Serum Lycopene, Other Carotenoids, and Prostate Cancer Risk: a Nested Case-Control Study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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Abstract

Background: **Reports from several studies have suggested that carotenoids, and in particular lycopene, could be prostate cancer–preventive agents. This has stimulated extensive laboratory and clinical research, as well as much commercial and public enthusiasm. However, the epidemiologic evidence remains inconclusive.**

Materials and Methods: **We investigated the association between prediagnostic serum carotenoids (lycopene, α-carotene, β-carotene, β-cryptoxanthin, lutein, and zeaxanthin) and risk of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a multicenter study designed to examine methods of early detection and risk factors for cancer. The study included 692 incident prostate cancer cases, diagnosed 1 to 8 years after study entry, including 270 aggressive cases, with regional or distant stage ($n = 90$) or Gleason score ≥ 7 ($n = 235$), and 844 randomly selected, matched controls. As study participants were selected from those who were assigned to annual standardized screening for prostate cancer, results are unlikely to be biased by differential screening, a circumstance that is difficult to attain under non–trial conditions.**

Results: **No association was observed between serum lycopene and total prostate cancer [odds ratios (OR), 1.14; 95% confidence intervals (95% CI), 0.82-1.58 for highest versus lowest quintile; *P* for trend, 0.28] or aggressive prostate cancer (OR, 0.99; 95% CI, 0.62-1.57 for highest versus lowest quintile; *P* for trend, 0.433). β-Carotene was associated with an increased risk of aggressive prostate cancer (OR, 1.67; 95% CI, 1.03-2.72 for highest versus lowest quintile; *P* for trend, 0.13); in particular, regional or distant stage disease (OR, 3.16; 95% CI, 1.37-7.31 for highest versus lowest quintile; *P* for trend, 0.02); other carotenoids were not associated with risk.**

Conclusion: **In this large prospective study, high serum β-carotene concentrations were associated with increased risk for aggressive, clinically relevant prostate cancer. Lycopene and other carotenoids were unrelated to prostate cancer. Consistent with other recent publications, these results suggest that lycopene or tomato-based regimens will not be effective for prostate cancer prevention.** (Cancer Epidemiol Biomarkers Prev 2007;16(5):962–8)

Introduction

Carotenoids have distinct antioxidative properties, protecting against free radicals that can damage DNA and other important biomolecules (1). Because oxidative stress increases with androgen exposure and age—factors related to prostate cancer risk—carotenoids may be particularly relevant for the prevention of this disease (2-7).

Carotenoids are synthesized in plants and bacteria to support photosynthesis (8). A variety of fruits and vegetables, in particular, deep-yellow/orange and red color, and dark-green leafy vegetables are typical sources of carotenoids (9). Lycopene, α-carotene, β-carotene, β-cryptoxanthin, lutein, and zeaxanthin represent the major carotenoids in the human diet.

Lycopene, the most potent antioxidant carotenoid (10, 11), has received particular scientific attention and stirred commercial and public enthusiasm regarding prostate cancer prevention, following reports (12, 13) of reduced prostate cancer risk with increasing intake of tomatoes and tomato products, the major source of this micronutrient (~80% of lycopene intake in the U.S. comes from tomatoes and tomato products; ref. 14). A recent meta-analysis (15) summarizing studies published up to 2003 reported a 10% to 20% reduction in prostate cancer risk with high tomato and lycopene intake, weighted strongly by findings from the large Health Professionals Follow-up Study (13, 16). More recently, we prospectively assessed the intake of >25 tomato-related food items in almost 30,000 men in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort (17), and found no overall association of dietary intake of tomatoes and lycopene with prostate cancer [1,338 cases, odds ratio (OR), 5th vs. 1st quintile of lycopene intake 0.95; 95% confidence intervals (95% CI), 0.79-1.13], although inverse associations were suggested for some processed tomato products commonly cooked with fat (17). Because the bioavailability of tomato-derived lycopene, an extremely lipophilic antioxidant (18), varies profoundly with heat and fat application (19-21), some studies (22-29) have relied on blood concentrations as an integrated measure of lycopene intake and absorption. Overall, results from these blood-based studies are inconclusive; some of the larger studies suggest the preventive effects of lycopene in subgroups with aggressive disease (16, 17, 22, 28), older men (29), or men without a family history of prostate cancer (29).

Initial blood-based studies (30-32) reported only on lycopene and β-carotene, whereas more recent studies (22-29) also included other serum carotenoids commonly found in humans, specifically α-carotene, β-cryptoxanthin, lutein, and zeaxanthin. Results from these more detailed evaluations of

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carotenoids (22-29) have also been inconsistent, which may be due in part to their limited sample size.

Here, we describe the results of a large nested case-control study of serum lycopene and other carotenoids and the incidence of prostate cancer in the PLCO Cancer Screening Trial, a randomized trial to evaluate the effectiveness of cancer screening and to investigate etiologic factors and early markers of cancer (33, 34). This study follows up on our previous findings for intake of tomato products evaluated by questionnaire (17) and, given the large sample size, further explores potential subgroup findings for serum lycopene, as suggested in previous studies.

Materials and Methods

Study Setting. Men in this nested case-control study were recruited as part of the PLCO Trial, between September 1993 and June 2001, at 10 centers in the U.S. (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC). At enrollment, men were between 55 and 74 years of age.

The nested case-control study was limited to men randomized to the screening arm of the trial. These men were offered prostate cancer screening by serum prostate-specific antigen (PSA) at entry and annually for 5 years and digital rectal examination (DRE) at entry and annually for 3 years. Men with a positive screening result (PSA test ≥4 ng/mL or DRE suspicious for prostate cancer) were referred to their medical-care providers for prostate cancer diagnostic evaluation. Furthermore, follow-up for recent diagnosis of cancer was conducted by annually mailed questionnaires. We acquired all medical and pathologic records related to prostate cancer diagnosis for all men suspect for prostate cancer by screening examination or annual questionnaire. Periodic search of the National Death Index was conducted and death certificates were obtained. Data were abstracted by trained medical record specialists. All participants were followed for the incidence of cancer and all causes of mortality for at least 13 years from their randomization date. Screening arm participants were asked to provide a blood sample at each screening visit. The institutional review boards of the U.S. National Cancer Institute and the 10 study centers approved the trial and participants provided written informed consent.

Study Population. Of the 38,350 men randomized to the screening arm of the trial, we excluded men reporting a history of prostate cancer, men without a valid prostate cancer screening (PSA test or DRE), men whose first valid prostate cancer screen was after October 1, 2001 (the censor date for this analysis), men who received a prostate cancer screening but for whom there was no subsequent contact (unless information from the National Death Index was available), men who did not complete a baseline risk factor questionnaire, men with an ethnic/racial background other than non–Hispanic White or non–Hispanic Black, men without a signed informed consent for etiologic studies on cancer, and men without any blood collections for etiologic studies at any of the screening visits. After exclusions, the analytic cohort included 28,243 men. All men were followed from their initial valid prostate cancer screen (PSA and/or DRE), to first occurrence of prostate cancer, loss-to-follow-up, death, or censor date (October 1, 2001), whichever came first. Cases are men diagnosed with adenocarcinoma of the prostate. Staging procedures corresponded to the tumor-node-metastasis stage of disease classification (35). Cases were defined as aggressive prostate cancer if they were stages III or IV (regionally invasive or distant metastatic disease) or Gleason score ≥7 based on the pathologic report of the patient's medical-care provider.

Among the 28,243 men, 1,320 prostate cancer cases were identified. For the present study, we further excluded non–Hispanic Black cases and cases diagnosed in the first year after blood draw, which leaves 803 cases in the study. For comparison, we selected controls (n = 949) by incidence-density sampling (36) with a case-control ratio of 1:1.2, frequency-matched by age at entry (5-year intervals), time since initial screening (1-year time windows), year of blood draw, and race/ethnicity.

Laboratory Analysis. Nonfasting blood specimens collected at the clinical centers were processed and frozen within 2 h of blood draw and stored at −70C°. Serum concentrations of carotenoids (lycopene, α-carotene, β-carotene, β-cryptoxanthin, lutein, and zeaxanthin) were determined using reversed-phase high-performance liquid chromatography, with UV detection (for details see ref. 37). Serum collected at study entry was available for 692 (86.2%) cases and 844 (88.9%) controls. Cases and their matched controls were analyzed in the same batch to minimize interassay variability. Blinded quality control samples were randomly inserted in each batch and monitored throughout the analysis. The coefficient of variation, estimated from 171 blinded duplicates, was 8.1% for lycopene, 5.8% for α-carotene, 9.5% for β-carotene, 13.9% for β-cryptoxanthin, 6.1% for lutein, and 9.2% for zeaxanthin. To investigate the reproducibility of serum carotenoid concentrations over time, for 46 control subjects we included a second serum sample drawn 1 year after study entry. Each of these 46 samples collected at year one was included in the same batch as the subject-paired serum sample collected at study entry.

Assessment of Questionnaire-Based Covariates. At enrollment, all participants were asked to complete a questionnaire including age, ethnicity, education, current and past smoking behavior, history of cancer and other diseases, use of selected drugs, recent history of screening exams, and prostate-related health factors. Usual dietary intake over the 12 months before enrollment was assessed with a 137-item food frequency questionnaire including 14 additional questions about intake of vitamin and mineral supplements and 10 additional questions on meat cooking practices (38). Dietary nutrient intake was calculated by multiplying the daily frequency of each consumed food item by the nutrient value of the sex-specific portion size (39), using the nutrient database from the U.S. Department of Agriculture (40). Total vitamin and mineral intake was calculated by using the sum of dietary and supplemental intake.

Statistical Analysis. Adjusted means (least squares means) were calculated by linear regression. The Wilcoxon rank sum test was used to test for differences between carotenoid concentrations between cases and controls. We used conditional logistic regression to estimate ORs and 95% CIs of prostate cancer, with serum carotenoids concentrations categorized as quintiles, based on the distribution among the controls. Tests for linear trend were based on quintile-specific median values expressed as a continuous variable, in conditional logistic regression analysis. The analyses were conditioned on the matching factors (age, time since initial screening, and year of blood draw), and adjusted for study center. We evaluated confounding by potential risk factors for prostate cancer, including family history of prostate cancer, educational attainment, physical activity, body mass index, aspirin and ibuprofen use, history of diabetes, smoking, intakes of alcohol, energy, fat, red meat, heterocyclic amines from meat (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine, PhIP), fruits, vegetables, cruciferous vegetables, vitamin E, and calcium, and serum selenium. None of the factors changed the β-coefficient of the risk estimates of any carotenoids by >10% and, therefore, none of these factors were included in the analyses. We considered serum cholesterol and month of

blood draw as potential confounders and investigated confounding by PSA and DRE screening (total number of screens and average number of screens/year); inclusion of these variables did not change the risk estimates by >10% and were also not retained in the final models. To assess effect modification by age (at study entry and age at diagnosis/censor date), smoking, and family history of prostate cancer, we did stratified analyses and evaluated the statistical significance of multiplicative interactions by comparison of the −2 log-likelihood statistic of the main effects model with that of the model that included the cross-product term. We calculated Spearman correlation coefficients to measure the correlation between serum carotenoid concentrations obtained at two different time points in 46 controls and between serum concentrations and dietary intake of carotenoids in all controls. Correlation coefficients were adjusted for the following factors that potentially affect carotenoid concentrations: month of blood draw, serum cholesterol concentration, smoking, body mass index, age, and energy intake.

Results

Among the 692 incident prostate cancer cases included in this analysis, 210 men were diagnosed in the second year of follow-up, 344 in year 3 and 4, and 138 men were diagnosed in years 5 to 8 (men diagnosed during the first year of follow-up were excluded from the study). The corresponding number for the 270 aggressive cases (i.e., stage III or IV prostate cancer or Gleason score of 7 or higher) and 90 stage III and IV cases included in the analysis were 75 and 26 cases in the second year, 135 and 44 cases in the third and fourth year, and 60 and 20 cases in years 5 to 8, respectively.

Compliance with the PLCO screening protocol was very high and did not vary by lycopene or β-carotene concentrations, as shown by the average annual number of prostate cancer screens (PSA and DRE; Table 1). The average age of controls was 65 years and younger men tended to have higher lycopene and lower β-carotene concentrations than older men. Increasing lycopene concentrations were associated with a lower probability of family history of prostate cancer, lower personal history of diabetes, and lower intake of vitamin D, but higher nonfasting serum cholesterol concentrations and higher intakes of red meat and vegetables. Men with high β-carotene concentrations tended to smoke less, be less obese, be more active, be less likely to have a personal history of diabetes, and have higher serum cholesterol concentrations. Those men also had a lower intake of fat, red meat, and PhIP, and higher intake of fruits and vegetables, calcium, vitamin D, and supplemental vitamin E.

Serum carotenoid concentrations, measured in 46 men at study entry and 1 year later were significantly correlated with correlation coefficients ranging between 0.49 and 0.77 (lycopene $r = 0.56$, α-carotene $r = 0.60$, β-carotene $r = 0.68$, β-cryptoxanthin $r = 0.77$, lutein $r = 0.58$, zeaxanthin $r = 0.49$; all $P < 0.05$), indicating relative stability in the rank order of these nutrients in the study population over time. Dietary intake and serum concentrations of the same carotenoid were modestly correlated, among controls (correlation coefficients: lycopene $r = 0.30$, α-carotene $r = 0.37$, β-carotene $r = 0.30$, β-cryptoxanthin $r = 0.46$, lutein + zeaxanthin $r = 0.32$; all $P < 0.0001$).

The range of carotenoid concentrations was wide, with 3-fold to 6-fold differences for specific carotenoids, at the medians of the first and fifth quintile in controls (Table 2). Serum concentrations of lycopene did not vary significantly between cases and controls; of the other carotenoids, only β-carotene concentrations were significantly greater in cases than controls ($P = 0.04$). In multivariate-adjusted analysis based on quintiles, lycopene was also not associated with prostate cancer incidence; men in the highest quintile had a nonsignificant 14% increase in prostate cancer risk, compared

Table 1. Description of baseline characteristics overall and according to quintiles of serum lycopene and β-carotene

Characteristic	Quintile of serum lycopene			Quintile of serum β-carotene			Overall
	1	3	5	1	3	5	
Controls (*n*)	168	168	168	168	168	168	844
Mean age at study entry, years (SD)	65.8 (0.4)	64.0 (0.4)	63.8 (0.4)	64.1 (0.4)	64.5 (0.4)	65.4 (0.4)	64.7 (0.2)
Average no. of screens /y*	0.97	0.95	0.96	0.96	0.97	0.97	0.96
Non–Hispanic White (%)	100	100	100	100	100	100	100
Family history of prostate cancer (%)	6.7	4.7	4.1	4.1	4.5	3.9	5.2
History of diabetes (%)	14.2	7.7	6.3	14.8	8.2	7.5	8.3
Serum cholesterol, mmol/L (SD)	5.3 (0.1)	6.1 (0.1)	7.1 (0.1)	5.4 (0.1)	6.3 (0.2)	6.6 (0.1)	6.1 (0.1)
Mean current body mass index, kg/m^2 (SD)	27.3 (0.3)	27.7 (0.3)	26.5 (0.3)	28.3 (0.3)	27.5 (0.3)	26.1 (0.3)	27.3 (0.1)
Smoking history (%)							
Never	32.7	23.3	32.4	21.6	27.1	40.7	30.0
Current	8.4	12.0	8.1	12.2	7.7	7.9	9.1
Former	51.0	57.1	48.8	55.2	55.1	40.6	51.5
Pipe/Cigar	6.2	6.2	9.2	9.8	8.8	9.2	9.4
Mean physical activity, h/wk (SD)	2.8 (0.1)	3.0 (0.1)	3.1 (0.1)	2.6 (0.1)	2.8 (0.1)	3.1 (0.1)	2.9 (0.1)
Aspirin use, ≥1 times/wk (%)	51.0	40.0	48.7	47.2	51.1	48.5	47.6
Mean intake (SD)							
Energy (kcal/d)	2405 (72)	2463 (72)	2395 (73)	2371 (71)	2332 (74)	2181 (73)	2347 (32)
Total fat (g/d)	78.8 (1.3)	81.8 (1.3)	81.2 (1.4)	81.9 (1.3)	79.6 (1.4)	76.8 (1.4)	79.2 (1.4)
Fruit, servings (2,000 kcal/d)	3.5 (0.2)	3.2 (0.2)	3.5 (0.2)	2.9 (0.2)	3.3 (0.2)	4.2 (0.2)	3.5 (0.1)
Vegetables, servings (2,000 kcal/d)	5.2 (0.2)	5.5 (0.2)	5.7 (0.2)	4.7 (0.1)	5.4 (0.2)	6.1 (0.2)	5.5 (0.1)
Red meat (g/d)	97.0 (4.5)	102.8 (4.5)	103.6 (4.6)	116.7 (4.4)	97.1 (4.6)	86.7 (4.5)	97.7 (2.6)
PhIP (ng/d)	237.1 (42.9)	309.9 (43.1)	224.7 (43.1)	294.4 (42.3)	215.0 (43.8)	208.2 (43.4)	219.6 (19.4)
Calcium (mg/d)	1150 (35)	1187 (35)	1168 (35)	1088 (34)	1129 (35)	1330 (35)	1166 (21)
Vitamin D (IU/d)	451.6 (25.1)	429.2 (25.2)	388.0 (25.2)	348.4 (24.2)	428.6 (25.0)	548.8 (24.8)	419.8 (11.5)
Supplement vitamin E use, ever, (%) †	52.8	47.0	49.3	38.6	47.4	70.0	48.6

NOTE: All values other than age were directly standardized for age. Intakes of total fat, fruit, vegetables, red meat, PhIP, calcium, and vitamin D were also standardized for energy intake.

*Average number of prostate cancer screening examinations (PSA or DRE) up to diagnosis of prostate cancer (cases) or selection as a control. Maximum period was limited to a period of active screening (years 0-5).

† Includes both single supplement and multivitamin use.

Table 2. Median and range of serum carotenoid concentrations (μg/dL) in prostate cancer cases and controls

	Cases (n = 692)		Controls (n = 844)		P*
	Median	10th-90th percentile	Median	10th-90th percentile	
Lycopene	64.4	30.5-110.1	62.2	30.5-108.2	0.31
α-Carotene	7.3	2.7-20.4	6.9	2.6-16.5	0.12
β-Carotene	16.0	6.5-46.3	15.2	6.1-38.6	0.04
β-Cryptoxanthin	6.8	3.2-15.9	6.8	2.9-16.7	0.51
Lutein	17.3	9.1-32.9	17.2	9.3-31.4	0.92
Zeaxanthin	5.8	3.1-10.5	5.9	3.2-10.3	0.66

*P values were calculated using the Wilcoxon rank sum test.

with men in the lowest quintile, with no indication of a linear trend (P_{trend} 0.28; Table 3). The other carotenoids were also not associated, overall, with risk of prostate cancer, except for higher β-carotene concentrations, which tended to be associated with an increased risk of prostate cancer, but results were not statistically significant.

Risks for aggressive prostate cancer were not related to serum carotenoid concentrations, except that high concentrations of β-carotene were associated with increased risk of aggressive disease (stages III or IV or Gleason score ≥ 7: OR, 1.67; 95% CI, 1.03-2.72 for highest versus lowest quintile; P_{trend} = 0.13; Table 4), with the strongest associations for stage III or IV prostate cancer (OR, 3.16; 95% CI, 1.37-7.31 for highest versus lowest quintile of β-carotene; P_{trend} = 0.02). This positive association with stage III and IV cancer was similar when restricted to cases diagnosed at least 4 years after blood collection.

Similar associations between serum carotenoids and prostate cancer were observed for subgroups characterized by age (<65 years and ≥65 years), smoking (ever versus never), family history of prostate cancer (yes versus no), or (for other carotenoids) serum β-carotene concentration (first versus second to fifth quintile; data not shown). Furthermore, ORs did not vary when the second year of follow-up or the last years without active screening (year 6+) were excluded (data not shown).

Simultaneous adjustment for all serum carotenoids resulted in very similar risk estimates, except for α- and β-carotene, which were less strongly positively associated with stage III and IV cancers. This finding may be explained by the high correlation between both carotenoids (r = 0.71).

Discussion

In this prospective analysis of serum carotenoids, including almost 700 cases, we observed no association between carotenoids and prostate cancer, except for β-carotene, which was associated with increased risk of aggressive prostate cancer, particularly regionally invasive or distant metastatic disease. None of the carotenoid-prostate cancer associations were modified by age, smoking, or family history of prostate cancer.

The Health Professionals Follow-up Study, a cohort study of dietary lycopene with almost 2,500 cases (16), observed an inverse association, whereas no association was found in two other cohorts (17, 41), including our study of >1,300 cases in the PLCO (17, 42-46). Among serum-based studies of circulating lycopene (22-26, 29, 47), the Physicians' Health Study reported that high lycopene concentrations were associated with lower risk of aggressive prostate cancer in the subgroup of men randomized to the placebo arm only (22). In the Health Professionals Follow-up Study, lycopene was inversely

Table 3. ORs of prostate cancer according to quintile of serum carotenoids

	Quintile					P_{trend}
	1*	2	3	4	5	
Lycopene						
Quintile median (μg/dL)	30.5	46.8	62.2	78.5	108.4	
No. of cases/controls	136/168	130/169	121/168	154/169	151/168	
OR (95% CI)†	1.00	1.00 (0.72-1.40)	0.93 (0.66-1.31)	1.16 (0.84-1.61)	1.14 (0.82-1.58)	0.28
α-Carotene						
Quintile median (μg/dL)	2.6	4.7	6.9	10.3	16.6	
No. of cases/controls	136/168	115/168	145/169	136/168	160/168	
OR (95% CI)†	1.00	0.89 (0.63-1.25)	1.06 (0.76-1.48)	1.04 (0.74-1.46)	1.18 (0.85-1.64)	0.17
β-Carotene						
Quintile median (μg/dL)	6.1	10.3	15.2	22.0	38.7	
No. of cases/controls	117/168	122/169	156/168	136/169	160/168	
OR (95% CI)†	1.00	1.03 (0.73-1.45)	1.36 (0.97-1.90)	1.14 (0.81-1.61)	1.30 (0.93-1.82)	0.16
β-Cryptoxanthin						
Quintile median (μg/dL)	2.9	5.0	6.8	9.5	16.8	
No. of cases/controls	139/168	139/169	123/168	132/169	158/168	
OR (95% CI)†	1.00	0.98 (0.71-1.36)	0.87 (0.62-1.22)	0.89 (0.64-1.25)	1.09 (0.78-1.52)	0.50
Lutein						
Quintile median (μg/dL)	9.3	13.3	17.2	22.4	31.5	
No. of cases/controls	151/168	116/169	149/168	127/169	148/168	
OR (95% CI)†	1.00	0.76 (0.54-1.06)	0.93 (0.67-1.28)	0.78 (0.56-1.09)	0.92 (0.66-1.27)	0.85
Zeaxanthin						
Quintile median (μg/dL)	3.2	4.6	5.9	7.6	10.3	
No. of cases/controls	142/168	139/169	140/168	128/169	143/168	
OR (95% CI)†	1.00	1.01 (0.72-1.40)	0.95 (0.69-1.33)	0.82 (0.59-1.15)	0.98 (0.70-1.37)	0.67

*Reference category.
† Adjusted for age, time since initial screening, year of blood draw, and study center.

Table 4. ORs of prostate cancer according to quintile of serum carotenoids

	Aggressive prostate cancer*		Stage III and IV prostate cancer	
	Cases/controls	OR (95% CI) †	Cases/controls	OR (95% CI) †
Lycopene				
Q1 ‡	53/168	1.00	17/168	1.00
Q2	43/169	0.74 (0.45-1.20)	12/169	0.61 (0.27-1.37)
Q3	53/168	0.95 (0.59-1.52)	23/168	1.15 (0.56-2.39)
Q4	68/169	1.22 (0.78-1.91)	22/169	1.16 (0.57-2.38)
Q5	53/168	0.99 (0.62-1.57)	16/168	0.96 (0.45-2.05)
P trend		0.43		0.62
α-Carotene				
Q1 ‡	51/168	1.00	13/168	1.00
Q2	43/168	0.94 (0.57-1.53)	13/168	1.33 (0.57-3.15)
Q3	62/169	1.21 (0.76-1.93)	21/169	1.96 (0.89-4.29)
Q4	57/168	1.19 (0.74-1.90)	21/168	1.93 (0.87-4.25)
Q5	57/168	1.11 (0.69-1.79)	22/168	2.07 (0.93-4.59)
P trend		0.58		0.09
β-Carotene				
Q1 ‡	38/168	1.00	9/168	1.00
Q2	62/169	1.53 (0.94-2.49)	22/169	2.40 (1.04-5.57)
Q3	50/168	1.37 (0.82-2.27)	14/168	1.53 (0.61-3.84)
Q4	52/169	1.39 (0.84-2.31)	17/169	1.78 (0.73-4.35)
Q5	67/168	1.67 (1.03-2.72)	28/168	3.16 (1.37-7.31)
P trend		0.13		0.02
β-Cryptoxanthin				
Q1 ‡	58/168	1.00	18/168	1.00
Q2	50/169	0.89 (0.56-1.40)	14/169	0.77 (0.36-1.66)
Q3	47/168	0.83 (0.52-1.33)	10/168	0.68 (0.29-1.60)
Q4	48/169	0.82 (0.51-1.31)	22/169	1.20 (0.58-2.47)
Q5	66/168	1.08 (0.69-1.71)	26/168	1.57 (0.78-3.16)
P trend		0.53		0.04
Lutein				
Q1 ‡	61/168	1.00	13/168	1.00
Q2	47/169	0.72 (0.45-1.15)	15/169	1.11 (0.47-2.60)
Q3	58/168	0.84 (0.54-1.31)	22/168	1.95 (0.88-4.32)
Q4	50/169	0.71 (0.44-1.14)	19/169	1.56 (0.70-3.48)
Q5	53/168	0.77 (0.49-1.22)	21/168	1.50 (0.68-3.33)
P trend		0.40		0.34
Zeaxanthin				
Q1 ‡	56/168	1.00	16/168	1.00
Q2	63/169	1.04 (0.66-1.63)	17/169	1.06 (0.48-2.33)
Q3	50/168	0.67 (0.42-1.09)	16/168	0.88 (0.40-1.94)
Q4	48/169	0.70 (0.44-1.13)	20/169	1.21 (0.57-2.56)
Q5	53/168	0.87 (0.54-1.39)	21/168	1.29 (0.61-2.72)
P trend		0.35		0.40

*Aggressive defined as stage III or IV *or* Gleason score ≥7 (n = 269).
† Adjusted for age, time since initial screening, year of blood draw, and study center.
‡ Reference category.

associated with prostate cancer in two subgroups: older men (≥65 years) and men without a family history of prostate cancer (29). Earlier findings of a nonsignificant inverse lycopene-prostate cancer association from the CLUE I study (23) were not confirmed on follow-up in CLUE I and CLUE II combined (24). Other prospectively designed nested case-control studies (25, 26, 47) also reported no association, whereas two retrospective case-control studies found inverse associations (27, 28). In some studies, low absolute or narrow range of intake or blood concentrations could have obscured associations (25, 41), however, two studies with low lycopene concentrations showed inverse associations (27, 28), and others (17, 24, 26, 27), including ours, with high intake (17) or blood concentrations, observed no association. Although if the potential cancer-preventive effect of lycopene is defined by a certain threshold, studies with a relatively high intake or blood concentrations could have missed such an effect. Overall, results on serum or plasma lycopene and prostate cancer are unpersuasive.

Supplementation in three randomized trials (48-50) with β-carotene showed inconsistent results for prostate cancer. For men in the Physicians' Health Study with low baseline serum β-carotene concentrations (lowest quartile), β-carotene supplementation (50 mg every other day for an average of 12 years) reduced prostate cancer risk (48), whereas in the Beta-Carotene and Retinol Efficacy Trial, daily supplementation with 30 mg of β-carotene and 25,000 IU vitamin A for up to 5 years was not related to risk (49), and supplementation in the Alpha-Tocopherol Beta-Carotene trial (20 mg β-carotene/d for 5-8 years) resulted in nonsignificant increases in prostate cancer incidence and mortality (50). Because the Alpha-Tocopherol Beta-Carotene trial was conducted in smokers, and animal studies showed that the combined exposure to tobacco smoke and high-dose β-carotene raises oxidative metabolites, induces P450 enzymes, diminishes retinol signaling, and enhances cell proliferation (51, 52), we explored β-carotene and smoking as codeterminants of prostate cancer, but found no evidence for such an interaction.

Observational studies also provide inconsistent findings for β-carotene. Some questionnaire-based case-control studies (42, 43, 45, 53-56) reported lower prostate cancer risks with high intake of β-carotene, however, other studies, including five cohort studies (13, 41, 46, 53, 57-65), did not. In blood-based observational studies, some showed no relation between β-carotene concentrations and prostate cancer (23, 24, 26, 32), whereas similar to ours, three studies (24, 25, 28) found increased risks, of which one was significant in blacks (28). Only two small case-control studies (65 and 118 cases)

reported an inverse association between serum β-carotene and prostate cancer (27, 47), whereas in the Health Professionals Follow-up Study inverse associations were limited to younger men (<65 years; ref. 29). These inconsistent findings are unlikely explained by the different blood concentrations between studies as most observational studies (25, 26, 28, 29, 32), including ours, had similar β-carotene concentrations, which were 8- to 20-fold lower (66) than observed after β-carotene supplementation in the three clinical trials, which also provided mixed results. Animal and *in vitro* studies further add to the complexity of β-carotene's effect on cancer: whereas antioxidative properties of β-carotene potentially reduce cancer risk, β-carotene also induces phase I carcinogen-activating enzymes associated with the generation of oxidative stress (52, 67). The inconsistent results for β-carotene in prostate cancer prevention and the potentially harmful effects of high-dose supplementation on lung cancer, heart disease, and death from all causes in smokers (68-71) should lead to caution in using β-carotene supplementation, at least at high doses.

Consistent with our study, blood-based studies (22, 24-26, 28, 29, 47), mostly nested within cohorts (22, 24-26, 29), observed no association between α-carotene, β-cryptoxanthin, lutein, or zeaxanthin and prostate cancer, except for two small case-control studies which showed an inverse relation (27, 47). Dietary studies summarized elsewhere (29) provide little evidence for a beneficial effect of these carotenoids with respect to prostate cancer prevention.

Serum concentrations of the individual carotenoids were similar to those of previous studies (22-28, 72) except for lycopene, which tend to be higher—possibly explained by age differences in the study populations—younger men may have a higher lycopene intake. Given the relatively wide range of carotenoid concentrations (3- to 6-fold difference between the median of the first and fifth quintile) it is unlikely that our null findings are explained by a limited variation in exposure concentrations.

The strengths of our study are standardized procedures for prostate cancer screening, prediagnostically collected serum samples, a large sample size, and detailed diagnostic data, which allowed us to stratify analyses by stage and grade and the fact that adjusting for many potential confounders did not affect the results. Because the study was conducted within the screening arm of the PLCO trial, all men were screened with a standardized protocol, which enabled us to control for the number of prostate cancer screens during the follow-up period, in a time-dependent manner. This might be difficult to achieve in a non–trial setting, as even with a comprehensive ascertainment of screening behavior, it can be difficult to distinguish between screening tests and exams carried out as part of diagnostic follow-up (73). Screen-detected early-stage prostate cancers might differ from clinically detected aggressive disease in their tumor characteristics and in underlying etiologic risk factors (74). However, all men in our study were annually screened and we stratified by aggressive/nonaggressive disease status.

A limitation of our study is measurement of only a single serum sample. Carotenoid measures at multiple time points would have resulted in more precise estimates of long-term exposure. For example, Kristal et al. (75) determined that using the mean of three measures of lycopene concentrations collected over 7 years yielded a reliability correlation of 0.82, providing a more robust measure of long-term intake. We observed moderate correlations between carotenoid concentrations measured a year apart (0.49-0.77), consistent with previous studies of repeated measures over time (72, 76). Accordingly, nondifferential measurement error, particularly for carotenoids with weaker correlations, such as zeaxanthin (0.49) or lycopene (0.56) may have weakened carotenoid-prostate cancer associations. A further limitation of this study is the relative short follow-up of up to 8 years. We cannot rule out that residual confounding could have affected our results despite our efforts to adjust for many potential confounders; however, this might be less likely for lycopene as high lycopene concentrations were generally associated with a less healthy lifestyle.

In summary, our results do not support the use of lycopene, β-carotene, or other carotenoids in prostate cancer prevention. Indeed, β-carotene may be related to increased risks for prostate cancer and is known to increase the risks of lung cancer and cardiovascular disease in smokers. Simple and inexpensive approaches to prostate cancer prevention would be of great public health significance, and it is unfortunate that the initial results on lycopene and tomato products from well-conducted studies could not be consistently replicated.

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