Published in final edited form as:

Cancer Causes Control. 2011 November ; 22(11): 1483–1495. doi:10.1007/s10552-011-9822-8.

Associations of serum vitamin A and carotenoid levels with markers of prostate cancer detection among US men

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Abstract

Associations of serum vitamin A and carotenoid levels with markers of prostate cancer detection were evaluated among 3927 U.S. men, 40–85 years of age, who participated in the 2001–2006 National Health and Nutrition Examination Surveys. Five recommended definitions of prostate cancer detection were adopted using total and free prostate specific antigen (tPSA and fPSA) laboratory measurements. Men were identified as high-risk based on alternative cut-offs, namely, tPSA>10 ng/ml, tPSA>4 ng/ml, tPSA> 2.5 ng/ml, %fPSA<25% and %fPSA<15%. %fPSA was defined as (fPSA÷tPSA)×100%. Serum levels of vitamin A (retinol, retinyl esters) and carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein+zeaxanthin, lycopene) were defined as quartiles and examined as risk/protective factors for PSA biomarkers. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using binary logistic models. After adjustment for known demographic, socioeconomic and lifestyle confounders, high serum levels of retinyl esters (tPSA>10 ng/ml: Q4vs.Q1→OR=0.38, 95% CI: 0.14–1.00) and α-carotene (%fPSA<15%: Q4vs.Q1→OR=0.49, 95% CI: 0.32–0.76) were associated with a lower odds whereas high serum level of lycopene (tPSA>2.5 ng/ml: Q4vs.Q1→OR=1.49, 95% CI: 1.01–2.14) was associated with a greater odds of prostate cancer detection. Apart from the three significant associations observed, no other exposure-outcome association was significant. Monitoring specific antioxidant levels may be helpful in early detection of prostate cancer.

Keywords

vitamin A; carotenoids; prostate cancer; prostate-specific antigen

INTRODUCTION

The burden of prostate cancer (PCa) remains a public health concern. PCa is the most commonly diagnosed non-dermatological cancer and the second leading cause of cancer-related death among U.S. men, with an estimated 217,730 new cases and 32,050 deaths in 2010 (1). In the U.S., a sharp rise in screen-detected PCa cases has been coupled with a more gradual decline in PCa deaths over the past 20 years (2). These secular trends have been attributed not only to aging of the U.S. population but also to adoption of serum prostate-specific antigen (PSA) testing as a routine method to screen for PCa (2, 3). Despite

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its low sensitivity and specificity, the PSA test is twice as likely as the digital rectal exam (DRE) to identify early-stage PCa (2). The American Cancer Society recommends that men should have the opportunity to make an informed decision about whether to be screened for PCa after discussion with their health care provider, who can inform them about uncertainties, risks, and potential benefits of PCa screening; discussion should start at age 50 years for average-risk men with an estimated life expectancy of 10 years or more, but can start as early as age 40 years for higher-risk men (<http://www.cancer.org/Cancer/ProstateCancer/MoreInformation/ProstateCancerEarlyDetection/prostate-cancer-early-detection-ac-s-recommendations>). The American Urological Association recommends offering PCa testing to asymptomatic men 40 years of age or older who wish to be screened with an estimated life expectancy of more than 10 years (<http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf>).

Although the U.S. Preventive Services Task Force recognizes that evidence for or against PCa screening is insufficient (4), the PSA test is routinely performed by clinical practitioners for the early detection of PCa, and this has resulted in a greater yield of localized PCa among U.S. men (5). Total PSA (tPSA) and free PSA (fPSA) are measured and percent free PSA (percentfPSA) is calculated. Whereas tPSA threshold values (tPSA>10 ng/ml, tPSA>4.0 ng/ml or tPSA >2.5 ng/ml) for recommending a prostate biopsy are still under debate (2, 5, 6), threshold values for percentfPSA (percentfPSA<25 percent or percentfPSA<15 percent) have been proposed as additional PCa screening tools (5, 6).

Dietary antioxidants which include vitamin A and carotenoids may provide an avenue for PCa prevention. Besides age and family history, few risk factors for PCa are currently established. Whereas the etiology of PCa is largely unknown (7–16), inflammation caused by infection, hormonal changes, physical trauma, urine reflux and dietary habits, is believed to play a role in prostate carcinogenesis (7, 17–20). Micronutrients with anti-oxidative properties are primarily obtained through dietary consumption of fruits and vegetables and are capable of scavenging harmful reactive oxygen species (ROS) that are generated during inflammatory processes. In sum, the biological mechanism underlying a protective role for vitamin A, carotenoids and other antioxidants against prostate carcinogenesis may include reversal of DNA damage by ROS (7).

To date, no studies using a representative sample of the U.S. population have examined levels of vitamin A (retinol, retinyl esters) and other carotenoids (α -carotene, β -carotene, β -cryptoxanthin, lutein, zeaxanthin, lycopene) as risk/protective factors for PSA biomarkers. Epidemiological evidence for the protective effect of lycopene – a carotenoid found in tomato and tomato-based products – against screen-detected PCa has yet to be established through randomized controlled trials (21). Recent studies based on the National Health and Nutrition Examination Surveys (NHANES) have described an inverse relationship between tPSA level and body mass index (BMI) (2, 22). Higher plasma volume and lower testosterone levels are physiological alterations that may explain this relationship as well as the delayed detection, reduced incidence and worse outcome of PCa among obese U.S. men (2, 23). One study suggested that regular use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce tPSA level, a further evidence linking inflammatory processes, and ultimately antioxidants, to PCa detection among U.S. men (7). Finally, one study reported a limited influence of diet and exercise on tPSA, but did not evaluate the potential role of antioxidants (23).

The purpose of this study is to analyze the cross-sectional associations of serum vitamin A and carotenoid levels with markers of PCa detection (tPSA and percentfPSA) among U.S. men, using 2001–2006 NHANES data.

MATERIALS AND METHODS

Data source

The NHANES is a cross-sectional, nationally representative survey designed to assess the health and nutritional status of the U.S. civilian non-institutionalized population (5). The survey is unique in that it combines interviews and physical examinations. Stratified, multistage, probability survey samples were obtained based on the selection of counties, blocks, households and persons within households (5), with over-sampling of individuals with low income, adults aged 60 years or older, African-Americans, and Mexican-Americans (24). Demographic, socioeconomic and health data were collected by trained staff using household interviews. In addition, a mobile examination center (MEC) run by health professionals collected numerous measurements including anthropometric, blood pressure, and laboratory tests, either on all or a sub-group of study participants. Since 1999, NHANES has become a continuous surveillance system. For the current analyses, we combined the 2001–2002, 2003–2004 and 2005–2006 NHANES datasets. Response rates for the 2001–2002, 2003–2004, and 2005–2006 surveys were 84 percent, 79 percent and 80 percent for the interview component, and 80 percent, 76 percent and 77 percent for the physical examination component, respectively (24). Informed consent was obtained for all participants and the institutional review board of the National Center for Health Statistics, Centers for Disease Control and Prevention approved all protocols for the NHANES (25).

Inclusion and exclusion criteria

A total of 4869 2001–2006 NHANES participants were eligible for PSA testing based on gender (male) and age (≥ 40 years). Of 4270 offered PSA testing, 4166 were willing to undergo PSA testing, 102 refused and 2 did not provide a response. A total of 38 subjects had missing data on exclusion criteria and 201 subjects fulfilled at least one of the exclusion criteria (Current infection or inflammation of the prostate gland ($n=50$); DRE in the past week ($n=60$); Prostate biopsy in the past 30 days ($n=10$); Cytoscopy in the past 30 days ($n=16$); History of PCa ($n=179$)) (5, 7). Of the remaining 3927 subjects who satisfied inclusion/exclusion criteria, 107 had missing data on tPSA and fPSA levels. Complete-case analyses were performed on subsets of 3820 subjects with known PSA laboratory measurements. Overall, subjects with known ($n=3820$) and missing ($n=107$) PSA biomarker data were similar in terms of age, education, marital status, household income and smoking history, but differed according to race (Hispanic: 8.6% vs. 5.7%; Non-Hispanic White: 79.1% vs. 72.4%; Non-Hispanic Black: 8.8% vs. 19.1%; Other: 3.6% vs. 2.8%; $P=0.01$).

Laboratory measurements

Blood samples were collected by venipuncture, centrifuged, and sera were frozen at -20°C within 1 hour of phlebotomy (5). Within 1 week, frozen specimens were sent on dry ice to the University of Washington Medical Center, Department of Laboratory Medicine, Immunology Division Laboratory (Seattle, WA), where they were kept at -70°C until analyzed (5).

Hybritech tPSA and fPSA monoclonal antibody assays (Hybritech, San Diego, CA) were applied on Beckman Coulter Access analyzer (Fullerton, CA) (2, 5, 6, 25). The coefficient of variation (CV) for tPSA test was less than 4.8 percent and that of fPSA was less than 5.5 percent (5). In this study, tPSA measurements were considered abnormal if found to exceed pre-specified cutpoints, namely 2.5 ng/mL, 4.0 ng/mL or 10.0 ng/mL (2, 5, 6). Similarly, percentfPSA measurements, defined as $(\text{fPSA} \div \text{tPSA}) \times 100$ percent, were considered abnormal based on two alternative cutpoints, namely <15 percent or <25 percent (5, 6).

High performance liquid chromatography with photodiode array detection was used to measure serum concentrations of retinol, α -tocopherol, γ -tocopherol, retinyl palmitate, retinyl stearate, α -carotene, trans- β -carotene, cis β -carotene, β -cryptoxanthin, lutein +zeaxanthin, trans-lycopene and total lycopene. In this study, vitamin A was measured as retinol and retinyl esters (sum of retinyl palmitate and retinyl stearate). Additionally, α -carotene, β -carotene (cis+trans), β -cryptoxanthin, lutein+zeaxanthin, total lycopene and total carotenoids were also examined. The CVs for vitamin A and β -carotene were previously reported to be less than 5%, whereas the CVs for other carotenoids were less than 11%. Furthermore, the lower limits of detection for retinol, retinyl esters and carotenes were 0.003 $\mu\text{g/mL}$, 0.005 $\mu\text{g/mL}$ and 0.003 $\mu\text{g/mL}$, respectively. Vitamin A and carotenoid measurements were analyzed in relation to tPSA and percentfPSA biomarkers, after categorization into quartiles (Q1, Q2, Q3, Q4).

Covariates

A priori confounders for the hypothesized relationships were identified from previously conducted research of similar populations of U.S. men that focused on determinants of abnormal PSA levels (7, 23, 25–27). These include age ('40–49', '50–59', '60–69', '70–79', '80+' years), race/ethnicity ('Hispanic', 'Non-Hispanic White', 'Non-Hispanic Black, Other'), education ('Less than High School', 'High School', 'More than High School'), marital status ('Ever married', 'Never married'), household income ('< \$20,000', '\$20,000') and BMI ('<25 kg/m^2 ', '25–<30 kg/m^2 ', '≥ 30 kg/m^2 '). Smoking history ('Current smoker', 'Former smoker', 'Never smoker') was considered but not included in the final model due to sample size limitations. Other obesity-related characteristics including insulin resistance, metabolic syndrome, physical exercise and dietary intake (total energy, percent carbohydrate and percent fat) were not considered as potential confounders due to large percentages of missing data.

Statistical analysis

Descriptive, bivariate and multivariate analyses were conducted using STATA version 8. Using survey commands, we applied recommended sub-sample weights for the period of 2001–2006. MEC exam weights were used for all analyses. Masked variance units were used to estimate variances through a Taylor series linearization method. The NHANES analytic guidelines which include sub-sample and MEC exam weights can be located at the following address: http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/analytical_guidelines.htm. Bivariate associations were analyzed using Pearson's Chi-square tests for independence and one-way analysis of variance tests. Unadjusted and fully-adjusted beta coefficients and odds ratios (OR) with their 95 percent confidence intervals (CI) were computed using *svylogit* and *svyreg* commands, taking sampling weights into consideration. These weights were defined to represent the U.S. civilian, non-institutionalized population while accounting for over-sampling of certain age and ethnic groups and interview non-response. Primary analyses were based on logistic regression (dichotomous outcomes) using quartiles for the exposures; further analyses were performed using linear regression (continuous outcomes) with exposures defined as quartiles, but also examining fractional polynomials and quadratic terms (28). Specifically, we compared the odds of PCa detection between the upper and lower quartiles (Q4 vs. Q1) of vitamin A and carotenoid levels. In addition, the associations of serum vitamin A and carotenoid concentrations with tPSA (Log_e transformed) and (fPSA÷tPSA)×100 percent were evaluated using least squares regression models. Sensitivity analyses were also conducted using multivariable linear regression models for log-transformed PSA biomarkers as a function of carotenoids defined as continuous variables, and quadratic terms of exposure variables were added to better characterize the non-linear associations between carotenoids and PSA biomarkers after

adjustment for confounders. Sampling weights were applied in all models. Two-sided statistical tests were performed at an alpha level of 0.05.

RESULTS

The study sample consisted of 3927 U.S. male adults with a mean (SEM) age of 55.13 (0.29) years. Nearly 79 percent were non-Hispanic White, 57 percent had more than high school education, 89 percent were ever married, 86 percent had a household income of \$20000 or higher, 25 percent were current smokers and 34 percent were obese (Table 1).

tPSA level was < 2.5 ng/mL, 2.5-<4.0 ng/mL, 4.0-<10 ng/mL and ≥ 10 ng/mL in 87.5 percent, 6.3 percent, 5.1 percent and 0.9 percent of the study sample, respectively. Whereas 65.2 percent had a percentfPSA ≥ 25.0 percent, 26.5 percent had a percentfPSA of 15-<25 percent and 8.3 percent had a percentfPSA of < 15 percent. Antioxidant concentrations ranged between 0.075 μmol/L for α-carotene and 2.32 μmol/L for retinol (Table 2).

As shown in Table 3 significant differences in log-transformed tPSA and percentfPSA levels were observed according to selected socio-demographic characteristics. When defined as dichotomous variables, tPSA levels consistently increased with age, but no similar trends were noted for percentfPSA. There were no significant racial or ethnic disparities, except for Hispanics who had the highest proportion of percentfPSA < 25 percent. Two biomarkers of PCa detection (tPSA > 2.5 ng/ml and percentfPSA < 15 percent) were inversely associated with level of education. A significantly higher proportion having tPSA > 2.5 ng/ml was found in the ever versus never married group of men. Having a household income of at least \$20000 was associated with a higher prevalence of tPSA > 4 ng/mL, tPSA > 2.5 ng/mL and percentfPSA < 15 percent. Current smokers had the lowest proportion of men having tPSA > 4 ng/mL, whereas BMI was inversely related to tPSA > 4 ng/mL and tPSA > 2.5 ng/mL.

As shown in Table 4 log-transformed tPSA differed significantly according to quartiles of retinol, α-carotene, β-carotene, lycopene and total carotenoids. Similarly, log-transformed percentfPSA differed according to quartiles of retinol alone. Cross-tabulation of PSA biomarkers (defined as dichotomous variables) against quartiles of retinol, retinyl esters and carotenoids suggested that two tPSA thresholds, namely tPSA > 4 ng/mL and tPSA > 2.5 ng/mL, were directly related to β-carotene and inversely related to lycopene.

Table 5 displays regression models for fully-adjusted associations of serum levels of retinol, retinyl esters and carotenoids with PSA levels. Multivariate logistic regression models suggested that high serum levels of retinyl esters (tPSA > 10 ng/ml: Q4 vs. Q1 → OR = 0.38, 95% CI: 0.14, 1.00) and α-carotene (percentfPSA < 15 percent: Q4 vs. Q1 → OR = 0.49, 95% CI: 0.32, 0.76) were associated with a lower odds of PCa detection. Whereas crude analyses implied an inverse relationship between high serum level of lycopene and PCa detection (tPSA > 2.5 ng/ml: Q4 vs. Q1 → OR = 0.64, 95% CI: 0.46, 0.88), the same exposure was found to be directly related to screen-detected PCa after adjustment for a priori confounders (tPSA > 2.5 ng/ml: Q4 vs. Q1 → OR = 1.49, 95% CI: 1.01, 2.14). Test-for-trend analyses in fully adjusted logistic regression models suggest that tPSA > 10 ng/mL was inversely associated with increasing levels of lutein+zeaxanthin ($P_{\text{trend}}=0.04$) and that %fPSA < 15 ng/ml was inversely associated with increasing levels of α-carotene ($P_{\text{trend}}=0.004$). Retinol and other carotenoids were not significantly associated with PSA biomarkers defined as dichotomous outcomes.

Finally, multiple linear regression models were constructed whereby outcomes were defined as continuous variables and exposures were defined as quartiles or continuous variables whereby fractional polynomials and quadratic terms were explored (continuous outcomes). After adjustment for known demographic, socioeconomic and lifestyle confounders, no

consistent trends could be identified through linear regression models for log-transformed tPSA and percentfPSA. When added to multivariable linear regression models, most quadratic terms were found to be statistically non-significant. One exception was the model where log-transformed percentfPSA was the dependent variable and beta-carotene was the independent variable. This finding may suggest that the relationship between β -carotene and percentfPSA is non-linear (data not shown).

DISCUSSION

In this cross-sectional study of U.S. men, we evaluated whether retinol, retinyl esters, α -carotene, β -carotene, β -cryptoxanthin, lutein, zeaxanthin, lycopene and total carotenoids were associated with PCa detection, using established threshold values for tPSA and percentfPSA. Multivariate logistic models were constructed after adjustment for age, race/ethnicity, education, marital status, household income and BMI. Three key results were obtained. First, the odds of having tPSA > 10 ng/ml were significantly reduced in the upper versus the lower quartiles of retinyl esters. Second, the odds of having percentfPSA < 15 percent were significantly reduced in the upper versus the lower quartiles of α -carotene. Third, the odds of having tPSA > 2.5 ng/ml were significantly increased in the upper versus the lower quartiles of lycopene.

The findings that serum levels of retinyl esters and α -carotene were inversely related to serum tPSA and percentfPSA threshold levels, respectively, are consistent with the idea that carotenoids have anti-oxidative properties that can reverse DNA damage produced by inflammatory processes leading to screen-detected PCa (29). This protective effect is unlikely due to physiological factors such as increased plasma volume or reduced testosterone levels, since BMI was taken into account in the multivariate analysis (2, 23).

Carotenoids are naturally occurring tetraterpenoid (40 carbon atoms) organic pigments found mostly in photosynthetic organisms, namely plants as well as some algae, fungi and bacteria (30). To date, over 600 carotenoids have been identified and classified as xanthophylls (lutein, zeaxanthin) which contain oxygen or carotenes (α -carotene, β -carotene, lycopene) which are devoid of oxygen (30). In humans, carotenoids can enhance the immune system and have anti-oxidative properties as they are efficient free-radical scavengers (30).

The finding that lycopene was positively associated with a tPSA threshold level is inconsistent with current knowledge (31–42). Previous studies have mostly implied either no association or a protective effect of lycopene against PCa. For instance, a recent meta-analysis of seven studies suggested that serum lycopene was inversely related to PCa risk [RR=0.74 (0.59–0.92)] (43). In our study, it is plausible that the distinct relationships observed between serum levels of lycopene and tPSA before and after adjustment for selected characteristics is due to strong confounding by at least one of the variables that we adjusted for. We performed separate analyses for each of the selected characteristics and identified age as being the strongest confounder, based on changes in the estimated odds ratios for the hypothesized relationship. In addition, adjusting for age, but not for other characteristics, was sufficient to change the direction of the relationship between lycopene and tPSA from inverse in the unadjusted model to direct in the adjusted model. In our study, unadjusted results overwhelmingly support an inverse association between lycopene and tPSA level, as hypothesized. However, this association changed to positive after simply adjusting for age. Confounding bias by older age is plausible as it is associated with both higher PSA levels and potentially higher lycopene intake (through supplements or diet) as a consequence of prostate health awareness. These relationships would result in an upward bias, as is seen in the adjusted models. Major epidemiologic studies of the inverse

association between lycopene intake and PCa were published in the late-1990's and early-2000's, which could have influenced lycopene intake among older men with higher PSA levels (and perhaps undiagnosed, underlying disease) in the current study period from 2001–2006. Furthermore, the effect of lycopene at the 2.5 ng/mL threshold was shown to be different from its effect at the 4 ng/mL and 10 ng/mL thresholds of tPSA. This finding implies the need for further investigation into the possibility of a non-linear relationship between lycopene and tPSA levels. According to Erdman and colleagues (44), lycopene has been shown to be the most potent *in vitro* antioxidant of all carotenoids tested; yet, *in vivo* studies do not support the hypothesis that lycopene (found at low concentrations in animal and human tissues) can protect against PCa through its anti-oxidative properties (44). The authors suggest alternative mediators of the protective effect of lycopene on screen-detected PCa, namely apoptosis, cell cycle inhibition, insulin-like growth factor 1 axis, gap junction communication, androgen status, detoxification enzymes and C-reactive protein (44).

The protective role of various carotenoids against chronic disease development remains controversial. Consumption of antioxidants, which include various carotenoids, through supplementation is not likely to be beneficial and excessive use of β -carotene may even be harmful (30). For instance, supplementation studies that used mega-doses of β -carotene have shown an increased risk of lung cancer among smokers (45–47). By contrast, the risk of dying from chronic diseases may be reduced among individuals who consume diets rich in carotenoids from natural sources, such as fruits and vegetables (30). Epidemiologic studies have shown that individuals who consume high levels of β -carotene in their diet and those with high levels of β -carotene in their blood have significantly reduced risk of lung cancer (30, 48–51). Because foods high in carotenoids are generally low in fat, gastrointestinal absorption and bioavailability of carotenoids may be enhanced by consumption of Gac fruit, crude palm oil, avocado fruit or oil (30).

Our study results should be interpreted with caution and in light of several limitations. First of all, we performed secondary analyses of the 2001–2006 NHANES, which is a series of cross-sectional studies. Thus, the temporal relationship between the main exposures (retinol, retinyl esters, carotenoids) and outcomes (tPSA and percentfPSA biomarkers) could not be ascertained through a cross-sectional design. Second, the 2001–2006 waves of NHANES did not include information on diagnosis and outcome of PCa, but only PSA test results. Third, a high percentage of NHANES men 40 years and older did not participate in PSA testing. Fourth, serum carotenoid levels may not correlate with actual levels of consumption through diet or supplementation. Finally, the statistically significant associations that were observed between selected carotenoids and PSA biomarkers cannot be ruled out as chance findings, given the large number of hypotheses being tested and the fact that two out of the three significant results were observed where the outcome was very sparse (tPSA > 10 ng/mL and percentfPSA < 15 percent).

In conclusion, serum levels of α -carotene, retinyl esters and lycopene were shown to be significantly associated with PSA biomarkers in the general population of U.S. men. Monitoring specific antioxidant levels may be helpful in early detection of PCa. Further studies are needed to elucidate the specific roles of carotenoids from various dietary sources for the purpose of PCa prevention.

Acknowledgments

ACKNOWLEDGMENTS AND FINANCIAL SUPPORT

This research was partly supported by the Intramural Research Program of the NIH, National Institute on Aging. We would like to thank Dr. Larry Brant and Dr. Joshua Goh for providing useful comments regarding the content of the manuscript.

Abbreviations

BMI	body mass index
CI	confidence interval
DRE	Digital rectal exam
fPSA	Free prostate-specific antigen
%fPSA	Percent free prostate-specific antigen
Q1	1 st quartile
Q2	2 nd quartile
Q3	3 rd quartile
Q4	4 th quartile
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PCa	Prostate cancer
PSA	Prostate-specific antigen
ROS	Reactive oxygen species
tPSA	Total prostate-specific antigen.

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Socio-Demographic and Lifestyle Characteristics of Study Participants – 2001–2006 National Health and Nutrition Examination Survey (N=3820)*

Table 1

	Sample Size	Population estimates
Age (years)	N=3820	Mean (SEM)
		55.09 (0.29)
	N=3820	Percent (SEM)
40–49	1115	39.4 (1.3)
50–59	827	29.4 (1.2)
60–69	840	16.5 (0.6)
70–79	655	10.3 (0.5)
80–85	383	4.1 (0.3)
Race and Ethnicity	N=3820	Percent (SEM)
Hispanic	805	8.6 (1.2)
Non-Hispanic White	2205	79.0 (1.6)
Non-Hispanic Black	709	8.8 (0.8)
Other	101	3.6 (0.4)
Education	N=3815	Percent (SEM)
Less than High School	1178	17.3 (0.9)
High School	876	25.6 (0.7)
More than High School	1761	57.1 (1.3)
Marital Status	N=3816	Percent (SEM)
Ever Married	3392	88.6 (0.7)
Never Married	424	11.4 (0.7)
Household income (\$)	N=3628	Percent (SEM)
< 20000	821	13.8 (0.8)
20000	2807	86.2 (0.8)
Smoking history	N=2644	Percent (SEM)
Current smoker	641	24.6 (1.2)
Former smoker	1069	37.4 (1.2)
Never smoker	934	37.9 (1.4)
Body mass index (kg/m2)	N=3713	Percent (SEM)
< 25	905	21.9 (0.8)

	Sample Size	Population estimates
25-<30	1621	43.8 (1.1)
30+	1187	34.2 (1.1)

SEM=Standard Error of the Mean;

* Out of 3927 subjects, 3820 (97.3%) had known tPSA level and 107 (2.7%) had missing data on tPSA level. These two groups differed significantly according to race, but none of the other socio-demographic characteristics.

Outcome and Exposure Characteristics of Study Participants – 2001–2006 National Health and Nutrition Examination Survey.

Table 2

	Sample Size	Population Estimates	Median (Inter-quartile range)
tPSA (ng/ml)	N=3820	Mean (SEM)	1.0 (0.6–1.9)
		Percent (SEM)	--
< 2.5	N=3820 3141	87.5 (0.7)	--
2.5-<4	323	6.3 (0.5)	--
4-<10	288	5.1 (0.4)	--
10+	68	0.9 (0.1)	--
% fPSA	N=3820	Mean (SEM)	28.8 (21.4–38.3)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
Retinol (μmol/L)	N=3823	Mean (SEM)	2.2 (1.9–2.6)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
Retinyl esters (μmol/L)	N=3586	Mean (SEM)	0.07 (0.05–0.1)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
α-carotene (μmol/L)	N=3817	Mean (SEM)	0.05 (0.03–0.09)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
β-carotene (μmol/L)	N=3709	Mean (SEM)	0.05 (0.1–0.4)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
β-cryptoxanthin (μmol/L)	N=3802	Mean (SEM)	0.2 (0.08–0.2)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
lutein+zeaxanthin (μmol/L)	N=3816	Mean (SEM)	0.3 (0.2–0.4)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
Lycopene (μmol/L)	N=3816	Mean (SEM)	0.4 (0.2–0.5)
		Percent (SEM)	--
< 15	N=3820 355	8.3 (0.6)	--
15-<25	1044	26.5 (1.0)	--
25+	2421	65.2 (1.3)	--
Total carotenoids (μmol/L)	N=3698	Mean (SEM)	1.1 (0.8–1.6)

%tPSA = Percent free prostate specific antigen; SEM=Standard Error of the Mean; tPSA = Total prostate specific antigen.

Table 3
Serum Prostate-Specific Antigen Levels by Socio-Demographic and Lifestyle Characteristics of Study Participants – 2001–2006 National Health and Nutrition Examination Survey

Total, Mean (SEM)	tPSA > 10 ng/ml (%)	tPSA > 4 ng/ml (%)	tPSA > 2.5 ng/ml (%)	%tPSA < 25% (%)	%tPSA < 15% (%)	tPSA Mean (SD)	%tPSA Mean (SD)
Age (years) (N=3820)							
40–49	0.23	1.40	3.40	32.02	7.86	0.93 (0.90)	31.3 (12.2)
50–59	0.51	3.36	8.81	36.05	7.73	1.33 (1.97)	30.2 (12.6)
60–69	1.54	9.14	20.72	39.54	8.72	2.06 (3.55)	29.6 (12.9)
70–79	2.76	19.40	33.15	32.68	9.98	2.89 (4.74)	30.3 (13.0)
80–85	5.24	25.36	40.31	37.89	10.6	4.32 (12.24)	31.3 (13.2)
P value	< 0.0001*	< 0.0001*	< 0.0001*	0.013*	0.54	< 0.0001**	0.013**
Race and Ethnicity (N=3820)							
Hispanic	0.96	4.18	10.96	43.14	11.97	1.85 (7.42)	28.4 (12.0)
Non-Hispanic White	0.95	6.24	12.66	34.10	7.67	1.88 (3.28)	31.1 (12.7)
Non-Hispanic Black	1.87	7.97	13.22	35.54	10.62	2.32 (5.64)	30.5 (13.3)
Other	0.0	3.21	9.55	27.66	6.98	1.34 (1.34)	33.6 (12.7)
P value	0.12	0.13	0.53	0.046*	0.11	0.08	< 0.0001**
Education (N=3815)							
Less than High School	1.49	8.49	16.96	35.99	10.98	2.42 (7.72)	29.8 (12.9)
High School	0.93	5.76	12.32	37.76	9.46	1.82 (3.13)	30.7 (12.9)
More than High School	0.88	5.54	11.61	33.08	6.94	1.69 (2.58)	30.8 (12.5)
P value	0.43	0.059	0.0023*	0.11	0.0071*	0.002**	0.036**
Marital Status (N=3816)							
Ever Married	1.05	6.33	13.00	34.83	8.22	1.99 (5.06)	30.5 (12.7)
Never Married	0.59	3.86	7.40	33.65	8.28	1.53 (3.08)	30.7 (13.1)
P value	0.32	0.078	0.0077*	0.73	0.97	< 0.0001**	0.98
Household income (\$) (N=3628)							

	tPSA > 10 ng/ml (%)	tPSA > 4 ng/ml (%)	tPSA > 2.5 ng/ml (%)	%tPSA < 25% (%)	%tPSA < 15% (%)	tPSA Mean (SD)	%tPSA Mean (SD)
< 20000	1.26	8.47	15.27	37.67	10.45	2.09 (4.17)	30.1 (13.0)
20000	0.90	5.73	11.85	34.25	7.90	1.87 (4.98)	30.7 (12.6)
P value	0.35	0.0002*	0.038*	0.29	0.037*	0.42	0.08
Smoking history (N=2644)							
Current smoker	0.63	3.46	10.10	37.52	9.50	1.56 (3.28)	29.5 (12.1)
Former smoker	0.92	7.33	14.09	31.50	7.26	2.00 (3.61)	31.6 (13.1)
Never smoker	0.90	6.63	12.64	31.94	7.04	1.92 (3.56)	31.5 (12.8)
P value	0.86	0.018*	0.18	0.13	0.33	0.0004**	0.004**
Body mass index (kg/m²) (N=3713)							
< 25	1.48	7.39	12.65	36.02	8.69	2.12 (4.07)	30.5 (12.9)
25-<30	1.05	6.70	13.94	34.07	8.42	2.00 (4.21)	30.3 (12.4)
30+	0.48	3.99	10.03	34.52	7.71	1.49 (2.11)	30.7 (12.9)
P value	0.15	0.0013*	0.013*	0.73	0.77	< 0.0001**	0.09

%tPSA = Percent free prostate specific antigen; SD=Standard deviation; tPSA = Total prostate specific antigen;

* $P < 0.05$ based on Chi-square tests of independence;

** $P < 0.05$ based on ANOVA test with log-transformed tPSA and %tPSA values.

Table 4

Logistic regression and one-way ANOVA models for unadjusted associations of serum levels of retinol, retinyl esters and carotenoids (defined as quartiles) with prostate specific antigen levels – 2001–2006 National Health and Nutrition Examination Survey*

	tPSA > 10 ng/ml (OR (95% CI), %)	tPSA > 4 ng/ml (%, OR (95% CI), %)	tPSA > 2.5 ng/ml (OR (95% CI), %)	%tPSA < 25% (OR 95% CI, %)	%tPSA < 15% (OR (95% CI), %)	tPSA Mean (SD)	%tPSA Mean (SD)
Retinol (μmol/L) (N=3810)							
Q1: 0.024–1.85	1.00, 1.3%	1.00, 5.8%	1.00, 12.7%	1.00, 38.9%	1.00, 8.7%	1.76 (3.36)	29.8 (12.6)
Q2: 1.85–2.21	0.42 (0.16–1.09), 0.5%	0.88 (0.58–1.32), 5.1%	0.79 (0.58–1.07), 10.3%	0.75 (0.56–0.99) *, 32.3%	0.94 (0.66–1.33), 8.2%	1.82 (3.21)	30.4 (12.8)
Q3: 2.21–2.62	0.98 (0.41–2.39), 1.2%	0.99 (0.64–1.53), 5.7%	0.88 (0.64–1.22), 11.5%	0.79 (0.65–0.97), 33.7%	1.05 (0.71–1.53), 9.1%	1.96 (4.13)	29.55 (11.71)
Q4: 2.62–8.76	0.79 (0.34–1.88), 0.9%	1.38 (0.88–2.17), 7.8%	1.23 (0.93–1.65), 15.3%	0.83 (0.66–1.04), 34.6%	0.81 (0.53–1.22), 7.2%	2.17 (7.18)	32.3 (13.5)
P value	0.24	0.09	0.008 *	0.13	0.46	0.0014 **	< 0.0001 **
Retinyl esters (μmol/L) (N=3573)							
Q1: 0.0059–0.048	1.00, 1.5%	1.00, 6.3%	1.00, 12.8%	1.00, 30.8%	1.00, 7.9%	1.93 (3.74)	30.9 (12.9)
Q2: 0.048–0.073	0.74 (0.31–1.76), 1.1%	1.04 (0.69–1.57), 6.5%	1.06 (0.81–1.38), 13.4%	1.25 (0.93–1.68), 35.8%	1.00 (0.62–1.65), 7.9%	2.03 (4.11)	30.6 (12.9)
Q3: 0.073–0.12	0.37 (0.11–1.21), 0.6%	0.93 (0.59–1.43), 5.9%	0.99 (0.74–1.37), 12.7%	1.33 (0.99–1.77), 37.1%	1.27 (0.77–2.11), 9.9%	1.67 (2.21)	30.1 (12.6)
Q4: 0.12–2.20	0.45 (0.19–1.09), 0.7%	0.86 (0.56–1.33), 5.5%	0.86 (0.67–1.12), 11.3%	1.22 (0.93–1.59), 35.2%	0.84 (0.53–1.35), 6.7%	2.02 (7.41)	30.6 (12.5)
P value	0.14	0.80	0.56	0.15	0.33	0.98	0.47
α-carotene (μmol/L) (N=3804)							
Q1: 0.0039–0.026	1.00, 1.2%	1.00, 5.8%	1.00, 11.8%	1.00, 36.2%	1.00, 10.2%	1.76 (3.41)	30.3 (13.2)
Q2: 0.026–0.048	0.62 (0.24–1.60), 0.7%	0.98 (0.67–1.42), 5.6%	0.97 (0.72–1.30), 11.5%	1.04 (0.78–1.38), 37.1%	0.80 (0.54–1.19), 8.4%	1.94 (3.98)	30.6 (13.1)
Q3: 0.048–0.089	0.63 (0.24–1.69), 0.8%	0.98 (0.66–1.46), 5.7%	1.08 (0.81–1.44), 12.6%	0.86 (0.69–1.08), 32.9%	0.80 (0.57–1.14), 8.3%	1.83 (3.27)	30.8 (12.5)
Q4: 0.089–1.80	1.14 (0.45–2.93), 1.3%	1.31 (0.89–1.92), 7.4%	1.23 (0.89–1.68), 14.1%	0.83 (0.60–1.14), 32.0%	0.54 (0.36–0.80), 5.8%	2.18 (7.24)	30.4 (12.0)
P value	0.41	0.32	0.39	0.37	0.038 *	0.0086 **	0.47

	tPSA > 10 ng/ml (OR (95% CI), %)	tPSA > 4 ng/ml (%, OR (95% CI), %)	tPSA > 2.5 ng/ml (OR (95% CI), %)	%tPSA < 25% (OR 95% CI), %)	%tPSA < 15% (OR 95% CI), %)	tPSA Mean (SD)	%tPSA Mean (SD)
β-carotene ($\mu\text{mol/L}$)							
(N=3696)							
Q1: 0.012–0.14	1.00, 0.5%	1.00, 4.9%	1.00, 9.9%	1.00, 36.5%	1.00, 9.0%	1.52 (2.11)	30.2 (12.9)
Q2: 0.14–0.24	2.38 (0.73–7.75), 1.1%	1.09 (0.75–1.58), 5.3%	1.25 (0.89–1.74), 12.2%	0.92 (0.70–1.19), 34.5%	1.08 (0.65–1.78), 9.6%	1.82 (3.76)	30.8 (13.1)
Q3: 0.24–0.40	3.02 (0.82–11.1), 1.4%	1.29 (0.86–1.94), 6.3%	1.47 (1.10–1.95), 13.9%	0.81 (0.65–1.02), 31.9%	0.63 (0.43–0.93), 5.9%	2.01 (3.38)	31.1 (12.9)
Q4: 0.40–6.39	2.12 (0.59–7.64), 1.0%	1.69 (1.08–2.67), 8.1%	1.53 (1.11–2.10), 14.5%	0.91 (0.74–1.14), 34.5%	0.94 (0.60–1.49), 8.5%	2.37 (7.86)	30.0 (12.1)
P value	0.27	0.047 *	0.028 *	0.36	0.13	<0.0001 **	0.22
β-cryptoxanthin ($\mu\text{mol/L}$)							
M(N=3789)							
Q1: 0.0025–0.080	1.00, 0.7%	1.00, 5.9%	1.00, 11.7%	1.00, 35.5%	9.5, 1.00	3.86 (12.84)	27.4 (12.9)
Q2: 0.080–0.13	1.97 (0.76–5.12), 1.3%	1.11 (0.78–1.59), 6.5%	1.13 (0.82–1.56), 13.1%	0.94 (0.77–1.15), 34.1%	0.79 (0.55–1.14), 7.7%	1.87 (3.23)	30.6 (13.2)
Q3: 0.13–0.22	1.87 (0.57–6.09), 1.2%	0.97 (0.66–1.43), 5.7%	1.15 (0.89–1.48), 13.3%	0.95 (0.77–1.16), 34.3%	0.83 (0.57–1.21), 8.0%	2.19 (7.74)	31.2 (12.7)
Q4: 0.22–2.73	1.19 (0.51–2.80), 0.8%	1.12 (0.76–1.67), 6.5%	1.03 (0.75–1.41), 12.0%	0.93 (0.78–1.12), 33.9%	0.77 (0.51–1.16), 7.5%	1.95 (3.38)	30.5 (12.5)
P value	0.43	0.84	0.69	0.89	0.43	0.18	0.12
lutein+zeaxanthin ($\mu\text{mol/L}$)							
(N=3803)							
Q1: 0.03–0.19	1.00, 0.7%	1.00, 5.9%	1.00, 11.2%	1.00, 33.2%	1.00, 8.7%	2.12 (7.72)	30.9 (13.4)
Q2: 0.19–0.27	1.99 (0.68–5.79), 1.5%	0.98 (0.68–1.42), 5.8%	1.27 (0.94–1.72), 13.8%	1.04 (0.84–1.27), 35.3%	1.07 (0.72–1.58), 9.3%	1.84 (3.27)	30.6 (12.6)
Q3: 0.27–0.37	1.54 (0.71–3.32), 1.1%	1.06 (0.74–1.52), 6.2%	1.19 (0.89–1.58), 13.1%	1.01 (0.76–1.32), 34.2%	0.88 (0.56–1.39), 7.8%	1.94 (3.13)	29.97 (12.60)
Q4: 0.37–1.95	0.84 (0.33–2.10), 0.6%	1.15 (0.81–1.63), 6.7%	1.07 (0.81–1.43), 11.9%	0.87 (0.71–1.06), 35.0%	0.76 (0.52–1.12), 6.8%	1.81 (3.12)	30.5 (12.3)
P value	0.19	0.81	0.30	0.88	0.38	0.19	0.57
Lycopene ($\mu\text{mol/L}$)							
(N=3803)							
Q1: 0.0067–0.23	1.00, 1.2%	1.00, 8.3%	1.00, 15.3%	1.00, 33.2%	1.00, 7.7%	2.38 (7.59)	30.8 (12.9)

	tPSA > 10 ng/ml (OR (95% CI), %)	tPSA > 4 ng/ml (%, OR (95% CI), %)	tPSA > 2.5 ng/ml (OR (95% CI), %)	%tPSA < 25% (OR 95% CI), %)	%tPSA < 15% (OR 95% CI), %)	tPSA Mean (SD)	%tPSA Mean (SD)
Q2: 0.23–0.35	0.76 (0.37–1.54), 0.9%	0.85 (0.61–1.19), 7.2%	0.89 (0.66–1.22), 13.9%	1.09 (0.88–1.36), 35.3%	1.09 (0.66–1.79), 8.3%	1.90 (3.33)	31.2 (13.2)
Q3: 0.35–0.52	0.34 (0.12–0.99), 0.9%	0.59 (0.39–0.89), 5.1%	0.75 (0.52–1.07), 11.9%	1.05 (0.81–1.35), 34.3%	1.19 (0.73–1.95), 9.0%	1.74 (3.36)	29.7 (12.4)
Q4: 0.52–1.49	0.44 (0.16–1.19), 1.1%	0.57 (0.39–0.83), 4.9%	0.64 (0.46–0.88), 10.3%	1.08 (0.83–1.40), 35.0%	1.02 (0.60–1.71), 7.8%	1.69 (3.18)	30.3 (12.3)
P value	0.85	0.007 *	0.033 *	0.33	0.84	0.0023 **	0.14
Total carotenoids (μmol/L)							
Q1: 0.082–0.81	1.00, 1.2%	1.00, 6.5%	1.00, 12.6%	1.00, 35.0%	1.00, 9.1%	1.94 (3.69)	30.8 (13.3)
Q2: 0.81–1.14	0.72 (0.26–2.04), 0.9%	0.94 (0.62–1.43), 6.2%	1.06 (0.78–1.44), 13.2%	1.06 (0.83–1.36), 36.5%	1.09 (0.66–1.79), 9.9%	1.75 (2.74)	30.5 (12.8)
Q3: 1.14–1.58	0.71 (0.25–1.99), 0.9%	0.70 (0.49–1.00), 4.7%	0.87 (0.64–1.17), 11.1%	0.86 (0.64–1.14), 31.6%	0.69 (0.43–1.13), 6.5%	1.78 (3.47)	31.2 (12.8)
Q4: 1.58–6.92	0.93 (0.41–2.10), 1.1%	1.14 (0.77–1.68), 7.3%	1.11 (0.82–1.50), 13.8%	0.98 (0.81–1.20), 34.7%	0.85 (0.52–1.39), 7.9%	2.25 (7.68)	29.7 (12.1)
P value	0.84	0.13	0.41	0.33	0.25	0.035 **	0.14

%tPSA = Percent free prostate specific antigen; SEM=Standard error of the mean; tPSA = Total prostate specific antigen;

* $P < 0.05$ based on Chi-square tests of independence;

** $P < 0.05$ based on one-way ANOVA tests with log-transformed tPSA and %tPSA values.

Table 5

Regression models for fully-adjusted associations of serum levels of retinol, retinyl esters and carotenoids (defined as quartiles) with prostate specific antigen levels – 2001–2006 National Health and Nutrition Examination Survey

	tPSA > 10 ng/ml		tPSA > 4 ng/ml		tPSA > 2.5 ng/ml		%tPSA < 25 ng/ml		%tPSA < 15 ng/ml	
Retinol (μmol/L)	OR (95% CI)	N=3416	OR (95% CI)	N=3509	OR (95% CI)	N=3509	OR (95% CI)	N=3509	OR (95% CI)	N=3509
Q1: 0.024–1.85	1.00		1.00		1.00		1.00		1.00	
Q2: 1.85–2.21	0.41 (0.14,1.23)		0.80 (0.50,1.28)		0.69 (0.48,0.97)		0.77 (0.58,1.03)		0.95 (0.64,1.40)	
Q3: 2.21–2.62	0.76 (0.25,2.31)		0.79 (0.48,1.31)		0.75 (0.52,1.11)		0.83 (0.68,1.00)		1.08 (0.71,1.66)	
Q4: 2.62–8.76	0.63 (0.22,1.79)		1.17 (0.68,2.01)		1.02 (0.73,1.44)		0.88 (0.69,1.13)		0.93 (0.58,1.49)	
P _{trend}	0.66		0.44		0.47		0.57		0.92	
Retinyl esters (μmol/L)	OR (95% CI)	N=3202	OR (95% CI)	N=3291	OR (95% CI)	N=3291	OR (95% CI)	N=3291	OR (95% CI)	N=3291
Q1: 0.0059–0.048	1.00		1.00		1.00		1.00		1.00	
Q2: 0.048–0.073	0.42 (0.13,1.30)		0.90 (0.53,1.54)		0.96 (0.67,1.38)		1.24 (0.91,1.70)		0.93 (0.54,1.58)	
Q3: 0.073–0.12	0.37 (0.09,1.38)		0.92 (0.60,1.42)		1.02 (0.76,1.37)		1.33 (0.99,1.80)		1.25 (0.74,2.10)	
Q4: 0.12–2.20	0.38 (0.14,1.00)		0.84 (0.53,1.33)		0.82 (0.60,1.12)		1.24 (0.92,1.66)		0.93 (0.56,1.53)	
P _{trend}	0.069		0.48		0.30		0.11		0.93	
α-carotene (μmol/L)	OR (95% CI)	N=3411	OR (95% CI)	N=3504	OR (95% CI)	N=3504	OR (95% CI)	N=3504	OR (95% CI)	N=3504
Q1: 0.0039–0.026	1.00		1.00		1.00		1.00		1.00	
Q2: 0.026–0.048	0.52 (0.18,1.55)		0.88 (0.58,1.34)		0.88 (0.65,1.21)		1.06 (0.79,1.41)		0.83 (0.55,1.25)	
Q3: 0.048–0.089	0.47 (0.15,1.44)		0.78 (0.52,1.17)		0.89 (0.66,1.20)		0.83 (0.65,1.05)		0.79 (0.53,1.19)	
Q4: 0.089–1.80	0.50 (0.16,1.61)		0.96 (0.62,1.49)		0.95 (0.67,1.35)		0.78 (0.56,1.12)		0.49 (0.32,0.76)	
P _{trend}	0.26		0.80		0.82		0.068		0.004	
β-carotene (μmol/L)	OR (95% CI)	N=3308	OR (95% CI)	N=3399	OR (95% CI)	N=3399	OR (95% CI)	N=3399	OR (95% CI)	N=3399
Q1: 0.012–0.14	1.00		1.00		1.00		1.00		1.00	
Q2: 0.14–0.24	1.98 (0.57,6.93)		0.92 (0.59,1.43)		1.04 (0.72,1.51)		0.93 (0.72,1.20)		1.17 (0.70,1.95)	
Q3: 0.24–0.40	1.94 (0.48,7.88)		0.92 (0.58,1.46)		1.11 (0.77,1.59)		0.83 (0.64,1.07)		0.67 (0.44,1.02)	
Q4: 0.40–6.39	0.67 (0.17,2.61)		0.95 (0.57,1.60)		0.98 (0.67,1.42)		0.87 (0.68,1.12)		0.95 (0.58,1.54)	

	tPSA > 10 ng/ml	tPSA > 4 ng/ml	tPSA > 2.5 ng/ml	%tPSA < 25 ng/ml	%tPSA < 15 ng/ml
P_{trend}	0.42	0.88	0.96	0.17	0.36
β-cryptoxanthin (μmol/L)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=3399	N=3492	N=3492	N=3492	N=3492
Q1: 0.0025–0.080	1.00	1.00	1.00	1.00	1.00
Q2: 0.080–0.13	1.85 (0.66,5.16)	1.04 (0.68,1.59)	1.12 (0.78,1.59)	0.98 (0.79,1.20)	0.83 (0.55,1.25)
Q3: 0.13–0.22	1.41 (0.35,5.67)	0.87 (0.56,1.36)	1.09 (0.81,1.49)	0.99 (0.79,1.25)	0.83 (0.53,1.28)
Q4: 0.22–2.73	0.89 (0.30,2.61)	1.14 (0.73,1.78)	1.04 (0.72,1.50)	0.93 (0.75,1.14)	0.76 (0.46,1.23)
P_{trend}	0.76	0.78	0.82	0.59	0.28
lutein+zeaxanthin (μmol/L)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=3411	N=3504	N=3504	N=3504	N=3504
Q1: 0.03–0.19	1.00	1.00	1.00	1.00	1.00
Q2: 0.19–0.27	1.87 (0.59,5.91)	1.08 (0.71,1.64)	1.38 (0.99,1.92)	1.08 (0.87,1.34)	1.17 (0.79,1.74)
Q3: 0.27–0.37	0.86 (0.34,2.17)	1.05 (0.70,1.56)	1.17 (0.83,1.65)	0.98 (0.74,1.31)	0.92 (0.58,1.44)
Q4: 0.37–1.95	0.52 (0.18,1.52)	1.16 (0.78,1.71)	1.03 (0.74,1.45)	0.83 (0.69,1.01)	0.78 (0.53,1.18)
P_{trend}	0.040	0.51	0.92	0.064	0.17
Lycopene (μmol/L)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=3411	N=3504	N=3504	N=3504	N=3504
Q1: 0.0067–0.23	1.00	1.00	1.00	1.00	1.00
Q2: 0.23–0.35	0.78 (0.36,1.70)	1.15 (0.82,1.61)	1.25 (0.94,1.68)	1.17 (0.94,1.44)	1.15 (0.69,1.90)
Q3: 0.35–0.52	0.28 (0.09,0.84)	0.95 (0.65,1.39)	1.26 (0.86,1.85)	1.16 (0.89,1.51)	1.28 (0.75,2.17)
Q4: 0.52–1.49	0.99 (0.35,2.76)	1.39 (0.92,2.09)	1.49 (1.04,2.14)	1.22 (0.92,1.61)	1.18 (0.67,2.06)
P_{trend}	0.67	0.23	0.057	0.22	0.54
Total carotenoids (μmol/L)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=3299	N=3390	N=3390	N=3390	N=3390
Q1: 0.082–0.81	1.00	1.00	1.00	1.00	1.00
Q2: 0.81–1.14	0.68 (0.21,2.14)	0.89 (0.54,1.49)	1.11 (0.82,1.49)	1.14 (0.89,1.47)	1.06 (0.61,1.85)
Q3: 1.14–1.58	0.75 (0.23,2.46)	0.79 (0.57,1.13)	1.00 (0.78,1.28)	0.88 (0.65,1.19)	0.72 (0.42,1.21)
Q4: 1.58–6.92	0.54 (0.20,1.42)	1.10 (0.70,1.73)	1.17 (0.82,1.68)	1.00 (0.80,1.26)	0.87 (0.51,1.47)
P_{trend}	0.31	0.75	0.50	0.48	0.29

CI=confidence interval; Q1=1st quartile; Q2=2nd quartile; Q3=3rd quartile; Q4=4th quartile; OR=odds ratio; tPSA = Total prostate specific antigen; %tPSA = Percent free prostate specific antigen;

* Multivariate regression models were adjusted for age ('40–49', '50–59', '60–69', '70–79', '80+', years), race/ethnicity ('Hispanic', 'Non-Hispanic White', 'Non-Hispanic Black, Other'), education ('Less than High School', 'High School', 'More than High School'), marital status ('Ever married', 'Never married'), household income ('<\$20,000', '\$20,000–\$24,999', '\$25,000–\$49,999', '\$50,000–\$99,999', '\$100,000 or more'), and body mass index ('<25 kg/m²', '25–29.9 kg/m²', '30 kg/m² or more').