Published in final edited form as:
Int J Cancer. 2008 September 1; 123(5): 1173–1180. doi:10.1002/ijc.23649.

Dietary α-, β-, γ- and δ-tocopherols in lung cancer risk

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Abstract

Studies of vitamin E and cancer have focused on the α-tocopherol form of the vitamin. However, other forms of vitamin E, in particular γ-tocopherol may have unique mechanistic characteristics relevant to lung cancer prevention. In an ongoing study of 1,088 incident lung cancer cases and 1,414 healthy matched controls, we studied the associations between 4 tocopherols (α-, β-, γ-, and δ-tocopherol) in the diet and lung cancer risk. Using multiple logistic regression analysis, the adjusted odds ratios (OR) and 95% confidence intervals (CI) of lung cancer for increasing quartiles of dietary α-tocopherol intake were 1.0, 0.63 (0.50–0.79), 0.58 (0.44–0.76) and 0.39 (0.28–0.53), respectively (p-trend < 0.0001). For dietary intake of β-tocopherol, the OR and 95% CI for all subjects were: 1.0, 0.79 (0.63–0.98), 0.59 (0.45–0.78) and 0.56 (0.42–0.74), respectively (p-trend < 0.0001). Similar results for dietary γ-tocopherol intake were observed: 1.0, 0.84 (0.67–1.06), 0.76 (0.59–0.97) and 0.56 (0.42–0.75), respectively (p- trend = 0.0002). No significant association between δ-tocopherol intake and lung cancer risk was detected. When the 4 tocopherols were summed as total tocopherol intake, a monotonic risk reduction was also observed. When we entered the other tocopherols in our model, only the association with dietary α-tocopherol intake remained significant; *i.e.*, increasing intake of dietary α-tocopherol accounted for 34–53% reductions in lung cancer risk. To the best of our knowledge, this is the first report of the independent associations of the 4 forms of dietary tocopherol (α-, β-, γ- and δ-tocohperol) on lung cancer risk. Given the limitations with case-control studies, these findings need to be confirmed in further investigations.

Keywords

dietary tocopherols; lung cancer risk; diet and lung cancer; vitamin E and lung cancer

Vitamin E is not a single nutrient, but a group of compounds which consists of 4 tocopherol isomers (α-, β-, γ- and δ-tocopherol) and 4 tocotrienol isomers (α-, β-, γ- and δ-tocotrienol), and functions as a lipophilic antioxidant that prevents lipid peroxidation.[1] Of all the natural isomeric forms of vitamin E, α-tocopherol has been the most extensively studied, probably because it is the most predominant form in plasma and tissues. In addition, the prevailing view has been that except for α-tocopherol, the other tocopherols do not contribute towards meeting vitamin E requirements, because although absorbed by humans, they are not converted to α-tocopherol and are poorly recognized by the α-tocopherol transfer protein (αTTP) in the liver.[2] However, while αTTP exhibits preferential affinity for α-tocopherol, there is now convincing evidence that αTTP interacts with both α- and γ-

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tocopherols as αTTP-null mice exhibit proportional decreases in both plasma α- and γ-tocopherols.[3]

While the different tocopherols have relatively similar antioxidant potency,[1] evidence is emerging that forms of vitamin E-like γ-tocopherol may have unique mechanistic characteristics not possessed by α-tocopherol, such as antiinflammatory activities, including inhibition of cyclooxygenase activity,[4] which are potentially relevant in lung cancer prevention. In addition, γ-tocopherol, unlike α-tocopherol, has been reported to inhibit proliferation of lung cancer cells.[5] However, to date, epidemiologic studies of vitamin E and lung cancer have focused only on the α-tocopherol form of vitamin E.

γ-tocopherol is an important form of vitamin E in the U.S. diet. Vegetable oils made from corn, soybean, and sesame are rich sources of γ-tocopherol, as are walnuts, pecans and peanuts. Therefore, in addition to α-tocopherol, the other forms of vitamin E deserve more research attention. Because of the antioxidant activities of the different tocopherols[1] and their potential importance in host defense against the initiation and progression of cancer, we hypothesized that dietary intake of α-, β-, γ- and δ-tocopherols would be protective against lung cancer. We therefore investigated the associations between α-, β-, γ- and δ-tocopherol intakes and risk of lung cancer in a large ongoing lung cancer case control study.

Material and methods

Study population

Our study population is comprised of 1,088 patients with lung cancer (cases) and 1,414 healthy controls who were frequency matched to the cases by age (±5 years) and smoking status (never, former and current) in an ongoing and previously described case–control study of lung cancer.[6] Newly diagnosed cases with histologically confirmed lung cancer were recruited prior to radiotherapy or chemotherapy from The University of Texas M.D. Anderson Cancer Center, Houston. There was no age, gender, ethnic or stage restrictions. Healthy controls without a previous diagnosis of cancer were recruited from the Kelsey–Seybold clinics, Houston's largest private multispecialty physician group of 23 clinics. All participants were U.S. residents. To date, the overall response rate among both the case patients and the control subjects has been approximately 75%. The study started in July 1995 and is still actively enrolling participants. This research was approved by both M.D. Anderson Cancer Center and Kelsey–Seybold Institutional Review Boards.

Epidemiologic and dietary data

Trained staff administered an extensive interview to all participants to obtain information on demographic factors and smoking history. Individuals who had smoked at least 100 cigarettes in their lifetimes were classified as ever-smokers; of those, former smokers had quit smoking at least 1 year before diagnosis (cases) or before the interview (controls). Individuals who smoked <100 cigarettes were classified as never smokers. Race/ethnicity information (white, Hispanic, African American) was self-reported. Subjects who reported drinking alcohol in amounts ranging from 0.1–15 g/d and >15 g/d were categorized as light and moderate-heavy drinkers, respectively. History of emphysema was based on the subject self-reporting a physician's diagnosis of emphysema. Body mass index (BMI) was estimated from self-reported weight (prior to diagnosis in patients) and height, and calculated as weight (kg) divided by height (m^2). Family history of cancer was defined as a first-degree relative ever being diagnosed with cancer.

Dietary data were collected from a modified version of the 135-item National Cancer Institute's Health Habits and History Questionnaire [HHHQ]) Food Frequency Questionnaire. The HHHQ includes a semi-quantitative food frequency list, an open-ended

food section, and other dietary-behavior questions pertaining to dining at restaurants and food preparation methods. The questionnaire has been shown to be a valid and reliable tool across various populations.[7,8] Study participants were asked about their diet during the year prior to diagnosis (cases) or the year prior to study enrollment (controls). Trained interviewers administered the food frequency questionnaires and registered dietitians reviewed them for completeness and outliers. Nutrient intake was calculated using the DIETSYS + Plus version 5.9 dietary analysis program (Block Dietary Data Systems, Berkeley, CA). We used SR-19, which, for the first time, has analytical values for α-, β-, γ- and δ-tocopherol. The SR-19 database is maintained by the US Department of Agriculture, Agricultural Research Service. For multiing-redient food items not available in SR19, nutrient values were derived from appropriate recipes from the Continuing Survey of Food Intakes by Individuals, 1994–96, 1998. Recipe adjustments were made, where required, for moisture changes and nutrient loss due to cooking.

Statistical analysis

Pearson's χ^2 test was used to compare the differences between patients and control subjects by gender, ethnicity, education, supplement and alcohol use, emphysema, and smoking status. Student's *t* test was calculated to compare differences in the mean age, smoking duration, number of cigarettes smoked per day, BMI (weight [kg]/height [m^2]), total energy intake, and dietary intakes of nutrients, such α-, γ-, β- and δ-tocopherol between cases and controls. In this study population, we included only individuals who fell within the cutoff points for reasonable caloric intake (ranging from 800–4,200 kcal for men and 600–3,500 kcal for women) per the method of Zhou et al.[9] Among 1,143 cases and 1,534 controls with complete dietary data, only 55 (4.8%) cases and 120 (7.8%) controls were excluded using the above mentioned gender-specific cut-offs for total energy intake.

Quartiles of α-, β-, γ- and δ-tocopherol intake (both crude and energy-adjusted) were based on distributions of dietary intake in control subjects. Energy-adjusted tocopherol quartiles were calculated by regressing dietary tocopherol intake on total calories and obtaining the residuals per the method of Willett and Stampher.[10] The residual value for each observation was then added to the mean dietary tocopherol value for our population.

Multiple logistic regression analysis was performed to calculate odds ratios (ORs) and 95% confidence intervals for associations between dietary α-, β-, γ- and δ-tocopherol and the risk of lung cancer, adjusting for age, gender, ethnicity, education, BMI, alcohol consumption (continuous), total calories (excluding alcohol calories), smoking duration, number of cigarettes smoked per day and family history of cancer in the first-degree relatives. The first quartile (lowest intake) was considered the referent category. Variables were included in the logistic regression models based on a priori knowledge of risk factors for lung cancer, and hence as potential confounders of the association between dietary tocopherols and lung cancer. Total calories were included in the models because they correlate with α-, β-, γ- and δ-tocopherol intake ($p < 0.0001$) and also because food sources of the tocopherols, such as many plant seeds, are energy-rich; the advantage of this model is that the full effects of total caloric intake can be observed.[10] We tested for trends in diet-lung cancer associations by treating dietary data as an ordinal variable using the Wald test.

Potential interactions between intakes of α-, β-, γ- and δ-tocopherols and lung cancer risk factors (for example, age, BMI, pack years) were tested on the multiplicative scale by entering the cross-product terms in the main effects multivariate models. We also conducted sub-group analyses defined by age, BMI (kg/m^2), smoking status (current, former and never smokers), alcohol (non-drinkers and drinkers), years of smoking, number of cigarettes smoked per day, vitamin/mineral supplement use (yes and no), history of cancer in first-degree relatives, lung cancer stage, and histology. BMI was stratified as ≤25 or >25 since a

number of studies have reported that BMI >25 is associated with reduced risk of lung cancer.[11–13] Years of smoking were dichotomized at the median-split (≤31 or >31) in the controls. Cigarettes smoked per day were dichotomized at ≤1 pack of cigarettes/day (≤20 cigarettes) or >1 pack of cigarettes per day (>20 cigarettes). Early stage lung cancers were defined as cases with stage I and II non-small cell lung cancer (NSCLC) and limited for small cell lung cancer. Late stage was defined as stages III and IV for NSCLC and extensive for small cell lung cancer. Lung cancer histology was categorized as adenocarcinoma, squamous cell carcinoma, nonsmall cell cancer (NSCLC) and small cell cancer.

We also computed Pearson and Spearman rank correlation coefficients in the control population between daily intakes of dietary α-, β-, γ- and δ-tocopherol. Therefore, in addition to estimating ORs from the models for α-, β-, γ- and δ-tocopherol, we constructed a second model for each tocopherol that included the other 3 tocopherols as covariates (model 2). Finally, we adjusted for vitamin C intake in our models because of the recognized redox relations between the tocopherols and vitamin C in endogenous oxidative stress.[14] The top food sources for α-, β-, γ- and δ-tocopherol were calculated by the DIETSYS + Plus dietary analysis program. We also computed adjusted odds ratios for food contributors of tocopherol intake and lung cancer risk. Statistical analyses were performed with SAS (version 8.0; SAS Institute, Cary, NC). All statistical tests were two-sided, and a *p*-value of less than 0.05 was considered statistically significant.

Results

Population characteristics (Table I)

Among 1,088 patients with lung cancer and 1,414 age-matched controls, mean ages of the cases and controls were 61.67 and 60.83 ($p = 0.05$), and well within the 5-year age matching criterion. Cases and controls did not differ by smoking status, the other matching criterion, although cases compared to controls reported a longer duration of smoking among both former ($p < 0.001$) and current smokers ($p = 0.01$). Further, cases who were current smokers, smoked more cigarettes per day than controls ($p < 0.0001$). Most (about 76–77%) of the cases and controls were Caucasians. Overall, controls were better educated than cases; more controls than cases had college and graduate level education. Cases also had a lower BMI than controls (26.69 *vs.* 28.47, $p < 0.01$). More controls than cases were users of multivitamin/mineral supplements and drank alcohol. More cases had a diagnosis of emphysema than controls. Compared with cases, controls had higher total caloric intake ($p < 0.01$), as well as higher intakes of α-($p < 0.01$), β-($p < 0.01$), γ-($p < 0.01$) and δ-tocopherol ($p < 0.01$), and therefore total tocopherol intake ($p < 0.0001$) across the total population, and in men and women separately.

Tocopherols and lung cancer risk (Table II)

The correlations between α-tocopherol and the other tocopherols were as follows: β-tocopherol ($r = 0.6$; $p < 0.001$), γ-tocopherol ($r = 0.5$; $p < 0.001$) and δ-tocopherol ($r = 0.3$; $p < 0.001$). When dietary intakes of α-, β-, γ- and δ-tocopherol were analyzed separately (Table I, model 1), increasing intakes of α-, β- and γ-tocopherol, but not δ-tocopherol, were associated with lower risk of lung cancer. With model 1, intakes of α-, β-, γ- and total tocopherols were inversely associated in a monotonic fashion with lung cancer risk. With increasing quartiles of intake, there were 37, 42 and 61% reductions in risk for α-tocopherol (*p*-trend < 0.0001); a 21, 41 and 44% reductions in risk for β-tocopherol (*p*-trend <0.0001); and a 16, 24 and 44% reductions in risk for γ-tocopherol (*p*-trend < 0.0002). The trend was borderline significant for δ-tocopherol ($p = 0.07$). For total tocopherols, the pattern was a 28, 37 and 55% reduction in risk for lung cancer by increasing quartile of intake ($p < 0.0001$). In model 2, for which the association of a specific tocopherol was adjusted for all the other

tocopherols, only the α-tocopherol association remained significant, with a monotonically decreasing 34, 36 and 53% reduction in lung cancer risk. Because vitamin C (ascorbic acid) is a major water-soluble antioxidant (reductant) in the cytosol that generates reduced vitamin E,[14] and also because in the current analysis, increased intake of vitamin C was associated with reduced lung cancer risk (data not shown), we constructed a third model (model 3) that included vitamin C. As shown in Table II, model 3 did not affect the magnitude or direction of the associations compared to model 1.

Stratified analysis (Table III)

In this section, only subgroup analyses for dietary α-tocopherol (models 1 and 2) are presented because we did not find independent associations for β-, γ- and δ-tocopherol intake in lung cancer risk using model 2 (Table II). In Table III, only data for those variables from stratified analyses that demonstrated a significant interaction with α-tocopherol in the multivariate model are presented.

In gender-specific analysis, for both models 1 and 2, increasing intakes of α-tocopherol were associated with significant trends for risk reduction. The associations were slightly more pronounced in women than men. Using the conservative model 2, the highest intake of α-tocopherol was associated with a 63 and 42% reduction in lung cancer risk in women and in men, respectively (data not shown).

A significant inverse trend for dietary α-tocopherol intake and lung cancer was observed in both age strata (Table III). Compared to those in the lowest quartile of intake, those in the highest quartile of dietary α-tocopherol intake had 47 and 54% reduced risks in younger and older subjects, respectively.

A significant inverse trend ($p < 0.05$) was evident among subjects in both BMI strata; lean subjects had 55, 55 and 69% reductions in risk for the second, third, and fourth quartiles of dietary α-tocopherol intake, respectively, whereas heavier subjects had 28, 25 and 45% reductions in lung cancer risk (data not shown).

In model 1, the protective effect of dietary α-tocopherol intake was observed across smoking strata; however, with model 2, the inverse trends for dietary α-tocopherol intake remained significant only among former and current smokers. A more pronounced risk reduction was seen in current smokers, for whom the highest compared to the lowest quartile of dietary α-tocopherol intake was associated with a 67% reduced risk. When stratified by duration of smoking, increasing intake of dietary α-tocopherol was more protective for participants with longer years of smoking. With model 2, those who smoked >31 years had a 70% reduction, whereas those who smoked ≤31 years had only a 39% risk reduction. Similar findings were observed when the data were stratified by number of cigarettes smoked per day (≤20 or >20 per day).

Dietary α-tocopherol intake was inversely associated with risk among both users and nonusers of vitamin/mineral supplements. The highest quartile of α-tocopherol intake was associated with a 42% reduced risk among users and a 60% reduction in risk in non-users. The inverse protective trend associated with higher levels of dietary α-tocopherol was significant ($p < 0.0001$) only in those who did not report physician-diagnosed emphysema history. There was no difference in the α-tocopherol-lung cancer association when stratified by family history of cancer, nor by early or late stage (data not shown). The following risk reductions were observed in the highest quartile of α-tocopherol intake: 46–53% for adenocarcinoma, 51–63% for squamous cell, 72–75% for non-small cell lung cancer (NSCLC) and 65–79% for small cell lung cancer.

Top food contributors

In our population, no single foods were major contributors to α-tocopherol intake, but several foods contributed small amounts of this nutrient in the diet. Peanut butter and salad dressings collectively provided 13–19% of α-tocopherol intake in the diet. 41–43% of β-tocopherol was derived from intakes of peanut butter, cookies, mayonnaise and sunflower seeds. Intakes of cookies, fried potatoes, reduced fat mayonnaise and chocolate candies contributed 61–69% of δ-tocopherols, while cookies, mayonnaise, chocolate candies and peanut butter or peanuts contributed 54–57% of γ-tocopherols. The tocopherols were also ubiquitous in several fruit and vegetables. When dietary intakes of specific food contributors of tocopherols were analyzed (Table IV, model 1), increasing intakes of peanut butter, salad dressing and total fruit and vegetables were associated with lower risk of lung cancer.

Discussion

To the best of our knowledge, this is the first study to compare dietary intakes of the different forms of tocopherols (α-, β-, γ-and δ-tocopherol) and lung cancer risk. Our principal findings were that, after accounting for the other forms of tocopherols and vitamin C intake, there was a strong inverse relationship between dietary α-tocopherol and lung cancer risk. To the extent possible, as explained in the methods, we have addressed the scientific validity of these findings because our models addressed the inter-correlations between the tocopherols and total calories.

Much of the research on vitamin E and lung cancer has centered on the role of α-tocopherol. The α-tocopherol, beta-carotene (ATBC) trial examined the effect of α-tocopherol (synthetic dl-α-tocopheryl acetate) or synthetic β-carotene on lung cancer incidence among 29,133 Finnish male smokers aged 50–69 years. After 5 to 8 years (median, 6.1 years), lung cancer incidence did not differ in the α-tocopherol compared to the placebo group.[15]

Several prospective cohort studies of dietary α-tocopherol and lung cancer risk have been published. The New York State cohort (n = 395 cases),[16] Netherlands cohort (n = 939 cases),[17] Finnish cohort (n = 117 cases),[18] NHANES 1 Follow-up (n = 248 cases),[19] Singapore Chinese Health cohort (n = 482 cases)[20] and the Nurses Health Cohort (n = 593 cases)[21] studies all reported nonsignificant reductions in lung cancer risk with increasing intake of dietary α-tocopherol. In a recent pooled analysis, vitamin E from foods was inversely associated with lung cancer risk, but the trend was also not statistically significant.[22]

Of 4 prospective studies[23–26] that assessed serum α-tocopherol levels and lung cancer risk, two[23,24] reported significant inverse association. In the ATBC trial of male smokers, a significant 19% reduction in lung cancer risk was observed among men who were in the highest *versus* lowest quintile of α-tocopherol concentrations at baseline.[23] In a nested case-control study within the Beta-Carotene and Retinol Efficacy Trial (CARET), a significant 48% reduction in lung cancer risk was observed in highest *versus* lowest quartile of α-tocopherol concentrations.[24] Yet in a nested case–control study[26] within the Japanese Collaborative cohort and the Yunnan Tin Miners prospective study,[25] no association was observed between serum α-tocopherol levels at baseline and lung cancer risk. Of the 3 studies[24–26] that described serum γ-tocopherol levels, none reported a significant association. The range in serum tocopherol levels varied across studies, and the studies with small range (for e.g., the Yunnan Tin Miners study[25]) may not have had the ability to detect a significant relationship.

Overall, the epidemiologic evidence to date suggests that low levels of both dietary and serum α-tocopherol may predispose to lung cancer risk. However, comparability of these

epidemiologic analyses may have been limited by various factors, such as use of different food composition databases, laboratory assays for α- and γ-tocopherol plasma/serum measurements, and differences in underlying lipoprotein levels, which are carriers of vitamin E. Our large lung cancer case–control study (n = 1,088 cases) adds meaningful data on α-, γ-, β- and δ-tocopherol to the literature. We found consistent independent associations for increased dietary α-tocopherol intake and risk reduction but did not find independent associations for γ-, β- and δ-tocopherol in lung cancer risk. In stratified analyses, in particular, we found that current smokers and those with longer duration of smoking were afforded greater protection from dietary α-tocopherol. Cigarette smoke, an established risk factor for lung cancer, is an important source of reactive oxygen species (ROS) in the lungs. Thus, 1 would expect that, in current compared to former smokers or those with a longer duration of smoking, dietary α-tocopherol intake would be less effective because it is plausible that ROS production from cigarettes may overwhelm the protective effects associated with α-tocopherol intake.

For dietary α-tocopherol intake, we observed protective trends in both nonusers and users of vitamin/mineral supplements. However, the amounts and frequency of use of vitamins/minerals were unavailable to compute total (dietary plus supplemental) α-tocopherol intake and to analyze in greater detail the associations of supplemental dose and risk.

Emphysema, which is strongly influenced by smoking,[27] is a chronic inflammatory condition[28] and a risk factor for lung cancer.[29] Dietary vitamin E (α-, γ-, β- and δ-tocopherol) has been shown to have potent antiinflammatory properties.[30] We observed significant protective trends against lung cancer risk with increased dietary intake of α-tocopherol largely in the subjects who did not report a diagnosis of emphysema. Chronic inflammation in emphysema results in a cycle of lung injury and repair that may overwhelm the antiinflammatory effects associated with dietary vitamin E intakes.

Similar inverse associations between α-tocopherol intake and lung cancer risk were noted for early and late stage disease, and histology. However, there were too few small cell lung cancers in each quartile of α-tocopherol intake for meaningful interpretation of the data.

When we assessed the top food contributors of α-tocopherol in our population as risk factors, as expected, we found a significant inverse association with increased intake of peanut butter, salad dressing and fruit and vegetables (Table IV). While these results validate our findings regarding α-tocopherol and lung cancer risk, it is also possible that other constituents in foods rich in tocopherols may be etiologically important.

We recognize the methological limitations investigating the association of dietary intake of the different forms of vitamin E and risk of lung cancer. Thus, we carefully constructed our models to account for the independent effects of the 4 different forms of dietary tocopherols and other dietary factors such as vitamin C intake. We also recognize that our study would be strengthened by more objective measurements of α-, β-, γ- and δ-tocopherol status, such as serum or cellular levels; however, serum samples are available only in a subset of subjects.

Our case–control study had other limitations. This study was originally designed to examine genetic susceptibility to lung cancer, while the present data represent secondary analysis. Like all case–control studies, our analysis raises concern about recall bias and residual confounding. In an attempt to reduce biased reporting of dietary intake in cases and controls, cases reported their diet during the year prior to diagnosis, and controls reported their diet during the year prior to enrollment into the study. The FFQ is practical for large epidemiology studies such as ours, but its use may introduce measurement error,[31,32] leading to biased estimates of the association between a given dietary factor and cancer. It

has been argued that because of misclassification errors, the FFQ is not always able to detect weak associations,[33,34] thereby attenuating the true association.

In an effort to improve the accuracy, our interviewers were trained in FFQ administration, while FFQ responses were reviewed and requeried by staff nutritionists. Portion sizes were assessed with visual aids. It is well recognized that the FFQ can reliably classify individuals by quartile of intake.[35] While recall bias may exist, in our study the control population consumed comparable daily mean dietary α-tocopherol intakes (6.1 and 6.5 mg/d for men and women, respectively) to values reported from a national sample of US adults (mean α-tocopherol intake: men, 6.7 mg/d; women, 4.7 mg/d).[36] The estimated average requirement (EAR) for vitamin E (α-tocopherol) is 12 mg/d and the recommended dietary allowance (RDA) is 15 mg/d. Thus, like national surveys, we found that even our healthy controls did not consume adequate amounts of vitamin E.[2]

It is well-known that estimates of dietary vitamin E intake are especially difficult to assess because dietary fat intake serves as an important carrier of vitamin E and is typically under-reported in dietary surveys. The quantity of fats or oils added during cooking is difficult to recall precisely but can contribute greatly to tocopherol intake and absorption. Additionally, respondents may not report the type of oils in preparation if they are not preparing their foods; as a result, default selections are made in the analysis that may improperly account for the tocopherol content of these foods. If indeed tocopherols are important in lung cancer prevention, underestimation of intake could drive the associations toward the null.

In conclusion, we report consistent inverse association between dietary α-tocopherol intake but no independent associations for β-, γ- and δ-tocopherol after adjustment for the other tocopherols and vitamin C. Our data should be useful in stimulating additional epidemiologic and basic science research in the relationship of different forms of vitamin E and cancer.

Acknowledgments

Grant sponsors: Flight Attendant Medical Research Institute (FAMRI); National Cancer Institute, National Institutes of Health, Department of Health and Human Services; Grant numbers: CA55769, CA86390, Lung SPORE CA70909.

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TABLE I

DISTRIBUTION OF SELECT DEMOGRAPHIC AND DIETARY VARIABLES BY CASE–CONTROL STATUS

Variable	Cases (*n* = 1,088)	Controls (*n* = 1,414)	*p*-value[1]
Age (years)			
Overall	61.67 (11.91)	60.83 (9.44)	0.05
Men	62.08 (11.48)	61.75 (8.65)	0.56
Women	61.16 (12.41)	59.95 (10.06)	0.06
Gender, *n* (%)			
Men	597 (54.87)	691 (48.87)	0.003
Women	491 (45.13)	723 (51.13)	
Smoking status, *n* (%)			
Never	238 (21.90)	303 (21.43)	0.10
Former	417 (38.36)	599 (42.36)	
Current	432 (39.74)	512 (36.21)	
Years smoked			
Former	32.85 (12.92)	27.76 (12.65)	<0.0001
Current	39.86 (11.97)	37.98 (10.94)	0.01
Cigarettes/day			
Former	25.34 (14.92)	25.13 (15.04)	0.82
Current	24.92 (11.90)	21.44 (12.11)	<0.0001
Ethnicity, *n* (%)			
Caucasian	829 (76.19)	1097 (77.58)	0.0007
Hispanic	53 (4.87)	109 (7.71)	
African American	206 (18.93)	208 (14.71)	
Education, *n* (%)			
Less high school	186 (17.10)	133 (9.41)	<0.0001
High school	294 (27.02)	272 (19.24)	
College	473 (43.47)	783 (55.37)	
Graduate school	135 (12.41)	226 (15.98)	
BMI (kg/m^2)			
Overall	26.64 (5.41)	28.39 (5.57)	<0.0001
Men	26.69 (4.77)	28.62 (5.01)	<0.0001
Women	26.58 (6.1)	28.16 (6.05)	<0.0001
Supplement use, *n* (%)			
Yes	640 (58.82)	948 (67.04)	<0.0001
No	448 (41.18)	466 (32.96)	
Alcohol drinker, *n* (%)			
Yes	910 (83.64)	1223 (86.49)	0.05
No	178 (16.36)	191 (13.51)	
Emphysema, *n* (%)			
Yes	183 (16.82)	81 (5.73)	<0.0001

Variable	Cases (*n* = 1,088)	Controls (*n* = 1,414)	*p*-value[1]
No	904 (83.09)	1332 (94.20)	
Unknown	1 (0.09)	1 (0.07)	
Total calories (kcal/day)			
Overall	2012 (718.24)	2087 (714.36)	0.009
Men	2248 (753.94)	2332 (734.22)	0.04
Women	1724 (549.26)	1852 (609.18)	0.0002
α-tocopherol (mg/day)[2]			
Overall	5.51 (2.52)	6.29 (3.03)	<0.0001
Men	5.26 (2.44)	6.1 (3.29)	<0.0001
Women	5.8 (2.58)	6.48 (2.75)	<0.0001
β-tocopherol (mg/day)[2]			
Overall	0.06 (0.04)	0.07 (0.06)	<0.0001
Men	0.05 (0.04)	0.07 (0.08)	0.0001
Women	0.06 (0.03)	0.07 (0.04)	0.02
γ-tocopherol (mg/day)[2]			
Overall	3.01 (1.47)	3.34 (1.79)	<0.0001
Men	2.9 (1.57)	3.28 (1.86)	<0.0001
Women	3.14 (1.32)	3.4 (1.72)	0.006
δ-tocopherol (mg/day)[2]			
Overall	0.54 (0.32)	0.58 (0.37)	0.004
Men	0.53 (0.35)	0.59 (0.40)	0.003
Women	0.56 (0.29)	0.58 (0.35)	0.36
Total tocopherol (mg/day)[2]			
Overall	9.12 (3.36)	10.29 (4.06)	<0.0001
Men	8.75 (3.38)	10.04 (4.35)	<0.0001
Women	9.57 (3.29)	10.53 (3.75)	<0.0001
Family history of cancer, *n* (%)			
Yes	326 (29.96)	399 (28.22)	<0.0001
No	762 (70.04)	1015 (71.78)	

For continuous variables, values are mean (SD).

[1]Calculated by *t* test for continuous variables or χ^2 test for categorical variables.

[2]Energy-adjusted.

TABLE II

ADJUSTED ODDS RATIOS FOR ASSOCIATIONS OF DIETARY TOCOPHEROL INTAKE AND LUNG CANCER RISK

	Quartile of dietary intake				*p*-value
	1	**2**	**3**	**4**	
α-tocopherol (mg/day)	≤4.13	4.14–5.60	5.61–7.73	>7.73	
Cases, *n*	419	260	243	166	
Controls, *n*	354	353	356	351	
Model 1	1	0.63 (0.50–0.79)	0.58 (0.44–0.76)	0.39 (0.28–0.53)	<0.0001
Model 2	1	0.66 (0.52–0.83)	0.64 (0.48–0.84)	0.47 (0.33–0.66)	<0.0001
Model 3	1	0.66 (0.52–0.83)	0.63 (0.48–0.83)	0.45 (0.32–0.62)	<0.0001
β-tocopherol (mg/day)	≤0.04	0.05–0.06	0.07–0.08	>0.08	
Cases, *n*	505	245	149	189	
Controls, *n*	483	326	255	350	
Model 1	1	0.79 (0.63–0.98)	0.59 (0.45–0.78)	0.56 (0.42–0.74)	<0.0001
Model 2	1	0.89 (0.70–1.12)	0.76 (0.56–1.03)	0.89 (0.61–1.30)	0.32
Model 3	1	0.80 (0.64–1.00)	0.60 (0.46–0.79)	0.57 (0.43–0.76)	<0.0001
γ-tocopherol (mg/day)	≤1.83	1.84–2.95	2.96–4.44	>4.44	
Cases, *n*	355	288	247	198	
Controls, *n*	356	353	352	353	
Model 1	1	0.84 (0.67–1.06)	0.76 (0.59–0.97)	0.56 (0.42–0.75)	0.0002
Model 2	1	0.89 (0.70–1.12)	0.85 (0.64–1.13)	0.68 (0.45–1.03)	0.10
Model 3	1	0.85 (0.67–1.07)	0.75 (0.58–0.97)	0.53 (0.40–0.72)	<0.0001
δ-tocopherol (mg/day)	≤0.28	0.29–0.49	0.50–0.78	>0.78	
Cases, *n*	341	296	221	230	
Controls, *n*	356	360	348	350	
Model 1	1	0.93 (0.74–1.17)	0.77 (0.60–1.0)	0.81 (0.61–1.07)	0.07
Model 2	1	1.05 (0.83–1.33)	0.96 (0.72–1.28)	1.22 (0.84–1.78)	0.55
Model 3	1	0.91 (0.72–1.14)	0.72 (0.56–0.93)	0.71 (0.53–0.95)	0.0073
Total tocopherol (mg/day)	≤6.68	6.69–9.34	9.35–12.95	>12.95	
Cases, *n*	390	275	238	185	
Controls, *n*	354	354	353	353	
Model 1	1	0.72 (0.57–0.90)	0.63 (0.48–0.82)	0.45 (0.33–0.62)	<0.0001

	Quartile of dietary intake				*p*-value
	1	**2**	**3**	**4**	
Model 2					
Model 3	1	0.75 (0.59–0.95)	0.67 (0.51–0.88)	0.50 (0.36–0.69)	<0.0001

Model 1, adjusted for age, gender, ethnicity, education, BMI, alcohol (continuous), total calories (excluding alcohol calories), smoke years, number of cigarettes/day and history of cancer.

Model 2, model 1 adjusted for the other tocopherol forms.

Model 3, model 1 adjusted for vitamin C.

Values inside parentheses are 95% CI.

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TABLE III

RISK ESTIMATES FOR DIETARY α-TOCOPHEROL (MG/D) AND LUNG CANCER DEFINED BY SELECTED VARIABLES

	Quartile of α-tocopherol (mg/day)				*p*-value
	1 (≤4.13)	**2 (4.14–5.60)**	**3 (5.61–7.73)**	**4 (>7.73)**	
Age					
≤60 (years)					
Cases, *n*	187	110	101	79	
Controls, *n*	161	159	157	146	
Model 1	1	0.64 (0.45–0.91)	0.64 (0.42–0.97)	0.55 (0.34–0.89)	0.02
Model 2	1	0.64 (0.44–0.91)	0.63 (0.41–0.97)	0.53 (0.31–0.91)	0.02
>60 (years)					
Cases, *n*	232	150	142	87	
Controls, *n*	193	194	199	205	
Model 1	1	0.59 (0.43–0.82)	0.54 (0.37–0.78)	0.31 (0.20–0.49)	<0.0001
Model 2	1	0.65 (0.47–0.90)	0.66 (0.44–0.97)	0.46 (0.28–0.75)	0.004
Smoking status					
Never					
Cases, *n*	86	57	56	39	
Controls, *n*	86	73	79	65	
Model 1	1	0.76 (0.46–1.26)	0.68 (0.39–1.20)	0.55 (0.28–1.06)	0.07
Model 2	1	0.80 (0.48–1.34)	0.80 (0.44–1.43)	0.76 (0.36–1.61)	0.45
Former					
Cases, *n*	147	98	97	75	
Controls, *n*	124	152	161	162	
Model 1	1	0.53 (0.36–0.79)	0.48 (0.31–0.75)	0.37 (0.22–0.62)	0.0002
Model 2	1	0.56 (0.38–0.83)	0.54 (0.34–0.85)	0.46 (0.26–0.81)	0.008
Current					
Cases, *n*	186	105	89	52	
Controls, *n*	144	128	116	124	
Model 1	1	0.66 (0.45–0.97)	0.58 (0.37–0.93)	0.32 (0.19–0.56)	0.0001
Model 2	1	0.67 (0.45–0.99)	0.60 (0.37–0.98)	0.33 (0.18–0.62)	0.001
Years smoking					

	Quartile of α-tocopherol (mg/day)				*p*-value
	1 (≤4.13)	**2 (4.14–5.60)**	**3 (5.61–7.73)**	**4 (>7.73)**	
≤31 (years)					
Cases, *n*	192	130	120	101	
Controls, *n*	204	199	191	184	
Model 1	1	0.67 (0.49–0.93)	0.61 (0.42–0.88)	0.50 (0.33–0.76)	0.001
Model 2	1	0.7 (0.51–0.97)	0.67 (0.46–0.98)	0.61 (0.38–0.97)	0.03
>31 (years)					
Cases, *n*	227	130	123	65	
Controls, *n*	150	154	165	167	
Model 1	1	0.57 (0.40–0.82)	0.51 (0.34–0.77)	0.26 (0.16–0.43)	<0.0001
Model 2	1	0.59 (0.42–0.85)	0.55 (0.36–0.84)	0.30 (0.17–0.52)	0.0001
Supplement use					
Yes					
Cases, *n*	226	150	149	115	
Controls, *n*	212	229	251	256	
Model 1	1	0.69 (0.51–0.94)	0.66 (0.47–0.92)	0.49 (0.33–0.72)	0.0005
Model 2	1	0.73 (0.54–0.98)	0.73 (0.52–1.03)	0.58 (0.38–0.88)	0.02
No					
Cases, *n*	193	110	94	51	
Controls, *n*	142	124	105	95	
Model 1	1	0.58 (0.40–0.85)	0.52 (0.32–0.84)	0.28 (0.16–0.51)	<0.0001
Model 2	1	0.63 (0.43–0.93)	0.62 (0.38–1.03)	0.40 (0.20–0.80)	0.01
Emphysema					
Yes					
Cases, *n*	66	45	48	24	
Controls, *n*	19	21	17	24	
Model 1	1	0.75 (0.33–1.70)	1.15 (0.44–2.99)	0.45 (0.15–1.38)	0.32
Model 2	1	0.78 (0.34–1.80)	1.30 (0.47–3.62)	0.65 (0.19–2.24)	0.75
No					
Cases, *n*	353	215	195	142	
Controls, *n*	335	332	339	327	

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	Quartile of α-tocopherol (mg/day)				*p*-value
	1 (≤4.13)	**2 (4.14–5.60)**	**3 (5.61–7.73)**	**4 (>7.73)**	
Model 1	1	0.61 (0.48–0.78)	0.53 (0.40–0.71)	0.39 (0.28–0.54)	<0.0001
Model 2	1	0.64 (0.50–0.82)	0.59 (0.44–0.79)	0.47 (0.32–0.67)	<0.0001
Stage					
Early					
Cases, *n*	115	80	57	55	
Controls, *n*	354	353	356	351	
Model 1	1	0.66 (0.48–0.90)	0.55 (0.38–0.79)	0.46 (0.30–0.71)	0.0002
Model 2	1	0.69 (0.50–0.94)	0.60 (0.41–0.87)	0.55 (0.34–0.88)	0.007
Later					
Cases, *n*	254	153	153	89	
Controls, *n*	354	353	356	351	
Model 1	1	0.58 (0.45–0.75)	0.59 (0.44–0.80)	0.34 (0.23–0.48)	<0.0001
Model 2	1	0.61 (0.47–0.79)	0.65 (0.48–0.89)	0.40 (0.27–0.60)	<0.0001
Histology					
Adenocarcinoma					
Cases, *n*	228	143	125	99	
Controls, *n*	354	353	356	351	
Model 1	1	0.65 (0.49–0.86)	0.57 (0.42–0.79)	0.47 (0.32–0.68)	<0.0001
Model 2	1	0.67 (0.51–0.89)	0.62 (0.44–0.86)	0.54 (0.36–0.81)	0.0019
Squamous					
Cases, *n*	93	63	59	41	
Controls, *n*	354	353	356	351	
Model 1	1	0.61 (0.41–0.93)	0.54 (0.33–0.86)	0.37 (0.21–0.67)	0.0009
Model 2	1	0.66 (0.43–0.99)	0.63 (0.38–1.02)	0.49 (0.26–0.92)	0.03
NSCLC					
Cases, *n*	72	39	41	18	
Controls, *n*	354	353	356	351	
Model 1	1	0.52 (0.33–0.82)	0.55 (0.33–0.94)	0.25 (0.12–0.50)	0.0003
Model 2	1	0.55 (0.35–0.87)	0.60 (0.34–1.05)	0.28 (0.13–0.61)	0.003
Small cell					

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	Quartile of α-tocopherol (mg/day)				*p*-value
	1 (≤4.13)	**2 (4.14–5.60)**	**3 (5.61–7.73)**	**4 (>7.73)**	
Cases, *n*	19	10	12	5	
Controls, *n*	354	353	356	351	
Model 1	1	0.46 (0.19–1.07)	0.50 (0.19–1.30)	0.21 (0.06–0.78)	0.03
Model 2	1	0.52 (0.22–1.24)	0.64 (0.23–1.77)	0.35 (0.08–1.46)	0.19

Model 1,adjusted for age, gender, ethnicity, education, BMI, alcohol (continuous), total calories (excluding alcohol calories), smoke years, number of cigarettes/day and history of cancer.

Model 2, model 1 adjusted for the other tocopherol forms.

Values inside parentheses are 95% CI.

In Table 3, data are only shown for variables that exhibit a significant interaction with α-tocopherol.

TABLE IV

ADJUSTED ODDS RATIOS FOR ASSOCIATIONS OF FOOD CONTRIBUTORS OF TOCOPHEROL INTAKE AND LUNG CANCER RISK

	Quartile of dietary intake				*p*-value
	1	**2**	**3**	**4**	
Peanut butter (mg/day)	<0.2	0.2–2.1	2.2–6.9	>6.9	
Cases, *n*	301	359	235	193	
Controls, *n*	352	400	332	330	
Model 1	1.00	1.08 (0.86–1.34)	0.87 (0.69–1.10)	0.73 (0.57–0.93)	0.004
Salad dressing[1] (mg/day)	<4.3	4.3–12.9	>12.9		
Cases, *n*	563	372	153		
Controls, *n*	704	412	298		
Model 1	1.00	1.14 (0.95–1.38)	0.72 (0.57–0.91)		0.06
Fruit and vegetables (mg/day)	<429.3	429.3–652.6	652.7–953.3	>953.3	
Cases, *n*	378	292	236	182	
Controls, *n*	354	353	354	353	
Model 1	1.00	0.88 (0.70–1.10)	0.75 (0.59–0.96)	0.60 (0.46–0.78)	<0.0001

Model 1, adjusted for age, gender, ethnicity, education, BMI, alcohol (continuous), total calories (excluding alcohol calories), smoke years, number of cigarettes/day and history of cancer.

[1]For salad dressing, we created tertiles because too few subjects were in the highest quartile of intake.