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Research Article

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Serum 25-Hydroxyvitamin D Concentrations and Risk of Prostate Cancer: Results from the Prostate Cancer Prevention Trial

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Abstract

Background: Epidemiologic studies have reported inconsistent associations of vitamin D and prostate cancer risk; however, few have adequately controlled for detection bias related to prostate-specific antigen (PSA) screening, and the results of many studies may be affected by occult prostate cancers among controls.

Methods: Data for this nested case–control analysis ($n = 1{,}695$ cases/1,682 controls) are from the Prostate Cancer Prevention Trial. Baseline serum was analyzed for 25-hydroxyvitamin D [25(OH)D]. The presence or absence of cancer was subsequently determined by prostate biopsy. Polytomous logistic regression models were used to estimate associations of 25(OH)D with risk of total, Gleason 2–6, Gleason 7, and Gleason 8–10 prostate cancer. Results are presented for placebo and finasteride arms separately and combined.

Results: There were no associations of serum 25(OH)D with total prostate cancer risk. For Gleason 2–6 cancers, results were inconsistent across treatment arms with a suggestion of increased risk in the placebo arm only; however, there was no dose–response relationship. For Gleason 8–10 prostate cancers, 25(OH)D concentrations were associated with a linear decrease in risk among combined treatment arms [quartile 4 vs. 1: OR, 0.55; 95% confidence interval (CI), 0.32–0.94; $P_{trend} = 0.04$]. These findings were somewhat stronger among men ≥65 versus 55–64 years at baseline (quartile 4 vs. 1: OR, 0.40; 95% CI, 0.18–0.88 vs. OR, 0.73; 95% CI, 0.35–1.52, respectively; $P_{interaction} = 0.52$).

Conclusions: Higher serum 25(OH)D may modestly increase risk of Gleason 2–6 disease and more substantially reduce risk of Gleason 8–10 prostate cancer.

Impact: Vitamin D may have different effects for different stages of prostate cancers. *Cancer Epidemiol Biomarkers Prev; 23(8); 1484–93. ©2014 AACR.*

Introduction

Prostate cancer is the most common cancer and the second leading cause of cancer deaths among men in the United States (1, 2). Despite the high prevalence of prostate cancer, there are very few known modifiable risk factors. There is considerable interest in the potential role for vitamin D in prostate cancer etiology. Vitamin D is a pro-hormone primarily recognized for its role in bone health (3); however, other identified functions include roles in cellular proliferation, differentiation, and apoptosis, all of which have relevance to cancer (4).

Many lines of evidence suggest an important role for vitamin D in the pathogenesis or progression of prostate cancer. Prostate cells express vitamin D receptors (VDR) and are able to convert 25-hydroxyvitamin D [25(OH)D], the primary circulating form of vitamin D, to the biologically active form of the vitamin, 1,25(OH)D (5). In experimental studies, 1,25(OH)D inhibits proliferation and induces differentiation, cell-cycle arrest, and apoptosis in prostatic cells, prostate cancer cell lines, and in animal models of prostate cancer (6–9). Two well-established risk factors for prostate cancer, older age and African American race, are associated with a decreased synthesis of vitamin D (10). In addition, ecologic studies indicate that ultraviolet radiation (UVR) exposure, one of the principal determinants of vitamin D status in humans, is inversely associated with prostate cancer risk (11).

Although there is strong biologic support for the association between vitamin D and prostate cancer, epidemiologic studies of the association of vitamin D concentration with risk have been inconsistent. Several observational studies reported an increased risk of prostate cancer among men with low (12, 13) or high (14–17) serum vitamin D concentrations, and one study found that men

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with the highest as well as lowest serum concentrations of vitamin D were at increased risk of prostate cancer (18). In contrast, many other studies found no association between vitamin D concentration and prostate cancer risk (19–32). Some of the inconsistencies in these studies may be related to small sample sizes or occult prostate cancer cases in the control group, and few studies were able to adequately control for detection bias, which often occurs in populations where screening via prostate-specific antigen (PSA) is common (33).

Here, we examine the association of serum 25(OH)D with prostate cancer risk using a nested case–control study of nearly 1,700 cases and 1,700 controls from the Prostate Cancer Prevention Trial (PCPT). In addition to the large sample size, several unique aspects of the PCPT address the limitations of previous studies: all participants underwent standardized annual prostate screening, the presence or absence of prostate cancer was established by biopsy, and cancer grade was determined by centralized, uniform pathology. Thus, detection bias and misclassification of disease was minimized, and pathologic grading of cases was rigorous.

Materials and Methods

Data for this nested case–control study are from the PCPT, a randomized double-blind, placebo-controlled trial of finasteride for the primary prevention of prostate cancer (34). Briefly, 18,880 men aged 55 years or older with normal digital rectal examination (DRE) results, PSA levels of 3 ng/mL or less, and no history of prostate cancer, severe lower urinary tract symptoms, or clinically significant coexisting conditions were randomized to receive finasteride (5 mg/d) or placebo. During the PCPT, participants underwent DRE and PSA determination annually, and men with an abnormal DRE or a PSA [adjusted for the effect of finasteride (ref. 35)] above 4.0 ng/mL were referred for a prostate biopsy. At the end of 7 years, all men not previously diagnosed with prostate cancer were asked to undergo an end-of-study biopsy per the primary trial protocol to determine the presence or absence of prostate cancer (34). Six core samples were collected under transrectal ultrasonographic guidance, and biopsies were reviewed for adenocarcinoma by both the local study site pathologist and a central pathology laboratory. In the case of discordant results, a referee pathologist reviewed cases until concordance was reached. Clinical stage was assigned locally, and tumors were graded centrally using the Gleason scoring system. All participants signed written informed consent, and the Institutional Review Board of the Fred Hutchinson Cancer Research Center (Seattle, WA), which serves as the statistical center for the PCPT, approved this study.

Case and control selection

Cases ($n = 1,695$) were all men with biopsy-confirmed prostate cancer, identified either by a "for-cause" (following a PSA > 4 ng/mL or abnormal DRE) biopsy ($n = 803$) or at the end-of-study biopsy ($n = 892$), who had baseline blood samples available for analysis. Controls ($n = 1,682$) were selected from men who had no evidence of prostate cancer on the end-of-study biopsy and had baseline blood samples. Controls were frequency matched to cases on distributions of age, first-degree family history of prostate cancer and PCPT treatment arm, and included all available non-Whites.

Data collection and laboratory methods

Information on age, race/ethnicity, family history of prostate cancer in first-degree relatives, level of physical activity, usual alcohol consumption, and history of smoking and diabetes was collected at baseline using standardized self-administered questionnaires.

Participants' height and weight were measured at the randomization clinic visit, and body mass index (BMI) was calculated as weight (kg)/height (m^2). One year after randomization, waist and hip circumferences were measured, and intakes of alcohol, vitamin D, and calcium were assessed using a food frequency questionnaire and a structured dietary supplement-use questionnaire (36, 37). Latitude from the Equator was assigned to each participant based on the study site from which the participant was randomized and using a publicly available database (38).

Nonfasting blood was collected at recruitment (3 months before randomization) into a tube without anticoagulant and kept at room temperature for 30 to 60 minutes before centrifugation. Following centrifugation, serum was extracted and shipped on dry ice overnight to a central repository. Upon receipt, the sample was thawed to remove an aliquot for PSA, total and high-density lipoprotein (HDL) cholesterol analysis, and the remaining serum was frozen in 0.5-mL aliquots. 25(OH)D concentration was measured from using one 0.5-mL serum sample.

Serum 25(OH)D concentration was measured using the LIAISON 25 OH Vitamin D TOTAL Assay (DiaSorin Inc.), following manufacturer's instructions. The lower limit of quantitation (LoQ) of the 25(OH)D assay is 4 ng/mL. No specimens had results below the LoQ. All batches were balanced for number of cases and controls, and laboratory personnel were blinded to case status. Assays were completed by the Fred Hutchinson Cancer Research Center Public Health Sciences Biomarkers Laboratory. The coefficient of variation (CV) for 86 blinded, embedded quality control samples from pooled specimens was 8.31%.

Statistical analysis

The distribution of characteristics for case and control participants was compared using t tests (for continuous variables) and χ^2 tests (for categorical variables). The distribution of serum 25(OH)D concentrations was right-skewed; therefore, values were log-transformed. Unadjusted linear regression models were used to determine whether participant characteristics were associated with log-transformed 25(OH)D concentrations.

Serum vitamin D concentrations were standardized for month of blood collection using the residual method (39), in which the residual from a regression model of month (12 categories) and 25(OH)D concentration was added to the population mean 25(OH)D concentration (60.74 nmol/L). The resulting month-standardized 25 (OH)D concentrations were then categorized into quartiles based on the distribution among controls. In addition, 25(OH)D was parameterized using clinically relevant cut points (37.5, 50, and 75 nmol/L; ref. 40); however, associations were similar to those using quartiles (data not shown).

Multivariate logistic and polytomous logistic regression models were used to estimate odds ratios and 95% confidence intervals for the associations of 25(OH)D concentration with risks of total, Gleason 2–6, Gleason 7, and Gleason 8–10 disease. Because finasteride reduces prostate cancer risk (34), and both vitamin D and finasteride are involved in androgen metabolism (41), analyses of the association between vitamin D and prostate cancer risk were conducted in the finasteride and placebo arm separately and combined. All models were adjusted for race (White, African American, other race). Analyses in combined PCPT arms were also adjusted for treatment (finasteride, placebo). Further control for matching variables, including age and family history of prostate cancer, as well as other factors believed to potentially confound the association between Vitamin D and prostate cancer risk in this cohort, including serum cholesterol concentration, BMI, physical activity, history of diabetes, latitude of study site, and total calcium intake, did not change the estimated effect by more than 10% and were not included in final models.

Because vitamin D synthesis is lower in older men (42) and obese men have lower concentrations of 25 (OH)D (43), analyses were also stratified by age (<65, ≥65 years) and BMI (<25, 25–29, ≥30 kg/m^2). In addition, analyses were stratified by whether the diagnostic biopsy was "for-cause" or not. Tests for linear trend across quartiles were based on an ordinal variable corresponding to rank (lowest to highest quartile). Tests for differences in associations across strata were based on interaction terms between 25(OH)D concentration and categorical indicator variables for treatment (finasteride, placebo), age (<65, ≥65 years), and a nominal variable for BMI (<25, 25–29, ≥30 kg/m^2). Sensitivity analyses were also completed removing cases diagnosed within 1 year of baseline. All tests were 2-sided and considered statistically significant at $P < 0.05$. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc.).

Results

Table 1 gives distributions of participants' characteristics and geometric mean of 25(OH)D concentrations. Participants were mostly White, overweight, sedentary, or minimally active, nondiabetic, former smokers, had no family history of prostate cancer, and were moderate drinkers (<30 grams of alcohol per day). Compared with controls, men with prostate cancer were more likely to be from a high latitude study site and were less likely to have a history of diabetes. 25(OH)D concentrations were lower among participants who were non-White, overweight or obese, less physically active, diabetic, current smokers, or from a higher latitude study site, and among participants who consumed less alcohol or calcium.

Table 2 gives associations of serum 25(OH)D concentration with total, Gleason 2–6, Gleason 7, and Gleason 8–10 prostate cancer in placebo and finasteride arms separately and combined. In the placebo arm, risk of total, Gleason 2–6, and Gleason 7 cancer tended to be increased for 25(OH)D concentrations ≥ 56.8 nmol/L (quartiles 3 and 4), whereas risk of Gleason 8–10 cancer tended to be decreased for increasing concentrations of 25(OH)D. The linear trend for Gleason 2–6 cancer was borderline significant ($P_{trend} = 0.05$); however, there were no clear monotonic trends in these associations. In the finasteride-only arm, increasing 25(OH)D concentrations were not associated with risk of total, Gleason 2–6, or Gleason 7 prostate cancer; however, there was a suggestive, but not significant, decrease in risk for Gleason 8–10 prostate cancer (Table 2). There were no statistically significant differences between placebo and finasteride arms in associations of 25(OH)D and risk of total, Gleason 2–6, Gleason 7, and Gleason 8–10 prostate cancer ($P_{interaction} = 0.58$, 0.77, 0.84, and 0.50, respectively); thus, results are also presented for treatment arms combined. In combined treatment arms, there was a suggestion of an increase in risk of Gleason 2–6 prostate cancer with increasing 25(OH)D concentrations, although the trend was borderline statistically significant and none of the point estimates for individual quartiles were significant. In addition, increasing 25 (OH)D concentrations were associated with a significant linear decrease in risk of Gleason 8–10 prostate cancer ($P_{trend} = 0.04$). Results were similar for sensitivity analyses excluding cases diagnosed within the first year (data not shown).

In combined PCPT treatment arms, associations of 25 (OH)D with risk of total, Gleason 2–6, and Gleason 7 prostate cancer were similar across strata defined by age; however, associations with risk of Gleason 8–10 prostate cancer tended to be stronger among older (≥65 years) men, although the difference between younger and older men was not statistically significant (Table 3). There were no statistically significant differences in associations of 25(OH)D with risk of total, Gleason 2–6, Gleason 7, or Gleason 8–10 prostate cancer across strata defined by BMI (Table 3). There was a suggestion that associations of 25(OH)D with Gleason 8–10 prostate cancer were stronger among cancers diagnosed "not-for-cause" [OR (95% CI) of Q4 vs. Q1 for 0.31 (0.10–1.01]; however, the number of Gleason 8–10 cases diagnosed "not-for-cause" is very small ($n = 27$) and no associations

Table 1. Baseline characteristics of PCPT participants

	n (%)	*n* (%)	*P*	Geometric mean[a] (95% CI)
Total sample	1,695	1,682		
Age, y			NR[b]	
55–59	452 (27)	453 (27)		53.7 (23.8–121.2)
60–64	548 (32)	538 (32)		57.6 (26.8–123.5)
65–69	409 (24)	416 (25)		57.5 (27.6–119.8)
70+	286 (17)	275 (16)		57.0 (26.6–122.2)
Race			NR[b]	
White	1,571 (93)	1,333 (79)		58.8 (28.6–120.9)
African American	82 (5)	171 (10)		39.5 (15.7–99.7)
Other	42 (2)	178 (11)		49.1 (22.9–105.6)
Family history of prostate cancer			NR[b]	
No	1,329 (78)	1,320 (78)		56.3 (25.8–122.7)
Yes	366 (22)	362 (22)		56.7 (26.9–119.7)
PCPT treatment arm			NR[b]	
Finasteride	708 (42)	711 (42)		55.3 (24.8–123.6)
Placebo	987 (58)	971 (58)		57.2 (27.1–120.8)
Baseline diabetes			<0.001	
No	1,618 (95)	1,556 (93)		57.0 (26.5–12.03)
Yes	77 (5)	125 (7)		47.8 (22.8–99.9)
BMI, kg/m^2			0.20	
Normal (<25)	466 (28)	417 (25)		60.9 (28.5–130.2)
Overweight (25–<30)	862 (51)	880 (53)		57.2 (27.0–121.2)
Obese (≥30)	351 (21)	368 (22)		49.2 (22.7–106.6)
Waist to hip			0.99	
0.77–<0.94	500 (33)	519 (34)		58.7 (27.1–127.2)
0.94–<0.98	500 (33)	519 (34)		56.4 (26.5–119.8)
0.98–1.18	501 (34)	515 (32)		53.8 (24.9–116.6)
Latitude of study site,[c] degrees			0.02	
21.3–<33.47	398 (23)	443 (26)		59.8 (28.5–125.5)
33.47–<38.49	425 (25)	429 (26)		56.5 (26.3–121.1
38.49–<41.69	412 (24)	429 (26)		55.5 (24.9–124.0)
41.69–48.73	460 (27)	381 (23)		54.0 (25.1–116.2)
Smoking status			0.59	
Never	601 (35)	573 (34)		57.2 (27–121.2)
Current	115 (7)	125 (7)		48.9 (20.3–117.6)
Former	979 (58)	984 (59)		56.9 (26.5–122.2)
Alcohol intake, g/d			0.84	
Non-drinker	381 (22)	392 (23)		55.3 (25.7–119.3)
>0–<30	1,161 (69)	1,142 (68)		56.6 (26.3–121.9)
≥30	153 (9)	148 (9)		57.9 (25.7–130.6)
Physical activity[d]			0.24	
Sedentary	286 (17)	291 (17)		50.1 (22.3–112.6)
Light	703 (42)	699 (42)		55.7 (25.8–120.3)
Moderate	554 (33)	511 (31)		59.2 (28.6–122.5)
Active	145 (8)	173 (10)		63.3 (30.4–131.8)
Calcium intake,[e] mg/d			0.28	
156–<697	364 (25)	377 (25)		50.9 (21.6–120.0)
697–<980	360 (25)	381 (25)		56.9 (27.3–118.6)
980–<1,364	351 (24)	390 (26)		56.7 (27.6–116.5)
1,364–4,075	387 (26)	354 (24)		62.0 (30.7–125.0)

(Continued on the following page)

Table 1. Baseline characteristics of PCPT participants (Cont'd)

	n (%)	*n* (%)	*P*	Geometric mean[a] (95% CI)
Vitamin D intake,[e] μg/d			0.30	
0.64–<4.31	358 (25)	383 (26)		51.8 (22.0–121.7)
4.31–<8.37	348 (24)	393 (26)		55.1 (25.6–118.7)
8.37–<14.64	379 (26)	362 (24)		57.7 (28.3–117.8)
14.64–42.27	377 (26)	364 (24)		61.8 (31.2–122.4)

Abbreviation: NR, not reported.

[a]Unadjusted.

[b]*P* values from matching or oversampling variables are not interpretable.

[c]Latitude defined as degrees north from Equator; 1° change in latitude is approximately equivalent to 69 miles; a latitude of 33°N is approximately equivalent to Long Beach, CA or Atlanta, GA; a latitude of 39°N is approximately equivalent to Sacramento, CA or Washington, DC and 42°N forms the California–Oregon and the New York–Pennsylvania borders.

[d]Sedentary: low activity index (calculated as the multiple of frequency, duration, and pace indices) and participated in intense activities less than once a week; Light: low activity index and participated in intense activities 4 times a week or less; Moderate: moderate or high activity index and participated in intense activities 4 times a week; Active: high activity index and participated in intense activities 5 or more times a week.

[e]From diet and supplements; for vitamin D, 1 μg = 40 IU.

for individual strata reached statistical significance (data not shown).

Discussion

In this nested case–control study in the PCPT, there were no associations of serum 25(OH)D and risk of total prostate cancer; however, there were differential associations among some subgroups. There was a suggestion of an increased risk of 25(OH)D concentrations with risk of Gleason 2–6 prostate cancer that was limited to the placebo arm; however, there was no evidence of a dose–response relationship. In addition, increasing 25 (OH)D concentrations were associated with a linear decrease in Gleason 8–10 prostate cancer risk. This association was consistent across subgroups defined by PCPT treatment arm (finasteride, placebo) and BMI (<25, 25–29, ≥30 kg/m^2) and was slightly stronger among older men (≥65 years).

Investigations of the association of vitamin D and prostate cancer risk are important to inform public health recommendations on vitamin D intake and solar exposure. The Institute of Medicine recently reviewed literature on vitamin D and risk of cancer and reported there was insufficient evidence to draw conclusions about a role for vitamin D in reducing prostate cancer risk (3). Despite the lack of evidence, popularized health reports and consumer literature emphasize the apparent widespread vitamin D insufficiency and deficiency. As a result, annual sales of vitamin D supplements have increased more than 10-fold, from $42 million in 2002 to $605 million in 2011 (44), and the prevalence of supplemental vitamin D use among men aged 60 and older has increased from 23.7% (1988–1994) to 44% (2003–2006; ref. 45). It is important to gain a better understanding of the risks and benefits of high vitamin D status on prostate cancer risk before recommendations can be made with respect to the use of supplemental vitamin D for prostate cancer prevention.

Two prior studies reported inverse associations of serum 25(OH)D and prostate cancer risk. In an update of the Health Professionals Follow-up Study (HPFS; $n = 1{,}260$ total cases), men in the highest quartile of 25(OH)D had a 57% lower risk of lethal prostate cancer ($P_{trend} = 0.002$) but no association with overall prostate cancer ($P_{trend} = 0.45$; ref. 13). In the Helsinki Heart Study ($n = 149$ total cases), men with 25(OH)D concentrations greater than 40 nmol/L had a 41% lower risk of total prostate cancer, and this association was stronger among younger men (<52 years; ref. 12). This study also reported that younger men with 25 (OH)D concentrations greater than 40 nmol/L had a lower risk of "non-localized" prostate cancer.

In contrast to HPFS and the Helsinki Heart Study, 5 previous studies have reported inconsistencies in the direction of associations between vitamin D concentration and risk of prostate cancer (14–18). One study of Nordic men ($n = 622$ cases) reported that risk of total prostate cancer was greatest among men with the lowest (≤19 nmol/L) and highest (≥80 nmol/L) 25(OH)D concentrations (18). Several other studies report positive associations between serum 25(OH)D and prostate cancer risk. In an initial report from the HPFS ($n = 684$ cases), risk of total and high-grade prostate cancer was 38% and 58% lower, respectively, among men with 25(OH)D concentrations lower than 15 ng/ml (37.44 nmol/L; ref. 17). In the Malmo Diet and Cancer Study, men with serum 25(OH)D between 91 and 106 nmol/L had the highest risk of total prostate cancer (16), and in the Alpha-Tocopherol Beta-Carotene study cohort ($n = 1{,}000$ cases), there was a significant dose–response increase in risk of total and

Table 2. Multivariable-adjusted associations of serum 25(OH)D concentrations and prostate cancer risk in the PCPT, by prostate cancer grade and treatment arm

	All cancer		Gleason 2–6		Gleason 7		Gleason 8–10	
	Case/control	OR[a] (95% CI)	Case/control	OR[a] (95% CI)	Case/control	OR[a] (95% CI)	Case/control	OR[a] (95% CI)
Placebo								
Q1[b]	193/233	Ref	136/233	Ref	33/233	Ref	16/233	Ref
Q2[b]	232/253	1.01 (0.78–1.33)	173/253	1.05 (0.78–1.40)	40/253	1.06 (0.65–1.77)	9/253	0.54 (0.23–1.27)
Q3[b]	276/231	1.32 (1.01–1.73)	204/231	1.35 (1.01–1.80)	48/231	1.40 (0.87–2.31)	12/231	0.81 (0.37–1.78)
Q4[b]	286/254	1.18 (0.91–1.53)	219/254	1.25 (0.94–1.66)	47/254	1.19 (0.73–1.97)	8/254	0.50 (0.20–1.22)
P_{trend}		0.08		0.05		0.33		0.22
Finasteride								
Q1[b]	165/188	Ref	89/188	Ref	46/188	Ref	24/188	Ref
Q2[b]	162/167	0.91 (0.66–1.26)	193/167	0.96 (0.66–1.40)	40/167	0.82 (0.51–1.34)	21/167	0.85 (0.45–1.60)
Q3[b]	173/188	0.78 (0.57–1.06)	100/188	0.83 (0.58–1.21)	43/188	0.70 (0.44–1.13)	20/188	0.63 (0.33–1.21)
Q4[b]	208/168	1.02 (0.74–1.39)	127/168	1.16 (0.81–1.67)	57/168	1.01 (0.64–1.59)	17/168	0.57 (0.29–1.12)
P_{trend}		0.90		0.52		0.94		0.07
Combined								
Q1[b]	358/421	Ref	225/421	Ref	79/421	Ref	40/421	Ref
Q2[b]	394/420	0.97 (0.79–1.18)	266/420	1.01 (0.81–1.28)	80/420	0.93 (0.66–1.31)	30/420	0.73 (0.44–1.21)
Q3[b]	449/419	1.07 (0.87–1.30)	304/419	1.13 (0.90–1.42)	91/419	1.01 (0.72–1.42)	32/419	0.75 (0.45–1.23)
Q4[b]	494/422	1.10 (0.90–1.35)	346/422	1.21 (0.97–1.52)	104/422	1.09 (0.78–1.52)	25/422	0.55 (0.32–0.94)
P_{trend}		0.20		0.06		0.48		0.04
$P_{interaction}$[c]		0.58		0.77		0.84		0.50

NOTE: Vitamin D standardized for month of blood draw before dividing into quartiles based on distribution in controls.

[a]ORs adjusted for age (continuous) and race (White, African American, other race); ORs for combined treatment arms also adjusted for treatment (finasteride, placebo).

[b]Quartile cutoff points of adjusted values: 44.7, 56.8, and 71.2 nmol/L.

[c]Interaction tested as the cross-product of 25(OH)D concentration rank (lowest to highest quartile) and an indicator for treatment (finasteride, placebo).

Table 3. Multivariable-adjusted associations for combined PCPT treatment arms of serum 25(OH)D concentrations and prostate cancer risk in the PCPT by age and BMI

	All cancer		Gleason 2–6		Gleason 7		Gleason 8–10	
	Case/control	OR[a] (95% CI)	Case/control	OR[a] (95% CI)	Case/control	OR[a] (95% CI)	Case/control	OR[a] (95% CI)
Age, y								
<65								
Q1[b]	213/260	Ref	139/260	Ref	47/260	Ref	20/260	Ref
Q2[b]	243/247	1.02 (0.78–1.33)	174/247	1.11 (0.82–1.48)	44/247	0.86 (0.55–1.36)	18/247	0.87 (0.44–1.71)
Q3[b]	256/253	1.01 (0.77–1.32)	188/253	1.12 (0.83–1.50)	43/253	0.80 (0.50–1.27)	14/253	0.65 (0.31–1.36)
Q4[b]	288/231	1.16 (0.89–1.52)	207/231	1.26 (0.94–1.68)	58/231	1.11 (0.72–1.73)	15/231	0.73 (0.35–1.51)
		0.28		0.15		0.65		0.30
65+								
Q1[b]	145/161	Ref	86/161	Ref	32/161	Ref	20/161	Ref
Q2[b]	151/173	0.89 (0.64–1.22)	92/173	0.87 (0.60–1.27)	36/173	1.02 (0.60–1.74)	12/173	0.56 (0.27–1.20)
Q3[b]	193/166	1.15 (0.84–1.57)	116/166	1.12 (0.78–1.61)	48/166	1.35 (0.82–2.25)	18/166	0.85 (0.43–1.69)
Q4[b]	206/191	1.03 (0.76–1.41)	139/191	1.14 (0.80–1.62)	46/191	1.09 (0.66–1.81)	10/191	0.40 (0.18–0.88)
		0.47		0.22		0.55		0.07
$P_{interaction}$		0.80		0.99		0.99		0.52
BMI[c]								
<25								
Q1[b]	66/94	Ref	47/94	Ref	10/94	Ref	7/94	Ref
Q2[b]	95/81	1.33 (0.84–2.09)	71/81	1.34 (0.81–2.20)	18/81	1.88 (0.81–4.37)	4/81	0.59 (0.16–2.15)
Q3[b]	145/110	1.49 (0.97–2.27)	101/110	1.39 (0.87–2.23)	26/110	1.96 (0.88–4.37)	8/110	0.81 (0.27–2.39)
Q4[b]	176/149	1.26 (0.84–1.90)	122/149	1.18 (0.76–1.86)	40/149	2.13 (0.99–4.59)	8/149	0.54 (0.18–1.59)
		0.79		0.66		0.08		0.34
25–<30								
Q1[b]	172/200	Ref	104/200	Ref	43/200	Ref	17/200	Ref
Q2[b]	212/225	0.99 (0.75–1.32)	140/225	1.07 (0.77–1.48)	41/225	0.78 (0.48–1.25)	19/225	1.00 (0.50–2.01)
Q3[b]	220/230	0.95 (0.72–1.27)	149/230	1.06 (0.77–1.47)	45/230	0.78 (0.49–1.25)	17/230	0.85 (0.41–1.74)
Q4[b]	258/225	1.11 (0.84–1.48)	188/225	1.33 (0.97–1.82)	48/225	0.83 (0.52–1.33)	12/225	0.60 (0.23–1.31)
		0.47		0.08		0.51		0.18
30+								
Q1[b]	120/127	Ref	74/127	Ref	26/127	Ref	16/127	Ref
Q2[b]	87/114	0.71 (0.48–1.05)	55/114	0.71 (0.45–1.11)	21/114	0.83 (0.44–1.58)	7/114	0.46 (0.18–1.17)
Q3[b]	84/79	1.00 (0.66–1.51)	54/79	1.00 (0.63–1.60)	20/79	1.16 (0.60–2.27)	7/79	0.66 (0.25–1.73)
Q4[b]	60/48	1.02 (0.64–1.64)	36/48	0.97 (0.57–1.66)	16/48	1.32 (0.63–2.73)	5/48	0.69 (0.23–2.05)
		0.76		0.89		0.37		0.44
$P_{interaction}$[d]		0.47		0.41		0.28		0.61

NOTE: Vitamin D standardized for month of blood draw before dividing into quartiles based on distribution in controls.

[a]ORs adjusted for age (except age-stratified models), race (White, African American, other race), and treatment (finasteride, placebo).

[b]Quartile cutoff points based on the distribution in controls in each strata.

[c]Thirty-three men missing BMI data were not included in BMI stratified analyses.

[d]Interaction tested as the cross-product of 25(OH)D concentration rank (lowest to highest quartile) and an indicator for age (<65, ≥65) or BMI (<25, 25–<30, ≥30).

aggressive prostate cancer across increasing quintiles of serum vitamin D (14). Also, in the Janus Serum Bank cohort ($n = 2{,}106$ cases), 25(OH)D concentrations were associated with a linear increase in risk of total prostate cancer, but only among men with blood collected in summer or autumn (15). In addition, numerous other nested case–control studies have reported no association between serum 25(OH)D concentrations and prostate cancer risk (19–32). Taken together, the totality of the evidence neither support nor refute a protective role for vitamin D in prostate carcinogenesis.

The reasons for the inconsistencies in results across studies are unclear. There are considerable differences in populations across these studies. Several were conducted in Northern European populations (12, 14–16, 18) in which the range of 25(OH)D concentration was smaller and the proportion with deficient 25(OH)D concentrations (<50 nmol/L) was greater; however, there was no consistency in the associations reported by these studies. It is possible that serum 25(OH)D concentrations are a marker of other health-related behaviors. For example, PSA screening is associated with healthy dietary behaviors and use of dietary supplements (46), and men who receive PSA screening are more likely to have prostate cancer detected (47); thus, results from studies that did not adjust for PSA screening may be biased. It is also possible that variations in assay techniques could account for some of the differences in findings across studies.

We hypothesized *a priori* that the association of 25(OH)D with prostate cancer risk might differ by PCPT treatment arm. In the PCPT, finasteride substantially reduced prostate cancer risk (34); therefore, we examined associations of 25(OH)D and prostate cancer separately by treatment arm. In addition, we investigated a potential interaction between 25(OH)D and finasteride. Finasteride inhibits the conversion of testosterone into dihydrotestosterone, and there is evidence to suggest the vitamin D plays a role in androgen signaling (48). For example, in animal and prostate cancer cell line studies, the effect of vitamin D on growth inhibition is androgen-dependent and is reversed after adding anti-androgens or castration (48). In addition, variants in the VDR and 5α−reductase type II genes combine to increase prostate cancer risk (49). Although there is strong biologic rationale to support these analyses, the associations of serum 25(OH)D and prostate cancer risk in the finasteride arm were only modestly attenuated in the PCPT, and there was no evidence of an interaction between serum 25(OH)D and treatment arm.

When stratified by Gleason score, we found a modest but significant inverse association of serum 25(OH)D concentration and risk of Gleason 8–10 cancer and a suggestive positive association for Gleason 2–6 cancer. Of the 15 nested case–control studies that stratified by stage or grade, 4 have reported inconsistent associations for 25(OH)D and risk of advanced prostate cancer. Ahonen and colleagues (12) reported that younger men (<52 years) with high (>40 nmol/L) 25 (OH)D had a lower risk of "nonlocalized" prostate cancer, and Shui and colleagues (13) found that men in the highest quartile of 25 (OH)D concentration had the lowest risk of "lethal" prostate cancer (metastases or prostate cancer–specific death). However, Mikhak and colleagues (17) found that men with sufficient (>37.5nmol/L) 25 (OH)D had an increased risk of high-grade (Gleason ≥7) cancer, and Albanes and colleagues (14) reported that men with the highest concentration of 25(OH)D had a 1.7-fold increased risk of aggressive (Gleason ≥ 8 or stage III or IV) disease. One additional study reported 25(OH)D concentrations greater than the lowest quintile were associated with increased risk of aggressive disease; however, the association was marginally statistically significant (22). No studies reported significant associations of 25(OH)D concentrations with risk of low-grade or nonaggressive prostate cancer. Ten additional nested case–control studies reported no association of 25(OH)D with high-grade or aggressive disease (18–21, 25–27, 30, 32).

Because serum 25(OH)D concentrations decline with age (50) and are lower in overweight and obese individuals due to sequestration of the fat-soluble vitamin in adipose tissue (43), we conducted exploratory analyses to examine whether the associations between 25(OH)D and prostate cancer risk differed by age or BMI. The association of 25(OH)D with risk of Gleason 8–10 cancer was slightly stronger among older than among younger men, although the numbers of cases among older men is small, associations were not linear and the differences between younger and older men were not statistically significant ($P_{\text{interaction}} = 0.52$). In the PCPT, obesity was associated with an increased risk of high-grade but decreased risk of low-grade cancer (51). Thus, it is possible that the effect of obesity on the association between 25(OH)D and prostate cancer risk differed for low- and high-grade cancer. The directions of associations of 25(OH)D with Gleason 2–6 and Gleason 7 differed slightly; however, these differences were not statistically significant ($P_{\text{interactions}} = 0.41$ and 0.28, respectively). There were no significant differences in associations of 25(OH)D with total or Gleason 8–10 cancer risk between normal weight, overweight, and obese men in this study.

There are several elements of the PCPT that serve to minimize bias in this study. First, all men in the PCPT had annual PSA and DRE tests, which substantially minimizes the potential for screening-related detection bias. Second, the absence or presence of prostate cancer was confirmed by biopsy in all men either during (cases only) or at the end of the trial; thus reducing the possibility that undetected cancers could affect study results. In addition, cancer grade was available for the majority of cases and was determined by centralized, uniform pathology. Finally, the PCPT recruited participants from more than 200 clinical sites, and thus represents a diverse U.S. geography.

Several limitations should also be noted. The use of a single measurement of vitamin D concentration may not be representative of an individual's long-term vitamin D

status; although, measurements of serum 25(OH)D collected over 5 years have been shown to be reasonably stable in healthy individuals over 5 years (52). The standardized screening protocol in the PCPT minimized the potential for detection bias, but it is possible that vitamin D status differed among men who were more likely to comply with a biopsy recommendation or elect to undergo the end of study biopsy. This, in part, may explain the slight positive association of 25(OH)D with risk of Gleason 2–6 prostate cancer. Although the end of study biopsy allowed confirmation of the absence of prostate cancer among controls, the majority of cancers detected were low-grade (77%), and the clinical significance of these cancers is unclear. Also, there were very few high-grade cancers diagnosed during the trial ($n = 127$); therefore, these results are based on a relatively small sample size. In addition, there were few African Americans in the PCPT, which is particularly relevant because African Americans have the highest risk of prostate cancer (1) and tend to have lower serum 25(OH)D concentrations (53). Even though we oversampled non-White controls, power was limited to detect differential associations among African Americans. Finally, few deaths from prostate cancer occurred in the PCPT, thus we were unable to examine mortality as an endpoint.

In conclusion, the findings from this large nested case–control study of vitamin D status and prostate cancer risk suggest a potential protective association between serum 25(OH)D concentration and risk of high-grade prostate cancer; however, these findings also suggest that serum 25(OH)D concentrations may be associated with an increased risk of low-grade prostate cancers. These differential associations require further study in sufficiently powered studies. While further research needs to be conducted to determine the most appropriate approaches for optimizing vitamin D status, particularly among older men who have decreased endogenous synthesis, these results suggest that the associations of vitamin D and prostate cancer risk may differ for low- and high-grade cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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