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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 abnormal PSA and/or digital rectal examination.

Experimental Design—Serum 25-hydroxyvitamin D (25-OH D) was obtained from 667 men, age 40-79, 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 (PCa), 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 ≥ 4+4 (OR = 3.66 [1.41, 9.50], p = 0.008) and tumor stage (stage ≥ cT2b vs. ≤ cT2a, OR = 2.42 [1.14, 5.10], p = 0.008). In African American (AA) men, we find increased odds of PCa 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 < 12ng/ml and Gleason ≥ 4+4 (OR = 4.89 [1.59, 15.07]; p = 0.006). There was an association with tumor stage ≥ cT2b vs. ≤ cT2a (OR: 4.22, [1.52 – 11.74], p = 0.003).

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The authors declare that there are no conflicts of interest.

Conclusions—In AA men, vitamin D deficiency was associated with increased odds of PCa diagnosis on biopsy. In both EA and AA men, severe deficiency was positively associated with higher Gleason grade and tumor stage.

Keywords

Vitamin D; Health Disparities; Environmental carcinogenesis/toxicology; Tumor promotion and progression; aggressive prostate cancer

Introduction

In the United States (US), prostate cancer (PCa) 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 PCa 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 UVB radiation levels correlated inversely with numerous cancers in Black Americans, including breast, colon, rectum, stomach, and esophagus (5). A recent study by Taskler et al demonstrated a negative association between prostate cancer incidence with ultraviolet radiation exposure in the US (6). For this reason, it has been hypothesized that vitamin D deficiency could play a role in the pathogenesis of PCa. 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 ultraviolet (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 and Hispanic counterparts (12, 13) in part due to lower skin synthesis from the 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 European Americans and AAs, including PCa (18)

Men undergoing prostate biopsy for elevated PSA or abnormal 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. 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 (19).

Methods

Subject Recruitment

Between February 2009 and February 2013, we enrolled 667 ambulatory men, age 40-79 years, from 5 urology clinics in Chicago, Illinois (3 academic, 1 public and 1 Veteran's

Administration) that were undergoing their first prostate biopsy for an elevated or abnormal serum prostate specific antigen (PSA) level or an abnormal digital rectal exam (DRE). The men were enrolled on the date of their biopsies and had their serum 25-hydroxyvitamin D (25-OH D) level drawn on the date of recruitment. We included only ambulatory, non-hospitalized 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 T tests for continuous variables and chi-square tests for categorical traits. There were small numbers of Hispanics, Asians and were excluded. We stratified the analyses by EA and AA race, since AA men have higher rates of positive biopsy (20), higher Gleason grade and stage at presentation (21), 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 non-cancer diagnosis, we created a best-fit unconditional binary logistic regression, using −2 log likelihood scores, with the dependent variable coded as case vs. non-cancer 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 (22). 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 <12ng/ml, <16ng/ml, < 20ng/ml and < 30ng/ml), and race-specific quartiles and tertiles. We present our stratified analyses as AA-race only and EA-race only since race likely confounds the relationship between vitamin D and PCa 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 ≥ 4+3 vs. Gleason < 4+3 and Gleason ≥ 4+4 vs. Gleason < 4+4.

We then employed binary regressions to evaluate associations between vitamin D deficiency and clinical tumor stage; specifically, we dichotomized clinical tumor stage as ≤ T2a versus ≥ T2b (23).

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 ≤ 3+3, Gleason 3+4, Gleason 4+3, Gleason ≥ 4+4).

Finally, we assessed for an association using ordinal logistic regression models between the 2007 National Comprehensive Cancer Network (NCCN) risk categories (based on pre-diagnosis PSA levels, tumor stage and Gleason grade) and vitamin D status using ordinal logistic regression (low risk, intermediate risk, high risk and ≥ very high risk). The NCCN risk guidelines for PCa are a clinical tool used for PCa 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-alpha reductase inhibitor (5-ARI) use on the biopsy outcomes.

This study was powered at 80% to detect an odds ratio of 1.6 for vitamin D deficiency PCa diagnosis using binary logistic regression modeling with a two-sided alpha 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., California).

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 vs. 56.5cm^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 < 20n/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). 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 (16.7ng/ml) relative to AA negative biopsies (19.3ng/ml, p = 0.04). The highest serum vitamin D level in EA men was 71ng/ml and was 45ng/ml for AA men.

Table 3 shows the distribution of the clinical features of the PCa cases. There was a reasonable distribution of high and low stage and grade disease with 55.9% having Gleason scores of ≤ 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 ≥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 ≥ intermediate risk category.

European American Analyses

In EA men, we found no associations between vitamin D status and PCa 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 < 20ng/ml (p= 0.16, Table 4A). Skin color, reported sun exposure and measured UV exposure were not associated with PCa diagnosis.

We used a binary logistic regression model for Gleason grade ≥ 3+4 and found that 25-OH D < 12ng/ml was not associated with ≥ 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 ≥ 3+4 (OR = 0.09, p = 0.005).

We used a binary logistic regression model for Gleason grade ≥ 4+4 and found that 25-OH D < 12ng/ml (OR: 3.66, 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 > 30kg/m^2), high calcium intake (i.e. > 1000mg/day) and 5-ARI use (see Table 4A). There were borderline associations found between 25-OH D < 12ng/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 4-level ordinal variable, (i.e. Gleason ≤ 3+3, Gleason 3+4, Gleason 4+3, Gleason ≥ 4+4). We note increased odds of higher Gleason grade with 25-OH D < 12ng/ml on ordinal logistic regression (p = 0.02). The best-fit model in EA men controlled for season, pre-biopsy PSA level, age, PCa 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 < 12ng/ml (OR: 2.42, 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 PCa risk categories using ordinal (data not shown) and binary logistic regression models (Table 4A). Four NCCN risk categories where 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 note increased odds of high and very high NCCN risk category with 25-OH D < 12ng/ml (p = 0.025).

The best-fit binary logistic regression model for ≥ intermediate vs. low NCCN risk category in EA (see Table 4A) controlled for age, season, greater than 34% positive biopsy cores (see CAPRA model), and 5-ARI use. We found a statistically significant multiplicative interaction between vitamin D < 12ng/ml and alcohol consumption (ever/never, p = 0.03). The interaction graph of vitamin D deficiency, alcohol use history and NCCN risk category suggests that people with current or former alcohol use and vitamin D < 12ng/ml have significantly lower odds of higher risk PCa relative to non-drinkers with vitamin D < 12ng/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 PCa diagnosis on biopsy and higher Gleason grade on biopsy among cancer patients (see Table 4A). Gleason grade 8-10 tumors (p = 0.55) and clinical stage ≥ 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 5ARI use in EA men (data not shown, p > 0.20).

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

African American Analyses

In AA men, we found increased odds of PCa diagnosis on prostate biopsy (Table 3) with vitamin D < 20ng/ml (OR = 2.43, CI: 1.20 - 4.94, p = 0.01) on binary logistic regression. In this model, we controlled for age, PSA, PCa 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 PCa diagnosis.

Using binary logistic regression we observed an association between 25-OH D < 12ng/ml and both Gleason ≥ 4+3 (OR = 4.20,CI: 1.51 -11.69; p = 0.006) and Gleason ≥ 4+4 (OR = 4.89, CI: 1.59 -15.07; p = 0.006). These models adjusted for season, age, PSA, marital status, tobacco use, and 5 alpha-reductase inhibitor use (data not shown).

Our ordinal regression analyses revealed that 25-OH D < 12ng/ml is positively associated with increased odds of higher Gleason grade disease (Gleason ≤ 3+3, Gleason 3+4, Gleason 4+3, Gleason ≥ 4+4; p = 0.002) when controlling for age, PSA, high school completion, season, 5 alpha-reductase inhibitor use, and current tobacco use.

Our binary logistic regression model for clinical stage ≤ T2a versus ≥ T2b show that 25-OH D < 12ng/ml (OR: 4.22, 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 < 12ng/ml was noted to be associated with higher clinical TNM tumor stage (T1, T2a, T2b/c, T3, T4, p = 0.02) when controlling for age, PSA, high school completion, season, marital status, 5 alpha-reductase inhibitor use, alcohol use and current tobacco use.

Again, we evaluated the association of vitamin D with the NCCN risk stratification in the PCa treatment guidelines in AA men. We also note increased odds of higher NCCN risk strata (low, intermediate, high, ≥ very high) with vitamin D < 12ng/ml on ordinal logistic regression (p = 0.002). The best-fit models in AA men controlled for season, age, PCa 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 ≥ intermediate risk category showed that vitamin D significantly interacted with alcohol use (see Table 4B, p = 0.02) after controlling for age, season, percentage of positive biopsy cores, and 5-ARI use.

Binary logistic regression analyses showed use of finasteride or dutasteride was associated with lower odds of prostate cancer diagnosis (see table 4B, OR = 0.08, 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 < 20ng/ml to define deficiency in the association of PCa diagnosis from our sensitivity analysis of different cut points. However, in evaluating the other biopsy outcomes we use 25-OH D < 12ng/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 abnormal PSA and/or abnormal digital rectal exam. First we show that vitamin D deficiency (25-OH D < 20ng/ml) was prevalent (41.2% of all men) in Chicago area men (Table 1). Moreover, vitamin D < 12ng/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 < 12ng/ml is positively associated with higher Gleason grade (Gleason ≥ 4+4), higher clinical stage (tumor stage ≥ 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 European American men.

Given the lack of association with PCa in EA men, it may be a poor biomarker in the general US population. It is likely that vitamin D is potentially a better biomarker for advanced disease since it is associated with higher grade and stage in both EA and AA men. Several studies have linked vitamin D deficiency to aggressive prostate cancer (24-28). Interestingly, in epidemiologic studies, low serum vitamin D has been linked to higher prostate cancer (PCa) incidence, but inconsistently (24, 28-33). The inconsistency may be due to the fact that early lifetime vitamin D deficiency likely affects cancer risk in later life (34) and a pre-diagnostic 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, 35) 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, pre-biopsy 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 ultraviolet 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 impacted 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, 36, 37). Adding more difficulty, there is evidence of a U shaped risk curve where both high and

low levels of vitamin D can increase prostate cancer risk (24). Sunlight exposure is the major source of vitamin D for most men and usually declines in older age (38, 39), but UV exposure varies dramatically in the world and the US. The largest positive epidemiologic study took place in Finland, a low UV environment, where the association was found (24). The correlation between pre-diagnostic vitamin D status and early vitamin D exposure would be stronger for AA men since 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, 36).

The inconsistency in the associations between vitamin D status and PCa 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 (25). 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 since men with elevated PSA or abnormal DRE are likely to be similar compared to cases and controls.

Another source of inconsistent associations may be due to the study sites UV exposure. 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 PCa risk (24, 40, 41) and that high levels were associated with higher Gleason grade tumors (24, 31, 42, 43). This study suggests that severe serum 25-hydroxyvitamin 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 71ng/ml (normal 25-OH D 20-80ng/ml). Among AA men, the highest serum 25-hydroxyvitamin D level was only 45ng/ml, making an evaluation of the effect of higher 25-OH D levels difficult. The low ultraviolet exposure in Chicago may partially explain the higher PCa 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 – 80ng/ml (44), then no one in our sample had elevated serum levels of 25-hydroxyvitamin D. This essentially allows for a simpler comparison between those with deficiency and those with normal levels. Indeed, many prior US 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 ≤ 15ng/ml as the deficiency cut point and the prior clinical cut points were < 20ng/ml and < 30ng/ml. These cut points only provided borderline statistical associations in our sample in EA men, but in AA men 25-OH D ≤ 15ng/ml does reach clinical significance in most of our analyses (data not shown). In fact, 25-OH D < 20ng/ml reached statistical significance for AA men for PCa diagnosis. In view of the prior studies, our data suggests that severe vitamin D deficiency (<12ng/ml) is associated with higher PCa 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 non-sustained among men of European ancestry (11, 45-48). Among men of African ancestry, the higher likelihood of sustained, chronic vitamin D deficiency should strengthen the associations found in epidemiologic studies.

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 (49-54). Low expression of the vitamin D receptor in prostate tumors has been linked to PCa aggressiveness and mortality (49).

Beer et al led a randomized controlled trial with a vitamin D analogue, which demonstrated a positive association with survival (50). In further support, a recent trial showed that men on active surveillance given 4000IU of vitamin D3 had significantly higher frequency of negative biopsies at one year relative to placebo (55). If vitamin D is involved in PCa 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 biological 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 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 PCa 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 PCa. 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 since 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 European Americans (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.

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Statement of 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.

Table 1

Demographic and clinical characteristics of patients with prostate cancer (PCa) and the negative biopsies

	PCa Cases (N = 383)	Negative Biopsies (N = 284)	
Continuous variables	**Median (SD)**	**Median (SD)**	**p-value[1]**
Age, years	62.0 (6.9)	61.0 (7.58)	**0.03**
Body-mass index, kg/m2	27.7 (5.0)	27.0 (4.8)	0.49
Serum PSA[3]	6.4 (654.0)	5.6 (12.0)	0.22
25-OH D serum level, ng/ml[4]	21.0 (10.0)	22.0 (11.0)	0.09
Vitamin D intake (IU)[5]	270.5 (3005.7)	232.7 (3263.3)	0.97
Calcium Intake (mg)	551.5 (2663.1)	619.5 (506.2)	0.35
Measured sun exposure	6.6 (8.0)	7.0 (7.2)	0.21
Education years post-high school	1.6	1.6	1.00
Prostate volume (cm^3)	42.9	56.5	**<0.001**

Categorical variables	**%**	**%**	**p-value[2]**
1st degree PCa fam. history	25.8	14.9	**0.001**
Abnormal DRE[6]	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 < 30ng/ml	78.1	75.2	0.43
25-OH D < 20ng/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 ≥ 30)	28.6	27.3	0.71
Tobacco-use	56.6	54.2	0.54

[1] Unpaired, two-sample t-test

[2] Chi-square analysis

[3] PSA = serum prostate specific antigen level (5-alpha reductase inhibitor-adjusted PSA value was calculated by doubling pre-biopsy PSA value)

[4] 25-OH D = serum 25 hydroxyvitamin D level drawn on date of enrollment

[5] IU International Units

[6] DRE = digital rectal examination.

Table 2

Serum 25-OH D Level Stratified By Season, Race/Ethnicity, Age, and Obesity

	PCa cases Mean (SD)	Negative Biopsies Mean (SD)	p-value[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	25.6 (12.0)	0.92
Age, years			
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

UV: Ultraviolet radiation

BMI: Body Mass Index.

[a]Unpaired, two-sample t-test

Table 3

Characteristics of prostate cancer cases in the cohort (N = 383)

Characteristic	PCa Cases
Clinical TNM Tumor Stage	**No. (%)**
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, No. (%)	
≤ 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)

TNM = Tumor, Node, Metastasis Staging System

NCCN = 2007 **National Comprehensive Cancer Network PCa Guidelines**

Table 4A

Regressions for the Association of Prostate Cancer and Serum 25-OH D Levels in European Americans

Biopsy Status: PCa[a] (n = 168) vs. Negative (n = 107)	**Stage: ≥ T2b (n = 32) vs. ≤ T2a (n = 136)**	**Gleason: ≥ 3+4 (n = 73) vs. ≤ 3+3 (n = 92)**	**Gleason: ≥ 4+4 (n = 25) vs. ≤ 4+4 (n = 140)**	**NCCN Risk: ≥ Intermediate (n = 104) vs. Low (n = 61)**
OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Serum 25-OH D < 20ng/ml 1.34 (0.90, 2.00)	**Serum 25-OH D < 12ng/ml 2.42 (1.14, 5.10)[c]**	Serum 25-OH D < 12ng/ml 1.54 (0.72, 3.31)	**Serum 25-OH D < 12ng/ml 3.66 (1.41, 9.50)[c]**	**Serum 25-OH D < 12ng/ml X Ever Drink[b]**
Season (high UV/low UV) 1.04 (0.71, 1.51)	Season (high UV/low UV) 0.97 (0.53, 1.76)	Season (high UV/low UV) 1.43 (0.85, 2.41)	Season (high UV/low UV) 0.84 (0.36, 1.95)	Season (high UV/low UV) 0.82 (0.46, 1.46)
Age 1.04 (1.01, 1.07)[b]	Age > 70 1.33 (0.58, 3.05)	Age > 70 1.69 (0.86, 3.32)	Age > 70 1.56 (0.53, 4.54)	Age > 70y/o 0.86 (0.38, 1.96)
Serum PSA 1.03 (1.01, 1.05)[b]	Serum PSA 1.00 (0.99, 1.00)	**Serum PSA 1.06 (1.03, 1.09)[c]**	Serum PSA 1.00 (1.00, 1.00)	High %Positive Cores[d] 0.66 (0.36, 1.22)
Family History 2.26 (1.41, 3.63)[c]	-	Family History 1.01 (0.57, 1.79)	High Ca^{2+} Intake 2.23 (0.88, 5.64)	-
Former Smoker 0.64 (0.38, 1.08)	Ever Smoke 1.18 (0.65, 2.16)	Ever Smoke 0.83 (0.49, 1.39)	Current Smoking 1.06 (0.35, 3.19)	-
-	Obesity 0.81 (0.40, 1.61)	-	Obesity 1.51 (0.60, 3.79)	-
5-ARI Use 0.29 (0.14, 0.59)[c]	5-ARI Use 0.88 (0.27, 2.85)	**5-ARI Use 0.09 (0.02, 0.47)[c]**	5-ARI Use 0.75 (0.16, 3.52)	5-ARI Use 1.30 (0.36, 2.81)

[a] Low risk refers to the National Comprehensive Cancer Network low and very low risk strata in the 2010 guidelines (PSA ≤ 10ng/ml, ≤T2a, ≤ Gleason 3+3)

[b] $P < 0.05$

[c] $P < 0.01$

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

Table 4B

Regressions for the Association of Prostate Cancer and Serum 25-OH D Levels in African Americans

Biopsy Status: PCa[a] (n = 168) vs Negative (n = 105)	**Stage: ≥ T2b (n = 47) vs. ≤ T2a (n = 118)**	**Gleason: ≥ 3+4 (n = 73) vs. ≤ 3+3 (n = 92)**	**Gleason: ≥ 4+4 (n = 25) vs. < 4+4 (n = 140)**	**NCCN Risk: ≥ Intermediate (n = 65) vs. Low (n = 100)**
OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Serum 25-OH D < 20ng/ml 2.43 (1.20, 4.94)[b]	**Serum 25-OH D < 12ng/ml 4.22 (1.52, 11.74)[c]**	**Serum 25-OH D < 12ng/ml 3.61 (1.17, 11.12)[b]**	**Serum 25-OH D < 12ng/ml 4.89 (1.59, 15.07)[c]**	**Serum 25-OH D < 12ng/ml X Ever Drink[b]**
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)[b]	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)[b]	Serum PSA 1.00 (0.99, 1.00)	Serum PSA 0.96 (0.91, 1.01)	**Serum PSA 2.14 (1.28, 3.58)[c]**	-
Family History 4.04 (1.68, 9.71)[c]	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)	-
>2drinks/day 0.49 (0.19, 1.28)	>2drinks/day 0.19 (0.02, 1.82)	**High %Positive Cores[d] 2.97 (1.08, 8.17)[b]**	Married (Yes) 0.46 (0.13, 1.59)	**High % Positive Cores[d] 2.90 (1.22, 6.91)[b]**
5-ARI Use 0.08 (0.02, 0.41)[c]	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)

[a] PCa = Prostate Cancer

[b] P < 0.05

[c] P < 0.01

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