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Dietary, Supplement, and Adipose Tissue Tocopherols Levels in Relation to Prostate Cancer Aggressiveness Among African and European Americans: The North Carolina-Louisiana Prostate Cancer Project (PCaP)

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Abstract

Background—Controversies remain over the safety and efficacy of vitamin E (i.e., α–tocopherol) supplementation use for the prevention of prostate cancer (CaP); however, associations of different tocopherol forms and CaP aggressiveness have yet to be examined.

Methods—This study examined whether food intake of tocopherols, vitamin E supplement use, and adipose tissue biomarkers of tocopherol were associated with CaP aggressiveness among African-American (AA, n=1,023) and European-American (EA, n=1,079) men diagnosed with incident CaP. Dietary tocopherols were estimated from a food frequency questionnaire, supplement use from questionnaire/inventory, and biomarkers from abdominal adipose samples measured using high-performance liquid chromatography. Odds ratios (ORs) and 95% confidence

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intervals (95% CIs) were estimated from logistic regression comparing high aggressive CaP to low/intermediate aggressive CaP, adjusting for covariates.

Results—Dietary intakes of α-and δ-tocopherol were related inversely to CaP aggressiveness among EAs [OR (95% CI), highest versus lowest quartile: α-tocopherol, 0.34 (0.17–0.69), P_{trend} = 0.006; δ-tocopherol, 0.45 (0.21–0.95) P_{trend} = 0.007]. Inverse associations between dietary and supplemental α-tocopherol and CaP aggressiveness were observed among AAs, though these did not reach statistical significance [OR (95% CI), highest versus lowest quartile: dietary α-tocopherol, 0.58 (0.28–1.19), P_{trend} = 0.20; supplemental α-tocopherol, 0.64 (0.31–1.21) P_{trend} = 0.15]. No significant association was observed between adipose tocopherol levels and CaP aggressiveness [OR (95% CI), highest versus lowest quartiles of α-tocopherol for EAs 1.43 (0.66–3.11) and AAs 0.66 (0.27–1.62)].

Conclusions—The inverse associations observed between dietary sources of tocopherols and CaP aggressiveness suggests a beneficial role of food sources of these tocopherols in CaP aggressiveness.

Keywords

prostate cancer; vitamin E; tocopherols; diet; supplement; adipose tissue; nutritional biomarkers

Introduction

Prostate cancer (CaP) is the leading invasive malignancy and has the second highest cancer mortality rate in American men [1]. International variations in CaP incidence as well as changes in the disease patterns among migrant populations in Western countries demonstrate the importance of environmental factors in the etiology of CaP, particularly the role of dietary factors [2–4]. Vitamin E, a fat-soluble micronutrient found in vegetable oils, seeds, nuts, leafy green vegetables and whole grains, is thought to have potent antioxidant and other biological functions that may inhibit prostate carcinogenesis [5, 6]. The potential beneficial effect of vitamin E in CaP is supported by mechanistic evidence that vitamin E contributes to the body's defenses against reactive oxygen species (ROS), which may play a role in CaP by causing oxidative damage to DNA and other important cellular constituents [5–8].

It has long been recognized that Vitamin E, the collective name for eight naturally occurring compounds consisting of four tocopherols (i.e., α–, β–, γ– and δ–tocopherol) and corresponding four tocotrienols, may protect against CaP [5, 6]. Previous studies, including randomized controlled trials (reviewed in [9–12]), have focused primarily on CaP incidence. These yielded conflicting findings. Lately, there has been increasing awareness of the remarkable heterogeneity of CaP. Owing to the widespread use of prostate-specific antigen (PSA) blood test for early detection, most newly diagnosed CaPs are latent disease and often remain indolent over a lifetime, similar to those observed at autopsy [13, 14]. Few (approximately 30%) of these tumors would progress aggressively and therefore be associated with poorer prognosis [15, 16]. Several reports indicate that the etiology of aggressive CaP may differ from that of non-aggressive CaP [17, 18], and may include

differences in dietary risk factors [19, 20]. Thus, prior conflicting findings on CaP incidence may be due to combining different disease subtypes in the analyses.

Distinguishing modifiable factors that lead to aggressive CaP rather than indolent disease is particularly important for addressing racial disparities in CaP, as African Americans (AAs) have greater burden of virulent CaP compared to European Americans (EAs)[21]. Therefore, this study examines whether higher intakes of tocopherols from diet and supplements (α–tocopherol equivalent), and higher adipose tissue tocopherol levels were inversely associated with CaP aggressiveness among AA and EA men in North Carolina and Louisiana.

Materials and Methods

Research Subjects

The North Carolina-Louisiana Prostate Cancer Project (PCaP) is a population-based, cross-sectional, case-only, incident CaP study, designed to investigate racial and geographical differences in CaP aggressiveness [22]. Using a rapid case ascertainment system, men with a first diagnosis of histologically confirmed adenocarcinoma of the prostate were recruited in North Carolina (NC) and Louisiana (LA) between July 1, 2004 and August 31, 2009. Residents of NC and LA were eligible if they resided within the study catchment areas, and were: (1) between 40–79 years old at diagnosis; (2) self-identified race as AA/Black or “Caucasian”/EA/White; (3) able to complete study interview in English; (4) did not live in an institution (e.g., nursing home); and (5) were mentally and physically able to complete the interview. Written informed consent was obtained from each research subject prior to participation. Approximately equal numbers of AAs and EAs were enrolled from NC (AAs n = 505; EAs n = 527) and LA (AAs n = 632; EA n = 603), with participation rates of 62% in NC, 72% for pre-Hurricane Katrina LA and 63% for post- Hurricane Katrina LA. Further details of the methods and designs of PCaP have been published [22]. The PCaP study protocols were approved by Institutional Review Boards (IRB) of the University of North Carolina at Chapel Hill, Louisiana State University Health Sciences Center, and the Department of Defense Prostate Cancer Research Program. The current analysis also was approved by the University of South Carolina IRB as exempt.

Study Variables and Definition of CaP Aggressiveness

Consenting research subjects completed structured, in-home, interviewer-administered questionnaires that included information on demographics, pre-diagnostic CaP screening history, comorbidities, family health history, healthcare access, and behavioral factors such as physical activity and smoking status. The interviewers, who were research nurses specifically trained for data collection, also obtained anthropometric measurements (height and weight) at the end of each interview using a standardized protocol. Data on clinical attributes of CaP including cancer stage at diagnosis, Gleason sum and prostate-specific antigen (PSA) level at diagnosis were abstracted from research subjects’ medical records obtained from diagnosing physicians. The medical records abstraction was done by trained personnel, and a random sample of the abstracted medical records (approximately 10%) were abstracted a second time by another staff member to ensure abstractor consistency. In PCaP, CaP aggressiveness is defined by a combination of Gleason sum, clinical stage and

PSA level at diagnosis as: (1) high aggressive (Gleason sum ≥8 or PSA >20 ng/mL, or Gleason sum ≥ 7 and clinical stage T3–T4); (2) low aggressive (Gleason sum < 7 and stage T1–T2 and PSA<10 ng/ml), and (3) intermediate aggressive CaP (all others). For the present analyses, a case-case study design was adopted to contrast research subjects with high aggressive CaP to those with low/intermediate aggressive CaP.

Dietary Assessment

Dietary data were obtained using the National Cancer Institute Dietary History Food Frequency Questionnaire [23], which was modified to include Southern foods. The modified 144-item questionnaire included questions on frequency of food intake, usual portion size, and food preparation methods in the 12 months prior to diagnosis with CaP. Responses to the questions were linked to an updated NCI nutrient database containing food compositions of α–, β–, γ–, and δ–tocopherol, and dietary intakes were estimated using the NCI Diet*Calc software [22].

Dietary Supplement Use

Information on dietary supplement use was solicited via a validated questionnaire [24] administered by the research nurses during in-home visits. Data on supplemental vitamin E intake were derived from response to questions about the use of multivitamins containing vitamin E and single-nutrient vitamin E supplements use. For multivitamins, research subjects were asked whether they had taken multivitamin supplements in the 12 months prior to CaP diagnosis (no, less than once a week, yes); and if yes, the frequency of use (1–2, 3–4, 5–6, 7 days/week). Forty-five percent of the research subjects reported multivitamin supplement use in the previous 12 months, and were asked to identify the most often used brand from a list of common multivitamin brands in the U.S., which included an open-ended option for unlisted brands. Subsequently, these research subjects were asked to provide the study nurse with the multivitamin supplement bottle for recording of nutrient contents and dose. Research subjects who were unable to provide the multivitamin bottle (about 5% of users) were assigned the vitamin E dose listed on manufacturer label of the stated brand. When the manufacturer label could not be found (less than 1%), research subjects were assigned the vitamin E dose of the most commonly used brand among multivitamin supplement users; this value was 50 IU (i.e., from Centrum Silver). In subsequent questions, research subjects were asked about the use of single-nutrient supplements; and if yes (13% of subjects), the frequency of use (same categories as above). Research subjects who were unable to provide the supplement bottle were asked to indicate the usual dose taken. Dose choices for single-nutrient vitamin E supplements were 30, 100, 200, 400, 600 or 800 IU/day, and an open-ended option for unlisted dose. Research subjects who reported using single-nutrient vitamin E supplement but could not provide the supplement bottle or unable to report usual dose (4% of users) were assigned the mode dose (i.e., 400 IU) among single-nutrient vitamin E supplement users. Total vitamin E supplement intake was estimated as the sum of vitamin E from single-nutrient supplement and multivitamins, and converted as 1 IU = 0.45 mg of α–tocopherol [25]. Total α–tocopherol exposure was subsequently calculated as the sum of dietary α–tocopherol intake and total vitamin E supplement intake (i.e., diet + supplement).

Adipose tissue sampling and analysis

Subcutaneous fat samples were obtained by a trained nurse from the abdominal area of consenting research subjects who were not allergic to the local anesthesia solution (2% lidocaine). After the overlying skin was anesthetized, a 15-gauge needle was inserted into the subcutaneous fat and suction was applied using 15 ml vacutainer tube. The aspirated tissue was trapped in the needle and luer lock adapter, which was placed in separate cryovials for transportation. The collected samples were transported on ice, immediately after collection, via overnight courier to the assigned facility for storage at −80°C. The samples were later assayed for tocopherol concentrations using high-performance liquid chromatography (HPLC, Craft Technologies) [26]. The average time between sample collection and storage was 24 hours, and average time from storage to analysis was 6 months. The adipose tissue concentrations of α–, γ–, and δ–tocopherol were expressed as mcg per gram of tissue at detection limit of 0.07 mcg/g.

Statistical analysis

The analytic population was drawn from 2,173 PCaP research subjects with complete data on CaP aggressiveness. Prior to data analysis, research subjects with implausibly low or high daily caloric intake (< 500 or > 6,000 kcals, n = 71) were excluded, leaving a final study sample of 2,102 (AAs n = 1,023, EAs n = 1,079). Of these research subjects, data on adipose tissue tocopherol levels were available for 945 subjects (AA n = 361, EAs n = 584).

Descriptive statistics were compared by level of CaP aggressiveness as means (continuous variables) and proportions (categorical variables) using t and χ^2 tests, respectively. All tocopherol exposure variables were categorized into quartiles, separately for AAs and EAs, based on distribution among low/intermediate aggressive cases in the respective race group. Consequently, analyses were performed separately for AAs and EAs. The decision to categorize the exposures separately by race based on preliminary analysis showing significant interaction between race and most of the dietary variables, indicating differential diet and supplement use patterns between AA and EAs. For example, P values for interaction between race, with total α-tocopherol and dietary γ–tocopherol were 0.02 and 0.04, respectively. Unconditional logistic regression was used to estimate crude (age-adjusted) and multivariable-adjusted odds ratios (ORs) and 95% confidence interval (CIs).

In selecting the multivariable-adjusted models, the following variables were considered as potential confounders based on review of the literature: pre-diagnostic PSA screening history (0, 1–7, >7 screenings); family history of CaP (number of affected first degree relatives: none *vs.* at least one); prevalence of comorbidities (Charlson Comorbidity Index: 0, 1, 2, ≥3); whether CaP treatment had started at time of interview (yes, no); smoking status (never, former, current); education (less than high school education, high school graduate/vocational school, some college/college graduate, graduate degree); annual household income (< $20,000, $20,001–$40,000, $40,001–$60,000, $60,001–$80,000, >$80,000, unknown); multivitamin use in the year prior to diagnosis (yes, no); non-steroidal anti-inflammatory drug (NSAID) use in the five years prior to diagnosis (yes, no); physical activity in the year prior to diagnosis [total metabolic equivalents (METs) of light, moderate and vigorous exercise categorized as: ≤10.2, 10.3–29.0, > 29.0 METs/week]; body mass

index (BMI: kg/m^2, continuous); study site (NC, LA); energy intake (kcal/day); dairy intake (servings/day); and alcohol intake (grams/day). These variables were first examined for confounding effect (i.e., ≥10% change in effect estimates of each exposure variable with age in the model). Next, variables determined to be confounders were placed in an elaborate model simultaneously for final model selection using a combination of the backward elimination method and likelihood ratio tests (LRTs) to remove one variable at a time. Through this process, the following variables were included in the final adjusted model for analysis of dietary tocopherols and vitamin E supplement use associations: age (continuous), pre-diagnostic PSA screening history, BMI, smoking status, education, income, NSAIDs use, dietary fat intake, and study site. Only pre-diagnostic PSA screening history was not determined to be a confounder; however, it was included in the final adjusted model because men who screen regularly tend to be diagnosed with incipient or early-stage disease rather than advanced disease [13]. Additional adjustments of family history of CaP, comorbidities and CaP treatment status were done for associations of adipose tocopherol levels and CaP aggressiveness. Tests for linear trend (P_{trend}) were performed by modeling the median values of each tocopherol category as continuous variable. Family history of CaP, pre-diagnostic PSA screening history, BMI and NSAIDs use were examined for potential effect modification by assessing stratum-specific ORs in stratified multivariable analyses, and including evaluation of interaction terms between these factors and the main exposures using likelihood ratio tests. All analyses were performed with SAS® version 9.3 (Cary, NC, USA) with statistical significance set at $\alpha = 0.05$ (two-tailed).

Results

Differences in distribution of research subject characteristics are presented by level of CaP aggressiveness separately for AAs and EAs in Table 1. AA subjects with high aggressive CaP were slightly older, had higher reported intakes of energy and dietary fat, included a greater proportion of current smokers and lower incomes, more often reported no PSA screening prior to diagnosis, but less often reported vitamin E supplement use compared to those with low/intermediate aggressive disease. EA subjects with high aggressive CaP also were older, had slightly higher BMI, and a higher proportion had started treatment for CaP by start of study as compared to those with low/intermediate aggressive CaP. In both AAs and EAs, research subjects with high aggressive CaP had a lower educational level than those with low/intermediate aggressive CaP. Differences in research subject characteristics among vitamin E supplement users and non-users also were noted (Supplementary Table 1).

Unadjusted mean differences in dietary, supplement and adipose tissue tocopherol levels are presented in Table 2 by race and by level of CaP aggressiveness. Overall, AA subjects tended to have higher dietary intake of γ– and δ–tocopherol, but lower intake of supplemental vitamin E as compared with EAs. Adipose tissue α–tocopherol concentration was 75% higher in EAs than AAs, but no significant difference was observed in γ– or δ–tocopherol concentration by race. Among EAs, no differences were observed in tocopherol levels from all three sources by the level of CaP aggressiveness; however, among AAs, research subjects with high aggressive CaP had lower supplemental vitamin E and total α–tocopherol intake compared to their counterparts with low/intermediate aggressive CaP.

Multivariable-adjusted ORs for high aggressive CaP were estimated by quartiles of dietary tocopherols and supplemental vitamin E intake with lowest quartiles as the referent group (Table 3). There was no significant association between dietary tocopherols or supplemental vitamin E intake in relation to CaP aggressiveness among AAs, although suggestions of inverse associations were observed, particularly in the highest quartiles of dietary α–tocopherol and total vitamin E supplement intake. Among EA subjects, a dose-response inverse association was observed between dietary α–tocopherol intake and CaP aggressiveness, showing 66% lower odds of high aggressive CaP in the highest quartile. However, neither vitamin E supplement intake nor total α–tocopherol intake (both diet and supplement sources) was associated with CaP aggressiveness among EAs. Dietary δ–tocopherol intake also was inversely and linearly associated with CaP aggressiveness among EAs. A nearly statistically significant inverse associations was observed in the highest quartile of β–tocopherol intake (OR = 0.56, 95% CI = 0.30–1.02), and marginally significant trend toward a lower odds of high aggressive CaP was observed with increasing intake of γ–tocopherol among EAs (P_{trend} = 0.05).

Research subjects included in the analysis of adipose tissue tocopherol levels and CaP aggressiveness (n = 945) differed from those excluded (n = 1157) on some sociodemographic characteristics (Supplementary Table 2). Although the two groups were similar in terms of CaP aggressiveness, those included had a somewhat higher BMI, included a lower proportion of AAs, a higher percentage of subjects from LA, and a slightly greater proportion had a positive family history of CaP as compared to those excluded. Those included also had higher levels of education and income, more often reported prior PSA screening, and fewer were current or former smokers compared to those excluded. In the analysis of adipose tocopherols and CaP aggressiveness, neither OR estimates nor linear trend tests showed statistically significant associations among AAs or EAs (Table 4); however, OR estimates for associations of adipose α-tocopherol were in the opposite direction in the two race groups [OR (95% CI), highest *versus* lowest quartile; were for AAs 0.66 (0.27–1.62), and EAs 1.43 (0.66–3.11)]. Because of the differences in the demographic characteristics highlighted above, additional analyses were performed by re-examining the association between dietary tocopherol intake and CaP aggressiveness only among research subjects with data on adipose tocopherol levels (Supplementary Table 3). Despite small sample size, these results were very similar to those reported in Table 3. Evaluation of potential modifying effects of family history of CaP, pre-diagnostic PSA screening history, smoking status, BMI and NSAIDs use did not show effect modification by these factors on the associations reported here (data not shown).

Discussion

In this population-based, case-only, study of CaP aggressiveness, higher dietary intakes of α– and δ–tocopherol were inversely associated with high aggressive CaP among EAs. Nearly significant inverse associations also were observed between higher dietary intake of γ– and β–tocopherol, and high aggressive CaP among EAs. Although there were significant differences in unadjusted mean levels of supplemental and total (diet and supplement) α–tocopherol intake by the levels of CaP aggressiveness among AAs, the inverse associations were not statistically significant in fully adjusted logistic regression models. Vitamin E

supplement use was not associated with CaP aggressiveness among EAs. Adipose tissue tocopherol levels also were not associated with CaP aggressiveness in either race.

Many reports indicate that tocopherols have strong chemopreventive properties that may protect against CaP, including functioning as antioxidant inhibitor of oxidative damage to DNA, lipids and proteins [5–8]. Other proposed mechanisms include enhancement of the immune system's surveillance capability and destruction of tumor cells, inhibition of protein kinase C, and modulation of apoptosis [6, 27–29]. However, clinical trials investigating the efficacy of supplemental α–tocopherol intake for the prevention of CaP have yielded contradictory results, with some showing beneficial effect [30], no benefit [31, 32], and even possible harm [27, 33]. In particular, the Alpha Tocopherol Beta-Carotene (ATBC) Cancer Prevention Trial, originally designed to investigate the ability of these two lipid-soluble antioxidants to reduce lung cancer incidence, reported a 32% reduced risk of CaP and 41% decreased mortality from CaP among Finnish male smokers taking 50 mg/day (approximately 50 IU/day) of supplemental vitamin E (α–tocopherol) over 5–8 years compared to placebo [30]. In contrast, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported a 17% increased risk of CaP among healthy males taking 400 IU/day of α–tocopherol over a 7-year median follow-up compared to placebo [27]. Two other clinical trials have reported no effect of vitamin E supplementation on CaP incidence [31, 32]. The epidemiologic data relating to tocopherols intake and CaP incidence also are equivocal (reviewed in [10–12]).

Data on tocopherols from diet, supplements, and adipose tissue provide complementary information about the role of tocopherols in CaP; however, as shown in this analysis, they can yield mixed results because these data represent different markers of tocopherol status. While dietary and supplement use questionnaires can provide estimates of usual intake patterns, typically they reflect intake in the more recent past [34]. On the other hand, fat-soluble antioxidants are known to selectively accumulate in human adipose tissue and tend to turn over at a low rate [35, 36]. Thus, adipose tissue is a relatively reliable marker of longer-term tocopherol status.

Dietary α–tocopherol intake has been associated with lower incidence of CaP in different populations [10, 11, 37], which concurs with the finding of the current study on CaP aggressiveness among EAs. The mean α–tocopherol intake level (10.5 mg/day) in this study also is comparable to that of a study conducted among AAs and EAs in NC [38]. Interestingly, though AAs and EAs had similar reported dietary intakes of α–tocopherol (Tables 2 and 3), a significant association was observed only among EAs. The relationship between dietary consumption of α–tocopherol and biologically effective dose depends on several factors including dietary habits and cooking methods. Exploratory analysis in PCaP showed that a greater proportion of EAs in the highest quartile of the dietary α–tocopherol consumption had higher intake of plant-based foods that are high in α–tocopherol such as nuts, seeds, olive oils and other healthy sources of α–tocopherol. By contrast, AAs in this category tended to consume higher amounts of foods from less healthy sources of α–tocopherol, particularly processed foods containing high amounts of saturated fat including fried potato and corn chips, and dark green vegetables prepared with lard and fatback. Besides differences in dietary patterns, there is strong evidence of racial differences in

metabolizing enzyme activities [39, 40] and genetic polymorphisms involved in oxidative DNA damage repair capacity [41, 42]—all of which may have influenced the results to some extent. Thus, the cancer prevention potential of α–tocopherol may be more complex than what is currently known about dietary consumption and CaP aggressiveness. This highlights the need for further work to better understand the underlying factors in order to address the racial disparity in this malignancy.

Despite the strong inverse association for dietary α–tocopherol among EAs, supplemental vitamin E and total α–tocopherol intake from both diet and supplements were not associated with CaP aggressiveness. Epidemiologic studies regarding vitamin E supplement use and CaP incidence have often reported null results [43–45]; few have reported protective associations, and these have been limited to smokers [46, 47] who may have greater need for vitamin E because of increased exposure to ROS from tobacco smoke [48]. In the present study, however, subgroup analysis did not show effect modification by smoking status, which may have been limited by small sample size, especially since analyses were stratified by race. The lack of significant associations for total α–tocopherol may be because research subjects who consumed large amounts of α–tocopherol from diet may have consumed small amounts from supplements or *vice versa*, which would lead to classification differences into low and higher quartiles when dietary and supplemental intakes were combined.

The results suggest that higher dietary intake of δ-tocopherol may decrease CaP aggressiveness. This apparent beneficial effect of δ-tocopherol, a relatively less common form of tocopherol found in castor and soybean oil and in processed foods such as potato chips [49], may be due to its reactive oxygen and nitrogen species scavenging activity [7, 50]. The marginally significant inverse associations for β– and γ–tocopherol observed among EAs suggest a potential beneficial role for these tocopherols or food sources of these tocopherols in CaP aggressiveness, but perhaps only at higher levels of intake. It must be noted that dietary intakes of γ–tocopherol were actually higher than α–tocopherol (Table 2), which is consistent with the general observation of higher amounts of γ–tocopherol than α–tocopherol in the American diet [51]. Nonetheless, blood concentrations of α–tocopherol are generally about ten times higher that γ–tocopherol, which has been attributed to the preferential transfer of α–tocopherol to the blood by the hepatic α–tocopherol transfer protein (α–TTP) [5, 52]. This suggests that higher dietary intake of the other tocopherols may be needed to increase their bioavailability and potential anticarcinogenic activities. Alternatively, α–tocopherol may have more potent anticarcinogenic properties than other tocopherols [50].

In general, EAs in this study had higher adipose tissue tocopherol concentrations than AAs. More strikingly, adipose α–tocopherol concentrations were 75% higher among EAs than AA. However, no significant association with CaP aggressiveness was observed for any of the adipose tocopherols in either race. Although what constitutes “normal” adipose tocopherol levels remains unclear, the mean adipose tocopherol levels among EA men were slightly higher than those reported in breast tissue from Malaysian women [53] and lower than those reported in adipose tissue from European males in the EURAMIC study [54]. This is the first study to examine adipose tocopherol levels in relation to CaP; thus, further investigation in larger studies would be useful.

Notable strengths of the present study include its design to measure CaP aggressiveness, which minimizes potential confounding by disease heterogeneity (i.e., the mixing of indolent and aggressive disease). The evaluation of three complementary measures of tocopherol intake allowed for a comprehensive assessment of tocopherol status in CaP aggressiveness. Additionally, the assessment of individual tocopherols rather than the mixing of tocopherols and tocotrienols helps delineate the role of each tocopherol in CaP aggressiveness. The use of a racially diverse population with approximately equal numbers of AAs and EAs also made it possible to explore whether associations between tocopherols and CaP aggressiveness differed by race. Moreover, the potential for selection bias and selective survival were minimized because participation rates were reasonably high at both study sites and research subjects were recruited shortly after diagnosis via rapid case-ascertainment; an average of five months from the time of diagnosis to time of interview.

The following limitations also are worth consideration. Imprecise measurements of dietary tocopherols could have influenced the study results to some extent. Because exposure assessment for tocopherols were done independent of the extent of CaP aggressiveness, differential misclassification bias is unlikely; however, non-differential exposure misclassification may have occurred, resulting in underestimation of ORs and failure to show modest associations [34]. Diet was assessed using a food frequency questionnaire. It is known that these structured instruments may be biased according to response sets [55], which in turn, may be related to psychological traits that either may exert a direct effect on cancer outcomes or indirectly affect other factors that may influence carcinogenesis [56]. The number of research subjects with adipose tissue tocopherol data was smaller than the overall study population. However, in sensitivity analyses, the results for dietary tocopherols were very similar in all research subjects compared to only those research subjects with data on adipose tocopherol levels. This consistency suggests minimal effect of missing data on the associations between adipose tocopherol levels and CaP aggressiveness. There is also the concern that adipose tocopherol levels may be altered by the presence of a tumor; however, a study examining the effect of breast tumor proximity on breast adipose tocopherol levels did not find significant differences in adipose tocopherol levels at different quadrants of breast tissue, including sites proximal and distal to the tumor [57]. Moreover, although adipose tocopherol levels are good markers for internal dose, they may not reflect prostatic tocopherol levels. Thus, results should be interpreted with this in mind. Other limitations include the lack of control for cholesterol levels, in particularly, low density lipoprotein which function as transport vehicles for tocopherols [5] and may be influenced by elevated low density lipoprotein (LDL) receptor activities in malignant cells [58]; as well as by abdominal adiposity which may influence the adipose tocopherol levels [59, 60]. Nonetheless, these might have been indirectly considered by adjusting for total dietary fat intake and BMI (which reflects general adiposity). The influence of individual differences in metabolism and absorption, interactions between individual tocopherols and other micronutrients, as well as potential modifying effects of genetic variants acting via similar mechanisms [35, 61, 62] were beyond the scope of this study. The possibility exists that some of the findings may be spurious owing to the sample size and multiple testing.

Conclusion

In summary, dietary intakes of α– and δ–tocopherol were inversely associated with CaP aggressiveness among EAs, suggesting a potential beneficial role of food sources of these tocopherols on CaP aggressiveness. Future work with larger number of high aggressive cases, repeated measures of tocopherol status, and involving evaluation of interaction between tocopherol status and functional gene polymorphisms in relevant genes, such as those involved in oxidative stress and DNA repair, may help to elucidate the etiologic relevance of tocopherols on CaP aggressiveness.

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Abbreviations

AA	African American
ATBC	Alpha Tocopherol Beta-carotene Cancer Prevention Trial
α–TTP	hepatic alpha-tocopherol transfer protein
BMI	Body mass index
CaP	Prostate cancer
CI	Confidence interval
EA	European American
HPLC	High-performance Liquid Chromatography
EURAMIC	European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Cancer of the Breast
IRB	Institutional Review Boards
LA	Louisiana
LSU	Louisiana State University (Health Sciences Center)
METs	Metabolic equivalents
NC	North Carolina
NCI-DHQ	National Cancer Institute Diet History Questionnaire

NSAIDS	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PCaP	North Carolina-Louisiana Prostate Cancer Project
PSA	Prostate-specific antigen
ROS	Reactive oxygen species
RR	Relative risk
SD	Standard deviation
SELECT	Selenium and Vitamin E Cancer Prevention Trial
UNC	University of North Carolina (Chapel Hill)

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Table 1

Distribution of demographic and patient characteristics by race and prostate cancer aggressiveness among men in the North Carolina-Louisiana Prostate Cancer Project (PCaP)

	African American n = 1,023					European American n = 1,079				
Characteristics	**High aggressive (n=206)**		**Low/intermediate aggressive (n=817)**		***P* value‡**	**High aggressive (n=164)**		**Low/intermediate aggressive (n=915)**		***P* value‡**
	Mean (SD)		**Mean (SD)**			**Mean (SD)**		**Mean (SD)**		
Age, years	63 (8)		62 (8)		0.004	67 (8)		64 (8)		<0.0001
Energy Intake, kcals/day	2799.6 (1232.4)		2593.0 (1146.0)		0.02	2339.3 (952.0)		2320.5 (865.7)		0.80
Dietary fat intake, grams/day	103.9 (52.1)		94.8 (48.4)		0.02	94.5 (42.4)		91.1 (39.2)		0.31
Body mass index (BMI), kg/m^2	29.9 (6.7)		29.2 (5.4)		0.16	30.5 (5.1)		29.0 (4.8)		0.0006
Study Site	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
NC	92	45	386	47	0.51	73	45	448	49	0.29
LA (pre & post Katrina)	114	55	431	53		91	55	467	51	
Family History of Prostate Cancer										
No affected 1st degree relative	157	76	606	74	0.55	136	83	696	76	0.05
At least 1 affected 1st degree relative	49	24	211	26		28	17	219	24	
Prostate Cancer Screening History										
0 screenings	120	58	307	38	<0.0001	40	24	153	17	0.06
1–7 screenings	53	26	338	41		68	42	405	44	
> 7 screenings	33	16	172	21		56	34	357	39	
Comorbidities										
0	88	43	382	47	0.39	84	51	503	55	0.07
1	53	26	216	26		31	19	214	23	
2	36	17	106	13		29	18	98	11	
≥ 3	29	14	113	14		20	12	100	11	
Started CaP treatment at start of study										
No	20	10	112	14	0.20	11	7	99	11	0.007

	African American n = 1,023					European American n = 1,079				
Characteristics	**High aggressive (n=206)**		**Low/intermediate aggressive (n=817)**		***P* value‡**	**High aggressive (n=164)**		**Low/intermediate aggressive (n=915)**		***P* value‡**
	Mean (SD)		**Mean (SD)**			**Mean (SD)**		**Mean (SD)**		
Yes	163	79	599	73		146	89	720	79	
Unknown	23	11	106	13		7	4	96	10	
Education										
Graduate/professional degree	50	24	239	29	0.004	71	43	377	41	0.01
Some college or college graduate	65	32	275	34		37	23	260	28	
High school grad or voc/tech school	85	42	243	30		27	16	81	9	
Less than high school education	6	3	59	7		29	18	197	22	
Income Level	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
≤ $20, 000	82	40	234	29	0.001	24	15	78	9	0.22
$20,001 – $40,000	52	25	212	26		33	20	184	20	
$40,001 – $60,000	20	10	132	16		24	15	154	17	
$60,001 – $80,000	12	6	70	8		20	12	124	13	
>$80,000	14	7	99	12		47	29	298	33	
Unknown	26	13	70	8		16	9	77	8	
Smoking Status										
Never	40	19	276	34	<0.001	59	36	330	36	0.76
Former smokers	107	52	390	48		87	53	501	55	
Current smokers	59	29	151	18		18	11	84	9	
NSAIDs Use										
No	84	41	364	45	0.33	56	34	305	33	0.85
Yes	120	59	446	55		108	66	608	67	
Vitamin E Supplement Use [a]										
No	141	68	488	60	0.02	65	40	396	43	0.38
Yes	65	32	329	40		99	60	519	57	

Prostate cancer aggressiveness defined by a combination of Gleason sum, clinical stage, and PSA level at diagnosis and classified as follows: High aggressive (Gleason sum ≥8 or PSA >20ng/ml or Gleason sum ≥7 AND clinical stage T3 –T4); Low/Intermediate aggressive: all other cases.

[a] Both single nutrient vitamin E supplements and multivitamins containing vitamin E.

Abbreviations: CaP – Prostate Cancer; SD – Standard deviation; NC –North Carolina LA – Louisiana; NSAIDs – Nonsteroidal anti-inflammatory drugs.

[‡] Test for differences between low/intermediate and high aggressive cancers were done using Student's t-test for continuous variables and chi-square tests for categorical variables.

Table 2

Unadjusted mean difference in tocopherol intake from diet and supplements, and adipose tissue tocopherol levels by race and level of prostate cancer aggressiveness

	African American n = 1,023	European American n = 1,079	% diff.[§]	African American			European American		
				High aggressive n = 206	Low/ intermediate Aggressive n = 817	P [†]	High aggressive n = 164	Low/ intermediate Aggressive n = 915	P [†]
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Dietary intake									
α–tocopherol (mg/day)	10.6 (5.9)	10.5 (5.3)	1	10.9 (6.5)	10.5 (5.8)	0.43	10.1 (5.3)	10.6 (5.3)	0.29
β–tocopherol (mg/day)	0.4 (0.2)	0.4 (0.2)	0	0.4 (0.3)	0.4 (0.2)	0.13	0.4 (0.2)	0.4 (0.2)	0.35
γ–tocopherol (mg/day)	21.0 (11.3)	18.6 (8.6)	11 [≠]	22.2 (11.7)	20.7 (11.2)	0.09	18.6 (9.1)	18.6 (8.5)	0.95
δ–tocopherol (mg/day)	3.0 (1.7)	2.7 (1.5)	10 [≠]	3.2 (1.8)	2.9 (1.7)	0.05	2.7 (1.5)	2.7 (1.5)	0.58
Supplemental vitamin E among supplement users [a] (α-tocopherol, mg/day)	53.5 (82.4)	76.6 (104.2)	− 43 [≠]	37.8 (54.2)	56.6 (86.6)	0.02	64.7 (94.2)	78.2 (101.4)	0.22
Supplemental vitamin E among multivitamin supplement users only [b] (α-tocopherol, mg/day)	18.5 (20.4)	22.3 (23.3)	− 20 [≠]	16.3 (9.9)	18.9 (21.8)	0.15	23.7 (26.0)	22.0 (22.8)	0.54
Supplemental vitamin E among single nutrient vitamin E supplement users only [c] (α-tocopherol, mg/day)	157.5 (100.5)	176.1 (101.6)	−12	110.4 (71.0)	166.0 (103.0)	0.06	177.0 (96.0)	176.0 (102.7)	0.96
Total α–tocopherol (diet + supplement, mg/day)	31.2 (57.8)	54.1 (85.2)	− 73 [≠]	22.8 (36.1)	33.3 (61.9)	0.002	49.2 (79.6)	55.0 (86.2)	0.42
Adipose tissue biomarkers [d]									
α–tocopherol (mcg/g)	86.6 (144.9)	151.4 (198.0)	− 75 [≠]	78.9 (138.0)	88.3 (146.6)	0.63	163.6 (221.3)	149.2 (193.7)	0.53
γ–tocopherol (mcg/g)	48.4 (74.1)	53.3 (54.5)	− 10	38.2 (38.2)	50.8 (79.9)	0.06	55.4 (56.5)	52.9 (54.1)	0.69
δ–tocopherol (mcg/g)	9.3 (10.2)	8.6 (7.8)	7	8.6 (9.9)	9.4 (10.3)	0.55	8.2 (6.6)	8.7 (8.0)	0.55

[a] Both multivitamin and single nutrient vitamin E supplement (African Americans, n = 394; European Americans, n = 618). Converted as 1 IU of Vitamin E = 0.45 mg α–tocopherol [25].

[b] Vitamin E intake from multivitamin supplements only (African Americans, n = 355; European Americans, n = 560). Converted as 1 IU of Vitamin E = 0.45 mg α–tocopherol [25].

[c] Vitamin E intake from single nutrient vitamin E supplements only (African Americans, n = 92; European Americans, n = 198). Converted as 1 IU of Vitamin E = 0.45 mg α–tocopherol [25].

[d] Among research subjects with data on adipose tocopherol levels (African Americans, n = 361; European Americans, n = 584).

[§] Percent difference between African Americans and European Americans

[‡] Significant p-values (< 0.05) for test of difference between African Americans and European Americans

[†] Chi-square test for difference by level of prostate cancer aggressiveness

Table 3

Associations between dietary and supplemental vitamin E intake and prostate cancer aggressiveness among African Americans (n = 1,023) and European Americans (n = 1,079).

			Crude [a]		Adjusted [b]	
	Cases/controls [c]	**% of cases/% of controls**	**OR (95% CI)**	**P (trend)**	**OR (95% CI)**	**p (trend)**
Dietary α–tocopherol mg/day (median)						
African American						
Q1: 0.51 – 6.37 (4.82)	51/205	25/25	1.00 (ref)	0.35	1.00 (ref)	0.20
Q2: 6.38 – 9.25 (7.72)	42/204	20/25	0.86 (0.55–1.35)		0.73 (0.43–1.22)	
Q3: 9.26 – 13.32 (10.85)	59/204	29/25	1.21 (0.79–1.85)		1.08 (0.62–1.86)	
Q4: 13.33 – 44.62 (17.13)	54/204	26/25	1.13 (0.73–1.74)		0.58 (0.28–1.19)	
European American						
Q1: 1.67 – 7.02 (5.55)	54/229	33/25	1.00 (ref)	0.18	1.00 (ref)	0.006
Q2: 7.03 – 9.54 (8.35)	35/229	21/25	0.66 (0.41–1.06)		0.54 (0.32–0.91)	
Q3: 9.55 – 12.79 (11.01)	39/229	24/25	0.77 (0.49–1.22)		0.51 (0.29–0.88)	
Q4: 12.80 – 53.18 (16.28)	36/228	22/25	0.68 (0.43–1.09)		0.34 (0.17–0.69)	
Vitamin E supplements [d] α–tocopherol, mg/day (median)						
African American						
Q1: non-users	141/488	68/60	1.00 (ref)	0.01	1.00 (ref)	0.15
Q2: 1.13 – 11.25 (10.13)	24/91	12/11	0.95 (0.58–1.55)		1.09 (0.65–1.84)	
Q3: 11.26 – 22.50 (22.50)	27/136	13/17	0.69 (0.44–1.09)		0.83 (0.51–1.34)	
Q4: 22.51 – 472.50 (180.00)	14/102	7/12	0.48 (0.26–0.87)		0.64 (0.34–1.21)	
European American						
Q1: non-users	65/396	40/43	1.00 (ref)	0.26	1.00 (ref)	0.38
Q2: 0.96 – 20.25 (13.50)	37/178	22/19	1.24 (0.79–1.94)		1.40 (0.87–2.24)	
Q3: 20.26 – 45.00 (22.50)	37/172	22/19	1.25 (0.80–1.95)		1.41 (0.88–2.27)	
Q4: 45.01 – 914.34 (193.50)	25/169	15/18	0.83 (0.50–1.37)		0.93 (0.55–1.58)	
Total α–tocopherol, Diet + supplement, mg/day (median)						
African American						

Prostate. Author manuscript; available in PMC 2016 October 20.

			Crude [a]		Adjusted [b]	
	Cases/controls [c]	**% of cases/% of controls**	**OR (95% CI)**	**P (trend)**	**OR (95% CI)**	**p (trend)**
Q1: 0.52 – 9.14 (6.64)	51/205	25/25	1.00 (ref)	0.27	1.00 (ref)	0.36
Q2: 9.15 – 15.83 (11.93)	60/204	29/25	1.24 (0.81–1.89)		1.27 (0.78–2.06)	
Q3: 15.84 – 28.54 (20.71)	52/204	25/25	1.07 (0.69–1.65)		0.88 (0.50–1.52)	
Q4: 28.55 – 482.37 (42.87)	43/204	21/25	0.87 (0.55–1.37)		0.89 (0.51–1.58)	
European Americans						
Q1: 2.40 – 11.40 (8.04)	43/229	26/25	1.00 (ref)	0.47	1.00 (ref)	0.55
Q2: 11.41 – 23.34 (15.56)	39/228	24/25	0.94 (0.58–1.51)		0.85 (0.50–1.42)	
Q3:23.35 – 39.69 (31.55)	44/230	27/25	0.98 (0.62–1.56)		0.99 (0.59–1.65)	
Q4:39.70 – 927.34 (201.33)	38/228	23/25	0.84 (0.52–1.36)		0.83 (0.49–1.40)	
Vitamin E supplement type (range, median, mg/day) [d]						
African American						
Non-users	141/488	69/60	1.00 (ref)	0.12	1.00 (ref)	0.59
Multivitamins only (1.13 – 180.00, 13.50)	51/251	25/31	0.72 (0.50–1.03)		0.85 (0.58–1.26)	
Single nutrient vitamin E supplement only (1.35 – 450.00, 180.00)	9/30	4/3	1.01 (0.47–2.18)		1.30 (0.56–3.01)	
Multivitamin + Single nutrient vitamin E supplement, (23.63 – 472.50, 193.50)	5/48	2/6	0.36 (0.14–0.93)		0.52 (0.19–1.38)	
European American						
Non-users	65/396	39/43	1.00 (ref)	0.14	1.00 (ref)	0.22
Multivitamins only (2.17 – 180.00, 20.48)	75/345	46/38	1.29 (0.89–1.85)		1.45 (0.98–2.15)	
Single nutrient vitamin E supplement only (0.96 – 450.00, 180.00)	8/50	5/5	0.91 (0.41–2.02)		0.96 (0.42–2.18)	
Multivitamin + Single nutrient vitamin E supplement, (23.63 – 914.85, 200.25)	16/124	10/14	0.71 (0.39–1.28)		0.81 (0.43–1.50)	
Dietary β–tocopherol mg/day (median)						
African American						
Q1: 0.03 – 0.25 (0.19)	53/208	26/26	1.00 (ref)	0.05	1.00 (ref)	0.22
Q2: 0.26 – 0.37 (0.31)	42/204	20/25	0.85 (0.54–1.33)		0.92 (0.56–1.50)	
Q3: 0.38 – 0.52 (0.44)	46/206	22/25	0.91 (0.58–1.41)		1.04 (0.62–1.77)	
Q4: 0.53 – 1.73 (0.69)	65/199	32/24	1.03 (0.92–2.12)		1.08 (0.73–2.59)	
European American						
Q1: 0.07 – 0.28 (0.22)	53/242	32/26	1.00 (ref)	0.44	1.00 (ref)	0.09

			Crude [a]		Adjusted [b]	
	Cases/controls [c]	% of cases/% of controls	OR (95% CI)	P (trend)	OR (95% CI)	p (trend)
Q2: 0.29 – 0.38 (0.33)	37/239	23/26	0.71 (0.44–1.12)		0.64 (0.39–1.05)	
Q3: 0.39 – 0.52 (0.45)	37/217	23/24	0.79 (0.50–1.26)		0.65 (0.39–1.11)	
Q4: 0.53 – 1.62 (0.63)	37/217	23/24	0.79 (0.50–1.26)		0.56 (0.30–1.02)	
Dietary γ–tocopherol mg/day (median)						
African American						
Q1: 0.03 – 12.37 (9.07)	46/204	22/25	1.00 (ref)	0.08	1.00 (ref)	0.59
Q2: 12.38 – 18.55 (15.48)	47/205	23/25	1.08 (0.68–1.70)		1.02 (0.61–1.71)	
Q3: 18.56 – 27.04 (22.78)	51/204	25/25	1.14 (0.73–1.78)		0.94 (0.53–1.69)	
Q4: 27.05 – 67.95 (33.75)	62/204	30/25	1.44 (0.94–2.22)		0.83 (0.39–1.80)	
European American						
Q1: 2.68 – 12.66 (9.83)	39/230	24/25	1.00 (ref)	0.82	1.00 (ref)	0.05
Q2: 12.67 – 17.35 (15.14)	47/228	29/25	1.26 (0.79–2.01)		1.14 (0.68–1.91)	
Q3: 17.36 – 22.85 (19.57)	41/229	25/25	1.10 (0.68–1.78)		0.77 (0.43–1.37)	
Q4: 22.86 – 55.13 (28.34)	37/228	22/25	1.00 (0.61–1.64)		0.52 (0.24–1.13)	
Dietary δ–tocopherol mg/day (median)						
African Americans						
Q1: 0.08 – 1.63 (1.22)	41/206	20/25	1.00 (ref)	0.04	1.00 (ref)	0.69
Q2: 1.64 – 2.56 (2.11)	52/204	25/25	1.33 (0.84–2.10)		1.25 (0.75–2.08)	
Q3: 2.57 – 3.71 (3.09)	48/204	23/25	1.21 (0.76–1.93)		0.92 (0.52–1.65)	
Q4: 3.72 – 13.09 (4.92)	65/203	32/25	1.64 (1.06–2.54)		0.97 (0.47–1.98)	
European American						
Q1: 0.34 – 1.69 (1.31)	36/231	22/25	1.00 (ref)	0.29	1.00 (ref)	0.007
Q2: 1.70 – 2.37 (2.05)	56/229	34/25	1.64 (1.03–2.60)		1.40 (0.85–2.30)	
Q3: 2.38 – 3.46 (2.84)	43/228	26/25	1.24 (0.76–2.01)		0.91 (0.52–1.60)	
Q4: 3.47 – 10.92 (4.29)	29/227	18/25	0.89 (0.52–1.50)		0.45 (0.21–0.95)	

Cases: high aggressive prostate cancers; Controls: low and intermediate aggressive cancers

[a] Adjusted for age

[b] additional adjustment for PSA screening history, BMI, smoking status, education, income, NSAIDs use, total dietary fat intake, and study site

[c] Some of the categories may not sum to the total sample size due to missing data

[d] Converted as 1 IU of Vitamin E = 0.45 mg α–tocopherol [25].

Table 4

Associations between adipose tissue tocopherol levels and prostate cancer aggressiveness among African (n = 361) and European (n = 584) Americans.

			Crude [a]		Adjusted [b]	
	Cases/Controls [c]	% of cases/% of controls	(OR 95% CI)	p (trend)	(OR 95% CI)	p (trend)
α–tocopherol mcg/g (median)						
African American						
Q1: 0.30 – 14.50 (6.45)	18/74	27/25	1.00 (ref)	0.41	1.00 (ref)	0.60
Q2: 14.51 – 36.30 (24.10)	13/73	20/25	0.74 (0.33–1.63)		0.58 (0.24–1.39)	
Q3: 36.56 – 108.90 (61.12)	22/74	33/25	1.18 (0.58–2.41)		0.98 (0.44–2.16)	
Q4: 108.91 – 1313.10 (183.27)	13/73	20/25	0.68 (0.31–1.50)		0.66 (0.27–1.62)	
European American						
Q1: 0.20 – 26.50 (12.50)	16/123	18/25	1.00 (ref)	0.71	1.00 (ref)	0.68
Q2: 26.51 – 78.80 (45.60)	26/123	29/25	1.54 (0.78–3.04)		1.54 (0.74–3.23)	
Q3: 79.81 – 204.70 (125.70)	26/123	29/25	1.39 (0.70–2.76)		1.58 (0.75–3.33)	
Q4: 204.71 – 1585.60 (328.90)	21/123	24/25	1.12 (0.55–2.27)		1.43 (0.66–3.11)	
γ–tocopherol mcg/g (median)						
African American						
Q1: 0.10 – 10.4 0 (5.29)	17/73	26/25	1.00 (ref)	0.60	1.00 (ref)	0.77
Q2: 10.41– 28.90 (18.10)	19/72	28/25	1.21 (0.58–2.54)		1.03 (0.45–2.35)	
Q3: 28.91– 64.10 (41.70)	15/72	23/25	0.86 (0.40–1.87)		0.72 (0.31–1.69)	
Q4: 64.11 – 972.90 (92.42)	15/72	23/25	0.90 (0.42–1.96)		0.93 (0.40–2.16)	
European American						
Q1: 0.20 – 13.40 (6.20)	16/122	18/25	1.00 (ref)	0.79	1.00 (ref)	0.91
Q2: 13.41 – 37.90 (23.90)	28/122	31/25	1.70 (0.87–3.32)		1.39 (0.68–2.83)	
Q3: 37.91 – 72.08 (52.10)	27/122	30/25	1.59 (0.81–3.12)		1.18 (0.57–2.46)	
Q4: 72.34 – 318.70 (110.74)	19/122	21/25	1.14 (0.55–2.33)		1.20 (0.56–2.55)	
δ–tocopherol mcg/g (median)						
African American						
Q1: 0.40 – 3.20 (2.00)	14/68	23/25	1.00 (ref)	0.45	1.00 (ref)	0.73

			Crude [a]		Adjusted [b]	
	Cases/Controls [c]	% of cases/% of controls	(OR 95% CI)	p (trend)	(OR 95% CI)	p (trend)
Q2: 3.21 – 6.43 (4.66)	20/67	33/25	1.39 (0.64–2.99)		1.46 (0.63–3.36)	
Q3: 6.44 – 11.54 (8.71)	14/67	23/25	0.97 (0.43–2.20)		1.17 (0.48–2.85)	
Q4: 11.55 – 101.40 (17.80)	12/67	20/25	0.86 (0.37–2.01)		1.01 (0.40–2.55)	
European American						
Q1: 0.30 – 2.99 (1.60)	17/117	20/25	1.00 (ref)	0.98	1.00 (ref)	0.81
Q2: 3.00 – 6.70 (4.60)	26/119	31/25	1.37 (0.70–2.68)		1.20 (0.58–2.49)	
Q3: 6.71 – 11.60 (8.69)	23/115	27/25	1.28 (0.64–2.55)		1.10 (0.52–2.32)	
Q4: 11.61 – 54.11 (16.10)	19/116	22/25	1.12 (0.55–2.29)		0.99 (0.46–2.13)	

[a] Adjusted for age

[b] Additional adjustment for education level, study site, BMI, smoking history, family history of CaP, PSA screening history, total fat intake, whether treatment started at time of interview, and comorbidities.

[c] Some of the categories may not sum to the total sample size due to missing data.