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Research Article

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Serum Retinol and Carotenoid Concentrations and Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial

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Abstract

Background: Findings from epidemiologic studies examining associations of serum retinol and carotenoids with prostate cancer risk have been inconsistent. This case–control study nested in the Prostate Cancer Prevention Trial evaluated associations of serum retinol and carotenoids with total, low-, and high-grade prostate cancer risk in a highly screened study population.

Methods: We used logistic regression adjusting for age, family history of prostate cancer, race, body mass index, and serum cholesterol to estimate ORs and 95% confidence intervals (CI) of prostate cancer by quartiles of serum retinol and carotenoids, separately in the placebo (975 cases/1,009 frequency-matched controls) and finasteride (708 cases/743 frequency-matched controls) arms of the trial.

Results: Serum retinol concentrations were associated with increased risk of total prostate cancer [OR (95% CI) comparing the highest quartile of serum retinol with the lowest: 1.30 (1.00–1.68)] and high-grade prostate cancer [OR (95% CI), 1.74 (1.14–2.68)] in the placebo arm of the trial only. Also in the placebo arm, there was a moderate positive association of α-carotene with risk of total prostate cancer [OR (95% CI), 1.32 (1.01–1.73)]. None of the other carotenoids was associated with prostate cancer risk in the placebo arm. No associations were observed for retinol and carotenoids in the finasteride arm.

Conclusion: In the placebo arm of this prospective study, high serum retinol and α-carotene concentrations were associated with increased risk of total and high-grade prostate cancers.

Impact: Men with higher levels of serum retinol and α-carotene may be at increased risk for prostate cancer. *Cancer Epidemiol Biomarkers Prev; 24(10); 1507–15. ©2015 AACR.*

Introduction

There has been substantial interest in the potential of antioxidant micronutrients for cancer prevention. Preclinical studies have shown that retinol, the biologically active form of vitamin A, may prevent cancer by regulating growth, differentiation, and apoptosis of normal and malignant cells, by increasing tissue levels of other antioxidants, such as selenium and α-tocopherol, or by regulating DNA transcription through the inhibition of DNA polymerase activity (1). Several carotenoids are vitamin A precursors, have potent antioxidant properties (2), and been shown to inhibit cell growth and induce apoptosis (1, 3).

Epidemiologic evidence for an association between these micronutrients and prostate cancer is inconsistent. Several prospective studies have reported no (4–11) or inverse (12–15) associations of serum retinol and carotenoids with prostate cancer risk, whereas others have shown positive associations (16–18). In part, these conflicting results may be due to differences in sample size. Many included fewer than 100 cases (13, 15, 16), possibly resulting in limited power to detect modest true associations. Furthermore, associations may differ by cancer grade, but only a few studies have investigated associations of retinol (8, 11, 18, 19) or carotenoids (8, 10, 20) with risk of prostate cancer by grade. Finally, differences in screening practices may also contribute to these disparate findings, and studies without a standardized screening protocol, or that are not able to match on or stratify by screening history, may be subject to screening-related detection bias.

The aim of this study was to address some of these limitations by examining associations of serum retinol and carotenoids, including α-carotene, β-carotene, and β-cryptoxanthin, with prostate cancer risk in a case–control study nested within the Prostate Cancer Prevention Trial (PCPT). The PCPT has several unique

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characteristics that minimize some of the aforementioned limitations of previous studies. First, the large sample size of this nested case–control study (975 cases/1,009 frequency-matched controls in the placebo arm, 708 cases/743 frequency-matched controls in the finasteride arm) allowed investigation of associations with low- and high-grade prostate cancer risk, as well as additional subgroup analyses by supplement use and reason for biopsy. In addition, the PCPT protocol included annual standardized prostate cancer screening and biopsy recommendations, as well as an end-of-study biopsy recommendation on all cancer-free men, which reduced the potential for screening-related detection bias. Finally, cancer grade was determined by centralized, uniform pathology, which minimized grade misclassification.

Materials and Methods

Study design and population

Data for this nested case–control study are from the PCPT, a multicenter, randomized, placebo-controlled SWOG-coordinated trial, testing whether the 5α-reductase type II inhibitor, finasteride, reduced risk of prostate cancer (21, 22). Between 1993 and 1997, across 221 study centers in the United States, 18,880 men were randomized to finasteride (5 mg/d) or placebo for 7 years. Eligible men were at least 55 years of age, had a prostate-specific antigen (PSA) level $\leq$3.0 ng/mL, a normal digital-rectal examination (DRE), no history of cancer (except nonmelanoma skin), or severe lower urinary tract symptoms.

During the PCPT, men were screened annually for prostate cancer by PSA and DRE. Men with abnormal DRE or finasteride-adjusted PSA levels $\geq$4.0 ng/mL were referred for a prostate biopsy (21). At the end of the study, all men who had not been previously diagnosed with prostate cancer were requested to undergo a prostate biopsy, regardless of PSA level or DRE status. All biopsies consisted of a minimum of 6 cores, taken under transrectal ultrasonographic guidance. Pathologic evaluation of prostate biopsy was conducted at each study site. In addition, pathologic evaluation was conducted centrally at the Prostate Diagnostic Laboratory, University of Colorado, to include determination of Gleason score, if cancer was present. Pathologists were blinded to trial arm and exposure information. In the case of discordant results, a referee pathologist reviewed cases until concordance was reached. Cancers were classified as "for-cause" if diagnosed after biopsy prompted by an abnormal DRE or elevated PSA, and "not-for-cause" if performed as an end-of-study biopsy. All participants signed written informed consent, and PCPT study procedures were approved by the Institutional Review Boards at each study site, and the Fred Hutchinson Cancer Research Center (Seattle, WA).

Case and control selection

Selection of cases and controls has been previously described (23, 24). Briefly, eligible cases (n = 1,809) were all men with biopsy-confirmed prostate cancer who had baseline blood samples available for analysis. Eligible controls (n = 1,809), selected from men who did not have prostate cancer detected on the end-of-study biopsy and had baseline blood samples, were frequency-matched to cases on distributions of age (5-year categories), treatment arm (finasteride or placebo), and family history of a first-degree relative with prostate cancer; controls were oversampled to include all nonwhites.

Data collection and laboratory methods

At baseline, men completed self-administered questionnaires on demographic, lifestyle, and medical factors, including age, race, alcohol consumption, smoking history, diabetes status, and family history of prostate cancer. Weight and height were measured at baseline, and body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. One year after randomization, men completed an additional questionnaire assessing the frequency of use of multivitamins and single dietary supplements in the previous 12 months. For the purposes of this study, men were considered supplemental vitamin A users if they reported using either vitamin A or β-carotene–containing supplements one or more times per week during the past 12 months, otherwise they were considered nonusers.

Nonfasting blood was collected approximately 3 months prior to randomization, and annually thereafter until diagnosis or the end of study. Venous blood was drawn into collection tubes without anticoagulant and stored at room temperature for 30 to 60 minutes before centrifugation. The serum fraction was then separated and frozen as quickly as possible before being shipped to the specimen repository where the samples were stored at −70°C until analysis (22, 25).

In a pilot study of 25 men from the PCPT with serum samples drawn in years 1, 5, and 7, the intraclass correlations for serum retinol, α-carotene, β-carotene, and β-cryptoxanthin were 64.2%, 73.7%, 46.3%, and 78.7%, respectively. To reduce intraindividual variability, we measured retinol and carotenoids in 250 μL serum samples that comprised equal parts of serum collected 1 and 4 years after randomization; samples from these years were pooled, and then refrozen at −70°C before analysis. Serum from alternative prediagnostic years was selected if men were missing a year 1 or year 4 sample (65 cases, 130 controls) or were diagnosed before year 4 (n = 255 cases), and a single, prediagnostic sample was used if 2 prediagnostic serum samples were unavailable (n = 75 cases, 3 controls). Men diagnosed with cancer before a postrandomization blood sample was collected were excluded (n = 44 cases), as were men with insufficient serum (n = 22 cases, 4 controls), men with missing laboratory values due to a labeling error (n = 44 cases, 35 controls), and men missing 1 or more covariates (n = 16 cases, 18 controls). The final sample size for the present analysis was 975 cases/1,009 controls in the placebo arm, and 708 cases/743 controls in the finasteride arm, and the mean (SD) length of time between serum sample collection and diagnosis (for cases) was 2.3 (1.2) years.

A hexane extract of serum was injected onto a C-18 Spherisorb ODS-2 HPLC column (3 μm, 3.0 × 125 mm, Waters PSS838528) using an Agilent 1100 LC system equipped with quaternary pump, electronic degasser, thermostatted column compartment (set at 25°C), automatic sampler, diode array detector, and ChemStation software. β-Cryptoxanthin was detected at 476 nm, α-carotene and β-carotene at 452 nm, and retinol at 325 nm. Standard curves were generated with commercially available pure chemicals; α-tocopherol acetate was used as the internal standard. Total cholesterol was measured using a Roche Cobas Mira Plus Chemistry Analyzer (Roche Diagnostics). All assays were completed by the Fred Hutchinson Cancer Research Center PHS Biomarker Laboratory, which participates in the National Institute of Standards and Technology Micronutrients Measurement Quality Assurance Program for fat-soluble vitamins and carotenoids in human plasma (26, 27). The weighted average coefficients of variation for pooled quality control samples were 8% for

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retinol, 13% for α-carotene, 13% for β-carotene, and 15% for β-cryptoxanthin.

Statistical analyses

Because finasteride was associated with a reduced risk of total prostate cancer, we hypothesized *a priori* that finasteride exposure would modify the association of retinol/carotenoids with prostate cancer risk; therefore, we examined all associations separately by treatment arm. Differences in baseline characteristics of study participants between case and control groups were tested using χ^2 and *t* tests for categorical and continuous variables, respectively. Geometric mean concentrations of serum retinol and carotenoids were adjusted for age, race, and family history of prostate cancer, and differences between prostate cancer cases and controls were assessed using *t* tests.

Multivariable polytomous logistic regression was used to estimate ORs and 95% confidence intervals (CI) for the associations of retinol and carotenoids with risk of low-grade (Gleason score 2–6) and high-grade (Gleason score 7–10) prostate cancers. Results did not materially change when we included Gleason 7 (3+4) cancers in our analyses of associations with "low-grade" cancers; therefore, to maintain consistency with previous PCPT analyses, all Gleason 7 cancers were considered high-grade for the purposes of this study. Tests for linear trend (P_{trend}) across quartiles of serum retinol and carotenoids were based on an ordinal variable corresponding to rank from lowest to highest. Stratum-specific quartile cutpoints were defined based on the distributions among controls.

All logistic regression models were adjusted for the matching variables age (continuous) and family history of prostate cancer (yes, no), the oversampling of non-whites (white, non-white), and BMI (continuous). Because retinol, α-carotene, β-carotene, and β-cryptoxanthin were correlated with serum cholesterol concentrations (r = 0.20, 0.17, 0.16, 0.18, respectively, all $P < 0.0001$), which was associated with risk of high-grade prostate cancer in this cohort (28), regression models were also adjusted for serum cholesterol. Further controls for other potential confounders, including physical activity and history of diabetes, did not change the estimated associations by more than 10% and, thus, were not included in final models.

Because serum retinol levels and/or prostate cancer risk may differ by indication for biopsy, use of vitamin A supplements (users versus nonusers), BMI, age, family history of prostate cancer, we examined associations in strata of these variables. The Wald χ^2 test was used to test for differences in associations across strata, based on interaction terms between serum retinol trend (as described above) and categorical indicator variables for trial arm, reason for biopsy, and supplement use.

Because of concern that serum retinol or α-carotene levels may have influenced prostate cancer detection using PSA (29), we determined the correlation (Pearson's *r*) between PSA and serum concentrations of retinol and carotenoids in controls from the placebo arm. Where the serum analyses were performed on pooled samples, the PSA value at the time of the second serum sample was used for comparison; otherwise, where one serum sample was used for retinol or α-carotene analyses, the PSA value at that time point was used.

All statistical tests were two sided, and $P < 0.05$ was considered statistically significant. SAS version 9.4 was used for all analyses (SAS Institute).

Results

Table 1 gives baseline demographic and lifestyle characteristics, stratified by treatment arm, of the prostate cancer cases overall and by grade, as well as for the controls. Cases and controls did not differ in the distribution of BMI, smoking status, and serum cholesterol, or by the matching variables age and family history of prostate cancer. In the placebo arm, cases were less likely than controls to be diabetic. Cases were more likely to be nonwhite than controls because of the oversampling of nonwhite controls. A much higher proportion of higher-grade cancers were diagnosed "for-cause" relative to low-grade cancers.

Table 2 gives geometric mean and distributions of serum retinol and carotenoids in total, low-grade, and high-grade prostate cancer cases and controls by treatment arm. In the placebo arm, serum α-carotene and β-carotene levels were marginally higher in total and low-grade prostate cancer cases relative to controls; serum α-carotene and β-carotene levels were not different between high-grade prostate cancer cases and controls. Serum retinol and β-cryptoxanthin did not differ between total, low-grade, or high-grade prostate cancer cases and controls in the placebo arm. Furthermore, there were no differences in serum retinol or carotenoids between total, low-grade, or high-grade prostate cancer cases and controls in the finasteride arm.

Table 3 gives multivariable-adjusted associations of serum retinol and carotenoids with risk of total, low-, and high-grade prostate cancer, stratified by treatment arm. In the placebo arm, serum retinol was positively associated with total and high-grade prostate cancer risk; the odds of total and high-grade prostate cancer were 30% and 74% higher, respectively, in the highest, relative to the lowest, quartile of serum retinol. In addition, serum α-carotene was associated with risk of total prostate cancer; the odds of developing total prostate cancer were 32% higher in the highest, relative to the lowest, quartile of serum α-carotene. There was suggestion of a positive association between quartile of serum α-carotene and risk of both low- and high-grade prostate cancers; however, neither of these associations reached statistical significance. There were no associations of β-carotene or β-cryptoxanthin with risk of total, low-, or high-grade prostate cancer in either the finasteride or placebo arms. There were no associations of serum retinol with prostate cancer risk in the finasteride arm. Furthermore, associations with high-grade cancers were not materially different when we restricted to Gleason 8–10 (data not shown).

The associations of retinol or carotenoids with prostate cancer risk did not differ when stratified by age, BMI, or family history of prostate cancer (data not shown); however, there were differences within strata of reason for biopsy and supplemental vitamin A use. Table 4 gives associations of retinol and α-carotene with prostate cancer risk stratified by reason for biopsy in the placebo arm only. When stratified by reason for biopsy, there were no associations of serum retinol with risk of prostate cancer among the "not-for-cause" detected cases, and an increased risk of total and high-grade prostate cancer among men diagnosed "for-cause," although the *P* interaction was not statistically significant. The odds of total and high-grade disease were 43% and 91% greater, respectively, than those in the highest, relative to lowest, quartile of serum retinol. In contrast, associations of α-carotene and prostate cancer risk were limited to cases diagnosed "not-for-cause." These associations were strongest for total and low-grade disease; the odds of developing total and low-grade disease were

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Table 1. Baseline characteristics of participants, stratified by prostate cancer grade and treatment arm, in the PCPT

	Finasteride					Placebo				
	Control ($n = 743$)	Total[a] cancer ($n = 708$)	Case Gleason 2–6 ($n = 422$)	Gleason 7–10 ($n = 257$)	P^b	Control ($n = 1,009$)	Total cancer ($n = 975$)	Case Gleason 2–6 ($n = 735$)	Gleason 7–10 ($n = 204$)	P^b
Age at baseline, mean (SD)	63.6 (5.6)	63.9 (5.6)	63.4 (5.5)	64.7 (5.7)	0.24	63.6 (5.6)	63.6 (5.5)	63.3 (5.4)	64.5 (5.5)	Frequency matched
55–59, *n* (%)	200 (26.9)	184 (26.0)	123 (29.1)	55 (21.4)	0.96	270 (26.8)	259 (26.6)	212 (28.8)	39 (19.1)	1.00
60–64	240 (32.3)	226 (31.9)	135 (32.0)	81 (31.5)		330 (32.7)	320 (32.8)	241 (32.8)	71 (34.8)	
65–69	180 (24.2)	175 (24.7)	101 (23.9)	67 (26.1)		244 (24.2)	238 (24.4)	175 (23.8)	49 (24.0)	
70+	123 (16.6)	123 (17.4)	63 (14.9)	54 (21.0)		165 (16.3)	158 (16.2)	107 (14.6)	45 (22.1)	
Race[c], *n* (%)										
White	541 (72.8)	655 (92.5)	392 (92.9)	234 (91.1)	<0.0001	848 (84.0)	906 (92.9)	693 (94.3)	180 (88.2)	<0.0001
Black	101 (13.6)	35 (4.9)	23 (5.5)	12 (4.7)		71 (7.0)	46 (4.7)	24 (3.3)	19 (9.3)	
Other	101 (13.6)	18 (2.5)	7 (1.7)	11 (4.3)		90 (8.9)	23 (2.4)	18 (2.4)	5 (2.5)	
BMI, mean (SD)	27.6 (4.0)	27.5 (3.8)	27.3 (3.8)	27.8 (3.8)	0.55	27.6 (4.0)	27.4 (4.1)	27.2 (4.1)	28.3 (4.1)	0.27
Normal (BMI <25), *n* (%)	200 (26.9)	189 (26.7)	121 (28.7)	62 (24.1)	0.91	244 (24.2)	282 (28.9)	225 (30.6)	45 (22.1)	0.05
Overweight (BMI 25 to <30)	377 (50.7)	354 (50.0)	211 (50.0)	130 (50.6)		549 (54.4)	502 (51.5)	379 (51.6)	102 (50.0)	
Obese (BMI $\geq$ 30)	166 (22.3)	165 (23.3)	90 (21.3)	65 (25.3)		216 (21.4)	191 (19.6)	131 (17.8)	57 (27.9)	
Any supplement use, *n* (%)	311 (50.7)	285 (49.8)	163 (48.7)	116 (53.7)	0.75	423 (50.6)	430 (54.4)	326 (55.0)	88 (53.0)	0.12
Cholesterol mg/dL, mean (SD)	216.0 (37.7)	216.8 (40.7)	216.1 (35.9)	217.3 (45.3)	0.71	212.0 (39.5)	215.2 (37.1)	215.5 (36.9)	214.7 (37.0)	0.06
Family history, *n* (%)	165 (22.2)	155 (21.9)	100 (23.7)	50 (19.5)	0.89	207 (20.5)	198 (20.3)	154 (21.0)	44 (21.6)	Frequency matched
Diabetes, *n* (%)	56 (7.5)	37 (5.2)	17 (4.0)	18 (7.0)	0.07	71 (7.0)	39 (4.0)	25 (3.4)	12 (5.9)	<0.01
Smoking status, *n* (%)										
Never smoker	257 (34.6)	243 (34.3)	160 (37.9)	78 (30.4)	0.84	345 (34.2)	356 (36.5)	270 (36.7)	75 (36.8)	0.45
Current smoker	57 (7.7)	49 (6.9)	26 (6.2)	20 (7.8)		77 (7.6)	65 (6.7)	53 (7.2)	11 (5.4)	
Former smoker	429 (57.7)	416 (58.8)	236 (55.9)	159 (61.9)		587 (58.2)	554 (56.8)	412 (56.1)	118 (57.8)	
Diagnosed on a for-cause biopsy	80 (10.8)	342 (48.3)	158 (37.4)	167 (65.0)	<0.0001	107 (10.6)	430 (44.1)	287 (39.0)	124 (60.8)	<0.0001
T stage										
T1a		92 (13.2)	66 (15.9)	18 (7.0)			137 (14.1)	107 (14.6)	13 (6.4)	
T1b		46 (6.6)	29 (7.0)	16 (6.2)			72 (7.4)	58 (7.9)	12 (5.9)	
T1c		358 (51.4)	221 (53.4)	130 (50.6)			517 (53.3)	403 (55.1)	109 (53.7)	
T2a		113 (16.2)	60 (14.5)	45 (17.5)			123 (12.7)	92 (12.6)	27 (13.3)	
T2b		39 (5.6)	19 (4.6)	19 (7.4)			48 (4.9)	26 (3.6)	18 (8.9)	
T2c		25 (3.6)	9 (2.2)	16 (6.2)			43 (4.4)	24 (3.3)	18 (8.9)	
T3		15 (2.2)	3 (0.7)	11 (4.3)			9 (0.9)	4 (0.5)	4 (2.0)	

[a]The number of high-grade and low-grade cancers does not equal the total number of cancer cases, due to the inclusion of ungraded cancers.
[b]Comparison between controls and total cancer cases.
[c]Non-white controls were oversampled.

59% and 49% greater, respectively, than those in the highest, relative to lowest, quartile of serum α-carotene. There was also an association of serum α-carotene with high-grade diseases detected not-for-cause (Table 4), although this association was not statistically significant.

Furthermore, several controls had an indication for biopsy (i.e., elevated PSA or abnormal DRE) at trial end ($n = 187$); therefore, we performed sensitivity analyses where we stratified both cases and controls by indication for biopsy. Results did not materially differ from those presented in Table 4.

Because of concern that serum retinol or α-carotene levels may have influenced PSA-based indications for biopsy (29), we also assessed associations of serum retinol and α-carotene with PSA. There were no associations of either serum retinol (Pearson $r = 0.01$, $P = 0.381$) or serum α-carotene with PSA (Pearson $r = -0.01$, $P = 0.64$).

Table 2. Geometric mean[a] (95% CI) of serum concentrations of retinol and carotenoids among prostate cancer cases and controls by treatment arm, in the PCPT

Serum concentration (μg/dL)	Control Mean (95% CI)	Case Mean (95% CI)	Gleason 2–6 Mean (95% CI)	Gleason 7–10 Mean (95% CI)
Placebo				
Retinol	0.67 (0.66–0.68)	0.68 (0.67–0.69)	0.68 (0.67–0.69)	0.69 (0.67–0.71)
α-Carotene	0.04 (0.04–0.05)	0.05 (0.05–0.05)[b]	0.05 (0.05–0.05)[b]	0.05 (0.04–0.05)
β-Carotene	0.23 (0.22–0.24)	0.24 (0.23–0.25)[b]	0.24 (0.23–0.26)[b]	0.23 (0.21–0.26)
β-Cryptoxanthin	0.08 (0.08–0.09)	0.08 (0.08–0.09)	0.09 (0.08–0.09)	0.08 (0.08–0.09)
Finasteride				
Retinol	0.68 (0.67–0.69)	0.67 (0.66–0.68)	0.68 (0.67–0.69)	0.67 (0.65–0.68)
α-Carotene	0.05 (0.04–0.05)	0.05 (0.04–0.05)	0.05 (0.04–0.05)	0.04 (0.04–0.05)
β-Carotene	0.23 (0.22–0.25)	0.24 (0.23–0.25)	0.24 (0.22–0.26)	0.23 (0.21–0.26)
β-Cryptoxanthin	0.08 (0.08–0.09)	0.08 (0.08–0.09)	0.09 (0.08–0.09)	0.08 (0.08–0.09)

[a]Geometric least squares means, adjusted for age, race, and family history.
[b]$P < 0.05$.

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Table 3. Associations of serum concentrations of retinol and carotenoids with total, low-grade, and high-grade cancers by treatment arm, in the PCPT[a]

	Total prostate cancer		Gleason 2–6		Gleason 7–10	
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	Case/control	OR (95% CI)
Retinol						
Placebo						
Q1[b]	205/260	Ref.	153/260	Ref.	42/260	Ref.
Q2	236/256	1.11 (0.86–1.44)	178/256	1.11 (0.84–1.47)	49/256	1.18 (0.75–1.85)
Q3	259/252	1.18 (0.91–1.53)	207/252	1.23 (0.93–1.63)	44/252	1.07 (0.68–1.71)
Q4	275/241	1.30 (1.00–1.68)	197/241	1.21 (0.91–1.60)	69/241	1.74 (1.14–2.68)
P trend		0.04		0.14		0.02
Finasteride						
Q1	164/179	Ref.	89/179	Ref.	67/179	Ref.
Q2	165/183	0.88 (0.64–1.20)	96/183	0.94 (0.65–1.35)	61/183	0.81 (0.53–1.22)
Q3	183/183	0.94 (0.69–1.28)	115/183	1.09 (0.76–1.56)	63/183	0.80 (0.53–1.20)
Q4	196/198	0.95 (0.70–1.30)	122/198	1.08 (0.75–1.54)	66/198	0.81 (0.53–1.22)
P trend		0.90		0.50		0.33
P interaction[c]		0.20		0.72		0.03
α-Carotene						
Placebo						
Q1	196/256	Ref.	145/256	Ref.	45/256	Ref.
Q2	245/256	1.16 (0.90–1.51)	190/256	1.20 (0.91–1.60)	48/256	1.04 (0.66–1.63)
Q3	263/249	1.28 (0.99–1.67)	197/249	1.27 (0.95–1.68)	55/249	1.24 (0.80–1.93)
Q4	271/248	1.32 (1.01–1.73)	203/248	1.29 (0.96–1.72)	56/248	1.36 (0.86–2.14)
P trend		0.03		0.10		0.13
Finasteride						
Q1	164/184	Ref.	95/184	Ref.	64/184	Ref.
Q2	168/180	0.95 (0.69–1.29)	93/180	0.92 (0.64–1.32)	68/180	0.96 (0.64–1.45)
Q3	198/190	1.06 (0.78–1.44)	119/190	1.08 (0.76–1.54)	67/190	0.94 (0.62–1.42)
Q4	178/189	0.95 (0.69–1.30)	115/189	1.04 (0.72–1.49)	58/189	0.81 (0.53–1.25)
P trend		0.92		0.63		0.35
P interaction		0.17		0.53		0.16
β-Carotene						
Placebo						
Q1	196/245	Ref.	143/245	Ref.	46/245	Ref.
Q2	255/266	1.13 (0.87–1.46)	192/266	1.15 (0.87–1.53)	50/266	0.99 (0.64–1.54)
Q3	274/253	1.28 (0.98–1.66)	205/253	1.27 (0.96–1.69)	61/253	1.35 (0.87–2.08)
Q4	250/245	1.18 (0.90–1.55)	195/245	1.22 (0.91–1.64)	47/245	1.07 (0.67–1.71)
P-trend		0.16		0.15		0.46
Finasteride						
Q1	159/193	Ref.	92/193	Ref.	59/193	Ref.
Q2	170/172	1.09 (0.80–1.49)	106/172	1.18 (0.82–1.69)	60/172	1.03 (0.68–1.58)
Q3	201/186	1.15 (0.85–1.57)	112/186	1.10 (0.77–1.57)	78/186	1.24 (0.82–1.87)
Q4	178/192	1.07 (0.78–1.47)	112/192	1.15 (0.80–1.65)	60/192	0.99 (0.64–1.53)
P trend		0.60		0.56		0.79
P interaction		0.61		0.64		0.93
β-Cryptoxanthin						
Placebo						
Q1	249/251	Ref.	187/251	Ref.	51/251	Ref.
Q2	221/257	0.84 (0.65–1.09)	171/257	0.86 (0.65–1.13)	44/257	0.85 (0.54–1.32)
Q3	274/250	1.08 (0.84–1.38)	202/250	1.05 (0.80–1.38)	64/250	1.25 (0.83–1.89)
Q4	231/251	0.90 (0.69–1.17)	175/251	0.89 (0.67–1.17)	45/251	0.95 (0.60–1.49)
P trend		0.89		0.74		0.70
Finasteride						
Q1	168/188	Ref.	99/188	Ref.	65/188	Ref.
Q2	179/181	1.07 (0.79–1.44)	102/181	1.03 (0.73–1.47)	67/181	1.03 (0.68–1.54)
Q3	196/186	1.27 (0.94–1.72)	119/186	1.32 (0.93–1.87)	68/186	1.12 (0.75–1.69)
Q4	165/188	1.09 (0.79–1.49)	102/188	1.13 (0.78–1.62)	57/188	0.98 (0.64–1.50)
P trend		0.38		0.29		0.95
P interaction		0.65		0.43		0.77

[a]Associations were adjusted for age, race, BMI, family history of prostate cancer, and serum cholesterol.

[b]Quartiles of serum concentration of retinol and carotenoids were defined based on values in all controls (finasteride and placebo arms combined). Quartiles 1, 2, 3, and 4, respectively, were defined using the following stratum-specific cutoffs. Retinol: <0.58 μg/dL, 0.58 to <0.67 μg/dL, 0.67 to <0.77 μg/dL, >0.77 μg/dL; α-carotene: <0.03 μg/dL, 0.03 to <0.04 μg/dL, 0.04 to <0.7 μg/dL, >0.7 μg/dL; β-carotene: <0.14 μg/dL, 0.14 to <0.23 μg/dL, 0.23 to <0.37 μg/dL, >0.37 μg/dL; β-cryptoxanthin: <0.06 μg/dL, 0.06 to <0.09 μg/dL, 0.09 to <0.12 μg/dL, >0.12 μg/dL.

[c]*P* value tests for interaction between serum quartile (as a trend ordinal value) and stratification factor.

Finally, we examined associations of serum retinol concentrations with prostate cancer risk, stratified by supplemental vitamin A use. Mean (SD) serum retinol concentrations were elevated in supplement users [0.72 (0.15) μg/dL], relative to nonusers [0.67 (0.14) μg/dL]. Table 5 gives associations of serum retinol and prostate cancer risk, stratified by supplement use. Associations of

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Table 4. Associations of serum concentrations of retinol and α-carotene with risk of total, lower-, and higher-grade prostate cancer, stratified by reason for biopsy, in the placebo arm of the PCPT[a]

Outcome	Cases/ controls	Total	Cases/ controls	Gleason 2–6	Cases/ controls	Gleason 7–10
Retinol						
For-cause						
Q1[b]	80/252	Ref.	55/252	Ref.	22/252	Ref.
Q2	100/253	1.19 (0.84–1.67)	65/253	1.11 (0.74–1.66)	30/253	1.31 (0.73–2.34)
Q3	123/252	1.41 (1.01–1.98)	90/252	1.47 (1.00–2.16)	28/252	1.23 (0.68–2.23)
Q4	127/252	1.43 (1.02–2.01)	77/252	1.24 (0.83–1.84)	44/252	1.91 (1.10–3.31)
P trend		0.02		0.16		0.02
Not-for-cause						
Q1	115/252	Ref.	94/252	Ref.	16/252	Ref.
Q2	128/253	1.05 (0.77–1.43)	105/253	1.04 (0.74–1.45)	18/253	1.12 (0.56–2.26)
Q3	144/252	1.12 (0.83–1.53)	120/252	1.12 (0.81–1.55)	20/252	1.26 (0.63–2.51)
Q4	158/252	1.21 (0.89–1.64)	129/252	1.17 (0.85–1.62)	26/252	1.64 (0.85–3.17)
P trend		0.18		0.29		0.12
P interaction[c,d]		0.98		0.296		0.94
α-Carotene						
For-cause						
Q1	102/253	Ref.	66/253	Ref.	31/253	Ref.
Q2	97/252	0.88 (0.63–1.23)	65/252	0.90 (0.61–1.33)	30/252	0.92 (0.54–1.58)
Q3	101/252	0.90 (0.64–1.25)	69/252	0.93 (0.63–1.38)	27/252	0.82 (0.47–1.44)
Q4	130/252	1.12 (0.81–1.56)	87/252	1.12 (0.76–1.64)	36/252	1.17 (0.68–2.00)
P trend		0.44		0.52		0.66
Not-for-cause						
Q1	91/253	Ref.	77/253	Ref.	13/253	Ref.
Q2	143/252	1.50 (1.09–2.07)	119/252	1.45 (1.03–2.04)	19/252	1.49 (0.71–3.12)
Q3	161/252	1.70 (1.23–2.34)	127/252	1.53 (1.09–2.16)	28/252	2.30 (1.14–4.64)
Q4	150/252	1.59 (1.14–2.21)	125/252	1.49 (1.05–2.12)	20/252	1.79 (0.84–3.82)
P trend		0.007		0.037		0.067
P interaction		0.73		0.94		0.44

[a]Associations adjusted for age, race, family history of prostate cancer, and serum cholesterol.
[b]Quartiles of serum concentration of retinol and carotenoids were defined based on values in all controls (finasteride and placebo arms combined). Quartiles 1, 2, 3, and 4, respectively, were defined using the following stratum-specific cutoffs. Retinol: <0.58 μg/dL, 0.58 to <0.67 μg/dL, 0.67 to <0.77 μg/dL, >0.77 μg/dL; α-carotene: <0.03 μg/dL, 0.03 to <0.04 μg/dL, 0.04 to <0.7 μg/dL, >0.7 μg/dL.
[c]To calculate interaction *P* value, controls are also stratified by reason for biopsy.
[d]*P* value tests for interaction between serum quartile (as a trend ordinal value) and stratification factor.

serum retinol and total and high-grade prostate cancer were strongest among supplemental vitamin A users, despite a statistically nonsignificant *P* interaction. Among men who reported regular supplemental vitamin A use, the odds of developing high-grade prostate cancer were 145% greater in the highest, relative to lowest, quartile of serum retinol. There was also a marginally nonsignificant 52% increased odds of total prostate cancer risk in the highest quartile of serum retinol, relative to those in the lowest. There were no associations of serum retinol with prostate cancer risk among supplement nonusers.

Table 5. Associations of retinol with risk of total, low-, and high-grade prostate cancer, stratified by supplemental retinol use, in the placebo arm of the PCPT[a,b]

	Total cancer		Gleason 2–6		Gleason 7–10	
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	Case/control	OR (95% CI)
User						
Q1[c]	86/110	Ref.	69/110	Ref.	15/110	Ref.
Q2	110/110	1.21 (0.81–1.79)	82/110	1.09 (0.71–1.68)	23/110	1.59 (0.78–3.23)
Q3	101/110	1.06 (0.71–1.58)	78/110	0.98 (0.63–1.51)	18/110	1.24 (0.59–2.63)
Q4	147/110	1.52 (1.03–2.25)	107/110	1.32 (0.87–2.01)	36/110	2.45 (1.24–4.85)
P trend		0.06		0.26		0.02
Nonuser						
Q1	91/116	Ref.	63/116	Ref.	24/116	Ref.
Q2	101/116	1.06 (0.72–1.57)	77/116	1.15 (0.75–1.77)	20/116	0.86 (0.45–1.66)
Q3	108/117	1.11 (0.75–1.63)	88/117	1.26 (0.83–1.92)	16/117	0.70 (0.35–1.40)
Q4	108/116	1.14 (0.78–1.68)	80/116	1.18 (0.77–1.80)	24/116	1.09 (0.58–2.05)
P trend		0.49		0.42		0.94
P interaction[d]		0.89		0.98		0.65

[a]Individuals were defined as supplement users if they reported using vitamin A supplements more than once per week. Supplement use data were missing for 215 cases and 182 controls.
[b]Associations adjusted for age, race, BMI, family history of prostate cancer, and serum cholesterol.
[c]Quartiles of serum retinol were defined based on values in all controls (finasteride and placebo arms combined). Quartiles 1, 2, 3, and 4, respectively, were defined using the following stratum-specific cutoffs: <0.60 μg/dL, 0.60 to <0.69 μg/dL, 0.69 to <0.78 μg/dL, >0.78 μg/dL.
[d]*P* value tests for interaction between serum retinol quartile (as a trend ordinal value) and supplemental retinol use.

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Discussion

In this prospective analysis of serum retinol, carotenoids, and prostate cancer risk, we found positive associations between serum retinol and total and high-grade prostate cancer, and between serum α-carotene and total prostate cancer, in the placebo arm of the PCPT. When examining associations stratified by reason for biopsy and supplement use, we found that associations with serum retinol were limited to men with a for-cause biopsy and those who reported supplement use. Associations of serum α-carotene with total prostate cancer risk were observed only among men with a not-for-cause biopsy. There were no other associations of serum carotenoids with prostate cancer risk. Furthermore, there were no associations of serum retinol or carotenoids with prostate cancer risk in the finasteride arm.

Our finding of an increased risk of prostate cancer with higher serum retinol concentrations is in agreement with results from two earlier cohort studies. In the Alpha Tocopherol Beta Carotene (ATBC) trial, high serum retinol concentrations were associated with increased risk of both total and aggressive prostate cancers (18), and in the Physician's Health Study (PHS), a positive association of serum retinol with total, but not aggressive, prostate cancer was reported (17). In addition, a recent pooled analysis, which included data from the PCPT, reported a 13% increase in prostate cancer risk in the highest quintile of serum retinol, relative to the lowest (T. Key and colleagues; unpublished data).

In contrast, several prospective studies have observed either no (4–11) or inverse (12–15) associations of serum retinol with prostate cancer risk. Two of the larger studies, the European Prospective Investigation into Cancer and Nutrition (EPIC; ref. 10) and the Prostate Testing for Cancer and Treatment (ProtecT; ref. 19) studies, found no significant association of plasma retinol with total prostate cancer risk. Conversely, the Prostate Lung Colorectal and Ovarian Cancer screening trial (PLCO) observed an inverse association in men randomized to the screening arm of the trial (11). Thus, epidemiologic evidence remains mixed regarding the association of serum retinol with prostate cancer risk.

Given that serum retinol concentrations are homeostatically regulated (30) and are not strongly associated with diet (31), it is unlikely that our findings can be wholly attributed to differences in dietary intake. Other factors that may affect serum retinol concentrations in a well-nourished population include age, male sex, and alcohol consumption, all of which have shown direct associations with serum retinol concentrations in the NHANES (32). In addition, serum retinol concentrations have shown marginal increases with vitamin A supplementation in a non-deficient population (33). In this study population, serum retinol concentrations were elevated in men who reported vitamin A supplement use, relative to those who did not.

This finding is in agreement with our observation that associations of serum retinol with prostate cancer risk were stronger in supplement users than supplement nonusers. There was a positive, nonmonotonic association of serum retinol and high-grade prostate cancer risk in supplement users only, which was only statistically significant for the highest quartile of serum retinol concentration. Therefore, supplement use may increase one's risk of prostate cancer by increasing serum retinol concentrations. Alternatively, supplemental and dietary retinol may have disparate effects on prostate cancer risk.

In additional stratified analyses, we found that associations of serum retinol with prostate cancer risk differed by reason for biopsy. The positive association of serum retinol with total and high-grade prostate cancer risk was limited to for-cause detected cancers; we observed nonsignificant positive trends of similar magnitude among not-for-cause detected cancers. Associations were strongest for high-grade cancers, and we note that a larger number of high-grade cancers were detected for cause; therefore, it is possible that these disparate findings might be explained by differences in statistical power between strata. It is unlikely that these associations may be attributed to detection bias, as we found no association of pooled serum retinol and PSA in PCPT placebo-arm controls.

Previous prospective studies of the association with serum α-carotene have largely been null (9, 10, 20), although some studies have suggested an inverse association (34). In the present study, we observed an increasing risk of total, low-, and high-grade prostate cancer with increasing α-carotene concentrations, but only the associations with total prostate cancer risk were statistically significant. Furthermore, we found that associations of serum α-carotene with total and low-grade prostate cancer risk were limited to not-for-cause detected cancers. It is also possible that elevated serum α-carotene could lead to decreased detection of for-cause cancers, as serum α-carotene has shown inverse associations with prostate cancer detection using PSA in NHANES (29). However, we found no association of serum α-carotene with PSA in this study population; therefore, we think that such detection bias is unlikely in this study population.

Finally, our finding of no association between serum β-carotene or β-cryptoxanthin and prostate cancer risk is consistent with results from several other studies, including the PHS and EPIC cohorts (10, 17, 35). In the PLCO, serum β-cryptoxanthin was not associated with total prostate cancer risk; however, serum β-carotene was positively associated with increased risk of aggressive prostate cancer (20). Furthermore, a positive association of serum β-carotene was also observed in the Finnish Kuopio Ischaemic Heart Disease Risk Factor Cohort (36).

There are several strengths of this study, including its primary strength, its relatively large size, which allowed us to examine associations with low- and high-grade prostate cancer risk. We found much stronger associations of serum retinol and α-carotene with risk of high-grade, relative to low-grade and total prostate cancer; it is possible that associations of serum retinol and carotenoids with prostate cancer risk may be obscured in studies that examine total prostate cancer risk only. The PCPT also had a standardized screening protocol, which limited detection bias and concerns of confounding due to associations of PSA screening with dietary patterns (37). Furthermore, disease misclassification was reduced in the PCPT; presence or absence of cancer was biopsy-confirmed for all participants in this nested case–control study, and cancer grade was determined by centralized, uniform pathology review. Finally, the use of pooled serum from years 1 and 4 provides an estimate of long-term serum retinol and carotenoid exposure, as compared with a single serum sample from baseline. This pooled serum sample may also better represent the etiologic time-period of interest.

There are also several features of the PCPT that must be considered when interpreting its results. First, because all study participants had low PSA at entry ($\leq$3 ng/mL), and were screened

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annually for prostate cancer using PSA and DRE, the number of high-grade cancers was limited, and the vast majority of the cancers were local stage cancers, which may not have become clinically relevant if not diagnosed on the end of study biopsy. However, despite the small number of high-grade cancers, we did observe significant associations with serum retinol. In addition, participants of the PCPT were primarily non-Hispanic whites, limiting our ability to examine differences by race or ethnicity. In this study, supplement use data were missing for 215 cases (13%) and 182 controls (10%); white men and men without a history of cigarette smoking were less likely to be missing data on supplement use. We do not expect this small proportion of missing data to affect our results. Finally, we cannot rule out the possible contribution of chance to our observed findings, especially given that we tested for differences between multiple subgroups. However, we do note that these findings agree with those from a large pooled analysis of prospective studies (T. Key and colleagues; unpublished data), which gives us confidence in the validity of this result.

In summary, in this nested case–control analysis, we found positive associations of serum retinol and α-carotene with total and high-grade prostate cancer risk, in men randomized to the placebo arm of the trial. Associations of retinol and prostate cancer risk differed by reason for biopsy and supplement use.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.M. Lippman, J. Schenk
Development of methodology: J. Schenk
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X. Song, M.S. Lucia, I.M. Thompson Jr
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.H. Nash, C. Till, S.M. Lippman, E.A. Platz, J. Schenk
Writing, review, and/or revision of the manuscript: S.H. Nash, C. Till, X. Song, M.S. Lucia, H.L. Parnes, I.M. Thompson Jr, S.M. Lippman, E.A. Platz, J. Schenk
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X. Song, H.L. Parnes, I.M. Thompson Jr, S.M. Lippman
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Serum Retinol and Carotenoid Concentrations and Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial

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