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Circulating 25-hydroxyvitamin D, vitamin D binding protein, and risk of advanced and lethal prostate cancer

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Abstract

We previously found that higher total 25-hydroxyvitamin D [25(OH)D] levels were associated with lower risk of lethal prostate cancer. However, the relationships of bioavailable 25(OH)D and vitamin D binding protein (VDBP) with risk of advanced and lethal prostate cancer are unclear. In a prospective case-control study of 156 pairs of advanced prostate cancer cases and controls, we directly measured prediagnostic circulating 25(OH)D and VDBP and calculated bioavailable 25(OH)D using a validated formula. We examined the association of bioavailable 25(OH)D and VDBP levels with risk of advanced and lethal prostate cancer and whether total 25(OH)D levels interacted with VDBP levels to affect the risk. Conditional logistic models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Compared to total 25(OH)D (P_{trend}=0.02), bioavailable 25(OH)D levels were not more strongly associated with risk of advanced prostate cancer (P_{trend}=0.14). Although VDBP levels were not associated with risk of advanced prostate cancer (P_{trend}=0.16), we observed an interaction between total 25(OH)D levels and VDBP levels in relation to risk of advanced prostate cancer ($P_{interaction}$=0.03). Compared to those with total 25(OH)D levels below the median and VDBP levels above the median (at highest risk), men with both levels above the median had a multivariable-adjusted OR of 0.31 (95% CI, 0.15-0.65) for advanced prostate cancer. We observed similar results when we restricted the analyses to 116 lethal prostate cancer cases and their controls. Our data suggest that VDBP levels may modify the association between total 25(OH)D levels and risk of advanced and lethal prostate cancer.

Keywords

25-hydroxyvitamin D; vitamin D binding protein; prostate cancer; free hormone hypothesis

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Introduction

Circulating 25-hydroxyvitamin D [25(OH)D] is the most commonly accepted blood biomarker for vitamin D status in epidemiologic studies. We have previously shown that higher circulating 25(OH)D levels were associated with lower risk of lethal prostate cancer.[1] Approximately 88% of circulating 25(OH)D is bound to vitamin D binding protein (VDBP), while 12% of 25(OH)D is loosely bound to albumin, leaving very little in its free form.[2] The relationship between circulating 25(OH)D and VDBP is complex. Experimental studies demonstrate that VDBP extends the half-life of circulating 25(OH)D, but may limit its biologic activity while bound,[3–5] compared to free and albumin-bound 25(OH)D (collectively referred to as “bioavailable” 25(OH)D), as put forward by the “free hormone hypothesis”.[6] Consistent with this hypothesis, several studies have found that bioavailable 25(OH)D levels were more strongly associated with serum calcium, parathyroid hormone levels and bone mineral density, compared to total 25(OH)D levels.[7–9]

Whether bioavailable 25(OH)D levels are more strongly associated with risk of advanced or lethal prostate cancer is unknown. In addition, VDBP circulates at much higher levels than 25(OH)D and may have an independent effect or modulate the effect of 25(OH)D on prostate carcinogenesis. In our study, we assessed prediagnostic circulating levels of total 25(OH)D, bioavailable 25(OH)D, and VDBP in order to examine the after questions: 1) whether VDBP levels were associated with risk of advanced or lethal prostate cancer, 2) whether VDBP levels modified the association between total 25(OH)D levels and risk of advanced or lethal prostate cancer, and 3) whether bioavailable 25(OH)D levels had a stronger association with risk of advanced or lethal prostate cancer than total 25(OH)D levels.

Methods

Study population

The Health Professionals Follow-Up Study is a prospective cohort that began in 1986 when 51,529 US male health professionals aged 40 to 75 years responded to a questionnaire about health-related behaviors and medical history. Information has been updated through biennial follow-up questionnaires. Blood samples were collected from 18,225 participants between 1993 and 1995.

Prostate cancers were identified initially from self-reports on questionnaires or death certificates and confirmed by medical records and pathology reports. Deaths were identified via mailings, telephone calls, and searches of the National Death Index. Information on clinical features at diagnosis was gleaned through review of medical records by study investigators blinded to exposure information. We sent men with prostate cancer additional questionnaires every 2 years to ascertain treatment, disease progression, and diagnosis of metastases.

We defined advanced stage prostate cancer as stage T3b, T4, N1, or M1 at diagnosis; development of distant metastasis during follow-up; or death as a result of prostate cancer

before the end of follow-up. Lethal cancers, a subset of advanced cancers, were those that caused death or metastasis to bone or other organs before the end of follow-up.

Between 1993 and 2004, 164 men were diagnosed with advanced prostate cancer after providing blood samples. For each confirmed case, we randomly selected a control who had not been diagnosed with prostate cancer at the time when the case was diagnosed. Because of the high screening rates in men who are diagnosed with prostate cancer, we required controls to have a prostate-specific antigen (PSA) test within 2.5 years before the date of diagnosis of their matched case to provide the opportunity for occult prostate cancers to be diagnosed. Controls were matched to cases on year of birth (±1 year), PSA test before blood collection (yes or no), time of blood collection in the day (midnight to before 9 $_{\text{a.m.}}$, 9 $_{\text{a.m.}}$ to before noon, noon to before 4 $_{\text{p.m.}}$, 4 $_{\text{p.m.}}$ to before midnight), season of blood collection (summer, fall, winter, spring), and year of blood collection (exact calendar year). Because the assay used in our study cannot accurately measure VDBP in African Americans,[10, 11] non-white participants were excluded, leaving 156 pairs of advanced prostate cancer cases (including 116 lethal prostate cancer cases) and controls for analysis. One control was measured for VDBP but not total 25(OH)D and was included only in the VDBP analysis. The participants of the study provided informed consent, and the Human Research Committee at the Harvard T.H. Chan School of Public Health approved our study.

Measurement of total 25(OH)D, VDBP, and albumin

EDTA preserved blood samples were collected via overnight courier. Approximately 95% of samples were received and processed within 24 h of blood collection; plasma, erythrocytes, and buffy coats were separated, aliquotted, and stored in liquid nitrogen freezers. Plasma 25(OH)D was measured by a radioimmunosorbent assay in the laboratory of Dr. Bruce Hollis (The Medical University of South Carolina, Charleston, SC),[12] in four batches (in 2001, 2003, 2004, and 2008, respectively), according to the diagnosis time of cases (blood collection to January 1996, February 1996 to January1998, February1998 to January 2000, February 2000 to January 2004). In blinded quality control samples, the mean intra-assay coefficient of variation (CV) was 5.4%, 5.6%, 14.8%, and 5.6% for batches 1 to 4, respectively. We standardized 25(OH)D levels by batch and season to account for extraneous variation by these variables. The correction method has been detailed elsewhere.[13] In brief, we regressed 25(OH)D levels on batch and season using a linear model and then calibrated 25(OH)D levels using the mean of the regression coefficients for batch and season. Plasma VDBP and albumin were measured in 2012 in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA) by an enzyme-linked immunosorbent assay (ELISA) based on a monocolonal antibody (R&D Systems) and a colorimetric assay (Roche Diagnostics), respectively. The mean CV was 7.8% and 3.0% for VDBP and albumin, respectively. For all assays, matched controls were assayed in the same batch of their cases in a blinded fashion.

Calculation of bioavailable 25(OH)D

We used the after equation to calculate bioavailable 25(OH)D:

$$\text{Bioavailable 25(OH)D} = \text{Total 25(OH)D} \times \frac{1 + \text{Albumin} \times \text{Ka}_{\text{Albumin}}}{1 + \text{Albumin} \times \text{Ka}_{\text{Albumin}} + \text{VDBP} \times \text{Ka}_{\text{VDBP}}},$$

where $Ka_{Albumin}$ is the affinity of albumin for 25(OH)D (6×10^5), Ka_{VDBP} is the affinity of VDBP for 25(OH)D (7×10^8),[2] and all concentrations are expressed in mol/L.

Two common single-nucleotide polymorphisms (SNPs) in *VDBP*, rs4588 and rs7041, give rise to three predominant haplotypes (GC1F, GC1S, and GC2). It is controversial whether the affinity of VDBP for 25(OH)D is affected by these haplotypes: three independent studies revealed no significant differences in the affinity,[14–16] whereas one study reported that the affinity of GC1F was four times higher than that of GC2 and double that of GC1S.[17] Therefore, we used a constant affinity to calculate bioavailable 25(OH)D in the main analyses, and conducted sensitivity analyses using a genotype-specific affinity. The two SNPs had been previously genotyped for another study.[1]

Statistical analyses

Spearman correlation coefficients between vitamin D-related biomarkers and lifestyle factors were estimated in controls. Conditional logistic models, taking into account the matched design, were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for advanced and lethal prostate cancer. Biomarkers were categorized into quartiles based on the levels in controls, and we tested for a linear trend across quartiles using an ordinal variable. In multivariable models, we adjusted for potential confounders, including family history of prostate cancer, body mass index (BMI), smoking status, vigorous physical activity, and alcohol intake measured on the 1994 questionnaire closest to blood collection. We also mutually adjusted for total 25(OH)D levels and VDBP levels in the same model. Covariates from the 1994 follow-up questionnaire were used as they were closest to the time of blood collection. If any covariate was missing on the 1994 questionnaire, we carried forward the covariate from previous questionnaires (1986-1992). To assess effect modification, we examined risk of advanced and lethal prostate cancer by combined categories of total 25(OH)D and VDBP levels (split at the median). Test of interaction between total 25(OH)D levels and VDBP levels was performed by entering their cross product in the model, evaluated by a likelihood ratio test. All analyses were performed with SAS software, version 9.4, and all p values are two sided.

Results

Table 1 shows selected characteristics of controls by quartile of total 25(OH)D, bioavailable 25(OH)D, and VDBP. Controls with higher total 25(OH)D levels had a lower BMI, reported higher vigorous physical activity, and were more likely to be ever smokers. Total 25(OH)D levels were not correlated with VDBP levels ($r = 0.12$; $p = 0.13$) but were correlated with bioavailable 25(OH)D levels ($r = 0.70$; $p < 0.001$) (Supporting Information Table S1). Bioavailable 25(OH)D levels were also correlated with VDBP ($r = -0.55$; $p < 0.001$) and albumin levels ($r = 0.16$; $p = 0.04$). In addition, both total 25(OH)D and bioavailable 25(OH)D levels were negatively correlated with BMI and positively correlated with vigorous physical activity (all $|r| \geq 0.20$; all $p < 0.02$).

Higher total 25(OH)D levels were associated with lower risk of advanced prostate cancer (Table 2). Compared to those in the bottom quartile of 25(OH)D, men in the top quartile had a multivariable-adjusted OR of 0.50 (95% CI, 0.24–1.03, $p_{trend} = 0.02$). The association

remained statistically significant when we restricted the analyses to the lethal prostate cancer cases and their controls (p_{trend} = 0.04; Table 2). Further adjustment for VDBP levels did not change these results (Table 2).

Compared to total 25(OH)D, bioavailable 25(OH)D levels were not more strongly associated with risk of advanced and lethal prostate cancer (p_{trend} = 0.14 and 0.05, respectively; Table 2). However, the results supported the inverse association between vitamin D status and prostate cancer risk, as men in the bottom quartile of bioavailable 25(OH)D had higher risk of prostate cancer compared to all others. We thus performed *post hoc* analysis to compare men in quartiles 2 to 4 combined to those in the bottom quartile: the multivariable-adjusted OR was 0.52 (95% CI, 0.29–0.92) for advanced prostate cancer and 0.40 (95% CI, 0.20–0.80) for lethal prostate cancer. In sensitivity analyses incorporating *VDBP* genotypes to calculate bioavailable 25(OH)D, our conclusions remained largely unchanged (Supporting Information Table S2).

VDBP levels were not associated with risk of advanced and lethal prostate cancer (p_{trend} = 0.16 and 0.48, respectively; Table 2). However, the pattern suggested a nonsignificantly higher risk of advanced prostate cancer in the bottom quartile of VDBP compared to all others. In *post hoc* analysis, the multivariable-adjusted OR was 0.59 (95% CI, 0.32–1.09), comparing men in quartiles 2 to 4 combined to those in the bottom quartile, yet our study had limited statistical power (estimated to be ≤65%[18]) to detect such a threshold effect.

Though significantly associated with VDBP levels, SNPs rs7041 and rs4588 were not associated with risk of advanced prostate cancer (p = 0.15 and 0.83, respectively). The null association between VDBP levels and risk of advanced prostate cancer remained unchanged after additional adjustment for these SNPs. We also performed sensitivity analyses by excluding patients carrying the phenotype GC1F-1F or GC1F-2 whose VDBP levels were much lower, and continued to observe no association with risk of advanced prostate cancer (data not shown).

We found a statistically significant interaction between total 25(OH)D levels and VDBP levels in relation to risk of advanced prostate cancer ($p_{interaction}$ = 0.03; Table 3). The inverse association with higher total 25(OH)D levels was more apparent when VDBP levels were also higher. Compared to those with total 25(OH)D levels below the median and VDBP levels above the median (at highest risk), the OR for advanced prostate cancer was 0.31 (95% CI, 0.15–0.65) in men with both levels above the median. The interaction persisted when we restricted the analyses to the lethal prostate cancer cases and their controls ($p_{interaction}$ = 0.02; Supporting Information Table S3).

Discussion

In this nested case-control study, we observed no overall association between VDBP levels and risk of advanced prostate cancer. However, we found an interaction between total 25(OH)D levels and VDBP levels such that men whose levels were high for both total 25(OH)D and VDBP had the lowest risk of advanced prostate cancer, while men with low total 25(OH)D levels and high VDBP levels had the highest risk. Contrary to the “free

hormone hypothesis", bioavailable 25(OH)D levels were not more strongly associated with risk of advanced prostate cancer than total 25(OH)D levels. We observed similar results when we restricted the analyses to the lethal prostate cancer cases and their controls.

Experimental studies demonstrate that VDBP has several important biological functions, including actin scavenging, macrophage activation, and chemotaxis.[19] In particular, VDBP-macrophage activating factor has a potent anti-angiogenic effect[20, 21] and can prevent tumor growth by inhibiting cancer cell proliferation and migration.[22, 23] A recent meta-analysis examined VDBP levels in relation to the overall risk of multiple cancers (basal cell carcinoma, bladder, breast, colon and rectum, endometrium, liver, esophagus, stomach, melanoma, pancreas, prostate, and kidney) and found borderline decreased risk in individuals with higher VDBP levels.[24] To date, four epidemiologic studies have assessed VDBP levels in relation to prostate cancer risk with mixed findings: one study found an inverse association between VDBP levels and prostate cancer risk in African Americans,[25] whereas the others reported a null association.[26–28] Notably, all these studies included both aggressive and non-aggressive diseases, yet none of the studies reported that the association between VDBP levels and prostate cancer risk was modified by disease aggressiveness.

Our results suggest that VDBP levels may modify the association between total 25(OH)D levels and risk of advanced and lethal prostate cancer. We observed that men whose levels were high for both total 25(OH)D and VDBP had the lowest risk of advanced and lethal prostate cancer. A previous study also reported an interaction between total 25(OH)D levels and VDBP levels in relation to risk of total prostate cancer in a cohort of Finnish smokers, in which, however, higher 25(OH)D levels were associated with higher risk of prostate cancer in men with higher VDBP levels.[26] Although our findings could be due to chance, several mechanistic explanations are possible. First, VDBP provides a reservoir for 25(OH)D, prolonging its half-life and thus increasing rather than decreasing vitamin D bioavailabilty. For example, individuals with high 25(OH)D levels as well as high VDBP levels may be less prone to vitamin D deficiency in seasons with less sun exposure. Second, VDBP may facilitate internalization of 25(OH)D into prostate epithelial cells. While it was long believed that only free 25(OH)D can enter target cells and modulate downstream biological events, recent studies suggest that the 25(OH)D-VDBP complex can also be internalized via megalin-mediated endocytosis.[29] Megalin is known to be expressed in epithelial cells of several organs including prostate.[30] Since bioavailable 25(OH)D is sparse in blood, total 25(OH)D could be a better reflection of 25(OH)D that influences prostate cancer development.

Strengths of our study include prediagnostic blood collection, detailed information on covariates, and relatively long-term and complete follow-up allowing for assessment of progression to lethal prostate cancer. We included only advanced prostate cancer cases because these are the more clinically relevant ones and we previously found an association between 25(OH)D levels and risk of lethal prostate cancer.[1] We were able to examine various vitamin D-related biomarkers as well as their interactions in relation to risk of advanced and lethal prostate cancer.

This work has several potential limitations. We measured 25(OH)D and VDBP at a single time point that may not represent their long-term status. However, VDBP levels are generally stable in adult life,[31] and previous studies have demonstrated a relatively high correlation for repeated measures of circulating 25(OH)D over time.[32–34] We did not directly measure bioavailable 25(OH)D. However, calculated free 25(OH)D levels are highly correlated with directly measured concentrations.[11] Recent studies suggest that ELISA based on a monocolonal antibody is incapable of measuring VDBP in African Americans, [10, 11] which would cause an error in the calculation of bioavailable 25(OH)D. Thus, we excluded non-white men to reduce this concern. Future research in men of other Ethnic groups is warranted, because rs4588 and rs7041 genotypes vary substantially by Ethnic group. Finally, we may have limited power to detect small effects due to the relatively small sample size.

In conclusion, our results do not support the hypothesis that bioavailable 25(OH)D levels have a stronger association with risk of advanced and lethal prostate cancer than total 25(OH)D levels. Although not directly associated with risk of advanced and lethal prostate cancer, VDBP levels may modify the association between total 25(OH)D levels and risk of advanced and lethal prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of controls at blood collection by quartile of total 25-hydroxyvitamin D, bioavailable 25-hydroxyvitamin D, and vitamin D binding protein

Characteristic	Quartile of total 25(OH)D				Quartile of bioavailable 25(OH)D[1]				Quartile of VDBP			
	1	2	3	4	1	2	3	4	1	2	3	4
Mean age, years	66.6	65.6	67.2	65.6	67.0	65.4	66.1	66.5	67.3	63.9	67.4	66.5
Mean body mass index, kg/m^2	27.2	26.7	25.9	23.8	26.9	26.4	25.1	25.2	26.1	26.0	26.3	25.2
Mean vigorous physical activity, MET-h/wk	6.3	8.3	11.3	15.9	9.3	6.4	9.8	16.3	12.9	7.6	11.8	11.1
Smoking status, %												
Never	60.5	48.7	48.7	43.6	65.8	43.6	51.3	41.0	51.3	38.5	51.3	61.5
Past	36.8	48.7	46.2	48.7	31.6	51.3	43.6	53.8	43.6	56.4	43.6	35.9
Current	2.6	2.6	5.1	7.7	2.6	5.1	5.1	5.1	5.1	5.1	5.1	2.6
Mean alcohol intake, g/d	9	19	13	13	15	14	12	14	11	15	14	14
Family history of prostate cancer, %	7.9	10.3	17.9	15.4	13.2	7.7	10.3	20.5	12.8	15.4	7.7	15.4
PSA test before blood collection, %	60.5	64.1	71.8	66.7	63.2	71.8	53.8	74.4	69.2	66.7	59.0	69.2
Vasectomy status, %	21.1	23.1	28.2	23.1	21.1	23.1	17.9	33.3	17.9	23.1	23.1	30.8
Mean sun exposure, UV-B flux	127	128	133	132	128	131	129	131	127	134	136	124
Mean intake												
Total energy, kcal/d	1926	2224	2172	1971	1987	2289	2091	1928	1987	2126	2143	2030
Vitamin D from foods, IU/d	217	285	297	264	214	280	312	256	261	256	297	246
Vitamin D from supplements, IU/d	122	199	107	221	125	201	152	170	208	119	151	181
Total lycopene, energy-adjusted, μg/d	6285	7230	6846	9818	7375	7192	7067	8573	6735	8062	6833	8549
Total calcium, energy-adjusted, mg/d	896	901	869	970	828	929	977	899	921	873	976	893
Red meat, servings/week	6	9	8	6	6	9	7	6	7	8	7	6
Fish, servings/week	2	2	2	2	2	2	2	2	2	2	2	2
Coffee, servings/d	2	2	2	2	2	2	2	2	2	2	2	2

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MET, metabolic equivalent; PSA, prostate-specific antigen; UV, ultraviolet; VDBP, vitamin D binding protein.

[1]Bioavailable 25(OH)D was calculated using total 25(OH)D, VDBP, and albumin levels and a constant affinity of VDBP for 25(OH)D

Table 2.

Odds ratios and 95% confidence intervals of advanced and lethal prostate cancer by quartile of total 25-hydroxyvitamin D, bioavailable 25-hydroxyvitamin D, and vitamin D binding protein

	Quartile of biomarker				p_{trend}
	1	2	3	4	
Advanced prostate cancer					
Total 25(OH)D					
Median (range), ng/mL	15.60 (≤18.49)	21.45 (18.54–24.28)	27.95 (24.31–30.47)	37.00 (≥30.78)	
No. of cases/controls	44/38	54/39	33/39	24/39	
Base model, OR (95% CI)[1]	1	1.19 (0.63–2.26)	0.78 (0.40–1.54)	0.54 (0.27–1.08)	0.03
Multivariable-adjusted model, OR (95% CI)[2]	1	1.24 (0.64–2.40)	0.78 (0.38–1.57)	0.50 (0.24–1.03)	0.02
Model further adjusted for VDBP, OR (95% CI)	1	1.23 (0.64–2.37)	0.79 (0.39–1.59)	0.49 (0.24–1.01)	0.02
Bioavailable 25(OH)D[3]					
Median (range), ng/mL	1.787 (≤2.253)	2.626 (2.255–2.887)	3.470 (2.888–3.980)	5.067 (≥4.008)	
No. of cases/controls	52/38	33/39	33/39	37/39	
Base model, OR (95% CI)[1]	1	0.59 (0.30–1.15)	0.58 (0.29–1.14)	0.67 (0.35–1.27)	0.21
Multivariable-adjusted model, OR (95% CI)[2]	1	0.47 (0.22–0.97)	0.50 (0.24–1.02)	0.58 (0.30–1.15)	0.14
VDBP					
Median (range), μg/mL	138.8 (≤186.6)	212.8 (188.0–239.6)	262.8 (239.8–296.0)	346.7 (≥298.0)	
No. of cases/controls	50/39	38/39	34/39	34/39	
Base model, OR (95% CI)[1]	1	0.69 (0.35–1.36)	0.61 (0.30–1.21)	0.59 (0.29–1.21)	0.14
Multivariable-adjusted model, OR (95% CI)[2]	1	0.66 (0.33–1.31)	0.61 (0.30–1.23)	0.62 (0.30–1.30)	0.21
Model further adjusted for 25(OH)D, OR (95% CI)	1	0.64 (0.31–1.29)	0.55 (0.27–1.14)	0.59 (0.28–1.26)	0.16
Lethal prostate cancer					
Total 25(OH)D					
Median (range), ng/mL	15.63 (≤18.49)	21.32 (18.54–24.22)	27.55 (24.31–30.32)	37.00 (≥30.78)	
No. of cases/controls	35/28	36/29	25/30	19/28	
Base model, OR (95% CI)[1]	1	0.95 (0.46–1.96)	0.69 (0.33–1.47)	0.57 (0.26–1.22)	0.09
Multivariable-adjusted model, OR (95% CI)[2]	1	1.07 (0.49–2.34)	0.63 (0.28–1.40)	0.50 (0.22–1.15)	0.04
Model further adjusted for VDBP, OR (95% CI)	1	1.07 (0.49–2.34)	0.63 (0.28–1.40)	0.50 (0.22–1.15)	0.04

	Quartile of biomarker				p_{trend}
	1	2	3	4	
Bioavailable 25(OH)D[3]					
Median (range), ng/mL	1.802 (≤2.253)	2.656 (2.255–2.887)	3.453 (2.888–3.980)	5.331 (≥4.087)	
No. of cases/controls	41/27	24/29	23/29	27/30	
Base model, OR (95% CI)[1]	1	0.49 (0.22–1.11)	0.47 (0.21–1.05)	0.57 (0.27–1.21)	0.13
Multivariable-adjusted model, OR (95% CI)[2]	1	0.38 (0.16–0.95)	0.34 (0.14–0.83)	0.45 (0.20–1.02)	0.05
VDBP					
Median (range), μg/mL	140.6 (≤186.6)	213.3 (188.0–237.9)	262.8 (239.8–296.0)	348.7 (≥299.4)	
No. of cases/controls	39/33	24/25	28/31	25/27	
Base model, OR (95% CI)[1]	1	0.78 (0.36–1.69)	0.71 (0.33–1.53)	0.72 (0.32–1.63)	0.39
Multivariable-adjusted model, OR (95% CI)[2]	1	0.65 (0.29–1.50)	0.70 (0.32–1.55)	0.85 (0.35–2.04)	0.62
Model further adjusted for 25(OH)D, OR (95% CI)	1	0.65 (0.28–1.54)	0.62 (0.27–1.39)	0.79 (0.32–1.95)	0.48

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

[1]OR (95% CI) from conditional logistic models conditioned on matching factors.

[2]OR (95% CI) from conditional logistic models conditioned on matching factors and adjusted for family history of prostate cancer, body mass index (<25.0, 25.0–29.9, ≥30.0 kg/m^2), vigorous physical activity (0, 0.1–5.9, 6.0–12.9, 13.0–25.9, ≥26.0 metabolic equivalent-h/week), and smoking status (never, past, current).

[3]Bioavailable 25(OH)D was calculated using total 25(OH)D, VDBP, and albumin levels and a constant affinity of VDBP for 25(OH)D.

Table 3.

Odds ratios and 95% confidence intervals of advanced prostate cancer by combined categories of total 25-hydroxyvitamin D and vitamin D binding protein[1]

		Total 25(OH)D[2]		$p_{interaction}$
		Low (<24.3 ng/mL)	High (≥24.3 ng/mL)	
VDBP[2]	Low (<239.8 μg/mL)	0.81 (0.42–1.59)	0.81 (0.38–1.74)	0.03
	High (≥239.8 μg/mL)	1	0.31 (0.15–0.65)	

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

[1]OR (95% CI) from conditional logistic models conditioned on matching factors and adjusted for family history of prostate cancer, body mass index (<25.0, 25.0–29.9, ≥30.0 kg/m^2), vigorous physical activity (0, 0.1–5.9, 6.0–12.9, 13.0–25.9, ≥26.0 metabolic equivalent-h/week), and smoking status (never, past, current).

[2]Cutpoints chosen based on median values in controls: 56 cases and 46 controls with low total 25(OH)D levels and low VDBP levels; 42 cases and 31 controls with low total 25(OH)D levels and high VDBP levels; 32 cases and 31 controls with high total 25(OH)D levels and low VDBP levels; 25 cases and 47 controls with high total 25(OH)D levels and high VDBP levels.