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Author Manuscript

Cancer Causes Control. Author manuscript; available in PMC 2010 September 1.

Published in final edited form as:

Cancer Causes Control. 2009 September ; 20(7): 1161–1171. doi:10.1007/s10552-009-9304-4.

Association of selenium, tocopherols, carotenoids, retinol, and 15-isoprostane F_{2t} in serum or urine with prostate cancer risk: the multiethnic cohort

Jasmeet K. Gill and Adrian A. Franke

Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813, USA

J. Steven Morris

Research Reactor Center, University of Missouri–Columbia, Columbia, USA

Robert V. Cooney, Lynne R. Wilkens, Loic Le Marchand, and Marc T. Goodman

Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813, USA

Brian E. Henderson

Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Laurence N. Kolonel

Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813, USA

Abstract

Objective—We examine the association of antioxidants and 15-isoprostane F_{2t} with risk of prostate cancer.

Methods—We conducted a nested case–control study of serum antioxidant biomarkers (selenium, tocopherols, carotenoids, and retinol) and a urinary oxidation biomarker (15-isoprostane F_{2t}) with risk of prostate cancer within the Multiethnic Cohort. Demographic, dietary, and other exposure information was collected by self-administered questionnaire in 1993–1996. We compared prediagnostic biomarker levels from 467 prostate cancer cases and 936 cancer free controls that were matched on several variables. Multivariate conditional logistic regression models were used to compute adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results—We observed that there was no overall association of serum concentrations of antioxidants and urinary concentrations of 15-isoprostane F_{2t} with risk of prostate cancer or risk of advanced prostate cancer. However, we did observe an inverse association for serum selenium only among African-American men (*p* trend = 0.02); men in the third tertile of selenium concentrations had a 41% lower risk (95% CI: 0.38–0.93) of prostate cancer when compared to men in the first tertile.

Conclusions—Overall, our study found no association of serum antioxidants or 15-isoprostane F_{2t} with the risk of prostate cancer. The observed inverse association of selenium with prostate cancer in African-Americans needs to be validated in other studies.

Keywords

Prostate cancer; Risk; Ethnicity; Cohort; Serum antioxidants

Introduction

Prostate cancer is the leading cancer among males in the US. Over 186,320 new cases were expected in 2008 [1]. Although it is well established that the risk of prostate cancer changes with age and differs across ethnicities, evidence for modifiable risk factors such as diet is limited and inconsistent. Oxidative stress has been linked to carcinogenesis [2] and many studies have focused on measures of exposure to antioxidants such as selenium, tocopherols, retinol, and carotenoids (particularly lycopene). The results from studies on antioxidants and prostate cancer have been inconsistent. A 2004 review of diet and prostate cancer risk illustrates the variations in results from prospective cohort studies using biomarkers to measure some or all of the aforementioned antioxidants. Three studies produced inverse effect estimates for one or more of the antioxidants (<0.80), two studies had effect estimates near 1.0, one study showed an increase in risk (>1.20), and two studies had effect estimates ranging from 0.50 to 1.08 [3]. Isoprostanes are compounds produced from the peroxidation of arachidonic acid by free radicals [4]. 15-isoprostane F_{2t} is a biologically active isoprostane known to be a reliable biomarker of lipid peroxidation [4], but, few epidemiologic studies have examined the association of circulating 15-isoprostane F_{2t} levels with the risk of cancer.

In this analysis we examined serum biomarkers for antioxidants (selenium, tocopherols, retinol, lycopene, and other carotenoids), as well as a urine biomarker of oxidation (15-isoprostane F_{2t}) in a nested case–control study of prostate cancer. Cases and controls were identified through the prospective Multiethnic Cohort Study of African-Americans, Caucasians, Japanese-Americans, Latinos, and Native-Hawaiians.

Materials and methods

Study population

Details of the Multiethnic Cohort (MEC) were described previously [5]. In brief, data were collected between 1993 and 1996 using a 26-page self-administered mail questionnaire sent to residents of Hawaii and California, mainly Los Angeles County. Subjects were identified through drivers' license records in both locations; in addition, voter registration records were used in Hawaii and Health Care Financing Administration files in California. African-Americans, Caucasians, Japanese-Americans, Latinos, and Native-Hawaiians were the primary targets for recruitment, but a small number of persons of other ethnicities were also enrolled in the study. Participation in the cohort was limited to people of ages between 45 and 75 years in 1993, except for Native-Hawaiians who were recruited at 42 years and older. The MEC dataset consists of 215,251 people, including 96,382 are men. The Institutional Review Boards of both the University of Hawaii and the University of Southern California approved the study.

Biospecimen sub-cohort

Participants for this nested case–control study were men from the MEC who had provided prediagnostic blood specimens primarily between 2001 and 2006 ($n = 29,009$). Cohort members were contacted by letter, and then by phone, to request biological specimens (blood and urine). For those who agreed, a short screening questionnaire (use of anticoagulants, blood clotting disorders, etc.) and updated information on a few items (including current smoking habits, weight, vitamin supplement use, colonoscopy/sigmoidoscopy) was administered by

phone. Specimens were collected at a clinical laboratory or in the subjects' home and were processed within four hours of collection. Blood samples were drawn in a fasting state for most cases (83%), and were separated into components (serum, plasma, buffy coat, red cells) under yellow light and stored in multiple 0.5 cc aliquots in vapor phase of liquid nitrogen freezers. First morning urines were collected in Los Angeles and overnight samples were collected in Hawaii. The urine samples were distributed into ten 2 ml aliquots for each subject and stored in freezers at -80°C .

Selection of cases and controls

Cases of prostate cancer, diagnosed after specimen collection, were identified through linkages with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the Hawaii Tumor Registry, all members of the Surveillance, Epidemiology, and End Results program supported by the National Cancer Institute. Advanced prostate cancer cases were defined as: (1) having either regional or distant spread, and/or (2) having a Gleason score ≥ 7 irrespective of tumor stage. A total of 467 prostate cancer cases were identified for this study. Controls were selected among the male biorepository participants, who were alive and free of prostate cancer at the age of diagnosis of the case. A control pool that met the matching criteria was created for each case, from which two controls were randomly selected. Matching criteria included geographic site (HI, LA), ethnicity, age at specimen collection (± 1 year), date (± 1 month) and time of day (± 2 h) of sample collection, and fasting status (<6, 6–7, 8–9, 10+ h). Two cases had an extra control matched to ensure availability of an appropriate urine specimen.

Laboratory analysis

Study samples were analyzed for selenium adjusted for sodium via neutron activation analysis. This procedure and the associated quality control practices used by this laboratory in epidemiology studies have recently been described [6]. Each sample was individually placed in the top-center position of a shuttle rabbit and irradiated for 5 s in the Row I position using the pneumatic-tube irradiation facility at the University of Missouri-Columbia Research Reactor (MURR). After a decay of 15 s, each sample was real-time counted for 30 s using a high-resolution gamma-rays spectrometer. The 161.9 keV gamma-rays from the decay of Se-77 m are used to determine Se concentrations by standard comparison.

Plasma concentrations of tocopherols, retinol, lycopene, and other carotenoids were determined by high-pressure liquid chromatography with photo diode array detection slightly modified from our earlier protocol [7] by using 0.3 ml plasma, followed by partitioning into hexane, drying, and redissolving in 0.15 ml of the HPLC mobile phase. Twenty microliter were injected onto a Gemini C18 analytical column ($150 \times 3.2 \text{ mm}^2$, $3 \mu\text{M}$) coupled to a Gemini C18 pre-column ($4 \times 3.0 \text{ mm}^2$, $10 \mu\text{M}$) (Phenomenex; Torrance, CA) using isocratic elution with a mobile phase of 665 ml methanol/218 ml dichloromethane/117 ml acetonitrile/2 ml aq. bis-tris propane (0.5 M pH 6.8) and containing 0.25 g/l BHT at 0.3 ml/min. Carotenoids and tocopherols (alpha, gamma + beta, and delta-tocopherol) were quantitated by absorbance at 450 and 295 nm, respectively. Beta-tocopherol could not be separated from gamma-tocopherol in this HPLC system. However, because the contribution of beta-tocopherol to the combined total is minor, the beta/gamma values in our tables reflect mostly gamma-tocopherol. All urine samples were measured for 15-isoprostane F_{2t} adjusted for creatinine using a radioimmunoassay. A solution of radiolabeled tracer (about 833 Bq/ml or 50,000 dpm/ml in the RIA buffer) solution was added to tubes containing a mix of the urine sample with bovine- γ -globulin and RIA buffer and an antibody solution. After incubating overnight and centrifugating the next day, the radioactivity of the samples were measured by a β -liquid scintillation counter (Packard TriCarb 2100 TR). Urinary creatinine concentrations were

measured with a Roche-Cobas MiraPlus chemistry analyzer using a kit from Randox Laboratories (Crumlin, UK) that is based on a kinetic modification of the Jaffe reaction.

Serum analysis was performed on 461 cases (99%) and 931 controls (99%) for selenium, and on 382 cases (82%) and 765 controls (82%) with fasting for 8 h or more for tocopherols, retinol, lycopene, and other carotenoids. Urinalysis for concentration of 15-isoprostane F_{2t} was performed on 290 cases (62%) and 543 controls (58%) who provided first morning or overnight urine samples. The remaining respondents (177 cases and 393 controls) did not provide the requested first morning or overnight urine sample. Therefore, they were asked to provide a spot urine sample which was inadequate for performing 15-isoprostane F_{2t} urinalysis. The intra-assay coefficients of variation were 2.3% for serum selenium, 1.5% for serum alpha-tocopherol, 1.9% for serum gamma-tocopherol, 1.5% for total serum tocopherol, 3.8% for serum retinol, 2.6% for serum beta-carotene, 2.3% for serum lycopene, 2.0% for beta-cryptoxanthin, 3.1% for lutein + zeaxanthin, 1.9% for total serum carotenoids, and 10.1% for urinary 15-isoprostane F_{2t} .

Statistical analysis

We applied multivariate conditional logistic regression models of prostate cancer incidence, with case-control matched sets as the strata variable, to estimate odds ratios (ORs) and 95% CIs. We created quartiles for each biomarker variable based on the distribution of cases and controls combined, and represented them with three indicator variables. Individual trend variables were created by assigning them the median values of each quartile grouping. We adjusted for the following covariates in our models: body mass index (≤ 25 , >25 to ≤ 30 , >30 kg/m^2), family history of prostate cancer in father and/or brother(s) (yes, no), years of education (continuous), age at blood draw (continuous), and number of fasting hours prior to blood draw (continuous). The latter two variables accounted for any systematic differences in these variables within matched sets. We repeated the analyses using only controls with PSA (prostate specific antigen) values ≤ 4.0 ng/ml and their matched cases to minimize any potential bias due to disease misclassification. We also performed analyses by using only advanced prostate cases and their matched controls. We examined effect modification in all case-control sets by BMI and smoking status using a likelihood ratio test comparing a model with interaction terms to a model with main effects only. We also performed analyses using tertiles of each biomarker for the three ethnic groups with adequate sample size (African-Americans, Japanese-Americans, and Latinos). We tested for the interaction of ethnicity with each biomarker using the Wald test.

Results

Means for body mass index and education were similar for cases and control subjects (Table 1). However, cases had a higher proportion of men with a family history of prostate cancer than control subjects (12.6% vs. 8.3%, respectively). Median values and interquartile ranges of the biomarkers were similar for cases and controls. Cases had slightly higher medians for four analytes—gamma-tocopherol, beta-carotene, total carotenoids, and retinol—while controls were slightly higher for the rest. The average time from date of specimen collection to diagnosis for cases was 2 years (data not shown).

We observed no association between serum selenium levels and risk of prostate cancer (Table 2). Although the ORs for serum selenium levels were all below one (OR = 0.82, 95% CI: 0.59–1.14, for the fourth quartile compared to first quartile), the trend was not monotonic or statistically significant (p trend = 0.25). We observed no association between serum concentrations of alpha-tocopherol, gamma-tocopherol, or total tocopherols and risk of prostate cancer. The odds ratios for the fourth quartile compared to the first quartile of serum

concentration were 0.95 (95% CI: 0.65–1.41), 0.95 (95% CI: 0.65–1.39), and 1.12 (95% CI: 0.75–1.67) for alpha-tocopherol, gamma-tocopherol, and total tocopherols, respectively.

Serum beta-carotene concentrations were not associated with risk of prostate cancer, though the ORs were inverse; men in the fourth quartile had an OR = 0.81 (95% CI: 0.55–1.18) when compared to men in the first quartile. Risk estimates for serum lycopene concentrations decreased monotonically with increased serum concentrations, but none of the risk estimates were statistically significant; for the fourth quartile compared to the first quartile, the odds ratio was 0.78 (95% CI: 0.53–1.14) and there was no statistically significant trend ($p = 0.16$). We observed no association between serum beta-cryptoxanthin or serum lutein + zeaxanthin and risk of prostate cancer. The odds ratios for the fourth quartile compared to the first quartile were 0.97 (95% CI: 0.66–1.43) and 1.08 (95% CI: 0.73–1.61), respectively. There was also no association between total serum carotenoids and risk of prostate cancer. For the fourth quartile compared to the first quartile, the odds ratio was 1.00 (95% CI: 0.67–1.49). Serum retinol was not associated with the risk of prostate cancer either. The odds ratio for the fourth quartile compared to the first quartile was 1.05 (95% CI: 0.70–1.58). Finally, urinary 15-isoprostane F_{2t} levels showed no association with prostate cancer risk; the odds ratio was 0.90 (95% CI: 0.55–1.49) for the fourth quartile compared to first quartile.

Further adjustment by smoking status did not materially change any of the results presented above (data not shown). When all of the analyses were restricted to control subjects with PSA values ≤ 4.0 and their matched cases, our conclusions were unchanged (data not shown). We also examined effect modification by BMI (< 25 and ≥ 25 kg/m²) and smoking status (never/ever smoker) and found no statistical evidence for differences across the strata (data not shown).

We repeated the analyses by ethnic groups (Table 3) to see whether the findings in Table 2 appeared consistent. Due to the limited sample size, we were unable to perform analyses on Native-Hawaiians and Caucasians. The results by ethnic group were most interesting for selenium. Although the overall analysis in Table 2 indicated a non-statistically significant decrease in risk of prostate cancer across quartiles of selenium concentrations, the ethnic-specific analysis was not so consistent. We observed no evidence of an inverse association between selenium and prostate cancer in Japanese-Americans and Latinos, but there was a statistically significant inverse association in the African-American men (p trend = 0.02). Men in the third tertile had a 41% lower risk of prostate cancer when compared to men in the first tertile (95% CI: 0.38–0.93). However, a test for interaction of selenium and ethnic group was not statistically significant (p interaction = 0.17).

As in Table 2, the ethnic-specific results for total tocopherols, gamma-tocopherol, and alpha-tocopherol confirmed the lack of any association with prostate cancer risk. Similar to the overall results, the ethnic-specific results in Table 3 for beta-carotene serum levels were mostly below 1.0 and not statistically significant. In Table 2, there was a suggestion of a decreasing trend in risk with increased serum concentrations of lycopene though the trend was not statistically significant (p trend = 0.16). However, in the ethnic-specific analysis, the results for lycopene were not consistent, and weakened this observation. The results for beta-cryptoxanthin varied across ethnic groups, with the Latino men having risk estimates well above 1.0 and the Japanese-American and African-American men with estimates below 1.0. However, the test for interaction was not statistically significant (p interaction = 0.48). Similar to the results in Table 2, the ethnic-specific results for lutein + zeaxanthin showed no association with risk of prostate cancer. We also observed no associations with retinol or 15-isoprostane F_{2t} and risk of prostate cancer across ethnic groups.

Table 4 shows results of an analysis restricted to men with advanced prostate cancer and their matched controls. The lack of association between any of the biomarkers and risk of prostate

cancer persisted and the risk estimates were generally similar to those for all prostate cancer cases in Table 2 with the exception of alpha-tocopherol and lutein + zeaxanthin. The risk estimates for alpha-tocopherol changed direction, but were still not statistically significant. For lutein + zeaxanthin, the odds ratio for advanced prostate cancer (Table 4) among men in the fourth quartile compared to the first quartile of serum concentration was double that of all prostate cancer cases (Table 2); however, both estimates were not statistically significant.

Discussion

In this study, we observed no clear associations between serum levels of selenium, alpha-tocopherol, gamma-tocopherol, total tocopherols, beta-carotene, lycopene, beta-cryptoxanthin, lutein + zeaxanthin, total carotenoids, retinol, or urinary 15-isoprostane F_{2t} and the risk of prostate cancer. We did observe an inverse association for serum selenium, but only among African-American men. Analyses restricted to men with advanced prostate cancer did not show any statistically significant associations. The findings were relatively unchanged when analyses were restricted to controls with normal PSA values and their matched cases. Thus, our data do not support the role of antioxidants as preventing initiation or progression of prostate cancer. Our general findings are in concordance with a recent null paper from our research group that examined dietary and supplemental intake of beta-carotene, lycopene, beta-cryptoxanthin, lutein, and alpha-tocopherol and prostate cancer incidence in the entire cohort [8].

Our overall null results on serum selenium agree with two prospective studies [9,10] but differ from the findings of two others [11,12]. One study found men in the highest quintile of serum selenium to be protected against prostate cancer when compared to the lowest quintile (OR = 0.38, 95% CI: 0.17–0.85), but no trend with serum concentration was observed [11]. The Physician's Health Study investigators observed a protective effect against prostate cancer for the 5th quintile of plasma selenium when cases were limited to those with baseline PSA levels >4.0 and to those with advanced prostate cancer [12]. However, we could not confirm the advanced prostate cancer finding in our study. Interestingly, a selenium intervention trial for skin cancer found selenium supplementation to decrease risk of prostate cancer by 50–65%, though this was not an a priori hypothesis [13,14].

We did observe a decreased risk of prostate cancer with increasing serum selenium levels among the African-American men in our study. Although our sample size was limited, we did run a model with Caucasian men to see if there was any association with selenium and observed no association with risk of prostate cancer. Interestingly, the African-American men in our study had the lowest mean selenium levels of all the ethnic groups (0.134 $\mu\text{g/g}$ compared to 0.139 $\mu\text{g/g}$ for Caucasians, 0.149 $\mu\text{g/g}$ for Japanese-Americans, 0.136 $\mu\text{g/g}$ for Latinos, and 0.139 $\mu\text{g/g}$ for Native-Hawaiians). The Physician's Health Study investigators observed a 51% decreased risk of prostate cancer (95% CI: 0.28–0.86) in their analysis of cases with baseline PSA >4 ng/ml [12]. Our sample size precluded testing the association further in African-American men with advanced prostate cancer or with PSA levels >4.0, however, the African-American men did have the highest PSA levels of all the ethnic groups. The ethnic differences we observed could also be indicative of ethnic-specific polymorphisms in selenoprotein gene families, such as glutathione peroxidases. The results of the large ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT) of chemoprevention for prostate cancer will be of particular interest with regard to prostate cancer risk, since it includes African-American men. Therefore, until we accrue more African-American cases or the SELECT trial publishes its ethnic-specific results, our finding will need to be interpreted with caution.

We also found that total serum tocopherol, alpha-tocopherol, and gamma-tocopherol were not associated with risk of prostate cancer, a result reported by several other prospective studies

[11,15-19] including the European Prospective Investigation into Cancer and Nutrition (EPIC) [20]. However, baseline serum alpha-tocopherol measurements were inversely associated with prostate cancer in the Alpha-tocopherol, Beta-carotene Cancer Prevention Study (ATBC) among smokers in Finland [21]. Men in the highest quintile of serum alpha-tocopherol had a 20% reduction in risk of prostate cancer (95% CI: 0.66–0.96) compared to men in the lowest quintile. An earlier nested case–control study within the ATBC also observed a decrease in risk of prostate cancer among men in the highest quintiles of alpha-tocopherol and gamma-tocopherol, though both were not statistically significant [22]. Two studies reported statistically significant decrease in the risk of prostate cancer for men in the highest quintile of gamma-tocopherol compared to the lowest quintile [11,17]. A Swiss study found low levels of tocopherol to be associated with an increased risk of prostate cancer mortality [23].

We observed no association between serum lycopene and prostate cancer risk, similar to four other prospective studies [16,17,20,24]. In contrast, the Physician's Health Study observed a 40% reduction in risk of all prostate cancer and a 60% reduction in risk of aggressive prostate cancer for men in the highest quintile of serum lycopene [19]. However, our advanced prostate cancer results and those of two other studies [20,24] were not in accordance with these findings.

We observed no association with total carotenoid serum concentrations, beta-carotene, beta-cryptoxanthin, or lutein + zeaxanthin concentrations, and risk of prostate cancer. Three prospective studies support our beta-carotene results [16,17,20]. However, a prospective study in Finland observed an 80% decrease in risk of prostate cancer among men in the highest quintile of serum beta-carotene [25] while a prospective study in the US found high serum beta-carotene to increase risk of prostate cancer [24]. Several studies support our null findings for beta-cryptoxanthin, and lutein + zeaxanthin [17,19,20,24].

Serum retinol levels were not associated with risk of prostate cancer in our study, a finding supported by several other studies [9,16,17,20,23,25]. In contrast, the Physician's Health Study observed a 56% increased risk of prostate cancer (95% CI: 1.07–2.27) for men in the fifth quintile compared to the first quintile of retinol concentration.

A unique aspect of this prospective study was the examination of urinary 15-isoprostane F_{2t} levels in association with prostate cancer risk. Studies of the oxidation and prostate cancer using sera have found greater levels of lipid peroxidation in prostate cancer cases when compared to controls and men with benign prostatic hyperplasia [26,27]. A recent study of breast cancer and urinary 15-isoprostane F_{2t} levels observed a statistically significant positive trend in risk of breast cancer with increasing 15-isoprostane F_{2t} levels [28]. Additional studies of prostate cancer and 15-isoprostane F_{2t} levels will be needed in the future to determine its value as a biomarker of risk.

Inconsistencies in the results of studies of circulating antioxidants with the risk of prostate cancer are difficult to reconcile. Population differences in diet and metabolism that might influence serum or urinary antioxidant concentrations is one possible source of variation between studies. However, median antioxidant values across studies were reasonably comparable. For example, the median lycopene values for cases and controls in our study (383.9 and 399.3 ng/ml for all cases and controls and 461.3 and 418.1 ng/ml for Caucasian cases and controls, respectively) was similar to values in three [16,17,19] of four prospective studies. Only one study [24] had lycopene values that were much higher than the other studies and they observed no association with risk of prostate cancer. Likewise, for beta-carotene, the Finnish study that found it to decrease risk of prostate cancer [25] had mean (no medians reported) beta-carotene values similar to [17] or lower than [16] studies—including ours—that found no association. Furthermore, the prospective study which found high beta-carotene levels to increase risk of prostate cancer [24] had median beta-carotene levels lower than our study, but

higher than the Finnish study [25]. Perhaps part of the reason for the inconsistencies is due to differences in time from blood draw to case ascertainment across studies, variations in laboratory methods, or uncontrolled confounding.

Our study had several strengths. It is a prospective study and specimens were collected before prostate cancer diagnosis. We were able to examine the consistency of risk estimates for three ethnic groups, African-Americans, Latinos, and Japanese-Americans. Other prospective studies consisted mainly of Caucasian men. A limitation of our study was the lack of power in the analysis of advanced prostate cancer and the analysis by ethnic groups. With the advent of regular PSA screening, most cases of prostate cancer are being diagnosed early, so that assembling large numbers of advanced cases is becoming increasingly difficult. However, in the future, as more cases accrue in large cohorts, these types of analyses will need to be re-examined.

Overall, our study found no association of selenium, tocopherols, lycopene, other carotenoids, or 15-isoprostane F_{2t} with the risk of prostate cancer. The observed inverse association of selenium with prostate cancer in African-Americans is intriguing, but needs to be validated in other studies, as do our null findings for 15-isoprostane F_{2t} .

Acknowledgments

This study has been supported by the National Cancer Institute grants P01 CA 33619 and R37 CA 54281. One of the authors (JKG) was supported by a postdoctoral fellowship on Grant R25 CA 90956.

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Table 1

Characteristics of cases and controls

	Cases	Controls
<i>Covariates</i>	<i>n</i> = 467	<i>n</i> = 936
Body mass index (kg/m ²), mean (SD)	26.2 (4.0)	26.5 (4.1)
Age at blood draw (years), mean (SD)	68.9 (7.1)	68.7 (7.1)
Fasting hours prior to blood draw, mean (SD)	11.8 (4.8)	11.9 (4.9)
High school education or less (%)	34.0	34.4
Family history of prostate cancer (%)	12.6	8.3
Ethnicity (%)		
African-American	46.9	46.8
Caucasian	13.1	13.1
Japanese-American	18.8	18.8
Latino	17.8	17.7
Native-Hawaiian	3.4	3.5
<i>Analytes median (interquartile range)</i>		
Selenium (µg/g)	0.13 (0.12–0.15)	0.14 (0.13–0.15)
Alpha-tocopherol (mg/dl)	1.41 (1.06–1.97)	1.42 (1.07–1.93)
Gamma-tocopherol (mg/dl)	0.17 (0.09–0.26)	0.16 (0.09–0.26)
Total tocopherols (mg/dl)	1.65 (1.33–2.18)	1.66 (1.33–2.11)
Beta-carotene (µg/dl)	24.3 (13.6–40.9)	23.7 (14.1–40.1)
Lycopene (µg/dl)	38.4 (27.5–52.7)	39.9 (28.9–54.3)
Beta-cryptoxanthin (µg/dl)	20.8 (14.1–31.8)	21.0 (13.4–32.6)
Lutein + zeaxanthin (µg/dl)	40.8 (32.8–53.2)	41.2 (32.3–52.4)
Total carotenoids (µg/dl)	158.9 (121.5–210.2)	157.5 (120.5–205.4)
Retinol (µg/dl)	117.6 (97.0–141.8)	115.1 (96.0–140.3)
15-isoprostane F _{2t} (ng/mg)	3.25 (2.54–4.54)	3.37 (2.71–4.41)

Table 2
Odds ratios and 95% CI for risk of prostate cancer across quartiles of serum selenium, tocopherols, lycopene, other carotenoids, retinol, and urinary 15-isoprostane F_{2t}

Variable	Quartiles of concentration levels				p trend
	1	2	3	4	
Selenium (µg/g)					
Median level	0.12	0.13	0.14	0.16	—
No. of cases	123	111	105	111	—
Base model OR ^a	1	0.83 (0.60–1.14)	0.76 (0.55–1.05)	0.82 (0.59–1.14)	0.27
Fully adjusted OR ^b	1	0.84 (0.61–1.16)	0.75 (0.53–1.04)	0.82 (0.59–1.14)	0.25
Alpha-tocopherol (mg/dl)					
Median level	0.90	1.24	1.62	2.51	—
No. of cases	93	94	88	97	—
Base model OR ^a	1	0.99 (0.69–1.42)	0.89 (0.62–1.29)	1.00 (0.69–1.47)	0.95
Fully adjusted OR ^b	1	0.95 (0.66–1.37)	0.83 (0.57–1.21)	0.95 (0.65–1.41)	0.89
Gamma-tocopherol (mg/dl)					
Median level	0.06	0.13	0.20	0.34	—
No. of cases	98	88	93	93	—
Base model OR ^a	1	0.80 (0.55–1.15)	0.98 (0.69–1.41)	0.91 (0.63–1.31)	0.91
Fully adjusted OR ^b	1	0.76 (0.53–1.11)	0.95 (0.66–1.38)	0.95 (0.65–1.39)	0.83
Total tocopherols (mg/dl)					
Median level	1.14	1.51	1.86	2.71	—
No. of cases	89	99	84	100	—
Base model OR ^a	1	1.14 (0.80–1.63)	0.92 (0.63–1.35)	1.16 (0.78–1.71)	0.55
Fully adjusted OR ^b	1	1.12 (0.79–1.61)	0.87 (0.59–1.28)	1.12 (0.75–1.67)	0.66
Beta-carotene (µg/dl)					
Median level	9.8	18.9	29.8	59.7	—
No. of cases	98	89	92	93	—
Base model OR ^a	1	0.86 (0.60–1.23)	0.87 (0.61–1.26)	0.89 (0.62–1.30)	0.73
Fully adjusted OR ^b	1	0.83 (0.58–1.20)	0.77 (0.53–1.13)	0.81 (0.55–1.18)	0.40
Lycopene (µg/dl)					

Variable	Quartiles of concentration levels				p trend
	1	2	3	4	
Median level	22.0	33.9	46.2	65.6	—
No. of cases	96	96	92	88	—
Base model OR ^a	1	0.96 (0.67–1.37)	0.89 (0.62–1.27)	0.80 (0.55–1.18)	0.23
Fully adjusted OR ^b	1	0.96 (0.67–1.38)	0.85 (0.59–1.22)	0.78 (0.53–1.14)	0.16
Beta-cryptoxanthin (µg/dl)					
Median level	13.8	22.1	30.8	56.2	—
No. of cases	85	104	92	91	—
Base model OR ^a	1	1.31 (0.92–1.86)	1.12 (0.78–1.61)	1.04 (0.71–1.51)	0.74
Fully adjusted OR ^b	1	1.36 (0.95–1.95)	1.19 (0.77–1.62)	0.97 (0.66–1.43)	0.43
Lutein + Zeaxanthin (µg/dl)					
Median level	26.9	36.8	46.3	62.5	—
No. of cases	90	98	88	96	—
Base model OR ^a	1	1.12 (0.78–1.59)	0.92 (0.64–1.33)	1.08 (0.74–1.60)	0.86
Fully adjusted OR ^b	1	1.15 (0.80–1.66)	0.97 (0.66–1.41)	1.08 (0.73–1.61)	0.89
Total carotenoids (µg/dl)					
Median level	100.4	139.1	180.4	256.8	—
No. of cases	89	94	92	97	—
Base model OR ^a	1	1.08 (0.76–1.54)	1.02 (0.71–1.47)	1.08 (0.73–1.59)	0.79
Fully adjusted OR ^b	1	1.06 (0.74–1.53)	0.97 (0.67–1.41)	1.00 (0.67–1.49)	0.87
Retinol (µg/dl)					
Median level	83.5	106.7	126.2	163.0	—
No. of cases	91	88	97	96	—
Base model OR ^a	1	0.98 (0.69–1.40)	1.19 (0.83–1.71)	1.16 (0.79–1.72)	0.34
Fully adjusted OR ^b	1	0.95 (0.66–1.37)	1.13 (0.78–1.64)	1.05 (0.70–1.58)	0.66
15-isoprostane F _{2t} (ng/mg)					
Median level	2.26	3.01	3.76	5.58	—
No. of cases	72	71	66	73	—
Base model OR ^a	1	0.63 (0.39–1.03)	0.60 (0.37–0.98)	0.81 (0.50–1.31)	0.84
Fully adjusted OR ^b	1	0.71 (0.43–1.17)	0.65 (0.39–1.08)	0.90 (0.55–1.49)	0.96

Variable	Quartiles of concentration levels				p trend
	1	2	3	4	
<p>Cases and controls were matched on geographic area, ethnicity, age at specimen collection, date and time of specimen collection, and fasting status. Cases with missing covariate data were excluded from the analyses ($n = 11$ for selenium, $n = 10$ for other antioxidants, $n = 8$ for 15-isoprostane F_{2t})</p> <p>^a Adjusted by conditional logistic regression for age at specimen collection and fasting hours prior to blood draw as continuous variables</p> <p>^b Adjusted by conditional logistic regression for age at specimen collection, fasting hours prior to blood draw, body mass index, family history of prostate cancer, and education</p>					

Table 3

Odds ratios and 95% CI for risk of prostate cancer by ethnicity, across tertiles of serum selenium, tocopherols, lycopene, other carotenoids, retinol, and urinary 15-isoprostane F_{2t}

Variable	Tertiles of serum concentration levels												<i>p</i> interaction ^b			
	African-Americans			Japanese-Americans			Latinos									
	1	2	3	1	2	3	1	2	3	1	2	3				
Selenium																
No. of cases	95	68	42	17	18	52	26	28	24							
Multivariate OR ^a	1	0.79 (0.53–1.18)	0.59 (0.38–0.93)	1	0.66 (0.30–1.45)	1.18 (0.57–2.43)	1	0.83 (0.42–1.65)	1.17 (0.56–2.45)							0.17
<i>p</i> trend		0.02			0.34			0.64								
Alpha-tocopherol																
No. of cases	69	52	30	14	22	45	26	20	23							
Multivariate OR	1	1.10 (0.64–1.63)	0.88 (0.49–1.57)	1	0.59 (0.25–1.38)	0.82 (0.38–1.79)	1	0.97 (0.44–2.14)	1.02 (0.45–2.28)							0.91
<i>p</i> trend		0.67			0.48			0.94								
Gamma-tocopherol																
No. of cases	45	43	63	38	27	16	22	23	24							
Multivariate OR	1	0.67 (0.39–1.16)	0.85 (0.51–1.41)	1	0.96 (0.51–1.83)	0.97 (0.42–2.21)	1	0.77 (0.37–1.59)	0.89 (0.41–1.92)							0.70
<i>p</i> trend		0.76			0.93			0.80								
Total tocopherols																
No. of cases	65	52	34	13	25	43	29	18	22							
Multivariate OR	1	0.95 (0.58–1.55)	1.12 (0.63–2.00)	1	0.97 (0.43–2.20)	1.19 (0.54–2.63)	1	0.92 (0.42–2.01)	0.74 (0.32–1.71)							0.98
<i>p</i> trend		0.69			0.91			0.49								
Beta-carotene																
No. of cases	52	48	51	17	20	44	31	22	16							
Multivariate OR	1	0.78 (0.47–1.30)	0.88 (0.53–1.47)	1	0.65 (0.28–1.51)	0.98 (0.46–2.09)	1	0.76 (0.36–1.61)	1.06 (0.43–2.64)							0.47
<i>p</i> trend		0.79			0.60			0.92								
Lycopene																
No. of cases	66	41	44	27	23	31	25	25	19							
Multivariate OR	1	0.65 (0.40–1.06)	0.70 (0.41–1.17)	1	0.52 (0.25–1.07)	0.68 (0.33–1.38)	1	1.08 (0.51–2.29)	1.23 (0.50–3.04)							0.33
<i>p</i> trend		0.18			0.34			0.63								
Beta-cryptoxanthin																
No. of cases	61	54	36	19	16	46	18	30	21							

Variable	Teriles of serum concentration levels												<i>p</i> interaction ^b
	African-Americans			Japanese-Americans			Latinos						
	1	2	3	1	2	3	1	2	3	1	2	3	
Multivariate OR	0.82 (0.51–1.31)	0.89 (0.51–1.56)	0.89 (0.51–1.56)	1	0.61 (0.26–1.40)	0.73 (0.35–1.53)	1	1.91 (0.85–4.26)	1.39 (0.57–3.41)	0.48			
<i>p</i> trend	0.70				0.68			0.64					
Lutein + Zeaxanthin													
No. of cases	54	57	40	12	31	38	28	19	22				
Multivariate OR	1.20 (0.75–1.92)	0.80 (0.46–1.37)	0.80 (0.46–1.37)	1	1.76 (0.73–4.19)	1.10 (0.45–2.70)	1	0.75 (0.35–1.60)	2.40 (1.00–5.78)	0.13			
<i>p</i> trend	0.40				0.64			0.06					
Total carotenoids													
No. of cases	63	47	41	13	25	43	27	28	14				
Multivariate OR	1	0.83 (0.52–1.31)	0.84 (0.50–1.40)	1	0.85 (0.38–1.91)	0.94 (0.43–2.07)	1	1.38 (0.68–2.83)	0.96 (0.40–2.28)	0.84			
<i>p</i> trend		0.51			0.99			0.94					
Retinol													
No. of cases	64	47	40	19	31	31	26	27	16				
Multivariate OR	0.88 (0.54–1.43)	0.75 (0.43–1.29)	0.75 (0.43–1.29)	1	0.88 (0.40–1.97)	1.03 (0.43–2.47)	1	1.42 (0.72–2.79)	1.11 (0.49–2.51)	0.42			
<i>p</i> trend	0.30				0.88			0.71					
15- <i>s</i> -proprastane F _{2t}													
No. of cases	38	36	37	37	25	9	13	16	19				
Multivariate OR	1	0.89 (0.41–1.90)	1.13 (0.52–2.43)	1	0.82 (0.38–1.78)	0.90 (0.40–2.02)	1	2.30 (0.67–7.93)	2.21 (0.68–7.15)	0.22			
<i>p</i> trend		0.67			0.85			0.31					

^a Cases and controls were matched on geographic area, ethnicity, age at specimen collection, date and time of specimen collection, and fasting status

^a Adjusted by conditional logistic regression for age at specimen collection, fasting hours prior to blood draw, body mass index, family history of prostate cancer, and education

^b *p*-value for Wald test of interaction between the three ethnic groups and each biomarker

Table 4
Odds ratios and 95% CI for risk of advanced^a prostate cancer across quartiles of serum selenium, tocopherols, lycopene, other carotenoids, retinol, and urinary 15-isoprostane F_{2t}^b

Variable	Quartiles of serum antioxidant levels				p trend
	1	2	3	4	
Selenium					
No. of cases	32	33	32	26	
Multivariate OR ^c	1	0.99 (0.52–1.89)	0.87 (0.44–1.72)	0.99 (0.46–2.15)	0.92
Alpha-tocopherol					
No. of cases	24	27	32	21	
Multivariate OR	1	1.28 (0.63–2.59)	1.16 (0.57–2.33)	1.13 (0.50–2.54)	0.87
Gamma-tocopherol					
No. of cases	30	27	24	23	
Multivariate OR	1	0.74 (0.36–1.50)	0.75 (0.38–1.50)	0.85 (0.40–1.82)	0.74
Total tocopherols					
No. of cases	25	30	29	20	
Multivariate OR	1	1.41 (0.72–2.77)	1.15 (0.57–2.30)	0.90 (0.40–2.01)	0.63
Beta-carotene					
No. of cases	28	25	23	28	
Multivariate OR	1	0.92 (0.45–1.87)	0.64 (0.30–1.34)	0.70 (0.31–1.55)	0.50
Lycopene					
No. of cases	37	26	21	20	
Multivariate OR	1	0.49 (0.16–1.51)	0.57 (0.21–1.57)	1.86 (0.65–5.31)	0.14
Beta-cryptoxanthin					
No. of cases	27	40	20	17	
Multivariate OR	1	1.72 (0.89–3.34)	0.79 (0.38–1.65)	0.87 (0.38–1.98)	0.47
Lutein + Zeaxanthin					
No. of cases	31	31	22	20	
Multivariate OR	1	1.21 (0.64–2.30)	1.07 (0.54–2.11)	2.03 (0.86–4.76)	0.17
Total carotenoids					
No. of cases	32	27	25	20	
Multivariate OR	1	1.30 (0.66–2.57)	1.08 (0.53–2.17)	0.90 (0.40–2.02)	0.76

Variable	Quartiles of serum antioxidant levels				p trend
	1	2	3	4	
Retinol					
No. of cases	35	27	21	21	
Multivariate OR	1	0.84 (0.44–1.63)	1.35 (0.64–2.85)	1.22 (0.54–2.73)	0.48
15-isoprostane F _{2t}					
No. of cases	18	17	18	21	
Multivariate OR	1	0.49 (0.16–1.51)	0.57 (0.21–1.57)	1.85 (0.65–5.31)	0.14

^a Advanced prostate cancer cases were defined as: (1) having either regional or distant spread and/or (2) having a Gleason score ≥ 7 irrespective of tumor stage

^b Cases and controls were matched on geographic area, ethnicity, age at specimen collection, date and time of specimen collection, and fasting status

^c Adjusted by conditional logistic regression for age at specimen collection, fasting hours prior to blood draw, body mass index, family history of prostate cancer, and education