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Circulating Levels of 25-hydroxyvitamin D and Prostate Cancer Prognosis

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Abstract

Objectives—Ecological, *in vitro,* and *in vivo* studies demonstrate a link between vitamin D and prostate tumor growth and aggressiveness. The goal of this study was to investigate whether plasma concentration of vitamin D is associated with survivorship and disease progression in men diagnosed with prostate cancer.

Methods and Materials—We conducted a population-based cohort study of 1,476 prostate cancer patients to assess disease recurrence/progression and prostate cancer-specific mortality (PCSM) risks associated with serum levels of 25(OH) vitamin D [25(OH)D].

Results—There were 325 recurrence/progression and 95 PCSM events during an average of 10.8 years of follow-up. Serum levels of 25(OH)D were not associated with risk of recurrence/progression or mortality. Clinically deficient vitamin D levels were associated with an increased risk of death from other causes.

Conclusions—We did not find evidence that serum vitamin D levels measured after diagnosis affect prostate cancer prognosis. Lower levels of vitamin D were associated with risk of non-prostate cancer mortality.

Keywords

Prostatic Neoplasms; Mortality; Prognosis; Vitamin D/blood*; Cohort Studies; Epidemiologic Studies; Humans; Male

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Conflict of Interest Statement

Drs. Holt, Feng, and Stanford and Mss. Fu and Kolb have no financial disclosures to report. Dr. Ronald Horst is founder, co-owner, and director of Heartland Assays LLC which carried out measurement of vitamin D status.

Introduction

Vitamin D is a potential modifiable factor that could decrease disease burden of prostate cancer (PCa) through improved patient prognosis. Both *in vitro* and *in vivo* studies have consistently shown that the active form of vitamin D, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D$] or calcitriol, affects prostate tumorigenesis. In primary prostate epithelial cells calcitriol has been shown to be anti-proliferative, pro-differentiating and pro-apoptotic [1–3]. In mouse models and human PCa xenografts calcitriol has caused a reduction in tumor size and volume, as well as inhibited invasiveness, metastasis, and angiogenesis [2–5].

The role of vitamin D in prostate tumor growth and aggressiveness is also supported by ecological studies. Several studies have reported inverse associations between prostate cancer-specific mortality (PCSM) and sunlight exposure, geographical latitude, and season of diagnosis [6–10]. There are, however, only a limited number of studies directly linking serum levels of vitamin D with either PCa prognosis or measures of PCa aggressiveness. Some, but not all, case-only studies have reported inverse associations between vitamin D levels and measures of tumor aggressiveness such as Gleason score and stage[11–13]. Two case-only studies have reported deceased risks of PCSM in men with higher levels of 25(OH)D, however one study used a hospital-based population comprising more clinically aggressive cases while the other study found risk of PCSM was attenuated after adjustment for Gleason score [13, 14].

To further clarify the potential association between vitamin D and PCa prognosis, we conducted a population-based cohort study of 25(OH)D in relation to survival and disease progression in men diagnosed with PCa. Serum samples were collected shortly after diagnosis and the cohort was then followed prospectively for outcomes.

Materials and Methods

Study Population

Study subjects were enrolled in one of two population-based prostate cancer case-control studies that have been described previously [15, 16]. Cases were newly diagnosed with histologically confirmed PCa in two study periods, either January 1, 1993 to December 31, 1996 (Study I, age range 40–64 years) or January 1, 2002 to December 31, 2005 (Study II, age range 35–74 years). PCa cases were identified from the metropolitan Seattle-Puget Sound population-based tumor registry that is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Of the 1,754 eligible, interviewed cases, we obtained peripheral blood samples for assessment of serum vitamin D from 1,476 cases (n=650 Study I; n=826 Study II).

Clinical and Follow-up Data

Baseline in-person interviews collected epidemiological data including age, race, weekly exercise, smoking status, weight, height, and medical history. Clinical information was extracted from the SEER cancer registry and supplemented through physician queries. Dietary intake of vitamin D and calcium was calculated using previously described food frequency questionnaires (FFQ) administered separately from the baseline interview for 1,338 (90.7%) of cases [17].

Recurrence/progression status was determined using two self-administered follow-up questionnaires that were sent to study participants in 2004–05 and 2010–11 and medical record reviews. The overall survey response level was 79.6%. Criteria used to determine recurrence/progression has been described previously, but briefly includes biochemical

(PSA), receipt of secondary treatment, or a positive bone scan, biopsy, CT or MRI, or a physician's diagnosis of PCa recurrence/progression [17]. Cases diagnosed with local/regional stage disease but deceased at the time of follow-up (n=47) or diagnosed with metastatic disease were also considered to have recurred/progressed. Vital status was obtained from the SEER registry and fatal PCa cases were confirmed through review of death certificates. Two categories were defined to capture specific phenotypes of PCa: 1) an aggressive phenotype that included patients with distant stage disease, Gleason score ≥8, or PSA ≥20 ng/mL, and 2) a lethal phenotype that included distant stage, cases that died of PCa, or cases that developed metastasis during follow-up.

Vitamin D Measurement

Blood samples were collected at time of interview (~10 months after diagnosis), kept cool, processed within 4–6 hours using standard protocols, and serum aliquots stored at −80°C until analysis. Measurement of 25(OH)D was used since its correlation to cutaneous synthesis and dietary intake of vitamin D is superior to the active form of the hormone, 1,25(OH)D, which has a short half-life and tight homeostatic control [18]. Quantitative determination of serum of 25(OH)D utilized the radioimmunosorbant DiaSorin LIAISON 25 OH Vitamin D TOTAL Assay developed by Heartland Assays; samples were shipped to Heartland Laboratory where assays were performed. The distribution of subjects was random across batches and the coefficient variation between replicates was 10%. In addition to including known positive and negative controls within each batch of samples assayed, blind duplicate samples (1%) distributed across batches were assayed.

Statistical Analysis

Cox proportional hazards (PH) regression models were used to examine associations between serum 25(OH)D with PCSM and other cause mortality. For estimating risk of PCa recurrence/progression, a modified weighted logistic regression model that allows for time-varying marker effects and uses inverse censoring probability as a weight to accommodate censored failure time, was employed at 5-year and 10-year time-points [19]. Vitamin D levels were categorized according to the latest guidelines published by the Food and Medicine Board at the National Institute of Medicine: deficient (< 12 ng/mL), insufficient (12–20 ng/mL), sufficient (≥20–50 ng/mL), and excessive (>50ng/mL) [20]. Models were adjusted for season of blood draw (winter, January-March; spring, April-June; summer, July-September; and autumn, October-December). In addition, concentrations of 25(OH)D were standardized within season of blood draw and z-scores used to create quartiles of vitamin D levels. Models were adjusted for age at diagnosis, race, weekly physical exercise (none, 1, 2–3, 4–5, or ≥6 times a week), smoking status (never, former, current), and body mass index [BMI, < 25 kg/m^2, 25–29.9 kg/m^2, ≥ 30.0 kg/m^2], Gleason score [2–6, 7(3+4), or 7(4+3) −10], stage at diagnosis (local, regional, or distant), and primary treatment [radical prostatectomy, radiation with or without androgen deprivation therapy (ADT), ADT only, other treatment, or active surveillance]. Dietary intake of vitamin D, calcium, and family history of PCa were assessed for confounding, but did not appreciably alter results so were omitted from the analysis. Sensitivity analysis was carried out limiting data to Caucasians. Effect modification was evaluated for BMI, primary treatment and measures of tumor aggressiveness using likelihood ratio tests.

Time to PCa recurrence/progression was defined as time from diagnosis to the first reported evidence of recurrence. For those with follow-up but without an event, the censoring date was when the most recent follow-up questionnaire was returned. For those who died of metastatic PCa prior to the follow-up surveys, time to recurrence/progression was imputed [17, 21]. For those diagnosed with metastatic disease, time to event was set at zero. Time to PCSM was defined as the time from diagnosis to death. Living cases were censored on date

of most recent linkage with the cancer registry, April 2012. Cases that died from other or unknown causes were censored at the time of death. This study was approved by Fred Hutchinson Cancer Research Center's Institutional Review Board, and all subjects signed informed consent. Analysis was done using the STATA statistical package (version 11, STATA Corp., College Station, TX).

Results

Within this population-based cohort of PCa cases, vitamin D deficiency was associated with African American race, family history of PCa, obesity (BMI ≥30 kg/m^2), less exercise, current smoking status, and lower levels of dietary intake of vitamin D and calcium (Table 1). Vitamin D status was not associated with Gleason score, stage, or diagnostic PSA level at the univariate level (Table 1) nor after adjustment for season of blood draw, age, race, exercise, smoking, or BMI (data not shown.) After adjusting for age and season of blood draw, the vitamin D deficient group were 50% more likely to be diagnosed with an aggressive phenotype as compared to the sufficient vitamin D group [Odds Ratio (OR) 1.5; 95% CI 1.0–2.3, p = 0.03]. Lethal PCa was not associated with vitamin D levels at the univariate level or after adjustment for season and other potential confounders.

There was an average of 10.8 years of follow-up (range 0.8–18.8 years) for the entire cohort during which 95 cases died of PCa and 172 cases died of other causes. Table 2 shows vital status by clinical strata of vitamin D levels. No significant differences were observed in risk of PCSM by clinically defined levels of vitamin D (Table 2), seasonally-adjusted quartiles or using log-transformed data of 25(OH)D levels (data not shown). Clinically deficient vitamin D cases had an increased risk of death from other causes. Cases with information on recurrence/ progression had an average 8.5 years of follow-up after diagnosis (range 0.3–17.6 years), during which 325 events were recorded. There was no association observed with risk of recurrence/ progression by vitamin D status (Table 2) or seasonally-adjusted quartiles (data not shown). Results did not change when limited to Caucasians or when dietary calcium intake was accounted for.

There were no significant risk differences observed for PCSM or recurrence/progression by vitamin D levels when models were stratified by measures of tumor aggressiveness or primary treatment (data not shown). There was evidence of effect modification of BMI with risk of PCSM (p = 0.02, BMI as continuous measure) but not with risk of recurrence/ progression. For cases with BMI of 25–29.9 kg/m^2 (overweight) there was a non-significant increased risk of PCSM for both clinically deficient and excessive vitamin D groups (HR 1.8; 95% CI 0.6–5.4 and HR 1.6; 95% CI 0.1–17.6, respectively). Vitamin D deficiency was inversely associated with PCSM in the normal weight category (BMI <25.0 kg/m^2), although there were only two events within this stratum (HR 0.1; 95% CI 0.001–0.02, p = 0.002).

Discussion

We did not find evidence that vitamin D levels alter PCa prognosis. Lower levels of vitamin D were associated with risk of non-PCa mortality, which is in line with other studies [11]. Based on evidence from *in vitro* and *in vivo* models and ecological studies, vitamin D is thought to represent a potentially modifiable exposure that could improve PCa prognosis. While findings reported here do not support this hypothesis, they do illustrate potential pitfalls with studies of circulating vitamin D levels and PCa outcomes.

Few PCa epidemiologic studies have focused on effects that vitamin D status may have on tumor propensity to grow and metastasize. Some case-only studies suggest an inverse

association between vitamin D status and tumor aggressiveness, however, these findings have not been supported by case-control studies [11–13]. A recent nested case-control study from Shui *et al.* showed that while there was no association observed with Gleason score or stage in men with vitamin D deficiency, there was an increased risk of lethal PCa [22]. We did not replicate this finding in our PCa cohort, and there was no association with Gleason score or stage; we did observe an association between vitamin D deficiency and the aggressive phenotype that incorporated PSA values. Two epidemiological studies have examined PCa outcomes utilizing a prospective design. A small Norwegian hospital-based study showed deceased risks of PCSM in men with higher levels of plasma 25(OH)D in samples collected after diagnosis [14]. That study was comprised of men who were undergoing treatment for their cancer, thus had a higher proportion of aggressive phenotypes as compared to our cohort. The Physicians Health and Health Professionals Follow-up study cohorts both reported an inverse association between vitamin D status and PCSM, however the association was null after adjustment for Gleason score [13].

There are several concerns, such as timing of the blood draw and relevant exposure thresholds, when interpreting results from these studies. If vitamin D status was measured post-diagnosis or post-treatment, both reverse causality and modification by treatment are possible, however, we did not observe an association with more aggressive tumor phenotypes or by primary treatment type. The relationship between serum vitamin D and prognosis may not be linear as assumed by many study designs, thus we examined seasonally-adjusted vitamin D status several ways to ascertain a potential dose effect both linearly and within a polynomial model, in addition to grouping vitamin D status into clinically relevant categories based on the latest recommendations by the Institutes of Medicine [23]. These categories include an “excessive vitamin D status” group based on emerging evidence linking adverse effects of high vitamin D levels, particularly at >150 nmol/L (>60 ng/mL) [20]. We observed a non-significant association with PCSM and risk of PCa recurrence/progression, as well as shorter average time to event in this group. The lack of statistical significance of risk estimates may be due to insufficient power given the limited number of outcome events. The grouping of vitamin D levels into clinically significant categories exacerbated the small number of events observed in the clinically deficient group; however, when the data were analyzed with vitamin D levels as quartiles there were still no significant associations observed. Lastly, serum levels may not represent local tissue exposure since prostate tissue can metabolize 25(OH)D into $1,25(OH)_2D$, which is not bound to the tight endocrine regulation of circulating $1,25(OH)_2D$ [24]. In addition, expression and action of enzymes that mediate metabolism and activity of vitamin D in prostate tissue is dynamic. For instance, higher vitamin D receptor (VDR) activity, which ultimately mediates response to calcitriol, in epithelial cells of prostate tumors is correlated with a reduced risk of lethal PCa, but does not correlate with serum 25(OH)D [25]. In a trial examining vitamin D supplementation at 4000 IU/day in active surveillance patients, over half the subjects had a decrease in number of positive cores and/or Gleason score after one year, yet there was no correlation between serum levels of 25(OH)D and the treatment response observed in the prostate tissue [26].

Looking beyond potential difficulties in measurement of circulating proteins, this study has several strengths. Heartland Laboratories has been instrumental in methodology development for accurate assessment of vitamin D status, lending validity to the exposure measurement. Although there was only one measure taken, reliability of a single measurement over a 5-year period has been shown [27]. Detailed covariate measurement permitted adjustment for seasonal variation in vitamin D levels, adjustment of confounders and assessment of effect modification. Both obesity and race are associated with poorer PCa outcomes and vitamin D deficiency, and we did observe different risk estimates across the BMI strata [28–30]. We were not able to access PCSM or risk of recurrence/progression in

African Americans due to small numbers; however, our results were not altered by excluding them from the analysis. Vitamin D status can be viewed as a marker for overall health and healthy lifestyle; indeed, we did observe that vitamin D deficiency was associated with less physical exercise and smoking which have both been linked to PCa prognosis. We were able to account for these factors, thus residual confounding from healthy lifestyle is likely to be minimal on our results. Lastly, the long follow-up period allowed for capture of both PCSM and recurrence/progression events that occurred more than 5 years after initial treatment. The active follow-up of this population-based cohort has one of the largest sample sizes of detailed information of long term PCa outcomes in the published literature.

Conclusions

In conclusion, these results demonstrate that circulating levels of vitamin D have little or no impact on PCa prognosis within the parameters of this study. Future studies should focus on the potential effects of vitamin D activity in PCa tissue specifically, attempt to establish a threshold of vitamin D tissue exposure for which there is a consequence on patient outcomes, and to better define how different phenotypes of the tumor may be affected by vitamin D exposure.

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Abbreviations and Acronyms

1,25(OH)$_2$D	1,25-dihydroxyvitamin D_3
25(OH)D	25(OH) vitamin D
ADT	androgen deprivation therapy
BMI	body mass index
FFQ	food frequency questionnaire
HR	hazard ratio
PCa	prostate cancer
PH	proportional hazards
PSA	prostate specific antigen
PCSM	prostate cancer-specific mortality

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Table 1

Distribution and univariate associations for selected characteristics of prostate cancer cases by clinically defined levels of vitamin D status

Clinically Defined Groups of Serum 25(OH)D					
	Deficient (<12 ng/mL) n = 124 (%)	**Insufficient (12–19.9 ng/mL) n = 390 (%)**	**Sufficient (20–50.9 ng/ml) n = 941 (%)**	**Excessive (≥51 ng/mL) n = 21 (%)**	**p-value [a]**
Age at Diagnosis (yrs), mean (SD)	60 (6.0)	59.2 (7.0)	60.0 (7.1)	62.6 (6.8)	0.07
Race					
Caucasian	80 (64.5)	335 (85.9)	889 (94.5)	21 (100)	<0.001
African American	44 (35.5)	55 (14.1)	52 (5.5)	0 (0)	
Family History of PC					
No	111 (89.5)	303 (77.7)	735 (78.1)	13 (61.9)	0.006
Yes	13 (10.5)	87 (22.3)	206 (21.9)	8 (38.1)	
Body Mass Index (kg/m^2)					
< 25.0	29 (23.4)	96 (24.6)	334 (35.5)	12 (57.1)	<0.001
25.0–29.9	58 (46.8)	199 (51)	454 (48.2)	7 (33.3)	
≥ 30.0	37 (29.8)	95 (24.4)	153 (16.3)	2 (9.5)	
Physical Exercise (time/week)					
0	50 (40.3)	112 (28.7)	161 (17.1)	5 (23.8)	<0.001
1	26 (21.0)	82 (21.0)	165 (17.5)	3 (14.3)	
2–3	22 (17.7)	124 (31.8)	334 (35.5)	6 (28.6)	
≥4	26 (20.0)	72 (18.5)	281 (29.9)	7 (33.3)	
Smoking Status					
Nonsmoker	45 (36.3)	150 (38.5)	390 (41.4)	10 (47.6)	<0.001
Former Smoker	45 (36.3)	182 (46.7)	447 (47.5)	10 (47.6)	
Current Smoker	34 (27.4)	58 (14.9)	104 (11.1)	1 (4.8)	
Total Dietary Vitamin D (ug/d)					
0.0–3.6	44 (35.5)	93 (23.8)	169 (18)	2 (9.5)	<0.001
3.6–5.6	29 (23.4)	81 (20.8)	216 (23)	6 (28.6)	
5.6–8.3	16 (12.9)	88 (22.6)	234 (24.9)	6 (28.6)	
> 8.3	19 (15.3)	83 (21.3)	245 (26)	7 (33.3)	
Missing	16 (12.9)	45 (11.5)	77 (8.2)	0 (0)	
Total Dietary Calcium (mg/d)					

Clinically Defined Groups of Serum 25(OH)D	Deficient (<12 ng/mL) n = 124 (%)	Insufficient (12–19.9 ng/mL) n = 390 (%)	Sufficient (20–50.9 ng/ml) n = 941 (%)	Excessive (≥51 ng/mL) n = 21 (%)	p-value [a]
0–563	44 (35.5)	94 (24.1)	189 (20.1)	1 (4.8)	<0.001
563–809	24 (19.4)	95 (24.4)	199 (21.1)	7 (33.3)	
809–1182	24 (19.4)	72 (18.5)	227 (24.1)	5 (23.8)	
>1182	16 (12.9)	84 (21.5)	249 (26.5)	8 (38.1)	
Missing	16 (12.9)	45 (11.5)	77 (8.2)	0 (0)	
Stage					
Local	97 (78.2)	300 (76.9)	736 (78.2)	17 (81)	0.94
Regional/Distant	27 (21.8)	90 (23.1)	205 (21.8)	4 (19)	
Gleason Score					
2–6	61 (49.2)	218 (55.9)	532 (56.5)	13 (61.9)	0.81
7 (3+4)	38 (30.6)	106 (27.2)	261 (27.7)	6 (28.6)	
7(4+3), 8–10	23 (18.5)	65 (16.7)	145 (15.4)	2 (9.5)	
Unknown	2 (1.6)	1 (0.3)	3 (0.3)	0 (0)	
Diagnostic PSA Level					
0–9.9 ng/mL	79 (63.7)	247 (63.3)	669 (71.1)	16 (76.2)	0.22
10+ ng/mL	34 (27.4)	101 (25.9)	214 (22.7)	4 (19)	
Unknown	11 (8.9)	42 (10.8)	58 (6.2)	1 (4.8)	
Aggressive Phenotype [b]					
Less	71 (57.3)	252 (64.6)	632 (67.2)	17 (80.9)	0.07
More	53 (42.7)	138 (35.4)	309 (32.8)	4 (19.1)	
Lethal Phenotype [c]					
No	111 (89.5)	358 (91.8)	842 (89.5)	19 (90.5)	0.63
Yes	13 (10.5)	32 (8.2)	99 (10.5)	2 (9.5)	

[a] Unadjusted p-values determined by X^2 or Anova.

[b] More aggressive phenotype includes cases diagnosed with distant stage disease, Gleason score ≥8, or a PSA ≥20.

[c] Lethal phenotype includes cases diagnosed with distant stage, cases that died of PCa, or cases with evidence of metastasis.

Table 2

Hazard ratios and odds ratios with 95% confidence intervals for prostate cancer mortality and recurrence/progression, respectively, according to clinically defined levels of vitamin D status

Levels of Serum 25(OH)D	**Deficient (<12 ng/mL) n = 124 (%)**	**Insufficient (12–19.9 ng/mL) n = 390 (%)**	**Sufficient (20–50.9 ng/ml) n = 941(%)**	**Excessive (>=51 ng/mL) n = 21 (%)**
Vital Status (n=1,476)				
Alive	90 (72.6)	316 (81.0)	788 (83.7)	15 (71.4)
Death from prostate cancer	10 (8.1)	19 (4.9)	64 (6.8)	2 (9.5)
Mean (range) time to PCSM, years	7.7 (0.6–15.9)	7.8 (1.3–17.1)	6.7 (1.1–16.0)	3.9 (1.8–6.0)
Partial adjusted Hazard Ratio, Model 1 (95% CI) [a]	1.1 (0.6–2.4)	0.7 (0.4–1.1)	reference	1.8 (0.4–7.5)
Partial adjusted Hazard Ratio, Model 2 (95% CI) [b]	0.9 (0.5–2.0)	0.6 (0.4–1.0)	reference	1.7 (0.4–7.0)
Adjusted Hazard Ratio (95% CI) [c]	1.2 (0.5–2.7)	0.8 (0.5–1.3)	reference	1.2 (0.3–5.3)
Death from other causes	24 (19.3)	55 (14.1)	89 (9.5)	4 (19.1)
Mean (range) time to non-PCa death, years	7.9 (1.5–16.7)	8.3 (0.8–17.4)	8.8 (1.2–16.4)	9.0 (3.6–17.0)
Partial adjusted Hazard Ratio (95% CI) [a]	2.4 (1.5–3.9)	1.5 (1.1–2.1)	reference	1.9 (0.7–5.1)
Adjusted Hazard Ratio (95% CI) [b]	**1.8 (1.1–3.0)**	1.3 (0.9–1.8)	reference	1.7 (0.6–4.6)
Recurrence/progression Status (n=1,150) [d]				
No event	54 (82.4)	187 (65.6)	532 (69.2)	14 (68.4)
Diagnosed with distant stage	3 (3.8)	8 (2.8)	26 (3.4)	1 (5.9)
Recurred/Progressed	22 (27.8)	90 (31.6)	211 (27.4)	2 (11.7)
Mean (range) time to recurrence/progression, years	5.1 (0.4–9.7)	5.5 (0.3–16.0)	5.5 (0.3–16.6)	1.8 (1.2–2.3)
Partial adjusted Odds Ratio (95% CI) [a,b]	1.1 (0.9–1.2)	1.0 (0.9–1.1)	reference	0.8 (0.6–1.1)
Adjusted Odd Ratio (95% CI) [c]	1.1 (0.9–1.2)	1.1 (1.0–1.2)	reference	0.8 (0.6–1.1)

[a] Adjusted for season of blood draw, age and race.

[b] Additionally adjusted for BMI, smoking status, and weekly exercise

[c] Additionally adjusted for stage, Gleason score and primary treatment.

[d] Cases without follow-up for recurrence/progression (n=326) are not shown.