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Clinical Cancer Research

Vitamin D Deficiency Predicts Prostate Biopsy Outcomes

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Abstract

Purpose: The association between vitamin D and prostate biopsy outcomes has not been evaluated. We examine serum vitamin D levels with prostate biopsy results in men with an abnormal prostate-specific antigen and/or digital rectal examination.

Experimental Design: Serum 25-hydroxyvitamin D (25-OH D) was obtained from 667 men, ages 40 to 79 years, prospectively enrolled from Chicago urology clinics undergoing first prostate biopsy. Logistic regression was used to evaluate the associations between 25-OH D status and incident prostate cancer, Gleason score, and tumor stage.

Results: Among European American (EA) men, there was an association of 25-OH D <12 ng/mL with higher Gleason score $\geq$ 4+4 [OR, 3.66; 95% confidence interval (CI), 1.41–9.50; $P = 0.008$] and tumor stage [stage $\geq$ cT2b vs. $\leq$ cT2a, OR, 2.42 (1.14–5.10); $P = 0.008$]. In African American (AA) men, we find increased odds of prostate cancer diagnosis on biopsy with 25-OH D < 20 ng/mL [OR, 2.43 (1.20–4.94); $P = 0.01$]. AA men demonstrated an association between 25-OH D < 12 ng/mL and Gleason $\geq$ 4+4 [OR, 4.89 (1.59–15.07); $P = 0.006$]. There was an association with tumor stage $\geq$ cT2b vs. $\leq$ cT2a [OR, 4.22 (1.52–11.74); $P = 0.003$].

Conclusions: In AA men, vitamin D deficiency was associated with increased odds of prostate cancer diagnosis on biopsy. In both EA and AA men, severe deficiency was positively associated with higher Gleason grade and tumor stage. *Clin Cancer Res; 20(9); 2289–99. ©2014 AACR.*

Introduction

In the United States, prostate cancer is the most common nondermatologic malignancy in men; however, there are significant racial disparities in incidence and mortality rates (1). The disease is 1.6 times more common among African American (AA) men, and AA men are 2.5 times more likely to die of the disease (2, 3). National public health priorities are now focused on uncovering the etiologies of cancer health disparities. It has been shown that prostate cancer incidence mirrors that of vitamin D deficiency being highest in northerly latitudes, and in people of older age and of African ancestry (4). Recently, Grant showed that residential solar ultraviolet B (UVB) radiation levels correlated inversely with numerous cancers in Black Americans, including breast, colon, rectum, stomach, and esophagus (5). A recent study by Taskler and colleagues demonstrated a negative association between prostate cancer incidence with UV radiation exposure in the United States (6). For this reason, it has been hypothesized that vitamin D deficiency could play a role in the pathogenesis of prostate cancer. Indeed, studies suggest higher cancer mortality rates for patients diagnosed in winter (7, 8) and at northern latitudes (9, 10). For the majority of individuals, approximately 90% of vitamin D is estimated to derive from sunshine, with the liver converting solar UV radiation into 25-hydroxyvitamin D3 (25-OH D3), the form of vitamin D typically measured in blood serum (11). AA men have lower serum vitamin D levels than their European American (EA) and Hispanic counterparts (12, 13), in part due to lower skin synthesis from the ultraviolet (UV) UV blocking effects of melanin in the skin (14–17). A recent epidemiologic study suggests that vitamin D deficiency may explain the disparity in cancer survival between EAs and AAs, including prostate cancer (18).

Men undergoing prostate biopsy for an elevated prostate-specific antigen (PSA) or abnormal digital rectal exam (DRE) are less likely to have significant differences in screening practices. Overall, we sought to examine the association of vitamin D status and prostate cancer diagnosis, Gleason grade, tumor stage, and National Comprehensive Cancer Network (NCCN) risk category in high-risk men (19). To our knowledge, there have been no studies evaluating the association of vitamin D status and the outcomes of prostate biopsies. We also evaluate these outcomes in an ethnically diverse population of ambulatory men in a city with low UV exposure (20).

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Translational Relevance

There is a critical need for new biologic markers for prostate cancer due to the low sensitivity and specificity of prostate-specific antigen for predicting incidence and aggressiveness of prostate cancer. This study is an evaluation of the impact of serum 25-hydroxyvitamin D on prostate cancer biopsy results from prospectively collected data from men enrolled from urology clinics at various medical academic centers in Chicago, Illinois. Vitamin D may interfere with carcinogenesis through the vitamin D receptor by several mechanisms, including inhibition of angiogenesis and cellular proliferation, and promotion of cellular apoptosis and differentiation. Our work supports the hypothesis that 25-hydroxyvitamin D is a potential biomarker that plays a clinically significant role in prostate cancer, and it may be a useful modifiable risk factor in the disease. Additionally, differences in serum 25-hydroxyvitamin D levels may explain ethnic disparities in prostate cancer–specific incidence, morbidity, and mortality.

Materials and Methods

Subject recruitment

Between February 2009 and February 2013, we enrolled 667 ambulatory men, ages 40 to 79 years, from five urology clinics in Chicago, Illinois (three academic, one public, and one Veteran's Administration) that were undergoing their first prostate biopsy for an elevated or abnormal serum PSA level or an abnormal DRE. The men were enrolled on the date of their biopsies and had their serum 25-OH D level drawn on the date of recruitment. We included only ambulatory, nonhospitalized men to avoid recruiting men too immobilized to get adequate sun exposure.

Statistical analysis

Sample characteristics for the cases and negative biopsies were compared using descriptive statistics and tested for significance using Student's *t* tests for continuous variables and χ^2 tests for categorical traits. There were small numbers of Hispanics, Asians and were excluded. We stratified the analyses by EA and AA race, because AA men have higher rates of positive biopsy (21), higher Gleason grade and stage at presentation (22), and higher prevalence of vitamin D deficiency (12, 13).

The vitamin D status of the cases and negative biopsies were analyzed in the context of the predictors of serum vitamin D, namely season, race, age, and body mass index (BMI).

For the analysis of vitamin D deficiency and cancer versus noncancer diagnosis, we created a best-fit unconditional binary logistic regression, using −2 log likelihood scores, with the dependent variable coded as case versus noncancer diagnosis. More than 10 tissues, including the prostate, have the ability to activate and metabolize serum 25-OH D. Cancer initiation and promotion are separate metabolic processes with potentially different responses to serum vitamin D (23). Thus, we performed a sensitivity analysis for defining vitamin D deficiency using clinically defined cut points, cut points used in the cancer literature (25-OH D <12 ng/mL, <16 ng/mL, <20 ng/mL, and <30 ng/mL), and race-specific quartiles and tertiles. We present our stratified analyses as AA-race–only and EA-race–only because race likely confounds the relationship between vitamin D and prostate cancer diagnosis.

We also created binary variables to evaluate associations between vitamin D deficiency and Gleason grade. Specifically, we used binary logistic regression models for Gleason $\geq$ 4+3 versus Gleason < 4+3 and Gleason $\geq$ 4+4 versus Gleason < 4+4.

We then used binary regressions to evaluate associations between vitamin D deficiency and clinical tumor stage; specifically, we dichotomized clinical tumor stage as $\leq$ T2a versus $\geq$ T2b (24).

Next, we used ordinal logistic regression models for the evaluation of vitamin D deficiency and Gleason grade, which included a four-level dependent variable, (i.e., Gleason $\leq$ 3+3, Gleason 3+4, Gleason 4+3, and Gleason $\geq$ 4+4).

Finally, we assessed for an association using ordinal logistic regression models between the 2007 NCCN risk categories (based on prediagnosis PSA levels, tumor stage, and Gleason grade) and vitamin D status using ordinal logistic regression (low risk, intermediate risk, high risk, and $\geq$ very high risk). The NCCN risk guidelines for prostate cancer are a clinical tool used for prostate cancer risk stratification and treatment recommendations (23). Confidence intervals are reported for the regressions in the tables and *P* values are used in the text. In addition, we also test for potential interactions between vitamin D deficiency and 5-α reductase inhibitor (5-ARI) use on the biopsy outcomes.

This study was powered at 80% to detect an OR of 1.6 for vitamin D deficiency prostate cancer diagnosis using binary logistic regression modeling with a two-sided α of 0.05 assuming a 50% prevalence of vitamin D deficiency. All participants provided written informed consent. The Institutional Review Boards of each participating site approved the protocol. Statistical analyses were conducted with SPSS 21 (IBM Corp.).

Results

The mean age of our study population was 62.0 years for the cases versus 61.0 years for the negative biopsy group (Table 1; $P = 0.03$). Prostate volume was significantly smaller among cases (42.9 cm^3 vs. 56.5 cm^3; $P < 0.001$) and the case group had a higher percentage of prostate cancer family history (25.8% vs. 14.9%, $P = 0.001$). Rates of vitamin D deficiency (25-OH D < 20 ng/mL) were similar between cases and negative biopsies (43.7% vs. 37.8%; $P = 0.17$); however, negative biopsies had fewer AAs and more Asian Americans and Hispanic Americans ($P = 0.01$).

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Table 1. Demographic and clinical characteristics of patients with prostate cancer and negative biopsies

	Prostate cancer cases ($N = 383$)	Negative biopsies ($N = 284$)	
Continuous variables, median (SD)			P[a]
Age, y	62.0 (6.9)	61.0 (7.58)	**0.03**
BMI, kg/m^2	27.7 (5.0)	27.0 (4.8)	0.49
Serum PSA[b]	6.4 (654.0)	5.6 (12.0)	0.22
25-OH D serum level, ng/mL[c]	21.0 (10.0)	22.0 (11.0)	0.09
Vitamin D intake (IU)	270.5 (3,005.7)	232.7 (3,263.3)	0.97
Calcium intake (mg)	551.5 (2,663.1)	619.5 (506.2)	0.35
Measured sun exposure	6.6 (8.0)	7.0 (7.2)	0.21
Education years after high school	1.6	1.6	1.00
Prostate volume (cm^3)	42.9	56.5	**<0.001**
Categorical variables (%)			P[d]
First degree prostate cancer family history	25.8	14.9	**0.001**
Abnormal DRE	33.9	29.9	0.27
Race/ethnicity			
African American ($n = 273$)	43.9	37.0	0.08
European American ($n = 275$)	41.8	40.5	0.74
Other ($n = 119$)	14.4	22.5	**0.01**
High school completed	87.6	83.0	0.09
25-OH D < 30 ng/mL	78.1	75.2	0.43
25-OH D < 20 ng/mL	43.7	37.8	0.17
Vitamin D supplement use	13.1	12.7	0.89
Married	58.1	62.9	0.21
Obesity (BMI $\geq$ 30)	28.6	27.3	0.71
Tobacco use	56.6	54.2	0.54

NOTE: P values in bold print have reached statistical significance ($P < 0.05$).

[a]Unpaired, two-sample t test.

[b]PSA = serum PSA level (5-ARI–adjusted PSA value was calculated by doubling prebiopsy PSA value).

[c]25-OH D = serum 25 hydroxyvitamin D level drawn on date of enrollment.

[d]χ^2 analysis.

Otherwise, the cases and controls were similar in most covariates (see Table 1).

The serum vitamin D characteristics between cases and negative biopsy participants are shown in Table 2. Of note, the mean 25-OH D level was lower in AA cases (16.7 ng/mL) relative to AA-negative biopsies (19.3 ng/mL, $P = 0.04$). The highest serum vitamin D level in EA men was 71 ng/mL and was 45 ng/mL for AA men.

Table 3 shows the distribution of the clinical features of the prostate cancer cases. There was a reasonable distribution of high and low stage and grade disease with 55.9% having Gleason scores of $\leq$3+3. There are no clinical T4 or N1 participants in the sample. However, our population did include some asymptomatic men with metastatic disease in our population and 23.8% of the sample fall into the high or $\geq$very high NCCN risk strata.

Below, we present the race-stratified analyses of the associations of vitamin D deficiency on prostate cancer diagnosed on biopsy, Gleason grade on biopsy, clinical tumor stage, and NCCN low-risk versus $\geq$ intermediate-risk category.

EA analyses

In EA men, we found no associations between vitamin D status and prostate cancer diagnosis on biopsy using quartiles, tertiles, and several cut points for deficiency (all $P >$ 0.15, data not shown). The best model for EA men included vitamin D < 20 ng/mL ($P = 0.16$, Table 4). Skin color, reported sun exposure, and measured UV exposure were not associated with prostate cancer diagnosis.

We used a binary logistic regression model for Gleason grade $\geq$ 3+4 and found that 25-OH D < 12 ng/mL was not associated with $\geq$ intermediate-grade disease on biopsy. This model controlled for age, PSA, season, tobacco use, family history, and 5-ARI use. There was a strong negative association with 5-ARI use and biopsy Gleason grade $\geq$ 3+4 (OR, 0.09; $P = 0.005$).

We used a binary logistic regression model for Gleason grade $\geq$ 4+4 and found that 25-OH D < 12 ng/mL (OR, 3.66, 95% confidence interval, CI, 1.41–9.50; $P = 0.008$) was associated with high-grade disease on biopsy. This model controlled for age, PSA, season, current tobacco use, obesity (BMI > 30 kg/m^2), high calcium intake (i.e.,

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Table 2. Serum 25-OH D level stratified by season, race/ethnicity, age, and obesity

	Prostate cancer cases, mean (SD)	Negative biopsies, mean (SD)	P^a
Season of blood draw			
Low UV (November–April)	21.2 (10.1)	22.1 (11.6)	0.48
High UV (May–October)	22.6 (9.8)	24.8 (11.9)	0.11
Race/ethnicity			
African American	16.7 (8.2)	19.3 (10.4)	**0.04**
Non–African American	25.7 (9.5)	25.6 (12.0)	0.92
Age, y			
Less than 55	20.3 (10.5)	21.6 (9.7)	0.54
55–69	22.2 (9.8)	23.7 (12.2)	0.19
70 or older	22.0 (10.2)	25.1 (12.8)	0.24
Obesity			
BMI < 30	22.6 (10.0)	24.7 (12.8)	0.07
BMI ≥ 30	20.7 (10.3)	21.9 (9.3)	0.50
BMI ≥ 35	19.0 (10.4)	25.5 (8.2)	0.68

NOTE: *P* values in bold print have reached statistical significance ($P < 0.05$).
[a]Unpaired, two-sample *t* test.

Table 3. Characteristics of prostate cancer cases in the cohort ($N = 383$)

Characteristic	Prostate cancer cases
Clinical TNM tumor stage, number (%)	
T1c (N0/x, M0/x)	228 (59.5)
T2a (N0/x, M0/x)	67 (17.5)
T2b/c (N0/x, M0/x)	68 (17.8)
T3a (N0/x, M0/x)	5 (1.3)
T3b (N0/x, M0/x)	3 (0.8)
N1	0 (0.0)
M1	8 (2.1)
Gleason score, number (%)	
≤G3+3	214 (55.9)
G3+4	85 (22.2)
G4+3	38 (9.7)
≥G4+4	48 (12.3)
Serum PSA level (ng/mL)	
≤10.0	273 (71.3)
10.1–20.0	56 (14.6)
>20.0	54 (14.1)
NCCN risk strata	
Very low/low	150 (39.2)
Intermediate	142 (37.1)
High/very high	91 (23.8)
Tumor type	
Prostate adenocarcinoma	383 (100)

Abbreviation: NCCN, 2007 NCCN Prostate Cancer Guidelines.

>1,000 mg/day), and 5-ARI use (see Table 4). There were borderline associations found between 25-OH D < 12 ng/mL and Gleason grade ≥ 4+3 ($P = 0.10$, data not shown).

We then tested for an association with Gleason grade on biopsy using a four-level ordinal variable (i.e., Gleason ≤ 3+3, Gleason 3+4, Gleason 4+3, and Gleason ≥ 4+4). We noted increased odds of higher Gleason grade with 25-OH D < 12 ng/mL on ordinal logistic regression ($P = 0.02$). The best-fit model in EA men controlled for season, prebiopsy PSA level, age, prostate cancer family history, 5-ARI use, marital status, current smoking and alcohol use, and high school completion.

Next, we used a binary logistic regression model for clinical stage ≤ T2a versus ≥ stage T2b and found that 25-OH D < 12 ng/mL (OR, 2.42, 95% CI, 1.14–5.10; $P = 0.008$) was associated with higher odds of clinical stage ≥ T2b disease among men with cancer. This model controlled for age, PSA, season, education, 5-ARI use, tobacco use, and obesity.

Then, we evaluated the association of vitamin D with the NCCN prostate cancer risk categories using ordinal (data not shown) and binary logistic regression models (Table 4). Four NCCN risk categories were used: very low risk/low risk, intermediate risk, high risk, and ≥ very high risk for an ordinal variable with these four levels. On ordinal logistic regression, we noted increased odds of high and very high NCCN risk category with 25-OH D < 12 ng/mL ($P = 0.025$).

The best-fit binary logistic regression model for ≥ intermediate versus low NCCN risk category in EA (see Table 4) controlled for age, season, greater than 34% positive biopsy cores (25), and 5-ARI use. We found a statistically significant multiplicative interaction between vitamin D < 12 ng/mL and alcohol consumption (ever/never, $P = 0.03$). The interaction graph of vitamin D deficiency, alcohol use

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Table 4. Regressions for the association of prostate cancer and serum 25-OH D levels in EAs

Biopsy status: prostate cancer[a] ($n = 168$) vs. negative ($n = 107$) OR (95% CI)	**Stage: $\geq$ T2b ($n = 32$) vs. $\leq$ T2a ($n = 136$) OR (95% CI)**	**Gleason: $\geq$ 3+4 ($n = 73$) vs. $\leq$ 3+3 ($n = 92$) OR (95% CI)**	**Gleason: $\geq$ 4+4 ($n = 25$) vs. < 4+4 ($n = 140$) OR (95% CI)**	**NCCN risk: $\geq$ intermediate ($n = 104$) vs. low ($n = 61$) OR (95% CI)**
Serum 25-OH D < 20 ng/mL	**Serum 25-OH D < 12 ng/mL**	Serum 25-OH D < 12 ng/mL	**Serum 25-OH D < 12 ng/mL**	**Serum 25-OH D < 12 ng/mL**
1.34 (0.90–2.00)	**2.42 (1.14–5.10)[b]**	1.54 (0.72–3.31)	**3.66 (1.41–9.50)[b]**	**X ever drink[c]**
Season (high UV/low UV)	Season (high UV/low UV)	Season (high UV/low UV)	Season (high UV/low UV)	Season (high UV/low UV)
1.04 (0.71–1.51)	0.97 (0.53–1.76)	1.43 (0.85–2.41)	0.84 (0.36–1.95)	0.82 (0.46–1.46)
Age	Age > 70	Age > 70	Age > 70	Age > 70 y/o
1.04 (1.01–1.07)[c]	1.33 (0.58–3.05)	1.69 (0.86–3.32)	1.56 (0.53–4.54)	0.86 (0.38–1.96)
Serum PSA 1.03 (1.01–1.05)[c]	Serum PSA	**Serum PSA1.06 (1.03–1.09)[b]**	Serum PSA	High % positive cores[d]
	1.00 (0.99–1.00)		1.00 (1.00–1.00)	0.66 (0.36–1.22)
Family history	—	Family history	High Ca^{2+} intake	—
2.26 (1.41–3.63)[b]		1.01 (0.57–1.79)	2.23 (0.88–5.64)	
Former smoker	Ever smoke	Ever smoke	Current smoking	—
0.64 (0.38–1.08)	1.18 (0.65–2.16)	0.83 (0.49–1.39)	1.06 (0.35–3.19)	
—	Obesity	—	Obesity	—
	0.81 (0.40–1.61)		1.51 (0.60–3.79)	
5-ARI use	5-ARI use	**5-ARI use**	5-ARI use	5-ARI use
0.29 (0.14–0.59)[b]	0.88 (0.27–2.85)	**0.09 (0.02–0.47)[b]**	0.75 (0.16–3.52)	1.30 (0.36–2.81)

NOTE: Bold print is used for covariates that have reached statistical significance with $P < 0.05$.

[a]Low risk refers to the NCCN low and very low risk strata, i.e., serum PSA < 10 ng/mL, clinical tumor stage $\leq$ cT2a, and biopsy Gleason score $\leq$ 3+3.

[b]$P < 0.01$.

[c]$P < 0.05$

[d]High percent positive refers to having greater than or equal to 34% of the biopsy cores that were obtained containing prostate adenocarcinoma.

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history, and NCCN risk category suggests that people with current or former alcohol use and vitamin D < 12 ng/mL have significantly lower odds of higher-risk prostate cancer relative to nondrinkers with vitamin D < 12 ng/mL alone (graph not shown). Heavy drinking was not significant in this model.

In EA men, we also evaluated 5-ARI use as part of the vitamin D analysis. Finasteride/dutasteride use was significantly negatively associated with prostate cancer diagnosis on biopsy and higher Gleason grade on biopsy among patients with cancer (see Table 4). Gleason grade 8 to 10 tumors ($P = 0.55$) and clinical stage $\geq$ T2b ($P = 0.74$) are not associated with 5-ARI use on logistic regression analyses (data not shown). Of note, there was no evidence of a significant interaction between vitamin D deficiency and 5-ARI use in EA men (data not shown, $P > 0.20$).

Ultimately, we reported the models using 25-OH D < 12 ng/mL to define deficiency in the association of deficiency from our sensitivity analysis of different cut points and prostate cancer diagnosis based on −2 log likelihood scores to define best-fit regression models to predict cancer diagnosis in EA men.

AA analyses

In AA men, we found increased odds of prostate cancer diagnosis on prostate biopsy (Table 3) with vitamin D < 20 ng/mL (OR, 2.43, 95% CI, 1.20–4.94; $P = 0.01$) on binary logistic regression. In this model, we controlled for age, PSA, prostate cancer family history, season, current cigarette use, alcohol use, and 5-ARI use. Skin color, reported sun exposure, and measured UV exposure are not associated with prostate cancer diagnosis.

Using binary logistic regression we observed an association between 25-OH D < 12 ng/mL and both Gleason $\geq$ 4+3 (OR, 4.20, 95% CI, 1.51–11.69; $P = 0.006$) and Gleason $\geq$ 4+4 (OR, 4.89, 95% CI, 1.59–15.07; $P = 0.006$). These models adjusted for season, age, PSA, marital status, tobacco use, and 5-ARI use (data not shown).

Our ordinal regression analyses revealed that 25-OH D < 12 ng/mL is positively associated with increased odds of higher Gleason grade disease (Gleason $\leq$ 3+3, Gleason 3+4, Gleason 4+3, and Gleason $\geq$ 4+4; $P = 0.002$) when controlling for age, PSA, high school completion, season, 5-ARI use, and current tobacco use.

Our binary logistic regression model for clinical stage $\leq$ T2a versus $\geq$ T2b shows that 25-OH D < 12 ng/mL (OR, 4.22, 95% CI, 1.52–11.74; $P = 0.003$) was associated with increased odds of higher clinical stage disease among men with cancer. This model similarly controlled for age, PSA, season, alcohol use, tobacco use, and percentage of positive cores on biopsy and 5-ARI use.

Using ordinal logistic regression, 25-OH D < 12 ng/mL was noted to be associated with higher clinical TNM (tumor–node–metastasis) stage (T1, T2a, T2b/c, T3, T4; $P = 0.02$) when controlling for age, PSA, high school completion, season, marital status, 5-ARI use, alcohol use, and current tobacco use.

Again, we evaluated the association of vitamin D with the NCCN risk stratification in the prostate cancer treatment guidelines in AA men. We also noted increased odds of higher NCCN risk strata (low, intermediate, high, and $\geq$ very high) with vitamin D < 12 ng/mL on ordinal logistic regression ($P = 0.002$). The best-fit models in AA men controlled for season, age, prostate cancer family history, 5-ARI use, smoking and alcohol use, and education. Similar to the models in EA men, binary logistic regression of vitamin D and low-risk category versus $\geq$ intermediate-risk category showed that vitamin D significantly interacted with alcohol use (see Table 5; $P = 0.02$) after controlling for age, season, percentage of positive biopsy cores, and 5-ARI use.

Binary logistic regression analyses showed that use of finasteride or dutasteride was associated with lower odds of prostate cancer diagnosis (see Table 5; OR, 0.08, 95% CI, 0.02–0.41; $P = 0.004$) in AA men. We also evaluated 5-ARI use in the analyses of Gleason grade, tumor stage, and NCCN risk category. Binary logistic regression analyses revealed that 5-ARI use was not significantly associated with Gleason grade, tumor stage, or overall NCCN risk category among AAs (all $P > 0.25$). There was no evidence for an interaction with vitamin D deficiency seen on logistic regressions or on ordinal regressions for Gleason grade, clinical tumor stage, or NCCN risk strata (all $P > 0.20$).

In AA men, we reported the models using 25-OH D < 20 ng/mL to define deficiency in the association of prostate cancer diagnosis from our sensitivity analysis of different cut points. However, in evaluating the other biopsy outcomes, we used 25-OH D < 12 ng/mL based on −2 log likelihood scores from the best-fit regression models to predict biopsy outcomes in AA and EA men.

Discussion

Our report is the first to describe the association of vitamin D deficiency and outcomes of prostate biopsies in high-risk men with an abnormal PSA and/or an abnormal DRE. First, we show that vitamin D deficiency (25-OH D < 20 ng/mL) was prevalent (41.2% of all men) in Chicago area men (Table 1). Moreover, vitamin D < 12 ng/mL, which represents severe vitamin D deficiency, is relatively common in Chicago comprising 15.7% of the sample. We also show that severe vitamin D deficiency is associated with increased odds of prostate cancer diagnosis among AA men undergoing initial prostate biopsy. We also show that 25-OH D < 12 ng/mL is positively associated with higher Gleason grade (Gleason $\geq$ 4+4), higher clinical stage (tumor stage $\geq$ cT2b), and overall NCCN risk category in both EA and AA men. These are novel findings and corroborate the animal and *in vitro* data suggesting a role for vitamin D in prostate cancer. We fail to show an association between vitamin D deficiency and prostate cancer diagnosis in EA men.

Given the lack of association with prostate cancer in EA men, it may be a poor biomarker in the general U.S. population. It is likely that vitamin D is potentially a better biomarker for advanced disease because it is associated with higher grade and stage in both EA and AA men. Several studies have linked vitamin D deficiency to aggressive

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Table 5. Regressions for the association of prostate cancer and serum 25-OH D levels in AAs

Biopsy status: prostate cancer ($n = 168$) vs. negative ($n = 105$) OR (95% CI)	**Stage: ≥ T2b ($n = 47$) vs. ≤ T2a ($n = 118$) OR (95% CI)**	**Gleason: ≥ 3+4 ($n = 73$) vs. ≤ 3+3 ($n = 92$) OR (95% CI)**	**Gleason: ≥ 4+4 ($n = 25$) vs. < 4+4 ($n = 140$) OR (95% CI)**	**NCCN risk: ≥ intermediate ($n = 65$) vs. low ($n = 100$) OR (95% CI)**
Serum 25-OH D < 20 ng/mL 2.43 (1.20–4.94)[a]	**Serum 25-OH D < 12 ng/mL 4.22 (1.52–11.74)[b]**	**Serum 25-OH D < 12 ng/mL 3.61 (1.17–11.12)[a]**	**Serum 25-OH D < 12 ng/mL 4.89 (1.59–15.07)[b]**	**Serum 25-OH D < 12 ng/mL X ever drink[a]**
Season (high UV/low UV) 1.22 (0.62–2.39)	Season (high UV/low UV) 1.41 (0.50–3.96)	Season (high UV/low UV) 1.72 (0.61–4.83)	Season (high UV/low UV) 1.13 (0.37–3.45)	Season (high UV/low UV) 1.36 (0.57–3.22)
Age 1.06 (1.01–1.11)[a]	Age > 70 0.38 (0.08–1.92)	Age > 70 2.26 (0.64–8.03)	Age 1.06 (0.99–1.14)	Age > 70 0.63 (0.19–2.09)
Serum PSA 1.04 (1.01–1.08)[a]	Serum PSA 1.00 (0.99–1.00)	Serum PSA 0.96 (0.91–1.01)	**Serum PSA 2.14 (1.28–3.58)[b]**	—
Family history 4.04 (1.68–9.71)[b]	High %positive cores 2.42 (0.91–6.44)	Family history 1.45 (0.52–4.04)	Family history 2.36 (0.71–7.83)	—
Current smoking 1.35 (0.61–2.98)	—	Ever smoke 0.69 (0.25–1.90)	Ever smoke 0.64 (0.18–2.19)	—
>2 drinks/day 0.49 (0.19–1.28)	>2 drinks/day 0.19 (0.02–1.82)	**High % positive cores[c] 2.97 (1.08–8.17)[a]**	Married (yes) 0.46 (0.13–1.59)	**High %positive cores[c] 2.90 (1.22–6.91)[a]**
5-ARI use 0.08 (0.02–0.41)[b]	5-ARI use 0.38 (0.03–5.17)	5-ARI use 0.36 (0.02–5.56)	5-ARI use 3.15 (0.42–23.41)	5-ARI use 0.67 (0.06–7.95)

NOTE: Covariates in bold print have reached statistical significance with $P < 0.05$.

[a]$P < 0.05$.

[b]$P < 0.01$.

[c]High percent positive refers to having greater than or equal to 34% of the biopsy cores that were obtained containing prostate adenocarcinoma.

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prostate cancer (26–30). Interestingly, in epidemiologic studies, low serum vitamin D has been linked to higher prostate cancer incidence, but inconsistently (24, 30–35). The inconsistency may be due to the fact that early lifetime vitamin D deficiency likely affects cancer risk in later life (36) and a prediagnostic vitamin D level may not be correlated with early-life vitamin D deficiency (5). In this study, serum vitamin D is being drawn on the day of the biopsy. We are using this measure as a proxy for early lifetime vitamin D deficiency or chronic deficiency in EA and AA men. We, and other investigators, have shown that the biggest determinant of serum 25-OH D level in Chicago for EA men was sun exposure (12, 37) and for AA men the major determinant was skin color. Sun exposure due to recreational activity may decline with aging, whereas skin color is relatively stable. Therefore, prebiopsy vitamin D deficiency is not necessarily strongly correlated with chronic deficiency in EA men, but should be more correlated in AA men. Of note, skin melanin content and reported and measured UV radiation exposure were not significant predictors of cancer status in our race-stratified analyses.

Studies that evaluate vitamin D status near cancer diagnosis may make it hard to detect the association with cancer and early vitamin D deficiency, especially in men of European ancestry. However, tumor progression would be affected by recent vitamin D deficiency, which may explain the consistent association with aggressive disease. Also men of European ancestry are less likely to be deficient relative to AA men, especially in their youth (13, 38, 39). Adding more difficulty, there is evidence of a U-shaped risk curve in which both high and low levels of vitamin D can increase prostate cancer risk (26). Sunlight exposure is the major source of vitamin D for most men and usually declines in older age (40, 41), but UV exposure varies dramatically in the world and the United States. The largest positive epidemiologic study took place in Finland, a low-UV environment, where the association was found (26). The correlation between prediagnostic vitamin D status and early vitamin D exposure would be stronger for AA men because a major vitamin D determinant is melanin skin content (i.e., skin color). Furthermore, AA men would rarely have high levels of vitamin D, which may make associations between cancer status and vitamin D deficiency easier to detect (12, 38).

The inconsistency in the associations between vitamin D status and prostate cancer in epidemiologic case–control studies is likely multifactorial. Most studies failed to account for skin color, sun exposure across study sites, season, and supplemental and dietary vitamin D intake (27). Another issue is that cases and controls could have unmeasured differences that could confound the relationship between vitamin D and prostate cancer diagnosis, which is lessened in this study because men with an elevated PSA or an abnormal DRE are likely to be similar compared with cases and controls.

Another source of inconsistent associations may be due to the study sites of UV exposure. Differences in UV exposure across study sites may lessen the likelihood of detecting associations between vitamin D and prostate cancer diagnosis. Few studies have been conducted in poor UV environments with prevalent severe deficiency. Some authors suggested that both high and low vitamin D levels could increase prostate cancer risk (26, 42, 43) and that high levels were associated with higher Gleason grade tumors (26, 33, 44, 45). This study suggests that severe serum 25-OH D deficiency is associated with higher Gleason scores, higher clinical stage and, subsequently, higher NCCN risk strata among AA and EA men among those with cancer in the study. We evaluated vitamin D using tertiles, quartiles, and quintiles, but never demonstrate higher odds of prostate cancer at higher levels of vitamin D. This is somewhat complicated by the fact that few EA men have levels that would be consider elevated, as the highest level in our sample was 71 ng/mL (normal 25-OH D, 20–80 ng/mL). Among AA men, the highest serum 25-OH D level was only 45 ng/mL, making an evaluation of the effect of higher 25-OH D levels difficult. The low UV exposure in Chicago may partially explain the higher prostate cancer incidence in the city. It may also allow us to better detect the effect of lower vitamin D levels relative to normal levels on odds of cancer diagnosis and higher-risk disease.

If normal serum 25-OH D is between 30 to 80 ng/mL (46), then no one in our sample had elevated serum levels of 25-OH D. This essentially allows for a simpler comparison between those with deficiency and those with normal levels. Indeed, many prior U.S. studies were conducted across multiple sites in varied UV conditions and some sites have been in sunnier climates, which could limit the number of men with severe and chronic deficiency. Of note, the prior Finnish studies used $\leq$15 ng/mL as the deficiency cut point and the prior clinical cut points were <20 and <30 ng/mL. These cut points only provided borderline statistical associations in our sample in EA men, but in AA men 25-OH D $\leq$ 15 ng/mL does reach clinical significance in most of our analyses (data not shown). In fact, 25-OH D < 20 ng/mL reached statistical significance for AA men for prostate cancer diagnosis. In view of the prior studies, our data suggest that severe vitamin D deficiency (<12 ng/mL) is associated with higher prostate cancer grade and stage. Epidemiologic studies that accrued non–AA patients in higher UV climates would have difficulty finding this degree of deficiency and may fail to find an association.

It is likely that genetic polymorphisms in vitamin D pathway genes, such as the *Vitamin D Receptor*, moderate the effect of vitamin D deficiency on tumor differentiation, proliferation, and progression. In EA men, the inconsistent associations in epidemiologic studies may be due to the varied frequencies of vitamin D–related polymorphisms. This would further complicate the fact that vitamin D deficiency is likely more occasional and nonsustained among men of European ancestry (11, 47–50). Among men of African ancestry, the higher likelihood of sustained, chronic vitamin D deficiency should strengthen the associations found in epidemiologic studies.

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There is a plethora of *in vitro*, animal, and clinical data suggesting potential mechanisms for the role of vitamin D in prostate differentiation and tumor progression (51–56). Low expression of the vitamin D receptor in prostate tumors has been linked to prostate cancer aggressiveness and mortality (51).

Beer and colleagues led a randomized controlled trial with a vitamin D analogue, which demonstrated a positive association with survival (52). In further support, a recent trial showed that men on active surveillance given 4,000 IU of vitamin D3 had significantly higher frequency of negative biopsies at 1 year relative to placebo (57). If vitamin D is involved in prostate cancer initiation or progression, it would provide a modifiable risk factor for primary prevention and secondary prevention to limit progression, especially in the highest risk group of AA men. Vitamin D analogues could be useful agents to use in men on active surveillance to delay treatment. Therefore, there is a critical need for large epidemiologic studies that investigate the biologic and environmental mediators of serum vitamin D and prostate cancer progression that includes men of African ancestry.

Limitations

The primary limitation of the study is the cross-sectional design. There is always a concern for residual confounding like serum testosterone levels. However, the men seem comparable on most of the known covariates and are different in terms of expected risk factors like PSA level and prostate cancer family history. We also acknowledge that a one-time serum measurement may not be representative of chronic vitamin D deficiency, which likely would be needed to predispose a man to prostate cancer. Nevertheless, for the majority of men who do not move between geographic regions, the stable UV exposure in Chicago may be a proxy for lifetime vitamin D exposure and reported sun exposure did not improve our models. Moreover, skin color is a major predictor of vitamin D deficiency in AA men and because this is likely to be relatively stable over time, the one-time serum measurement of deficiency is likely more correlated with chronic deficiency in AA men than in EAs (14, 16). Finally, prostate cancer initiation and aggressiveness are multifactorial, and our observational design allowed us to identify associations, not causality.

Conclusion

AA men had higher rates of vitamin D deficiency than EA men and deficiency is common across racial groups in Chicago. In AA men, vitamin D deficiency was associated with increased odds of prostate cancer in men undergoing biopsy. In both EA and AA men, severe deficiency was associated with higher Gleason grade disease, higher tumor stage, and higher risk of prostate cancer recurrence according to NCCN criteria. The use of vitamin D deficiency as a biomarker of advanced disease should be further evaluated.

Disclosure of Potential Conflicts of Interest

W.J. Catalona is a consultant/advisory board member for Beckman Coulter and has received commercial research support from Beckman Coulter, DeCode Genetics, and Ohmx. No potential conflicts of interest were disclosed by the other authors.

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