HHS Public Access

Author manuscript

Prostate. Author manuscript; available in PMC 2016 October 26.

Published in final edited form as:

Prostate. 2016 September ; 76(12): 1053–1066. doi:10.1002/pros.23189.

Carotenoid Intake and Adipose Tissue Carotenoid Levels in Relation to Prostate Cancer Aggressiveness among African-American and European-American Men in the North Carolina-Louisiana Prostate Cancer Project (PCaP)

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Abstract

Background—Associations between carotenoid intake and prostate cancer (CaP) incidence have varied across studies. This may be due to combining indolent with aggressive disease in most studies. This study examined whether carotenoid intake and adipose tissue carotenoid levels were inversely associated with CaP aggressiveness.

Methods—Data on African-American (AA, n=1,023) and European-American (EA, n=1,079) men with incident CaP from North Carolina and Louisiana were analyzed. Dietary carotenoid intake was assessed using a detailed food frequency questionnaire, and abdominal adipose tissue

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Disclosure Statement: The authors have no conflict of interest to disclose.

samples were analyzed for carotenoid concentrations using high-performance liquid chromatography. Multivariable logistic regression was used in race-stratified analysis to calculate odds ratios (ORs) and 95% confidence intervals (95%CI) comparing high aggressive CaP with low/intermediate aggressive CaP.

Results—Carotenoid intake differed significantly between AAs and EAs, which included higher intake of lycopene among EAs and higher β–cryptoxanthin intake among AAs. Comparing the highest and lowest tertiles, dietary lycopene was associated inversely with high aggressive CaP among EAs (OR=0.55, 95%CI: 0.34–0.89, P_{trend}=0.02), while an inverse association was observed between dietary β–cryptoxanthin intake and high aggressive CaP among AAs (OR=0.56, 95%CI: 0.36–0.87, P_{trend}=0.01). Adipose tissue α–carotene and lycopene (*cis* + *trans*) concentrations were higher among EAs than AAs, and marginally significant inverse linear trends were observed for adipose α–carotene (P_{trend}=0.07) and lycopene (P_{trend}=0.11), and CaP aggressiveness among EAs only.

Conclusions—These results suggest that diets high in lycopene and β–cryptoxanthin may protect against aggressive CaP among EAs and AAs, respectively. Differences in dietary behaviors may explain the racial differences in associations.

Keywords

prostate cancer; carotenoids; α–carotene; β–carotene; β–cryptoxanthin; lutein; lycopene; zeaxanthin; supplements; adipose tissue; nutritional biomarkers

Introduction

Prostate cancer (CaP) remains the most commonly occurring invasive malignancy and the second leading cause of cancer death among American men (1). Accumulated data on the relation between diet and cancer incidence indicate that about 30–40% of all cancer cases may be preventable through healthy diet and weight control (2,3). Greater intake of vegetables and, to a lesser extent, fruits has been associated with lower risk of various malignancies, which include CaP (4,5). However, identifying the beneficial nutrients or bioactive compounds responsible for the suggested protection conferred by vegetables and fruit intake against CaP remains a challenge. Carotenoids are biologically active phytochemicals found in many plant foods, and they are thought to contribute to the inverse association between vegetables and fruit intake and CaP risk (5,6). Despite this evidence, findings from case-control and cohort studies summarized in recent reviews (7,8) indicate that the overall association between carotenoid intake and CaP risk is equivocal.

Lycopene and β–carotene are the most commonly studied carotenoids in relation to CaP. Lycopene, a carotenoid devoid of vitamin A activity, has the strongest evidence for beneficial association with CaP (9–12), although study results have varied (13,14). Early studies focused primarily on β–carotene, a pro-vitamin A carotenoid; however, two large intervention trials conducted in Finland (15) and in the United States (16) failed to show a beneficial effect of β–carotene supplementation on CaP incidence in secondary analyses. One reported a 23% increased risk of CaP in the β–carotene intervention group *versus* placebo (15), and the other, which examined effects of β–carotene and retinol supplements

in tandem because of their close metabolic relationship, found a 52% increased risk of aggressive CaP (Gleason ≥7 or stage III/IV) in the intervention group compared to placebo (16). The elevated risks associated with β–carotene supplementation were not evident in follow-up studies (16,17), and observational studies have conflicted on associations between β–carotene and CaP risk (6–8). Carotenoids, such as α–carotene, β–cryptoxanthin, lutein, and zeaxanthin, have been associated with modest reductions in CaP risk, but as with lycopene and β–carotene, findings have been mixed (18–20).

Data are scarce on the relationship between carotenoid intake and CaP aggressiveness (as opposed to overall CaP incidence) (9,14). As suggested by Giovannucci et al. (12), the dietary risk factors for aggressive CaP may differ from those for non-aggressive disease, and thus, some carotenoids may differentially influence aggressive *versus* non-aggressive CaP. Given the inconsistent findings, and increased interest in identifying modifiable risk factors for aggressive CaP, particularly among African Americans (AAs), a population with a high incidence of aggressive CaP (21), this study investigated associations of dietary, supplemental and adipose tissue carotenoid levels in relation to CaP aggressiveness among AA and European-American (EA) men in North Carolina and Louisiana.

Materials and Methods

Research Subjects

A population-based, case-control study was conducted using data from the North Carolina-Louisiana Prostate Cancer Project (PCaP). One of the primary aims of PCaP, a multidisciplinary, cross-sectional, case-only, incident CaP study, was to investigate and compare factors associated with CaP aggressiveness among AAs and EAs. Residents of the study catchment areas in North Carolina and Louisiana were eligible to participate in PCaP if they had a first, histologically confirmed, diagnosis of adenocarcinoma of the prostate between July 1, 2004 and August 31, 2009, were 40–79 years of age at the time of diagnosis, and self-identified their race as AA/Black or “Caucasian American”/White (EA). Other eligibility criteria included having sufficient cognitive and physical functions to consent and complete the study interview in English, and not residing in an institution (e.g., nursing home). PCaP enrolled 2267 research subjects of whom approximately half were EAs (n= 1130) and half were AAs (n = 1137). All research subjects provided written informed consent before participating in the study. Participation rates were 62% in North Carolina, 72% for pre-Hurricane Katrina Louisiana and 63% for post-Hurricane Katrina Louisiana. Further details of the PCaP methods and design can be found elsewhere (22). The PCaP study protocols were approved by Institutional Review Boards of all collaborating institutions (22), and the current study also received Institutional Review Board approval from the University of South Carolina.

Data Collection

Structured, in-person interviews were conducted by trained research nurses, usually in the home of the research subject or at a place of his choosing. Trained interviewers solicited information that included demographic and socioeconomic factors, personal health history, family history of CaP, pre-diagnostic CaP screening habits, comorbidities, smoking history,

physical activity, usual diet, and use of dietary supplements and non-steroidal anti-inflammatory drugs (NSAIDs). Research nurses obtained measurements of research subjects' height and weight at the end of each interview using a standardized protocol. Information on the clinical stage, Gleason sum and prostate-specific antigen (PSA) level at diagnosis as well as disease-directed treatments were extracted from the research subjects' medical records that were obtained from diagnosing physicians. Watchful waiting (i.e., active surveillance of the progression of CaP) was not considered as a form of treatment in this study. The medical record abstractions were performed by trained personnel and included a double abstraction of a randomly selected sample (approximately 10%) to ensure consistency among abstractors. CaP aggressiveness was defined in PCaP as high aggressive (Gleason sum ≥8 or PSA >20 ng/mL or Gleason sum ≥7 and clinical stage T3–T4), low aggressive (Gleason sum < 7 and clinical stage T1-T2 and PSA <10 ng/ml), and intermediate aggressive (all others). These categories were used in case-case analyses contrasting high aggressive CaP cases with low/intermediate aggressive cases.

Dietary Carotenoid Intake

Dietary carotenoid intakes were assessed using the National Cancer Institute Diet History Food-frequency Questionnaire (NCI-DHQ) (23), which was modified to include Southern foods. The modified 144-item DHQ solicited detailed information about usual diet in the year before the diagnosis of CaP, which included frequency of food intake, portion size, and food preparation methods. Responses to the questions were linked to an updated NCI nutrient database through which the research subjects' usual daily intakes of various nutrients including α– and β–carotene, β–cryptoxanthin, lutein-zeaxanthin and lycopene were estimated using NCI Diet*Calc software (22).

Data on supplemental carotenoid intake were derived using a standardized questionnaire (24). Research subjects were asked about multivitamin and single-nutrient supplement use in the year preceding their diagnosis of CaP (no, less than once per week, yes) and those who answered "yes" were queried about the frequency of use (1–2, 3–4, 5–6, 7 days/week). Responses to the questionnaire were recorded by nurse interviewers who also undertook an inventory of nutrient contents and listed dose information from manufacturer label of each supplement type. When the supplement bottle was not available, research subjects were asked the usual dose taken. Average daily intakes of supplemental β–carotene, lutein and lycopene were estimated based on contributions from multivitamin and single-nutrient supplements as frequency (days per week) x dose (in μg) x number of pills taken at each time / 7. Total daily intake of β–carotene, lutein and lycopene were estimated as the sum of intakes from diet and supplement (diet + supplement) for each carotenoid.

Adipose Tissue Carotenoid Concentration

Approximately two grams of subcutaneous abdominal adipose tissue samples were obtained from consenting research subjects by trained nurses after anesthetizing the overlying skin with 2% lidocaine solution. PCaP research nurses, who were specifically trained for adipose tissue sampling, followed a standardized procedure that inserted a 15-gauge needle into the subcutaneous fat and applied negative pressure using a 15 ml vacutainer tube after prepping the overlying skin. The aspirated tissue was trapped in the needle and luer lock adapter,

which was placed in a separate cryovial and transported on ice via overnight courier to a designated storage facility where aliquots were prepared and stored at –80°C until assayed. Individual carotenoids were measured using high-performance liquid chromatography (HPLC) at the nutrition analyses laboratory of Craft Technologies, Inc. (Wilson, NC) using methods described by Craft et al. (25). The adipose tissue concentrations of α–carotene, cis- and trans-β–carotene, α–cryptoxanthin, β-cryptoxanthin, lutein, zeaxanthin, and cis- and trans-lycopene were quantified at minimum detection limit 0.003 μg/g of tissue.

Statistical Analyses

Before any analysis was performed, research subjects with incomplete data on CaP aggressiveness (n = 94) and those with implausible values for energy intake (< 500 or ≥6000 kcal/day, n = 71) were excluded from the total PCaP sample of 2267. The remaining 2,102 research subjects were included in the analyses; however, data on adipose tissue carotenoid levels were available for only 939 cases (EAs n = 581, AAs n = 358). All analyses were performed separately for AAs and EAs.

Descriptive statistics were expressed as means for continuous variables and proportions for categorical variables using *t*-tests and Chi-square tests, respectively. The carotenoid variables were categorized into tertiles according to distribution among low/intermediate aggressive cases, and unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for high aggressive CaP for increasing tertiles with the lowest tertile as the referent group. Trend tests were performed by assigning each tertile its median value expressed as a continuous variable in the logistic regression models. All associations were examined in crude (age-adjusted) and multivariable-adjusted models. The following known or suspected risk factors for CaP aggressiveness were considered for inclusion in the multivariable-adjusted models: age (continuous), body mass index (BMI, kg/m^2); family history of CaP in a first degree relative (none *vs.* at least one); pre-diagnostic PSA screening history (0, 1–7, >7 screenings); number of comorbidities (0, 1, 2, ≥3); whether CaP treatment had started at the time of the interview (yes, no); smoking status (never, former, current); education (less than high school education, high school graduate/some college, college graduate); annual household income (<$20,000, $20,001-$40,000, $40,001-$70,000, >$70,000); NSAIDs 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]; dietary fat intake (grams/day); alcohol intake (grams/day) and study site (NC, LA). Covariates that altered ORs of the main exposure variables by at least 10% were included in a full model for final model selection using the backward elimination method. Models were constructed separately by race. When a factor was determined to be a confounder in one race but not the other, that factor was included in each of the race-stratified analyses. Of the potential covariates, age, PSA screening history, BMI, smoking status, education, income, NSAIDs use, total fat intake, and study site were included in the final multivariable-adjusted models. Further adjustment for family history of CaP, comorbidities, and CaP treatment status were done in models examining associations between adipose carotenoid levels and CaP aggressiveness.

Stratified analyses by BMI (<24.9, normal weight; 25–29.9, overweight; ≥30 kg/m^2, obese) and smoking status were performed to evaluate whether the associations were modified by these factors. The evaluation of effect modification included interaction terms between BMI and smoking status variables and each of the carotenoids examined by likelihood ratio tests based on models with and without an interaction term. All statistical tests were two-sided and p-values less than 0.05 were considered statistically significant except for interaction p-values in the exploratory stratified analyses, where significance level was set at 0.10 in order to accommodate the small sample size of the stratified groups. All analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC).

Results

In both AAs and EAs, research subjects with high aggressive CaP were older and less educated compared to those with low/intermediate aggressive CaP (Table I). EA research subjects with high aggressive CaP had a slightly higher BMI and were more likely to have started treatment for CaP compared to EAs with low/intermediate aggressive CaP. AA research subjects with high aggressive CaP tended to have a higher reported intake of energy and dietary fat, were less likely to have had at least one pre-diagnostic PSA screening, and included a greater proportion of current and former smokers and low incomes compared to AAs with low/intermediate aggressive CaP.

Mean difference in carotenoid levels by CaP aggressiveness

Reported daily intake of carotenoids varied significantly between AAs and EAs (Table II). EAs tended to have higher intakes of α–carotene, supplemental β–carotene and lutein, and higher intake of lycopene from diet and supplements. AAs had higher dietary intakes of β–carotene, β–cryptoxanthin and lutein + zeaxanthin. Of note, rates of supplemental carotenoid intake were higher in EAs than AAs. For example, among AAs, 23% of AAs reported supplemental intake of lycopene and 30% reported supplemental β-carotene intake, while among EAs, 28% reported supplemental lycopene intake and 42% reported supplemental β-carotene intake. Adipose tissue carotenoid levels were generally higher in EAs than AAs with significant differences in the levels of zeaxanthin and lycopene (both *cis* and *trans* isoforms). Few significant differences in unadjusted mean carotenoid intake or adipose levels were observed by CaP aggressiveness among EAs or AAs.

Dietary and supplemental carotenoid intake and CaP aggressiveness

Substantial differences in carotenoid intake between AAs and EAs required the use of different cut-points to categorize each carotenoid by race; hence, results are presented separately for AAs and EAs (Table III). Among EAs, dietary lycopene intake was associated with a decrease in odds of high aggressive CaP; OR was 0.55 (95% CI: 0.34–0.89, P_{trend} = 0.02) in the highest *versus* lowest tertile after adjustment for multiple covariates. Although supplemental lycopene use was not associated with CaP aggressiveness among EAs, total lycopene intake from diet and supplements was related inversely to high aggressive CaP (OR = 0.56, 95% CI: 0.34–0.90, highest *versus* lowest tertile, P_{trend} = 0.03). These significant associations were not observed among AAs. However, dietary β–cryptoxanthin intake was

associated with 45% lower odds of high aggressive CaP among AAs only. None of the other carotenoids was significantly associated with CaP aggressiveness in either race.

Adipose tissue carotenoid levels and CaP aggressiveness

Evaluation of associations between adipose tissue carotenoid levels and CaP aggressiveness showed a marginally significant inverse linear trend toward lower odds of high aggressive CaP for the associations of adipose α–carotene (P_{trend} = 0.07) and lycopene (*cis* + *trans*, P_{trend} = 0.11) among EAs. No associations were observed between adipose carotenoid levels and CaP aggressiveness among AAs. Research subjects with data on adipose tissue carotenoid levels were similar to those without data on adipose carotenoids in the extent of CaP aggressiveness; however, they differed in BMI, race, CaP screening history, education, income, smoking status and study site (Supplemental Table I). These differences necessitated an alternate analysis of dietary carotenoid intake and CaP aggressiveness among research subjects who had adipose carotenoid data. The results from this analysis were similar to those presented in Table III (Supplementary Table II), which suggested minimal impact of missing adipose tissue data on the observed associations. In the stratified analyses, the associations between all measured carotenoids and CaP aggressiveness did not vary by smoking status or BMI (data not shown).

Discussion

This population-based study examined associations between carotenoid intake and adipose tissue carotenoid levels in relation to CaP aggressiveness among AAs and EAs in North Carolina and Louisiana. Inverse associations were observed between intake of lycopene and CaP aggressiveness among EAs, and between β–cryptoxanthin intake and CaP aggressiveness among AAs. Marginally significant linear trends in the direction of reduced odds of high aggressive CaP were observed for higher adipose abdominal tissue levels of α–carotene and lycopene (*cis* + *trans*) among EAs only. Subgroup analysis did not show evidence of effect modification by smoking status or BMI in either race.

A number of studies have suggested that carotenoid intake may play a beneficial role in CaP incidence; however, the overall evidence remains inconclusive (reviewed in (7,8)). Carotenoids are broadly categorized as pro-vitamin A (i.e., α–carotene, β–carotene, and β–cryptoxanthin) or non-pro-vitamin A (i.e., lutein, zeaxanthin and lycopene) depending on whether they are converted into retinol in the body (26). Both groups of carotenoids have been shown in *in vitro* and *in vivo* studies to have biological functions that could prevent or suppress the progression of cancer (27). Proposed mechanisms by which carotenoids may influence CaP aggressiveness include modulation of gene expression, induction of apoptosis, suppression of angiogenesis, and enhancement of antitumor immune responses (26,27). Equivocal findings in the literature may result from the focus on CaP incidence (6–8,19,28). Moreover, populations included in prior studies were predominantly of European decent, therefore the study results may not be necessarily applicable to AAs. Although the current study shows some differences in carotenoid associations with CaP aggressiveness between AAs and EAs, comparisons were made within each race. This analytic approach minimizes

confounding by unmeasured sociocultural factors, and possibly, biological factors that are inherently different between AAs and EAs (21,29).

The current finding for lycopene among EAs is consistent with previous studies that suggested that lycopene may be beneficial in reducing the risk and aggressiveness of CaP. In a prospective cohort study of male health professionals, higher lycopene intake was associated 21% lower risk of CaP and higher intake of tomato and tomato products (the primary sources of lycopene) also was associated with 53% reduced risk of advanced CaP (18). Gann et al. (30) reported a lower risk of aggressive CaP in men with high plasma lycopene levels. In another prospective study, Kirsh et al. (13) reported an inverse association between lycopene intake and CaP incidence among men with a family history of CaP. Reports from some case-control studies suggest that lycopene may reduce the risk of CaP (19,31), although others have failed to show an association (14,32). In addition to tomatoes and tomato-based foods, lycopene can be obtained in modest amounts from watermelon, guava, and papaya. Lycopene is considered the most potent antioxidant carotenoid because of its singlet oxygen quenching ability (33). The bioavailability of lycopene increases with thermal treatment of tomatoes, such as steaming, boiling or stewing, processing of tomatoes with oil, or simultaneous ingestion of tomato-based foods and fat (34). Thus, the potential benefits of lycopene depend on food processing and dietary habits, which may partly explain the discrepancy in lycopene associations between AAs and EAs. The consumption of lycopene from food and supplements, and adipose lycopene concentrations were higher in EAs than AAs (Table II), which suggest that the potential benefits of lycopene in relation to CaP aggressiveness may be acquired only at higher levels of intake.

The difference in lycopene associations between AAs and EAs also may have been influenced by gene-diet interactions that may vary by race. Goodman et al. (35), reported that polymorphic variants in *XRCC1*, a gene involved in base excision repair of DNA damage, may be associated with reduced ability of lycopene to decrease the risk of CaP. Accumulating evidence suggests that lycopene may play a more critical role in angiogenesis, tumor migration and apoptosis (36,37), molecular pathways that are relevant to CaP aggressiveness (38). Therefore, evaluating race-specific interactions between lycopene and functional polymorphisms in genes involved in these pathways may help unravel how lycopene might influence differentially CaP aggressiveness in different population subgroups.

β–cryptoxanthin, which is commonly found in tangerines, oranges, grapefruit, mangoes, fruit juices and red peppers (39), was inversely associated with CaP aggressiveness, but only among AAs, whose intake of β–cryptoxanthin were 37% higher than EAs (Table II). Studies have reported inverse (31,40) or positive (28,41) associations between β–cryptoxanthin and CaP risk. Reviews of the literature do not provide compelling evidence for or against a protective association between β–cryptoxanthin and CaP (6–8). Perhaps examining β–cryptoxanthin associations with different CaP phenotypes, as done in this study, may help delineate the role of β–cryptoxanthin in prostate carcinogenesis. The associations of α–carotene, β–carotene and lutein + zeaxanthin, and CaP incidence also have varied across

studies (6,18–20). Evaluations of these carotenoids in relation to CaP aggressiveness are rare (10,12,14), but evolving, and may help clarify their role in CaP.

Adipose tissue biomarkers of nutrient intake have been used to assess disease risk (42,43) and continues to receive increased attention because of the ability of adipose tissue to reflect long-term nutritional status. However, the uptake and turnover rates of carotenoids in adipose tissues remain unclear (44). The suggestion that higher adipose α–carotene and lycopene concentrations are related inversely to CaP aggressiveness warrants further investigation in larger studies, partly because of the possibility that adipose α–carotene and lycopene may have acted as markers for increased consumption of fruits and vegetables or as surrogates for a healthy lifestyle in general.

Cigarette smoking has been associated with depletion of circulating carotenoid levels (45) and high BMI appears to increase the body's carotenoids requirement (46); however, neither of these factors were found to have modifying effect on the associations between carotenoids intake and CaP aggressiveness. This is the first study to examine effect modification of carotenoids by smoking or BMI in relation to CaP aggressiveness. Some studies have suggested that β–carotene supplements may increase the risk of CaP among smokers (15). Thus, further evaluation in larger samples is needed to help tease out the potential interaction between carotenoids intake and smoking or BMI in relation to CaP aggressiveness.

Diet was assessed using a food frequency questionnaire. These structured instruments may be biased according to response sets (47) which, in turn, may be related to psychological traits that either exert a direct effect on cancer outcomes or indirectly affect other factors that may influence carcinogenesis (48). Other limitations of the current study include the fact that carotenoids likely do not act alone, and thus, the results reported here may reflect interactions among individual carotenoids or interactions with other food components or genetic variants (35). Because the diet assessment instrument was administered after diagnosis of CaP, post-diagnosis changes in dietary patterns could have influenced dietary recall and may have affected the results to some extent. This should be considered in the interpretation of results. Moreover, self-report of diet can be problematic, especially when asking research subjects to report dietary intake from the year prior to completing the questionnaire. Such recall inaccuracies would have resulted in non-differential misclassification because the research subjects were not likely to consider their disease aggressiveness in answering questions relating to food and supplements intake. Furthermore, laboratory personnel involved in the analyses of adipose carotenoid levels were blinded to the CaP attributes of the samples. Therefore, non-differential, rather than differential, misclassification may have attenuated the ORs to some extent. Some carotenoids may exert their beneficial effects in the early stages of carcinogenesis (27). The one-year reference period for the dietary and supplement use assessment may not be etiologically relevant to CaP, but can provide an estimate of usual dietary patterns (23); adipose tissue concentrations reflect longer-term exposure. Metabolic alterations in nutritional status of cancer patients have been documented (44) and therefore cancer-induced metabolic abnormalities may have affected the measured carotenoid levels. However, it has been observed that adipose tissue carotenoid levels are less susceptible to changes due to the presence of a tumor (49). Adipose carotenoid levels have been correlated inversely with body fat percentage (50). The

potential confounding effect of body fat burden was considered by adjusting for BMI (in the BMI unstratified analyses). Despite these limitations, the design of the study uniquely captures the complex pathological and clinical attributes of CaP, and the findings of this analysis add to the limited knowledge of the potential role of carotenoids in CaP aggressiveness within specific race groups.

Conclusions

This analysis shows a statistically significant inverse association between lycopene intake and CaP aggressiveness among EAs, and between β–cryptoxanthin and CaP aggressiveness among AAs. There was a suggestion that higher adipose tissue α–carotene and lycopene (*cis* + *trans*) levels also were inversely related to CaP aggressiveness among EAs. The results suggest that certain carotenoids may have greater beneficial impact among obese individuals with the possibility of detrimental effects among normal weight men, findings that warrant further investigation in larger studies. Although some of the findings vary by race, this was likely due to the variations in the levels of carotenoid intake between AAs and EAs. Overall, the findings support suggestions that a higher consumption of fruits and vegetables, which are the main sources of carotenoids, may be inversely associated with CaP aggressiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the North Carolina Central Cancer Registry, the Louisiana Tumor Registry, and the PCaP staff, advisory committees and participants for their important contributions. The authors also thank the dedicated staff, participant recruiters, and nurse-interviewers of the North Carolina-Louisiana Prostate cancer Project (PCaP). The authors acknowledge the UNC BioSpecimen Facility and the LSUHSC Pathology Lab for storage and sample disbursement (https://genome.unc.edu/bsp).

Funding: The North Carolina-Louisiana Prostate Cancer Project (PCaP) was carried out as a collaborative study supported by the Department of Defense contract DAMD 17-03-2-0052. These analyses were conducted while Dr. Samuel Antwi was a graduate student at the University of South Carolina. He was supported partially by a SPARC (Support to Promote Advancement of Research and Creativity) grant from the Office of the Vice President for Research at the University of South Carolina, and a graduate scholar fellowship grant from the Center for Colon Cancer Research, University of South Carolina. He was also supported by National Cancer Institute grant (2R25CA092049-11).

Abbreviations

AA	African American
BMI	Body mass index
CaP	Prostate cancer
CI	Confidence interval
EA	European American
NCI-DHQ	National Cancer Institute Diet History Food Frequency Questionnaire
NSAIDS	Non-steroidal anti-inflammatory drugs

OR	Odds ratio
PCaP	North Carolina-Louisiana Prostate Cancer Project
PSA	Prostate-specific antigen

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65(1):5–29. [PubMed: 25559415]
2. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. Journal of the National Cancer Institute. 1981; 66(6):1192–1308.
3. Popkin BM. Understanding global nutrition dynamics as a step towards controlling cancer incidence. Nature Reviews Cancer. 2007; 7(1):61–67. [PubMed: 17186019]
4. Liu B, Mao Q, Cao M, Xie L. Cruciferous vegetables intake and risk of prostate cancer: A meta-analysis. International Journal of Urology. 2012; 19(2):134–141. [PubMed: 22121852]
5. Chan JM, Giovannucci EL. Vegetables, fruits, associated micronutrients, and risk of prostate cancer. Epidemiologic reviews. 2001; 23(1):82–86. [PubMed: 11588858]
6. Young C, Yuan H-Q, He M-L, Zhang J-Y. Carotenoids and prostate cancer risk. Mini reviews in medicinal chemistry. 2008; 8(5):529–537. [PubMed: 18473940]
7. Vance TM, Su J, Fontham ET, Koo SI, Chun OK. Dietary antioxidants and prostate cancer: a review. Nutrition and cancer. 2013; 65(6):793–801. [PubMed: 23909722]
8. Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. Journal of Clinical Oncology. 2005; 23(32):8152–8160. [PubMed: 16278466]
9. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. Journal of the National Cancer Institute. 2002; 94(5): 391–398. [PubMed: 11880478]
10. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ. Lower Prostate Cancer Risk in Men with Elevated Plasma Lycopene Levels: Results of a Prospective Analysis. Cancer Research. 1999; 59(6):1225–1230. [PubMed: 10096552]
11. Ansari M, Ansari S. Lycopene and prostate cancer. 2005.
12. Giovannucci E. A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. Experimental Biology and Medicine. 2002; 227(10):852–859. [PubMed: 12424325]
13. Kirsh VA, Mayne ST, Peters U, Chatterjee N, Leitzmann MF, Dixon LB, Urban DA, Crawford ED, Hayes RB. A prospective study of lycopene and tomato product intake and risk of prostate cancer. Cancer Epidemiology Biomarkers & Prevention. 2006; 15(1):92–98.
14. Kristal AR, Arnold KB, Neuhouser ML, Goodman P, Platz EA, Albanes D, Thompson IM. Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. American journal of epidemiology. 2010; 172(5):566–577. [PubMed: 20693267]
15. Heinonen OP, Koss L, Albanes D, Taylor PR, Hartman AM, Edwards BK, Virtamo J, Huttunen JK, Haapakoski J, Malila N. Prostate cancer and supplementation with α-tocopherol and β-carotene: incidence and mortality in a controlled trial. Journal of the National Cancer Institute. 1998; 90(6): 440–446. [PubMed: 9521168]
16. Neuhouser ML, Barnett MJ, Kristal AR, Ambrosone CB, King IB, Thornquist M, Goodman GG. Dietary supplement use and prostate cancer risk in the Carotene and Retinol Efficacy Trial. Cancer Epidemiology Biomarkers & Prevention. 2009; 18(8):2202–2206.
17. Virtamo J, Pietinen P, Huttunen J, Korhonen P, Malila N, Virtanen M, Albanes D, Taylor P, Albert P. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. JAMA: the journal of the American Medical Association. 2003; 290(4):476–485. [PubMed: 12876090]
18. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retino in relation to risk of prostate cancer. Journal of the National Cancer Institute. 1995; 87(23):1767–1776. [PubMed: 7473833]

19. McCann SE, Ambrosone CB, Moysich KB, Brasure J, Marshall JR, Freudenheim JL, Wilkinson GS, Graham S. Intakes of selected nutrients, foods, and phytochemicals and prostate cancer risk in western New York. Nutrition and cancer. 2005; 53(1):33–41. [PubMed: 16351504]
20. Lewis JE, Soler-Vilá H, Clark PE, Kresty LA, Allen GO, Hu JJ. Intake of plant foods and associated nutrients in prostate cancer risk. Nutrition and cancer. 2009; 61(2):216–224. [PubMed: 19235037]
21. Freedland SJ, Isaacs WB. Explaining racial differences in prostate cancer in the United States: sociology or biology? The Prostate. 2005; 62(3):243–252. [PubMed: 15389726]
22. Schroeder JC, Bensen JT, Su LJ, Mishel M, Ivanova A, Smith GJ, Godley PA, Fontham ET, Mohler JL. The North Carolina-Louisiana Prostate Cancer Project (PCaP): Methods and design of a multidisciplinary population-based cohort study of racial differences in prostate cancer outcomes. The Prostate. 2006; 66(11):1162–1176. [PubMed: 16676364]
23. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, McIntosh A, Rosenfeld S. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires the Eating at America's Table Study. American Journal of Epidemiology. 2001; 154(12):1089–1099. [PubMed: 11744511]
24. Satia-Abouta J, Patterson RE, King IB, Stratton KL, Shattuck AL, Kristal AR, Potter JD, Thornquist MD, White E. Reliability and validity of self-report of vitamin and mineral supplement use in the vitamins and lifestyle study. American Journal of Epidemiology. 2003; 157(10):944–954. [PubMed: 12746248]
25. Craft NE, Wise SA, Soares JH Jr. Optimization of an isocratic high-performance liquid chromatographic separation of carotenoids. Journal of Chromatography A. 1992; 589(1):171–176.
26. Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2005; 1740(2):101–107. [PubMed: 15949675]
27. Gerster H. Anticarcinogenic effect of common carotenoids. International journal for vitamin and nutrition research Internationale Zeitschrift fur Vitamin-und Ernahrungsforschung Journal international de vitaminologie et de nutrition. 1992; 63(2):93–121.
28. Jain MG, Hislop GT, Howe GR, Ghadirian P. Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. Nutrition and cancer. 1999; 34(2):173–184. [PubMed: 10578485]
29. Wallace TA, Prueitt RL, Yi M, Howe TM, Gillespie JW, Yfantis HG, Stephens RM, Caporaso NE, Loffredo CA, Ambs S. Tumor Immunobiological Differences in Prostate Cancer between African-American and European-American Men. Cancer Research. 2008; 68(3):927–936. [PubMed: 18245496]
30. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ. Lower prostate cancer risk in men with elevated plasma lycopene levels results of a prospective analysis. Cancer research. 1999; 59(6):1225–1230. [PubMed: 10096552]
31. Jian L, Du CJ, Lee AH, Binns CW. Do dietary lycopene and other carotenoids protect against prostate cancer? International Journal of Cancer. 2005; 113(6):1010–1014. [PubMed: 15514967]
32. Hodge AM, English DR, McCredie MR, Severi G, Boyle P, Hopper JL, Giles GG. Foods, nutrients and prostate cancer. Cancer Causes & Control. 2004; 15(1):11–20. [PubMed: 14970730]
33. Stahl W, Sies H. Physical Quenching of Singlet Oxygen and cis-trans Isomerization of Carotenoidsa. Annals of the New York Academy of Sciences. 1993; 691(1):10–19. [PubMed: 8129279]
34. Gärtner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. The American Journal of Clinical Nutrition. 1997; 66(1):116–122. [PubMed: 9209178]
35. Goodman M, Bostick RM, Ward KC, Terry PD, van Gils CH, Taylor JA, Mandel JS. Lycopene intake and prostate cancer risk: effect modification by plasma antioxidants and the XRCC1 genotype. Nutrition and cancer. 2006; 55(1):13–20. [PubMed: 16965236]
36. Zu K, Mucci L, Rosner BA, Clinton SK, Loda M, Stampfer MJ, Giovannucci E. Dietary Lycopene, Angiogenesis, and Prostate Cancer: A Prospective Study in the Prostate-Specific Antigen Era. Journal of the National Cancer Institute. 2014

37. Palozza P, Colangelo M, Simone R, Catalano A, Boninsegna A, Lanza P, Monego G, Ranelletti FO. Lycopene induces cell growth inhibition by altering mevalonate pathway and Ras signaling in cancer cell lines. Carcinogenesis. 2010; 31(10):1813–1821. [PubMed: 20699249]
38. Chung LW, Baseman A, Assikis V, Zhau HE. Molecular insights into prostate cancer progression: the missing link of tumor microenvironment. The Journal of urology. 2005; 173(1):10–20. [PubMed: 15592017]
39. Maiani G, Periago Castón MJ, Catasta G, Toti E, Cambrodón IG, Bysted A, Granado-Lorencio F, Olmedilla-Alonso B, Knuthsen P, Valoti M, Böhm V, Mayer-Miebach E, Behsnilian D, Schlemmer U. Carotenoids: Actual knowledge on food sources, intakes, stability and bioavailability and their protective role in humans. Molecular Nutrition & Food Research. 2009; 53(S2):S194–S218. [PubMed: 19035552]
40. Chang S, Erdman J, John W, Clinton SK, Vadiveloo M, Strom SS, Yamamura Y, Duphorne CM, Spitz MR, Amos CI, Contois JH. Relationship between plasma carotenoids and prostate cancer. Nutrition and cancer. 2005; 53(2):127–134. [PubMed: 16573373]
41. Schuurman AG, Goldbohm RA, Brants HA, van den Brandt PA. A prospective cohort study on intake of retinol, vitamins C and E, and carotenoids and prostate cancer risk (Netherlands). Cancer Causes & Control. 2002; 13(6):573–582. [PubMed: 12195647]
42. Kohlmeier L, Kark JD, Gomez-Gracia E, Martin BC, Steck SE, Kardinaal AF, Ringstad J, Thamm M, Masaev V, Riemersma R. Lycopene and myocardial infarction risk in the EURAMIC Study. American Journal of Epidemiology. 1997; 146(8):618–626. [PubMed: 9345115]
43. Kabagambe EK, Furtado J, Baylin A, Campos H. Some dietary and adipose tissue carotenoids are associated with the risk of nonfatal acute myocardial infarction in Costa Rica. The Journal of nutrition. 2005; 135(7):1763–1769. [PubMed: 15987862]
44. Kohlmeier L, Kohlmeier M. Adipose tissue as a medium for epidemiologic exposure assessment. Environmental health perspectives. 1995; 103(Suppl 3):99.
45. Handelman GJ, Packer L, Cross CE. Destruction of tocopherols, carotenoids, and retinol in human plasma by cigarette smoke. The American journal of clinical nutrition. 1996; 63(4):559–565. [PubMed: 8599320]
46. Andersen LF, Jacobs DR, Gross MD, Schreiner PJ, Dale Williams O, Lee D-H. Longitudinal associations between body mass index and serum carotenoids: the CARDIA study. British journal of nutrition. 2006; 95(02):358–365. [PubMed: 16469154]
47. Hebert JR, Ma Y, Clemow L, Ockene IS, Saperia G, Stanek EJ, Merriam PA, Ockene JK. Gender differences in social desirability and social approval bias in dietary self-report. American Journal of Epidemiology. 1997; 146(12):1046–1055. [PubMed: 9420529]
48. Ellison GL, Coker AL, Hebert JR, Sanderson S, Royal CD, Weinrich SP. Psychosocial stress and prostate cancer: a theoretical model. Ethnicity & disease. 2000; 11(3):484–495.
49. Rautalahti M, Albanes D, Hyvönen L, Piironen V, Heinonen M. Effect of sampling site on retinol, carotenoid, tocopherol, and tocotrienol concentration of adipose tissue of human breast with cancer. Annals of nutrition and metabolism. 1990; 34(1):37–41. [PubMed: 2331139]
50. Chung H-Y, Ferreira ALA, Epstein S, Paiva SA, Castaneda-Sceppa C, Johnson EJ. Site-specific concentrations of carotenoids in adipose tissue: relations with dietary and serum carotenoid concentrations in healthy adults. The American journal of clinical nutrition. 2009; 90(3):533–539. [PubMed: 19587090]

Table I

Characteristics of research subjects by race and prostate cancer aggressiveness

	European American n = 1,079					African American n = 1,023				
Characteristics	**High aggressive CaP (n=164)**		**Low/intermediate aggressive CaP (n=915)**			**High aggressive CaP (n=206)**		**Low/intermediate aggressive CaP (n=817)**		
	Mean (SD)		**Mean (SD)**		***P* value‡**	**Mean (SD)**		**Mean (SD)**		***P* value‡**
Age, years	67 (8)		64 (8)		<0.0001	64 (8)		62 (8)		0.004
Energy Intake, kcals/day	2339 (952)		2320 (866)		0.80	2800 (1232)		2593 (1146)		0.02
Dietary Fat Intake, grams/day	94 (42)		91 (39)		0.31	104(52)		95(485)		0.02
Body Mass Index (BMI), kg/m^2	30 (5)		29 (5)		0.0006	30 (7)		29 (55)		0.16
	N	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Study Site										
North Carolina	73	45	448	49	0.29	92	45	386	47	0.51
Louisiana	91	55	467	51		114	55	431	53	
Family History of Prostate Cancer										
No affected 1st degree relative	136	83	696	76	0.05	157	76	606	74	0.55
At least 1 affected 1st degree relative	28	17	219	24		49	24	211	26	
PSA Screening History										
0 screenings	40	24	153	17	0.06	120	58	307	38	<0.0001
1–7 screenings	68	42	405	44		53	26	338	41	
> 7 screenings	56	34	357	39		33	16	172	21	
Comorbidities										
0	84	51	503	55	0.05	88	43	382	47	0.39
1	31	19	214	23		53	26	216	26	
2	29	18	98	11		36	17	106	13	
≥ 3	20	12	100	11		27	14	109	14	
Started CaP treatment at start of study										
No	11	7	99	11	0.007	20	10	112	14	0.20
Yes	146	89	720	79		163	79	599	73	

	European American n = 1,079					African American n = 1,023				
Characteristics	**High aggressive CaP (n=164)**		**Low/intermediate aggressive CaP (n=915)**			**High aggressive CaP (n=206)**		**Low/intermediate aggressive CaP (n=817)**		
	Mean (SD)		**Mean (SD)**		***P* value‡**	**Mean (SD)**		**Mean (SD)**		***P* value‡**
Unknown	7	4	96	10		23	11	106	13	
Education										
Less than high school education	27	17	81	9	0.005	85	41	243	30	0.001
High school graduate/ some college	79	48	432	47		102	50	438	54	
College graduate	58	35	402	44		19	9	135	16	
Income Level										
≤ $20, 000	24	15	78	9	0.11	82	40	234	29	0.0005
$20,001 – $40,000	33	20	184	20		52	25	212	26	
$40,001 – $70,000	38	23	217	24		24	12	171	21	
>$70,000	53	32	359	39		22	11	130	16	
Unknown	16	10	77	8		26	12	70	8	
Smoking Status										
Never	59	36	330	36	0.76	40	19	276	34	<0.001
Former smoker	87	53	501	55		107	52	390	48	
Current smoker	18	11	84	9		59	29	151	18	
NSAID Use										
No	56	34	305	33	0.85	84	41	364	45	0.33
Yes	108	66	608	67		120	59	446	55	

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.

Abbreviations: CaP – Prostate Cancer; NSAIDs – Nonsteroidal anti-inflammatory drugs; PSA – prostate-specific antigen; SD – Standard deviation.

‡Test for differences between high and low/intermediate CaP performed using Student t-test for continuous variables and chi-square tests for categorical variables.

Prostate. Author manuscript; available in PMC 2016 October 26.

Table II

Unadjusted mean difference in carotenoids from diet, supplements, and adipose tissue by race and prostate cancer aggressiveness

	European American n = 1,079	African American n = 1,023	% diff.[§]	European American			African American		
				High aggressive CaP n = 164	Low/intermediate aggressive CaP n = 915	p[†]	High aggressive CaP n = 206	Low/intermediate aggressive CaP n = 817	p[†]
Carotenoids	**Mean (SD)**	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
α–carotene μg/day									
dietary	661.9 (741.7)	596.3 (730.2)	10 ≠	610.0 (874.3)	671.1 (715.5)	0.39	597.6 (829.4)	595.9 (703.6)	0.98
β–carotene μg/day									
dietary	3914 (3028)	4789 (3899)	−22 ≠	3831 (3096)	3929 (3017)	0.70	4835 (3951)	4777 (3888)	0.85
supplement [a]	442.1 (1607)	235.0 (859.2)	47 ≠	300.9 (447.3)	467.4 (1734)	0.01	192.8 (1065)	245.6 (799.5)	0.50
diet + supplement	4356 (3478)	5024 (4028)	−15	4132 (3196)	4397 (3526)	0.37	5027 (4170)	5023 (3994)	0.99
β–cryptoxanthin μg/day									
dietary	162.9 (134.3)	223.5 (204.3)	−37 ≠	160.8 (117.8)	163.3 (137.1)	0.81	199.3 (171.8)	229.6 (211.4)	0.03
Lutein + zeaxanthin μg/day									
dietary	3230 (2708)	4231 (3533)	−31 ≠	3204 (2706)	3235 (2710)	0.89	4133 (3150)	4256 (3625)	0.63
supplement (lutein) [a]	81.7 (126.5)	45.5 (123.4)	44 ≠	84.0 (116.1)	81.3 (128.3)	080	32.8 (83.1)	48.8 (131.4)	0.03
diet + supplement	3312 (2737)	4277 (3550)	−29 ≠	3288 (2723)	3316 (2740)	0.90	4166 (3151)	4305 (3645)	0.62
Lycopene μg/day									
dietary	6716 (7842)	5539 (7791)	17 ≠	5994 (5770)	6845 (8154)	0.10	5440 (8294)	5564 (7664)	0.84
supplement [a]	85.3 (201.3)	66.7 (142)	22 ≠	85.0 (133.4)	85.3 (211.2)	0.97	60.5 (117.6)	68.3 (147.2)	0.42
diet + supplement	6801 (7855)	5606 (7794)	18 ≠	6079 (5773)	6931 (8168)	0.10	5500 (8303)	5632 (7666)	0.83
Adipose tissue carotenoid levels μg/g	N = 581 Mean (SD)	N = 358 Mean (SD)		N = 89 Mean (SD)	N = 492 Mean (SD)		N = 66 Mean (SD)	N = 292 Mean (SD)	
α–carotene	0.04 (0.05)	0.03 (0.05)	25	0.03 (0.06)	0.04 (0.05)	0.26	0.03 (0.03)	0.03 (0.05)	0.33
cis–β-carotene	0.10 (0.14)	0.10 (0.15)	0	0.09 (0.16)	0.10 (0.14)	0.42	0.10 (0.17)	0.09 (0.14)	0.81
trans–β-carotene	0.19 (0.27)	0.16 (0.27)	16	0.16 (0.27)	0.19 (0.28)	0.32	0.17 (0.32)	0.16 (0.26)	0.79
α–cryptoxanthin	0.03 (0.03)	0.02 (0.02)	33	0.02 (0.02)	0.03 (0.03)	0.16	0.02 (0.02)	0.02 (0.03)	0.49

		European American n = 1,079	African American n = 1,023	% diff.§	European American			African American		
					High aggressive CaP n = 164	Low/intermediate aggressive CaP n = 915	p†	High aggressive CaP n = 206	Low/intermediate aggressive CaP n = 817	p†
Carotenoids		**Mean (SD)**	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
	β–cryptoxanthin	0.09 (0.11)	0.08 (0.10)	11	0.08 (0.09)	0.09 (0.11)	0.28	0.07 (0.08)	0.08 (0.10)	0.84
	Lutein	0.21 (0.22)	0.20 (0.24)	5	0.18 (0.17)	0.21 (0.23)	0.20	0.19 (0.23)	0.20 (0.24)	0.82
	Zeaxanthin	0.10 (0.16)	0.07 (0.08)	30 ≠	0.08 (0.07)	0.10 (0.17)	0.03	0.07 (0.08)	0.08 (0.09)	0.46
	Lycopene (*cis* + *trans*)	0.35 (0.40)	0.28 (0.34)	20 ≠	0.28 (0.32)	0.36 (0.42)	0.04	0.28 (0.32)	0.28 (0.35)	0.93
	cis-lycopene	0.22 (0.26)	0.17 (0.21)	23 ≠	0.17 (0.20)	0.22 (0.27)	0.05	0.17 (0.20)	0.17 (0.22)	0.96
	all-trans-lycopene	0.13 (0.15)	0.10 (0.13)	23 ≠	0.10 (0.12)	0.13 (0.15)	0.05	0.11 (0.12)	0.10 (0.13)	0.84

Abbreviations: CaP – prostate cancer; SD – standard deviation

[a] Among supplement users only

[§] Percent difference in carotenoid levels between European Americans and African Americans

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

[†] Student's t-test for difference by level of prostate cancer aggressiveness

Table III

Odds ratios (ORs) and 95% confidence intervals (CIs) for associations between dietary and supplemental carotenoids intake and prostate cancer aggressiveness among European-American and African-American men

European American					African American				
Carotenoid levels	**High aggressive/ low-intermediate aggressive CaP 164/915**	**OR (95% CI) [a]**	**OR (95% CI) [b]**	**P[†]**	**Carotenoid levels**	**High aggressive/ low-intermediate aggressive CaP 206/817**	**OR (95% CI) [a]**	**OR (95% CI)[b]**	**P [†]**
α–carotene									
Dietary μg/day									
27.20 – 324.13	64/305	1.00 (ref)	1.00 (ref)		11.83 – 262.11	71/273	1.00 (ref)	1.00 (ref)	
324.14 – 626.76	48/305	0.74 (0.49–1.12)	0.72 (0.47–1.11)		262.12 – 585.99	63/272	0.89 (0.61–1.30)	0.79 (0.52–1.21)	
626.77 – 9812	52/305	0.80 (0.53–1.20)	0.76 (0.49–1.18)	0.33	586.00 – 9558	72/272	1.05 (0.72–1.52)	0.99 (0.64–1.52)	0.77
β–carotene									
Dietary μg/day									
194.86 – 2328	61/305	1.00 (ref)	1.00 (ref)		286.48 – 2544	61/273	1.00 (ref)	1.00 (ref)	
>2328 – 4046	44/305	0.68 (0.45–1.04)	0.67 (0.43–1.05)		>2544 – 5156	69/272	1.16 (0.79–1.70)	1.07 (0.70–1.62)	
>4046 – 25124	59/305	0.91 (0.61–1.35)	0.92 (0.60–1.43)	0.96	>5156 – 32901	76/272	1.22 (0.84–1.78)	1.12 (0.72–1.73)	0.64
Supplement μg/day									
non-users	91/536	1.00 (ref)	1.00 (ref)		non-users	153/564	1.00 (ref)	1.00 (ref)	
63.00 – 600.00	61/301	1.20 (0.84–1.71)	1.39 (0.96–2.02)		63.00 – 590.00	26/92	1.08 (0.67–1.74)	1.22 (0.74–2.03)	
600.01 – 16470	12/78	0.88 (0.46–1.69)	1.00 (0.50–1.97)	0.44	590.01 – 15600	27/161	0.62 (0.40–0.98)	0.76 (0.48–1.21)	0.37
Diet + supplement μg/day									
346 .80 – 2566	60/304	1.00 (ref)	1.00 (ref)		286.48 – 2773	67/273	1.00 (ref)	1.00 (ref)	
>2566 – 4458	48/306	0.76 (0.50–1.15)	0.76 (0.49–1.18)		>2773 – 5405	69/272	1.05 (0.72–1.53)	0.98 (0.65–1.47)	
>4458 – 25512	56/305	0.87 (0.58–1.30)	0.88 (0.56–1.37)	0.75	>5405 – 32901	70/272	1.02 (0.70–1.49)	0.96 (0.62–1.49)	0.88
β–cryptoxanthin									
Dietary μg/day									
6.04 – 86.14	51/305	1.00 (ref)	1.00 (ref)		3.53 – 116.43	87/273	1.00 (ref)	1.00 (ref)	
86.15 – 180.62	52/305	1.00 (0.65–1.52)	1.00 (0.64–1.55)		116.44 – 243.34	65/272	0.75 (0.52–1.08)	0.74 (0.50–1.11)	
180.63 – 1082	61/305	1.18 (0.78–1.77)	1.11 (0.71–1.72)	0.62	243.34 – 1594	54/272	0.63 (0.43–0.92)	**0.56 (0.36–0.87)**	**0.01**

European American					African American				
Carotenoid levels	**High aggressive/ low-intermediate aggressive CaP 164/915**	**OR (95% CI) [a]**	**OR (95% CI) [b]**	**P[†]**	**Carotenoid levels**	**High aggressive/ low-intermediate aggressive CaP 206/817**	**OR (95% CI) [a]**	**OR (95% CI)[b]**	**P [†]**
Lutein + Zeaxanthin									
Dietary μg/day									
289.67 – 1830	60/305	1.00 (ref)	1.00 (ref)		112.25 – 2299	64/273	1.00 (ref)	1.00 (ref)	
>1830 – 3253	44/305	0.71 (0.47–1.09)	0.71 (0.45–1.12)		>2299 – 4408	72/272	1.15 (0.79–1.68)	1.11 (0.74–1.68)	
>3253 – 30165	60/305	1.01 (0.68–1.50)	1.05 (0.67–1.63)	0.49	>4408 – 36608	70/272	1.10 (0.75–1.61)	1.08 (0.70–1.65)	0.82
Supplement (lutein) μg/day[C]									
non-users	106/617	1.00 (ref)	1.00 (ref)		non-users	177/671	1.00 (ref)	1.00 (ref)	
users	58/298	0.90 (0.64–1.28)	0.79 (0.55–1.14)		users	29/137	1.34 (0.87–2.06)	1.03(0.65–1.63)	
Diet + supplement μg/day									
289.67 – 1907	59/305	1.00 (ref)	1.00 (ref)		112.25 – 2309	63/273	1.00 (ref)	1.00 (ref)	
>1907 – 3318	46/305	0.75 (0.49–1.15)	0.75 (0.48–1.18)		>2309 – 4461	74/272	1.20 (0.82–1.75)	1.19 (0.78–1.79)	
>3318 – 31665	59/305	1.01 (0.69–1.50)	1.04 (0.69–1.63)	0.56	>4461 – 37558	69/272	1.10 (0.75–1.61)	1.09 (0.71–1.67)	0.85
Lycopene									
Dietary μg/day									
344.77 – 3605	70/305	1.00 (ref)	1.00 (ref)		21.52 – 2390	61/273	1.00 (ref)	1.00 (ref)	
>3605 – 6299	48/305	0.73 (0.48–1.09)	0.67 (0.44–1.02)		>2390 – 5003	70/272	1.23 (0.84–1.81)	1.27 (0.83–1.94)	
>6299 – 100250	46/305	0.74 (0.49–1.12)	**0.55 (0.34–0.89)**	**0.02**	>5003 – 85677	73/272	1.29 (0.88–1.89)	1.22 (0.77–1.93)	0.58
Supplement μg/day									
non-users	114/664	1.00 (ref)	1.00 (ref)		non-users	161/630	1.00 (ref)	1.00 (ref)	
64.28 – 250.00	17/126	1.91 (0.80–4.57)	2.14 (0.87–5.24)		64.28 – 250.00	12/88	0.86 (0.39–1.89)	0.97 (0.43–2.22)	
250.01 – 5000	33/125	1.09 (0.74–1.60)	1.22 (0.82–1.83)	0.27	250.01 – 1000	33/99	0.97 (0.65–1.45)	1.14 (0.74–1.73)	0.57
Diet + supplement μg/day									
344.77 – 3649	70/305	1.00 (ref)	1.00 (ref)		21.52 – 2448	62/273	1.00 (ref)	1.00 (ref)	
3649 – 6352	48/305	0.72 (0.48–1.08)	0.67 (0.44–1.02)		>2448 – 5064	70/272	1.22 (0.83–1.79)	1.21 (0.80–1.85)	
6352 – 100551	46/305	0.74 (0.49–1.12)	**0.56 (0.34–0.90)**	**0.03**	>5064 – 85677	72/272	1.25 (0.85–1.84)	1.16 (0.73–1.84)	0.70

Abbreviation: CaP – prostate cancer

[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] Categorized into two levels because limited variability in dose did not allow for creation of meaningful tertile categories

[†] Multivariable-adjusted trend *P* value

Table IV

Associations between adipose tissue carotenoid levels and prostate cancer aggressiveness among European Americans and African Americans

European American n = 581					African American n = 358				
Carotenoids	**High aggressive/ low-intermediate aggressive CaP [a] 89/492**	**OR (95% CI) [b]**	**OR (95% CI) [c]**	**P†**	**Carotenoids**	**High aggressive/ low-intermediate aggressive CaP [a] 66/292**	**OR (95% CI) [b]**	**OR (95% CI)[c]**	**P†**
α–carotene μg/g									
0.003 – 0.015	26/128	1.00 (ref)	1.00 (ref)		0.003 – 0.012	16/54	1.00 (ref)	1.00 (ref)	
0.016 – 0.039	30/116	1.15 (0.63–2.08)	1.52 (0.78–2.94)		0.013 – 0.025	7/53	0.34 (0.11–1.09)	0.45 (0.15–1.34)	
0.040 – 0.454	12/112	0.49 (0.24–1.03)	0.58 (0.25–1.32)	0.07	0.026 – 0.450	13/49	1.07 (0.39–2.92)	1.13 (0.43–3.00)	0.70
cis–β-carotene μg/g									
0.003 – 0.032	28/138	1.00 (ref)	1.00 (ref)		0.003 – 0.028	23/71	1.00 (ref)	1.00 (ref)	
0.033 – 0.088	27/134	0.89 (0.49–1.61)	1.06 (0.57–1.99)		0.029 – 0.073	7/71	0.60 (0.12–1.74)	0.74 (0.28–1.22)	
0.089 – 1.233	27/135	0.88 (0.49–1.59)	1.16 (0.60–2.25)	0.65	0.074 – 1.163	24/71	0.93 (0.47–1.83)	1.13 (0.52–2.44)	0.71
trans–β-carotene μg/g									
0.003 – 0.061	33/154	1.00 (ref)	1.00 (ref)		0.003 – 0.045	21/88	1.00 (ref)	1.00 (ref)	
0.062 – 0.171	34/152	0.95 (0.56–1.64)	1.11 (0.62–1.99)		0.046 – 0.126	17/88	0.85 (0.42–1.73)	0.70 (0.32–1.53)	
0.172 – 2.408	21/151	0.58 (0.32–1.06)	0.75 (0.39–1.45)	0.31	0.127 – 2.322	22/88	0.97 (0.49–1.91)	1.12 (0.52–2.39)	0.57
α–cryptoxanthin μg/g									
0.003 – 0.013	23/113	1.00 (ref)	1.00 (ref)		0.003 – 0.010	15/62	1.00 (ref)	1.00 (ref)	
0.014 – 0.025	18/112	0.73 (0.37–1.45)	0.84 (0.41–1.75)		0.011 – 0.024	14/62	0.92 (0.41–2.07)	0.94 (0.39–2.33)	
0.026 – 0.219	20/115	0.82 (0.42–1.60)	0.97 (0.46–2.02)	0.99	0.025 – 0.165	12/61	0.82 (0.35–1.90)	1.03 (0.40–2.68)	0.93
β–cryptoxanthin μg/g									
0.003 – 0.037	30/151	1.00 (ref)	1.00 (ref)		0.003 – 0.030	22/86	1.00 (ref)	1.00 (ref)	
0.038 – 0.089	32/148	1.03 (0.59–1.79)	1.19 (0.64–2.19)		0.031 – 0.070	17/82	0.82 (0.41–1.67)	0.71 (0.32–1.61)	
0.090 – 0.909	25/146	0.83 (0.46–1.49)	0.92 (0.48–1.76)	0.67	0.071 – 0.638	19/83	0.90 (0.45–1.78)	1.00 (0.46–2.19)	0.77
Lutein μg/g									
0.004 – 0.078	28/161	1.00 (ref)	1.00 (ref)		0.003 – 0.069	23/95	1.00 (ref)	1.00 (ref)	
0.079 – 0.219	31/161	1.22 (0.69–2.14)	1.26 (0.69–2.31)		0.070 – 0.204	22/94	0.96 (0.50–1.85)	0.95 (0.47–1.95)	

European American n = 581						African American n = 358				
Carotenoids		**High aggressive/ low-intermediate aggressive CaP [a] 89/492**	**OR (95% CI) [b]**	**OR (95% CI) [c]**	**P†**	**Carotenoids**	**High aggressive/ low-intermediate aggressive CaP [a] 66/292**	**OR (95% CI) [b]**	**OR (95% CI)[c]**	**P†**
	0.220 – 1.457	29/159	1.01 (0.57–1.79)	1.27 (0.68–2.35)	0.51	0.205 – 2.033	20/94	0.89 (0.46–1.73)	1.02 (0.49–2.12)	0.92
Zeaxanthin µg/g										
	0.003 – 0.038	28/156	1.00 (ref)	1.00 (ref)		0.003 – 0.028	24/93	1.00 (ref)	1.00 (ref)	
	0.039 – 0.098	40/157	1.42 (0.83–2.44)	1.73 (0.96–3.09)		0.029 – 0.073	20/93	0.83 (0.43–1.61)	0.87 (0.42–1.83)	
	0.099 – 2.985	20/154	0.76 (0.41–1.43)	0.96 (0.49–1.88)	0.78	0.074 – 0.713	19/91	0.83 (0.42–1.63)	1.01 (0.47–2.17)	0.89
Lycopene (*cis* + *trans*) µg/g										
	0.004 – 0.137	35/153	1.00 (ref)	1.00 (ref)		0.004 – 0.100	23/91	1.00 (ref)	1.00 (ref)	
	0.138 – 0.371	34/152	1.02 (0.60–1.73)	1.23 (0.69–2.18)		0.101 – 0.272	15/87	0.74 (0.36–1.51)	0.69 (0.31–1.56)	
	0.372 – 3.164	17/152	**0.51 (0.27–0.96)**	0.64 (0.34–1.31)	0.11	0.273 – 3.013	23/88	1.08 (0.56–2.07)	1.11 (0.53–2.35)	0.62
cis-lycopene µg/g										
	0.003 – 0.080	33/155	1.00 (ref)	1.00 (ref)		0.003 – 0.059	25/92	1.00 (ref)	1.00 (ref)	
	0.081 – 0.234	37/157	1.14 (0.67–1.93)	1.52 (0.85–2.71)		0.060 – 0.168	16/88	0.74 (0.37–1.49)	0.74 (0.34–1.63)	
	0.235 – 2.049	18/152	0.57 (0.31–1.07)	0.79 (0.40–1.54)	0.30	0.169 – 1.879	22/90	0.94 (0.49–1.80)	0.97 (0.46–2.02)	0.96
all-trans-lycopene µg/g										
	0.003 – 0.050	35/158	1.00 (ref)	1.00 (ref)		0.003 – 0.037	22/95	1.00 (ref)	1.00 (ref)	
	0.051 – 0.137	33/154	0.99 (0.58–1.69)	1.11 (0.63–1.99)		0.038 – 0.102	17/90	0.84 (0.42–1.70)	0.85 (0.39–1.85)	
	0.138 – 1.115	18/154	0.54 (0.29–1.01)	0.69 (0.36–1.36)	0.25	0.103 – 1.134	22/92	1.07 (0.55–2.07)	1.10 (0.51–2.34)	0.72

[a] Some categories may not sum to total number of subjects because of missing data

[b] Adjusted for age

[c] additional adjustment for PSA screening history, BMI, smoking status, education, income, NSAIDs use, total dietary fat intake, study site, family history of prostate cancer, comorbidities, and prostate cancer treatment status.

† Multivariable-adjusted trend p-values