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Serum 25-Hydroxyvitamin D, Vitamin D Binding Protein, and Prostate Cancer Risk in Black Men

Tracy M. Layne, PhD, MPH[1,2], **Stephanie J. Weinstein, PhD**[2], **Barry I. Graubard, PhD**[2], **Xiaomei Ma, PhD**[1,3], **Susan T. Mayne, PhD**[1,3], and **Demetrius Albanes, MD**[2]

[1]Chronic Disease Epidemiology Department, Yale School of Public Health, New Haven, Connecticut [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland [3]Yale Comprehensive Cancer Center, Yale University, New Haven, Connecticut

Abstract

BACKGROUND—Few studies have prospectively examined the relationship between vitamin D status and prostate cancer risk in black men, a group at high risk for both low vitamin D status and prostate cancer.

METHODS—Among black men in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, we identified 226 prostate cancer cases and 452 controls matched on age at randomization (±5 years), date of blood draw (±30 days), calendar year of cohort entry, and time since baseline prostate cancer screening (±1 year). Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between serum 25-hydroxyvitamin D [25(OH)D], vitamin D binding protein (DBP), the 25(OH)D:DBP molar ratio, and prostate cancer risk.

RESULTS—Serum 25(OH)D was not associated with overall prostate cancer (Q4 vs Q1: OR, 0.73; 95% CI, 0.40–1.33; *P* for trend = .25), although there were apparent inverse associations for nonaggressive disease (global *P* = .03, clinical stage I/II, and Gleason score <7) and among men ≥62 years old (*P* for interaction = .04) that were restricted to Q3. Interestingly, serum DBP was significantly inversely associated with prostate cancer risk (Q4 vs Q1: OR, 0.45; 95% CI, 0.20–1.00; *P* for trend = .03), whereas the 25(OH)D:DBP molar ratio was not. Results were similar

Corresponding author: Tracy M. Layne, PhD, MPH, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6E324, Bethesda, MD 20892; Fax: (240) 276-7837; tracy.layne@nih.gov.
Susan T. Mayne's current address: Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, Maryland.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosure.

AUTHOR CONTRIBUTIONS

Conceptualization: **Susan T. Mayne**, **Demetrius Albanes**. Methodology: **Barry I. Graubard, Susan T. Mayne**, **Demetrius Albanes**. Writing (Original Draft): **Tracy M. Layne**. Writing (Review and Editing): **Tracy M. Layne, Stephanie J. Weinstein, Barry I. Graubard, Xiaomei Ma, Susan T. Mayne, Demetrius Albanes**. Funding Acquisition: **Xiaomei Ma, Susan T. Mayne, Demetrius Albanes**. Supervision: **Susan T. Mayne**, **Demetrius Albanes**.

when we mutually adjusted for 25(OH)D and DBP, and we found no evidence of interaction between the two.

CONCLUSION—Our study suggests higher (versus lower) circulating DBP may be independently associated with a decreased prostate cancer risk in black men independent of 25(OH)D status.

Keywords

25-hydroxyvitamin D; vitamin D binding protein; prostate cancer; African American/black men; racial/ethnic cancer disparities

INTRODUCTION

Along with family history of prostate cancer and older age, black race (ie, African ancestry) is an established risk factor for prostate cancer.[1] Black men in the United States have 70% higher incidence and more than double the prostate cancer mortality compared with white men and experience some of the highest rates of prostate cancer globally.[2] This excess disease burden is compounded by diagnoses at earlier ages and of greater aggressiveness.[3] At the same time, the higher prevalence of low vitamin D status in black individuals compared with other racial/ethnic groups[4] is attributable to both higher melanin content in darker skin, which reduces the synthesis of vitamin D_3 from 7-dehydrocholesterol in response to solar ultraviolet B radiation,[5] and lower dietary and supplemental vitamin D intake.[6] The fact that black men compared with white men experience higher prostate cancer rates and lower vitamin D status is of interest given the possible etiological role of the latter in this malignancy.[7]

Regardless of the source, vitamin D undergoes two hydroxylation steps, first in the liver to synthesize 25-hydroxyvitamin D [25(OH)D], the accepted biomarker of vitamin D status, then in the kidney where the biologically active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] is produced.[8] Approximately 99% of 25(OH)D is bound to serum proteins, primarily vitamin D binding protein (DBP), leaving a small fraction of unbound or “free” 25(OH)D.[9] The anti-carcinogenic potential of vitamin D demonstrated in laboratory studies of prostate cells[7,8] contrasts with data from a meta-analysis of epidemiological studies conducted in predominantly non-Hispanic white men. These data suggest that higher circulating vitamin D increases prostate cancer risk,[10] a finding that would seem to conflict empirically with the low vitamin D status and high prostate cancer rates experienced by black men.[7] There remains, however, a paucity of research examining the relationship between black race, vitamin D status, and prostate cancer risk.[11–17]

In this prospective nested case-control study, we examine the association between prostate cancer risk and serum vitamin D status among black men in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

SUBJECTS AND METHODS

Study Population

The PLCO Trial is a large-scale randomized cancer screening trial that enrolled approximately 155,000 men and women aged 55–74 years between 1993 and 2001 from 10 screening centers across the United States.[18] Men assigned to the screening arm had prostate-specific antigen (PSA) measured at baseline and annually for 5 years thereafter, as well as a digital rectal examination at baseline and annually for 3 years.[18] Men with elevated serum PSA levels (ie, PSA >4.0 ng/mL) or suspicious digital rectal examination findings were referred for diagnostic evaluation. Incident prostate cancers were ascertained from annually mailed questionnaires completed by participants and subsequently confirmed through medical record reviews.[18] Approval for the study was obtained from the institutional review boards of the National Cancer Institute and each of the screening centers, and participants provided written informed consent.

Case and Control Selection

The screening arm of the trial included 1713 self-identified non-Hispanic black men who had no history of prostate cancer, completed the baseline questionnaire, and had serum available. Among these men, we identified 226 cases of incident prostate cancer diagnosed through the end of follow-up on December 31, 2009. Controls (n = 452) were selected from among black men with available serum who were cancer-free at the time of the case diagnosis, and matched 2:1 to cases on age at randomization (±5 years), date of blood draw (±30 days), calendar year of study entry, and time since baseline prostate cancer screening (±1 year).

Serum 25(OH)D and DBP

Nonfasting baseline blood was collected at each screening visit, processed, and stored at −70°C.[19] All samples were blinded, and case-control matched sets were assayed within the same batch at Heartland Assay, LLC (Ames, IA). Each batch contained serum quality control material. Serum 25(OH)D was measured by way of liquid chromatography/mass spectrometry. DBP concentrations were measured by commercial enzyme-linked immunosorbent assay (ELISA) (GenWay, San Diego, CA) using a polyclonal antibody in a sandwich format. The interassay coefficient of variation was 9.4% for 25(OH)D and 19.5% for DBP. The intraassay coefficient of variation was 10.9% for 25(OH)D and 16.7% for DBP.

Covariates

Participants in the screening arm of the study completed a questionnaire at study entry capturing information on race/ethnicity, education, smoking habits, physical activity, medical history, family history of cancer, and prostate health (eg, history of benign prostatic hypertrophy), and a separate dietary/supplement use questionnaire.

Statistical Analysis

Case and control distributions of select baseline characteristics were compared using Wilcoxon rank-sum and chi-square tests for continuous and categorical variables, respectively. The primary analyses used conditional logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between 25(OH)D, DBP, and the 25(OH)D:DBP molar ratio and overall prostate cancer, with unconditional logistic regression used for stratified analyses to retain case-control sets with different subgroup classification. To address seasonal variation in 25(OH)D, we created season-specific exposure categories based on the distribution among controls, with separate quartiles created for lighter months (May-October) and darker months (November-April), then combined them for analysis. We also season-standardized 25(OH)D by regressing log-transformed 25(OH)D concentrations on week of blood draw using a locally weighted polynomial regression method[20] and analyzed the association using predefined clinical cut-points (<25, 25–<37.5, 37.5–<50, 50–<75 [referent], ≥75 nmol/L). Quartiles of 25(OH)D:DBP, a proxy for unbound circulating 25(OH)D,[21] and DBP (nmol/L), which does not vary by season,[22] were calculated based on the distribution in the controls.

Potential confounders included: study center, PSA, body mass index (18.5–<25.0, 25–30, and >30 kg/m^2), smoking status (nonsmoker, current smoker, or former smoker), physical activity (hours per week [none, <1, 1, 2, 3, or 4+]), history of diabetes, family history of prostate cancer, marital status (married/living as married, widowed, separated/divorced, and never married), education (less than high school, high school graduate, some college/vocational, college graduate, postgraduate), and calcium and vitamin D intake (dietary and supplements). Only baseline PSA resulted in a >10% change in the parameter estimate for vitamin D. Additionally, although uncorrelated with 25(OH)D (Pearson correlation coefficient $r = -0.02$, $P = .68$), PSA was higher among men in the first quartile of 25(OH)D relative to those in Q2–Q4. Exclusion of outlying PSA values (>2 SD) did not alter findings; therefore, these values were retained. Our analyses therefore included examination of three models: 1) conditioned on matching factors only; 2) model 1 mutually adjusted for 25(OH)D or DBP; and 3) model 2 adjusted for baseline PSA. All subsequently reported ORs and 95% CIs are based on model 3.

In secondary analyses, we stratified by aggressive disease (Gleason sum ≥7 or tumor-node-metastasis clinical stage III or IV) and nonaggressive disease (clinical stage I and II with Gleason sum <7), median DBP for the associations with 25(OH)D and 25(OH)D:DBP, median 25(OH)D for the DBP association, median age at entry (62 years), body mass index (27.6 kg/m^2), and season of blood draw. Cross-product terms between the main vitamin D effect (quartiles) and subgroup factors (binary based on medians for continuous variables) were added to models to test effect modification. To examine whether the association between vitamin D and prostate cancer differed by disease aggressiveness while also maintaining the case-control match set and adjusting for covariates, we tested whether the beta coefficients obtained from disease-specific (aggressive vs nonaggressive disease) conditional logistic regression models differed. Sensitivity analyses were conducted restricting to men (and their matched controls) with ≥1 and ≥2 years between their baseline blood collection and diagnosis. Linear trends were evaluated by modeling ordinal

categorical variables or category-specific medians as continuous variables and testing the statistical significance using the Wald test. All analyses used a 2-sided alpha (type I error) level of 0.05, and were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 226 prostate cancer cases, 101 were aggressive and 125 were nonaggressive. The average age at baseline was 63 years, and the median time from blood collection to prostate cancer diagnosis was 4.1 years, with 66 cases (~29%) diagnosed within the first 2 years. The median serum concentrations for 25(OH)D and DBP were 46.1 nmol/L (range, 7.5–164.3) and 7316 nmol/L (range, 2584–14149), respectively, and the median dietary and total vitamin D intakes were 170 and 265 IU/d, respectively.

Selected baseline characteristics are presented in Table 1. Only serum PSA differed significantly between cases and controls (median, 3.2 ng/mL and 1.0 ng/mL, respectively), with family history of prostate cancer, and most other factors, including 25(OH)D and DBP, being similar. Among controls, DBP was uncorrelated with 25(OH)D ($r = 0.08$, $P = .10$), but inversely correlated with 25(OH)D:DBP ($r = -0.44$, $P < .0001$). Baseline age was modestly correlated with 25(OH)D ($r = 0.17$, $P = .0004$), DBP ($r = -0.10$, $P = .03$), and their molar ratio ($r = 0.20$, $P < .0001$).

Season-specific serum 25(OH)D was not associated with overall prostate cancer risk in multivariate models (Q4 vs Q1: OR, 0.73; 95% CI, 0.40–1.33; *P* for trend = .25) (Table 2). We obtained similar results using season-standardized quartiles, clinically defined cut-points, and season-specific quintiles of 25(OH)D as defined in a previous analysis of white men in the PLCO Trial[23] (Supporting Table 1). Serum DBP was inversely associated with prostate cancer risk (Q4 vs Q1: OR, 0.45; 95% CI, 0.20–1.00; *P* for trend = .03), including after adjustment for 25(OH)D. We observed no risk association for the 25(OH)D:DBP molar ratio (Table 2).

With regard to our secondary analyses, we found no association between serum 25(OH)D and aggressive prostate cancer risk, whereas a U-shaped association was evident for risk of nonaggressive disease, with a statistically inverse OR in Q3 (global $P = .03$, *P* for difference in the beta coefficients by aggressiveness = .09) (Table 3). The inverse association for DBP did not differ by cancer aggressiveness (*P* for difference in the beta coefficients by disease aggressiveness = .89) (Table 3). The associations between prostate cancer and 25(OH)D and 25(OH)D:DBP were not modified by DBP (*P* for interaction=.22 and .37, respectively). The DBP risk association also was not modified by 25(OH)D [Q4 vs Q1: below median 25(OH)D: OR, 0.90; 95% CI, 0.42–1.91; above median 25(OH)D: OR, 0.75; 95% CI:0.34–1.67; *P* for interaction = .81), and the associations for 25(OH)D, DBP, and their molar ratio did not differ by season of blood draw (*P* for interaction > .05 for each). Age modified the association between 25(OH)D and prostate cancer (*P* for interaction = .04) such that 25(OH)D appeared to be inversely associated with prostate cancer risk in older men, but again restricted to Q3 (Supporting Table 2). Family history of prostate cancer, history of diabetes, physical activity, and smoking status did not modify the vitamin D associations (data not shown). Sensitivity analyses restricted to cases (and their matched controls)

diagnosed ≥1 year after blood collection revealed somewhat stronger inverse associations for 25(OH)D (OR, 0.61, 0.44, and 0.62 for Q2, Q3, and Q4, respectively, vs Q1; *P* for trend = .14) and similarly for ≥2 years (OR, 0.54, 0.39, and 0.58; *P* for trend = .12). Similar inverse patterns of association were also observed for DBP (≥1 year OR, 1.05, 0.70, and 0.47; *P* for trend = .05; ≥2 year OR, 1.19, 0.78, and 0.52; *P* for trend = .08) (data not shown).

DISCUSSION

The present study is one of the few prospective examinations of the association between vitamin D and prostate cancer in black men, and to our knowledge, it is the first to evaluate the influence of the vitamin D binding protein (DBP) and estimated "free" or unbound 25(OH)D in this population. Serum 25(OH)D and 25(OH)D:DBP were not associated with overall prostate cancer risk, although 25(OH)D appeared inversely associated with nonaggressive disease, with a similar pattern of association in older men. There was a significantly lower prostate cancer risk among men with higher circulating DBP concentrations, which represents a novel finding.

Most research regarding the association between vitamin D and prostate cancer has been conducted in predominately white populations or has been adjusted for race/ethnicity without providing race-specific risk estimates.[24] Overall, these studies do not support an inverse risk relation, with a meta-analysis of 21 studies (including 20 prospective studies) of nearly 12,000 mostly non-Hispanic white cases finding that higher circulating 25(OH)D was related to higher prostate cancer risk (pooled OR, 1.17; 95% CI, 1.05–1.30).[10] This meta-analysis included the analysis of white men in the PLCO Trial, which showed a positive association between 25(OH)D status and risk of aggressive disease.[23] The present analysis of black men in the PLCO Trial suggests a weak inverse association with nonaggressive disease and a nonsignificant positive association with aggressive disease, consistent with the previous study of white men in the PLCO Trial.[23]

Previous investigations of black men have been largely retrospective[12,14,17] or cross-sectional analyses,[13] both of which are limited with respect to establishing a temporal relationship between vitamin D and prostate cancer risk. Only two race-specific studies examined the association between prediagnostic circulating 25(OH)D and prostate cancer risk in black men.[15,16] A nested case-control analysis within the Multiethnic Cohort Study found no association based on 136 black cases, the racial group with the lowest plasma 25(OH)D (<50 nmol/L vs ≥75 nmol/L; OR, 1.03; 95% CI, 0.64–1.66).[15] Similarly, the case-cohort analysis of 250 black cases in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed no association between vitamin D status and overall prostate cancer risk (≥75 nmol/L vs <37.5 nmol/L; hazard ratio [HR], 0.84; 95% CI, 0.50–1.40). However, higher vitamin D status did appear related to lower risk of Gleason 7–10 prostate cancer (≥75 nmol/L vs <37.5 nmol/L; HR, 0.47; 95% CI, 0.19–1.18; *P* for trend = .048).[16] In the current study, we observed a suggestive inverse association between 25(OH)D and non-aggressive prostate cancer risk, that was strongest and statistically significant in Q3 (40–68 nmol/L) versus Q1 (<39 nmol/L). This is not unlike the U-shaped pattern of association observed among all men in SELECT, which was also stronger and statistically significant in

Q3 (58.2–72.9 nmol/L) versus Q1 (<44.1 nmol/L) for total, Gleason 2–6, Gleason 7–10, and Gleason 8–10 prostate cancer.[16]

Beyond its role as the primary transport protein for 25(OH)D, one of the biological functions of DBP (or group-specific component, Gc protein) involves macrophage activation[25] through the inflammation-primed macrophage-activating factor (MAF), with Gc-MAF[26] having been shown to inhibit angiogenesis and growth/proliferation in pancreatic[27] and prostate malignant cells.[28] Racial differences in common variants in *GC*, the gene encoding DBP, have been established,[25] and one of the three common *GC* phenotypes, Gc 1F-1F, which is most common in populations of African descent (and least common in European populations),[25] has the highest Gc-MAF activity.[26] The potential antiangiogenic and antiproliferative activity of Gc-MAF, with notably higher activity in Gc1F-1F carriers, could partially explain the inverse association between DBP and prostate cancer risk in the present analysis. It might also account for the finding in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of white men where DBP was only associated (inversely) with prostate cancer risk in men with lower 25(OH)D.[29] This finding appears consistent with the inverse association between DBP and prostate cancer observed in the present study of black men with relatively low 25(OH)D.

Our study has several strengths, including the prospective design, which allowed us to overcome issues of temporality common in previous evaluations of the association between vitamin D and prostate cancer in black men. In addition to measuring 25(OH)D, which captures all sources of vitamin D exposure, we examined the influence of its primary transport carrier, vitamin D binding protein. The limitations of our study include the relatively small sample size and low power for the secondary analyses. As such, results from this study should be interpreted cautiously, and larger prospective studies or consortia of black populations will be better equipped to address the relationship between vitamin D and prostate cancer in this racial group. Our primary results may have also been influenced by some men having preclinical disease at baseline; however, the consistent inverse pattern of associations for serum 25(OH)D and DBP observed when excluding cases with fewer than 1 or 2 years between baseline and diagnosis suggests the findings were not biased in this manner. Findings from our secondary analyses are of interest, including those regarding age and disease aggressiveness, but were particularly underpowered and should be considered hypothesis-generating. With regard to the measurement of DBP, the polyclonal assay performed suboptimally, likely attenuating the observable associations. Use of this newly developed assay was necessary, however, to avoid spuriously low DBP concentrations obtained with the more commonly used monoclonal assay, which, unlike the polyclonal assay, does not recognize a range of genetically determined DBP protein isoforms common in black populations.[30]

In this prospective study of black men, a group at high risk of both vitamin D deficiency and prostate cancer, we found that serum DBP was inversely associated with prostate cancer risk independent of 25(OH)D status. This finding, as well as the suggestive inverse association observed between 25(OH)D and nonaggressive disease, require replication in other studies and investigation of potential biological mechanisms. Further prospective research is needed

to clarify whether (and how) race modifies the association between vitamin D and prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Selected Baseline Characteristics of Study Cases and Controls

Characteristics	Cases (n = 226)	Controls (n = 452)	P[a]
Age, y, mean (SD)	62.8 (5.3)	62.7 (5.1)	.94
PSA, ng/mL, mean (SD)[b]	5.8 (11.8)	1.6 (1.8)	<.0001
Height, cm, mean (SD)	177.5 (6.5)	178.4 (7.6)	.18
Body mass index, kg/m^2, mean (SD)	28.2 (4.5)	28.0 (4.6)	.57
Current smokers, n (%)	37 (16.4)	91 (20.2)	.49
History of diabetes, n (%)	33 (14.6)	87 (19.4)	.13
Family history of prostate cancer, n (%)	20 (8.9)	37 (8.3)	.95
Vitamin D supplement use, n (%)	11 (6.4)	20 (5.5)	.69
Calcium supplement use, n (%)	10 (5.9)	37 (10.1)	.10
Total vitamin D, IU/d, mean (SD)[c]	409 (27)	417 (18)	.79
Total calcium, mg/d, mean (SD)[c]	945 (31)	982 (21)	.32
Serum 25(OH)D, nmol/L, mean (SD)	48.1 (21.7)	49.6 (23.3)	.56
Serum DBP, nmol/L, mean (SD)	7229 (1760)	7440 (1878)	.16
25(OH)D:DBP ratio, ×10^3, mean (SD)	7.0 (3.7)	7.1 (4.2)	.98
Season of blood collection, n (%)			.51
Lighter months (May–October)	106 (46.9)	224 (49.6)	
Darker months (November–April)	120 (53.1)	228 (50.4)	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; DBP, vitamin D binding protein; PSA, prostate-specific antigen; SD, standard deviation.

[a] Wilcoxon or chi-square test.

[b] Among men with PSA < 2 SD from the mean.

[c] Adjusted for total energy intake; includes dietary and supplemental sources.

TABLE 2

Odds Ratios and 95% Confidence Intervals for the Association Between Serum 25(OH)D, DBP, and 25(OH)D:DBP and Total Prostate Cancer

	Q1	Q2	Q3	Q4	*P*-Trend
25(OH)D[a]					
No. of cases/controls	66/114	52/112	49/113	59/113	
OR (95% CI)[b]	1.0 (ref)	0.78 (0.49–1.25)	0.72 (0.45–1.17)	0.88 (0.56–1.38)	.58
OR (95% CI)[c]	1.0 (ref)	0.81 (0.50–1.30)	0.78 (0.48–1.26)	0.94 (0.60–1.49)	.79
OR (95% CI)[d]	1.0 (ref)	0.70 (0.37–1.30)	0.50 (0.26–0.94)	0.73 (0.40–1.33)	.25
DBP					
Range, nmol/L	≤6136	>6136-≤7394	>7394-≤8628	>8628	
No. cases/ controls	64/113	63/113	56/113	43/113	
OR (95% CI)[b]	1.0 (ref)	0.85 (0.51–1.41)	0.68 (0.38–1.21)	0.51 (0.28–0.95)	.02
OR (95% CI)[c]	1.0 (ref)	0.86 (0.52–1.44)	0.71 (0.39–1.29)	0.53 (0.28–0.99)	.04
OR (95% CI)[d]	1.0 (ref)	0.93 (0.49–1.76)	0.68 (0.32–1.47)	0.45 (0.20–1.00)	.03
25(OHD:DBP, $\times 10^3$					
Range, nmol/L	≤4.3	>4.3-≤6.4	>6.4-≤8.9	>8.9	
No. of cases/controls	59/115	51/111	62/114	54/112	
OR (95% CI)[b]	1.0 (ref)	0.90 (0.55–1.45)	1.06 (0.64–1.73)	0.93 (0.55–1.57)	.93
OR (95% CI)[d]	1.0 (ref)	1.12 (0.62–2.02)	0.81 (0.43–1.54)	0.73 (0.37–1.44)	.23

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; DBP, vitamin D binding protein; OR, odds ratio; Q, quartile.

[a]Season-specific quartiles (nmol/L). Darker months (November-April): Q1, ≤28.5; Q2, >28.5–40.3; Q3, >40.3–55.8; Q4, >55.8. Lighter months (May–October): Q1, ≤38.8; Q2, >38.8–51.8; Q3, >51.8–67.8; Q4, >67.8.

[b]Conditional logistic regression analyses conditioned on matching factors: age at randomization, date of blood draw, calendar year of cohort entry, and time since baseline prostate cancer screening.

[c]Additional mutual adjustment for DBP or 25(OH)D.

[d]Further adjustment for baseline PSA.

TABLE 3

Odds Ratios and 95% Confidence Intervals for the Association Between Serum 25(OH)D, DBP, and 25(OH)D:DBP and Aggressive and Nonaggressive Prostate Cancer

	Q1	Q2	Q3	Q4	*P*-Trend
Aggressive prostate cancer					
25(OH)D[a]					
No. of cases/controls	23/46	20/55	30/50	28/51	
OR (95% CI)[b]	1.0 (ref)	0.74 (0.35–1.58)	1.26 (0.58–2.71)	1.10 (0.55–2.21)	.53
OR (95% CI)[c]	1.0 (ref)	0.82 (0.38–1.78)	1.51 (0.67–3.41)	1.26 (0.62–2.60)	.35
OR (95% CI)[d]	1.0 (ref)	0.89 (0.32–2.51)	1.39 (0.45–4.30)	1.16 (0.43–3.14)	.66
DBP					
Range, nmol/L	≤6136	>6136-≤7394	>7394-≤8628	>8628	
No. of cases/controls	28/54	30/51	25/50	18/47	
OR (95% CI)[b]	1.0 (ref)	1.06 (0.49–2.29)	0.84 (0.36–1.95)	0.62 (0.24–1.58)	.25
OR (95% CI)[c]	1.0 (ref)	1.03 (0.47–2.26)	0.77 (0.32–1.85)	0.54 (0.20–1.45)	.17
OR (95% CI)[d]	1.0 (ref)	1.14 (0.42–3.07)	0.75 (0.23–2.46)	0.39 (0.10–1.51)	.16
25(OH)D:DBP, $\times 10^3$					
Range, nmol/L	≤4.3	>4.3-≤6.4	>6.4-≤8.9	>8.9	
No. of cases/controls	22/44	22/55	33/52	24/51	
OR (95% CI)[b]	1.0 (ref)	0.85 (0.40–1.82)	1.33 (0.61–2.93)	0.97 (0.42–2.23)	.83
OR (95% CI)[d]	1.0 (ref)	0.81 (0.31–2.13)	1.02 (0.35–3.03)	0.64 (0.20–2.06)	.52
Nonaggressive prostate cancer					
25(OH)D[a]					
No. of cases/controls	43/68	32/57	19/63	31/62	
OR (95% CI)[b]	1.0 (ref)	0.89 (0.48–1.64)	0.49 (0.26–0.92)	0.79 (0.44–1.44)	.20
OR (95% CI)[c]	1.0 (ref)	0.89 (0.48–1.65)	0.50 (0.27–0.95)	0.81 (0.44–1.49)	.23
OR (95% CI)[d, e]	1.0 (ref)	0.69 (0.31–1.54)	0.27 (0.11–0.63)	0.59 (0.27–1.30)	.08
DBP					
Range, nmol/L	≤6136	>6136-≤7394	>7394-≤8628	>8628	

	Q1	Q2	Q3	Q4	*P*-Trend
No. of cases/controls	36/59	33/62	31/63	25/66	
OR (95% CI)[b]	1.0 (ref)	0.71 (0.36–1.41)	0.56 (0.25–1.27)	0.44 (0.19–1.00)	.05
OR (95% CI)[c]	1.0 (ref)	0.72 (0.36–1.46)	0.59 (0.26–1.35)	0.45 (0.20–1.05)	.06
OR (95% CI)[d]	1.0 (ref)	0.71 (0.30–1.69)	0.53 (0.19–1.47)	0.37 (0.13–1.03)	.05
25(OH)D:DBP, $\times 10^3$					
Range, nmol/L	≤4.3	>4.3-≤6.4	>6.4-≤8.9	>8.9	
No. of cases/controls	37/71	29/56	29/52	30/61	
OR (95% CI)[b]	1.0 (ref)	0.98 (0.52–1.85)	0.88 (0.46–1.67)	0.92 (0.47–1.80)	.77
OR (95% CI)[d]	1.0 (ref)	1.60 (0.73–3.50)	0.65 (0.28–1.48)	0.78 (0.33–1.83)	.31

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; DBP, vitamin D binding protein; OR, odds ratio; Q, quartile.
Difference in the beta coefficients for the association by disease aggressiveness: 25(OH)D, $P = .09$; DBP, $P = .89$.

[a] Season-specific quartiles (nmol/L). Darker months (November-April): Q1, ≤28.5; Q2, >28.5–40.3; Q3, >40.3–55.8; Q4, >55.8. Lighter months (May–October): Q1, ≤38.8; Q2, >38.8–51.8; Q3, >51.8–67.8; Q4, >67.8.

[b] Conditional logistic regression analyses conditioned on matching factors: age at randomization, date of blood draw, calendar year of cohort entry, and time since baseline prostate cancer screening.

[c] Additional mutual adjustment for DBP or 25(OH)D.

[d] Further adjustment for baseline PSA.

[e] Global P-value for the overall association with risk from the conditional logistic regression model in superscript d <.05.