate.

[2] Adjusted for age at the time of randomization, serum cholesterol, smoking history (years smoked and cigarettes smoked per day), and history of diabetes mellitus, (29,092 cohort members with complete serum data; $n = 318$ cases).

[3] Dietary variables were energy-adjusted and adjusted for age at time of randomization, energy intake, smoking history (years smoked and cigarettes smoked per day), and history of diabetes mellitus (27,111 cohort members with complete dietary data; $n = 306$ cases).

and saturated fat were inversely associated with serum AT ($P < 0.05$). Compared with noncases, cases were older, had smoked for more years, more often had a history of diabetes mellitus, and had a higher intake of total and saturated fat ($P < 0.05$; data not shown).

After adjustment for age, smoking, serum cholesterol, and history of diabetes mellitus, men with the highest concentrations of serum AT had a 48% reduction in pancreatic cancer risk (quintile 5 compared with quintile 1, HR: 0.52; 95% CI: 0.34, 0.80; *P* for trend = 0.04; **Table 2**) and a 9% reduction in risk per

25% change in serum AT (HR: 0.91; 95% CI: 0.84, 0.99; $P = 0.04$). The associations for serum AT were similar for a 2-y lag analysis (quintile 5 compared with quintile 1, $n = 294$ cases; HR: 0.52; 95% CI: 0.34, 0.81: P for trend $= 0.04$; continuous HR: 0.91; 95% CI: 0.83, 1.00). Approximately 55% of the pancreatic cancer cases were documented as being histologically confirmed. The risks of the histologically confirmed (quintile 5 compared with quintile 1, $n = 174$; HR: 0.49; 95% CI: 0.28, 0.86; P for trend $= 0.24$; continuous HR: 0.94; 95% CI: 0.83, 1.04) and nonconfirmed (quintile 5 compared with quintile 1, $n = 144$; HR: 0.55; 95% CI: 0.29, 1.08; P for trend $= 0.07$; continuous HR: 0.88; 95% CI: 0.77, 1.01) pancreatic cancer cases were similar. No significant associations of pancreatic cancer with intake of tocopherols or tocotrienols were observed.

Polyunsaturated fat intake significantly modified the association between serum AT and pancreatic cancer (**Table 3**; P for interaction ≤ 0.05), such that significant inverse associations were most pronounced in subjects with a high polyunsaturated fat intake. Baseline serum AT was inversely associated with pancreatic cancer in all the intervention groups except the AT+BC group (**Table 4**; P for interaction $= 0.25$ for the categorical test and 0.02 for the continuous test), and no significant interaction of the association by AT compared with no AT was observed. There were no significant interactions of serum AT and pancreas cancer risk by history of diabetes mellitus, smoking habits, alcohol consumption, age, or follow-up time (P for interaction > 0.05).

DISCUSSION

We found that, relative to lower concentrations, higher prediagnostic serum AT concentrations were associated with a significant 48% reduction in incident exocrine pancreatic cancer risk, but no associations were observed for dietary intakes of tocopherols or tocotrienols in a cohort of male smokers. In addition, the inverse serum AT association was more pronounced in men with a high polyunsaturated fat intake than in those with a low intake.

The significant interaction that we observe between serum AT and pancreatic cancer by polyunsaturated fat intake is consistent with animal studies. Rodent models that examined the association between AT and pancreatic cancer showed that AT administration inhibits pancreatic carcinogenesis and metastasis when animals are fed diets high in polyunsaturated fat (21% of energy from soybean oil) (11–13), but not when fed diets high in saturated fat (20% of energy from lard) (14, 15). The different results for AT between the 2 models could be explained by the fact that polyunsaturated fats are putative prooxidants. Polyunsaturated fat has been shown to promote pancreatic cancer in rodents (34–36), although most epidemiologic studies, including the ATBC Study, have not shown significant associations between polyunsaturated fat intake and pancreatic cancer (16). The primary antioxidant function of vitamin E is to prevent cellular damage by quenching free radicals formed from polyunsaturated fatty acids reacting with oxygen in lipid membranes (5). Animals fed diets high in polyunsaturated fat may be more susceptible to the effects of lipid peroxidation and, consequently, AT administration is more effective. In particular, in *N*-nitrosobis-2-oxypropylamine–induced pancreatic cancer in Syrian hamsters fed diets high in polyunsaturated fat, AT inhibited preneoplastic pancreatic lesions (11), decreased the incidence of liver metastasis (11, 12), and increased glutathione peroxidase (12) and superoxide dismutase activity in pancreatic carcinomas (12, 13). The authors of these animal experiments hypothesized that the protection may have been mediated by the lipid peroxidation–preventive effects of AT and the accumulation of hydrogen peroxides in pancreatic tissue (13). There is also evidence that AT requirements may be greater with high polyunsaturated fat

TABLE 3
Hazard ratios (HRs) and 95% CIs for pancreatic cancer based on baseline serum α-tocopherol by polyunsaturated fat intake in male smokers[1]

			HR (95% CI)			
	No. of cases	Person-years	Joint effect	Stratified effect	*P* for trend	*P* for interaction
High polyunsaturated fat intake, >9.9 g/d						
Quintile of serum α-tocopherol						
<9.4 mg/L	30	22,332	1.00 (reference)	1.00 (reference)		0.05
≥9.4 to <10.8 mg/L	26	32,278	0.59 (0.35, 1.00)	0.61 (0.36, 1.04)		
≥10.8 to <12.2 mg/L	22	38,889	0.40 (0.23, 0.70)	0.42 (0.24, 0.75)		
≥12.2 to <14.2 mg/L	47	43,775	0.71 (0.43, 1.16)	0.78 (0.46, 1.32)		
≥14.2 mg/L	28	51,599	0.32 (0.18, 0.58)	0.38 (0.20, 0.73)		
Continuous HR[2]	153	188,877	—	0.86 (0.75, 0.97)	0.02	0.02
Low polyunsaturated fat intake, ≤9.9 g/d						
Quintile of serum α-tocopherol						
<9.4 mg/L	47	46,799	0.70 (0.44, 1.12)	1.00 (reference)		
≥9.4 to <10.8 mg/L	31	42,334	0.49 (0.29, 0.82)	0.66 (0.42, 1.06)		
≥10.8 to <12.2 mg/L	21	27,208	0.36 (0.20, 0.64)	0.47 (0.27, 0.81)		
≥12.2 to <14.2 mg/L	30	32,100	0.57 (0.32, 1.00)	0.72 (0.42, 1.24)		
≥14.2 mg/L	24	23,906	0.57 (0.31, 1.08)	0.69 (0.37, 1.29)		
Continuous HR[2]	153	182,347	—	0.97 (0.85, 1.10)	0.64	

[1] Stratified analysis is based on median split cutoffs of energy-adjusted polyunsaturated fat intake. HRs were adjusted for age at randomization, serum cholesterol, smoking history (years smoked and cigarettes smoked per day), history of diabetes mellitus, and energy intake (27,074 subjects with complete serum and dietary data; $n = 306$ cases). P for interaction $= 0.05$ for categorical stratified analysis.

[2] Continuous variables were standardized to the average size of the 2 central quartiles. Therefore, this is the HR associated with a 25% change in serum concentrations relative to the cohort distribution. P for interaction $= 0.02$. The P for trend is based on the P value of the continuous risk estimate.

TABLE 4
Hazard ratios (HRs) and 95% CIs for pancreatic cancer based on baseline serum α-tocopherol by study intervention in male smokers[1]

Intervention and baseline serum α-tocopherol	No. of cases	Person-years	HR (95% CI)		*P* for trend	*P* for interaction
			Joint effect	Stratified effect		
Placebo						
<9.7 μg/L	29	23,408	1.00 (reference)	1.00 (reference)		0.25
≥9.7 to <11.5 μg/L	12	26,414	0.36 (0.18, 0.71)	0.38 (0.19, 0.76)		
≥11.5 to <13.6 μg/L	23	25,972	0.70 (0.40, 1.23)	0.78 (0.42, 1.44)		
≥13.6 μg/L	18	24,497	0.56 (0.30, 1.05)	0.67 (0.32, 1.40)		
Continuous HR[2]	82	100,291	—	0.87 (0.72, 1.05)	0.13	0.02
β-Carotene only						
<9.7 μg/L	22	23,262	0.76 (0.44, 1.36)	1.00 (reference)		
≥9.7 to <11.5 μg/L	16	24,513	0.52 (0.28, 0.97)	0.62 (0.32, 1.20)		
≥11.5 to <13.6 μg/L	10	25,019	0.31 (0.15, 0.65)	0.34 (0.15, 0.76)		
≥13.6 μg/L	17	25,603	0.49 (0.26, 0.92)	0.46 (0.21, 1.03)		
Continuous HR[2]	65	98,397	—	0.79 (0.65, 0.97)	0.03	
α-Tocopherol only						
<9.7 μg/L	29	24,233	0.96 (0.57, 1.61)	1.00 (reference)		
≥9.7 to <11.5 μg/L	17	24,654	0.55 (0.30, 1.00)	0.58 (0.31, 1.07)		
≥11.5 to <13.6 μg/L	24	25,361	0.74 (0.43, 1.30)	0.79 (0.44, 1.42)		
≥13.6 μg/L	25	25,350	0.73 (0.41, 1.30)	0.78 (0.40, 1.52)		
Continuous HR[2]	95	99,599	—	0.87 (0.74, 1.02)	0.09	
α-Tocopherol and β-carotene						
<9.7 μg/L	20	22,545	0.71 (0.40, 1.25)	1.00 (reference)		
≥9.7 to <11.5 μg/L	16	24,548	0.52 (0.28, 0.96)	0.75 (0.38, 1.47)		
≥11.5 to <13.6 μg/L	17	25,858	0.50 (0.27, 0.93)	0.72 (0.36, 1.46)		
≥13.6 μg/L	23	25,380	0.68 (0.38, 1.22)	0.99 (0.47–2.09)		
Continuous HR[2]	76	98,330	—	1.10 (0.95, 1.27)	0.20	
No α-tocopherol						
<9.4 μg/L	43	37,013	1.00 (reference)	1.00 (reference)		0.26
≥9.4 to <10.8 μg/L	28	40,578	0.57 (0.35, 0.92)	0.56 (0.35, 0.92)		
≥10.8 to <12.2 μg/L	17	40,927	0.34 (0.19, 0.60)	0.33 (0.18, 0.59)		
≥12.2 to <14.2 μg/L	36	40,198	0.71 (0.44, 1.14)	0.69 (0.41, 1.14)		
≥14.2 μg/L	23	39,972	0.42 (0.24, 0.74)	0.40 (0.22, 0.77)		
Continuous HR[2]	147	198,688	—	0.83 (0.73, 0.96)	0.009	0.10
α-Tocopherol						
<9.4 μg/L	39	37,085	0.89 (0.58, 1.37)	1.00 (reference)		
≥9.4 to <10.8 μg/L	31	39,368	0.66 (0.41, 1.05)	0.75 (0.46, 1.20)		
≥10.8 to <12.2 μg/L	27	39,972	0.55 (0.33, 0.90)	0.63 (0.37, 1.05)		
≥12.2 to <14.2 μg/L	43	40,960	0.80 (0.51, 1.27)	0.93 (0.57, 1.52)		
≥14.2 μg/L	31	40,544	0.56 (0.33, 0.95)	0.66 (0.37, 1.17)		
Continuous HR[2]	171	197,929	—	0.98 (0.88, 1.09)	0.68	

[1] Stratified analysis is based on study intervention group. HRs were adjusted for age at randomization, serum cholesterol, smoking history (years smoked and cigarettes smoked per day), and history of diabetes mellitus. For the categorical interactions, the 2 × 2 factorial group *P* for interaction = 0.25, and the α-tocopherol compared with α-tocopherol intervention *P* for interaction = 0.26.

[2] Continuous variables were standardized to the average size of the 2 central quartiles. Therefore, this is the HR associated with a 25% change in serum concentrations relative to the cohort distribution. The *P* for trend is based on the *P* value of the continuous risk estimate. For the continuous interactions, the 2 × 2 factorial group *P* for interaction = 0.02, and the α-tocopherol compared with no α-tocopherol intervention *P* for interaction = 0.10.

intakes in humans (37). The results of these experimental studies and our finding that significant inverse associations between serum AT and pancreatic cancer were most pronounced in subjects with a high polyunsaturated fat intake may reinforce the biological plausibility that AT potentially plays a role in pancreatic cancer carcinogenesis.

The inverse association that we observed between serum AT and pancreatic cancer is stronger than that for the dietary intake of vitamin E and the AT trial supplement in the ATBC Study (22). As with all dietary intake studies, dietary intakes determined from a food-frequency questionnaire are not precise. Therefore, measurement error related to dietary assessment and the vitamin E nutrient database was likely and may have contributed to inaccurate risk estimates and attenuated associations between tocopherol and tocotrienol intakes and pancreatic cancer. Serum concentrations may be more biologically meaningful than dietary intake estimates because they are more accurately measured and reflect nutritional status and the combined effects of intake, absorption, and utilization as well as the effect of oxidative stress (eg, from cigarette smoke) on the depletion of serum and tissue sources (26, 38). In particular, smokers have a high uptake and subsequent turnover of antioxidants (26, 38). The Spearman correlation coefficients for serum AT and AT intake in the ATBC population was 0.24 ($P < 0.0001$) and was similar to that of other studies (39). Supplementation with AT during the randomized ATBC Study resulted in little or no effect

on pancreatic cancer rates: a 4% reduction for AT alone (95% CI: −44, 67%) and 0% change (95% CI: −48, 73%) for AT+BC compared with the placebo group (22). In contrast, men who received only the BC supplement had significantly lower pancreatic cancer rates (−54%; 95% CI: −77, −8%) (22). It is the latter finding that accounted for an apparent nonsignificantly higher risk in the overall AT group (AT alone and AT+BC compared with BC alone and placebo: 34%; 95% CI: −12, 105%) (22). Pancreatic cancer was not the primary endpoint of the trial, and with only 89 participants developing pancreatic cancer during the 6-y intervention period, the test of this hypothesis was underpowered (22). In stratified analyses, serum AT was inversely associated with pancreatic cancer in all of the intervention groups except the AT+BC group. Care needs to be taken to not overinterpret this interaction given the relatively small number of cases within each randomization group and the fact that most of our cases occurred during the posttrial follow-up of the ATBC Study. The beneficial and adverse effects of AT and BC disappeared for all cancers during the postintervention follow-up (40).

Several epidemiologic studies have examined serum AT or vitamin E intake and pancreatic cancer; however, most included relatively few pancreatic cancer cases. Two previous prospective nested case-control studies (18–20, 41) examined the relation of serum AT to pancreatic cancer. The first, conducted in Washington County, MD, measured prediagnostic serum AT in 22 cases and 44 matched controls during 9 y of follow-up and showed no association (18, 19). The second, conducted in Finland, also used prediagnostic serum from 28 cases (17 men, 11 women) that developed during an average follow-up of 8 y (20, 41). A significant 4.8–6.8-fold increased risk was observed for the 3 lowest compared with the 2 highest quintiles of AT, particularly among men (20, 41). A large case-control study (n = 451 cases, 1552 matched controls) in Shanghai, China, observed significant inverse associations between vitamin E intake and pancreatic cancer in men (high compared with low quartile, odds ratio: 0.57; 95% CI: 0.35, 0.93; P for trend = 0.006) but not in women (17).

The strengths of our study included its prospective nature, with AT status assessed up to 19 y before cancer diagnosis. Baseline AT was measured in all cohort members, and the number of pancreatic cancer cases was larger than in previous prospective studies. Serum cholesterol was also measured in all ATBC Study participants, which enabled us to adjust for blood lipids in our analyses (39). Because the cases arose from the larger cohort, our study had internal validity and there was no survival bias of cases or selection bias of controls. Our findings in smokers, however, may not be generalizable to populations that include nonsmokers and women. In particular, the association between serum AT and pancreatic cancer may be different in populations not exposed to factors that induce oxidative stress, such as cigarette smoke (26, 27). Residual confounding by cigarette smoking was possible but unlikely because all subjects were current smokers at baseline, self-reported current smoking is highly accurate in adults (42–44), and the smoking exposures were not confounders or effect modifiers of the AT association. In addition, the inverse association between serum AT and pancreatic cancer remained (quintile 5 compared with quintile 1, n = 87 cases; HR: 0.38; 95% CI: 0.17, 0.84; P for trend = 0.11) when our analysis was restricted to only men who reported smoking exactly 20 cigarettes/d. A single measurement of AT may not reflect long-term exposure, and, over time, subjects could have changed their intake of vitamin E–containing foods or altered other behaviors that could influence vitamin E status and potentially contribute to inaccurate risk estimates with extended follow-up. However, a single measurement can reflect intake over several weeks, and within-person variability studies support it exhibiting long-term stability with diet over 4–6 y (39, 45). Finally, we cannot exclude the possibility that a dietary correlate to serum AT that is not controlled, particularly another tocopherol, could explain the association we observed.

In conclusion, our results support the hypothesis that higher concentrations of serum AT may protect against pancreatic carcinogenesis in smokers. Further research is needed to evaluate our findings in other populations, particularly relative to exposure factors that influence endogenous oxidative stress.

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