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ORIGINAL REPORT

Associations Between Serum Vitamin D and Adverse Pathology in Men Undergoing Radical Prostatectomy

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A B S T R A C T

Purpose

Lower serum vitamin D levels have been associated with an increased risk of aggressive prostate cancer. Among men with localized prostate cancer, especially with low- or intermediate-risk disease, vitamin D may serve as an important biomarker of disease aggression. The aim of this study was to assess the relationship between adverse pathology at the time of radical prostatectomy and serum 25-hydroxyvitamin D (25-OH D) levels.

Methods

This cross-sectional study was carried out from 2009 to 2014, nested within a large epidemiologic study of 1,760 healthy controls and men undergoing prostate cancer screening. In total, 190 men underwent radical prostatectomy in the cohort. Adverse pathology was defined as the presence of primary Gleason 4 or any Gleason 5 disease, or extraprostatic extension. Descriptive and multivariate analyses were performed to assess the relationship between 25-OH D and adverse pathology at the time of prostatectomy.

Results

Eighty-seven men (45.8%) in this cohort demonstrated adverse pathology at radical prostatectomy. The median age in the cohort was 64.0 years (interquartile range, 59.0 to 67.0). On univariate analysis, men with adverse pathology at radical prostatectomy demonstrated lower median serum 25-OH D (22.7 *v* 27.0 ng/mL, $P = .007$) compared with their counterparts. On multivariate analysis, controlling for age, serum prostate specific antigen, and abnormal digital rectal examination, serum 25-OH D less than 30 ng/mL was associated with increased odds of adverse pathology (odds ratio, 2.64; 95% CI, 1.25 to 5.59; $P = .01$).

Conclusion

Insufficiency/deficiency of serum 25-OH D is associated with increased odds of adverse pathology in men with localized disease undergoing radical prostatectomy. Serum 25-OH D may serve as a useful biomarker in prostate cancer aggressiveness, which deserves continued study.

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INTRODUCTION

Recent population-based studies suggest that there is a relationship between vitamin D deficiency and increased prostate cancer (PCa) risk.[1] In addition, there is literature that demonstrates that vitamin D deficiency is also associated with aggressive PCa.[2,3] Interestingly, the prevalence of vitamin D deficiency in a cohort of men in Chicago, Illinois—a low UV exposure location—was 41.2%, and the prevalence of deficiency was significantly higher among black men.[4] The relationship between vitamin D and PCa may explain some disparities seen in PCa, especially among black men.

The majority of men diagnosed with PCa in the United States present with PCa localized to the prostate gland. The current treatment paradigm is shifting to managing these men with a surveillance protocol. Active surveillance as a management strategy of low-risk PCa—defined by the criteria of Epstein et al[5] and D'Amico et al[6]—is an evolving strategy that relies on risk stratification and diagnostic testing. It is unclear whether there are high-risk populations, such as black men, who would benefit from additional screening tests before management with a surveillance protocol. However, useful clinical risk factors have been extrapolated from pathologic findings from radical prostatectomy specimens.[7,8] For example, a review

of the radical prostatectomy database at Johns Hopkins Hospital demonstrated that black men with very low-risk PCa were more likely to have adverse pathology at prostatectomy compared with men of European descent.[9]

There is limited literature on the relationship between vitamin D and pathologic findings at the time of radical prostatectomy.[10] The aim of this study was to determine whether serum 25-hydroxyvitamin D (25-OH D) correlates with adverse pathology at radical prostatectomy among a diverse population of men from a large, urban population.

METHODS

This cross-sectional, observational study evaluating the associations of serum 25-OH D status with adverse pathology in men undergoing radical prostatectomy was carried out from 2009 to 2014. It was nested within a large epidemiologic study of 1,760 healthy controls and men undergoing PCa screening that evaluated environmental and biologic mediators of vitamin D and PCa risk. A total of 812 men between the ages of 40 and 79 years underwent prostate core biopsy for increasing prostate specific antigen (PSA) levels and/or an abnormal finding on digital rectal examination. All participants were prospectively enrolled through outpatient urology clinics from three academic (Northwestern University, University of Chicago, University of Illinois at Chicago) and two public (Jesse Brown VA Medical Center and Cook County Hospital) institutions in Chicago, Illinois.

One hundred ninety men were included in our study after undergoing radical prostatectomy for diagnosis of clinically localized PCa within 1 year of their positive prostate biopsy. Genitourinary pathologists reviewed all pathologic specimens. Men with a diagnosis of PCa were excluded from analysis if they received adjuvant therapy prior to radical prostatectomy or if they underwent treatment at a nonstudy institution. All study participants provided written consent, and the institutional review board at each participating institution approved the protocol.

Clinical and Environmental Data

Trained research coordinators collected all patient data via patient questionnaires and independent chart review. 25-OH D was collected by a peripheral serum sample at the time of enrollment by a trained research coordinator or clinic phlebotomists. Serum 25-OH D levels were measured using the DiaSorin Liaison 25-OH Vitamin D TOTAL Assay platform (DiaSorin, Stillwater, MN) by a direct, competitive chemiluminescent immunoassay. Relevant clinical covariates included age, first-degree family history of PCa, and tobacco use. Indicators of socioeconomic status were collected through a combination of a questionnaire and medical record review. Information on ethnicity and race was collected by self-identification and was characterized as black, white, or other. In addition, body mass index (BMI) was calculated from the measurement of standing height (in meters) and weight (in kilograms) of all participants at enrollment.

Cancer-specific clinical data, including biopsy result (ie, Gleason score, number of positive cores, and percentage of core involvement), clinical stage (tumor, node, metastasis classification), and PSA were recorded, and men in the cohort were classified according to the National Comprehensive Cancer Network (NCCN) risk classification groups.[11] Patients were then evaluated on the basis of the presence or absence of adverse pathologic features at the time of radical prostatectomy. Adverse pathology was defined by the presence of dominant Gleason pattern 4, the presence of any pattern 5, and pathologic stage $\geq$ pT3aN0M0.[12] All analyses were stratified by ethnicity/race and NCCN risk classification.

Statistical Analysis

Descriptive statistics were used to characterize important covariates, including age, serum 25-OH D level, serum PSA level, race, BMI, tobacco use, income, first-degree PCa family history, marital status, education, and 5 alpha-reductase inhibitor (5-ARI) use among men with and without adverse pathology at radical prostatectomy. 5-ARI–adjusted PSA values were calculated by doubling the prebiopsy PSA value.[13] A sample size of 190 patients—assuming a 1:1 case-control ratio—in a population with a prevalence of adverse pathology of 35% had a power of 87.7% to detect an OR of 2.5 or greater.

Continuous covariates were compared using a Wilcoxon rank sum test, and categorical variables were compared using a χ^2 test. Multivariate analysis was conducted using binary logistic regression to further evaluate the association of 25-OH D with adverse pathology. All multivariate analyses were adjusted for season of blood draw (ie, high *v* low ultraviolet exposure), race, and NCCN risk category. Covariates were added to the model in an additive fashion, and covariates were kept in the model if $P < .10$. All statistical tests were two-sided, with significance defined at .05. Additional regressions were conducted, stratified by NCCN category to assess trends within risk groups. Statistical analyses were conducted with Stata 12.1 (StataCorp, College Station, TX)

RESULTS

Overall, 45.8% (87) of the men in this cohort demonstrated adverse pathology at radical prostatectomy. The median age of men with adverse pathology was 65.0 years (interquartile range [IQR], 60.0 to 69.0 years), and the median age was 62.0 years (IQR, 60.0 to 69.0 years) for the men without adverse pathology ($P = .005$). Similarly, men with adverse pathology demonstrated a statistically significant higher median BMI (28.9 kg/m^2 *v* 27.7 kg/m^2; $P = .04$) and serum PSA (6.8 ng/mL *v* 4.4 ng/mL; $P < .001$). In addition, men with adverse pathology at radical prostatectomy demonstrated lower median serum 25-OH D (22.7 ng/mL; IQR, 15.9 to 29.0) compared with their counterparts (27.0 ng/mL; IQR, 20.0 to 34.0; $P = .007$). Men with adverse pathology were also more likely to have a serum 25-OH D level less than 30 ng/mL (80.5% *v*. 57.3%; $P = .001$) and were more likely to self-identify as black ($P = .03$). All other covariates did not demonstrate any significant differences on analysis (Table 1).

Pretreatment patient characteristics are listed in Table 2. Overall, 34.7% (66) of the men in this cohort met NCCN very low- or low-risk criteria; 68.4% (130) of the men presented with cT1c disease, 41.1% (78) had a Gleason score of 3 + 3 PCa, and 83.2% (158) had a PSA level of less than 10 ng/mL. At the time of prostatectomy, 31.6% of the men demonstrated extraprostatic disease (pT3), with 10.0% having seminal vesicle invasion on final pathology (Table 3).

On multiple logistic regression, a serum 25-OH D level of less than 30 ng/mL (odds ratio [OR], 2.51; 95% CI, 1.18 to 5.33; $P = .02$) was associated with adverse pathology in a model controlling for age, serum PSA, and abnormal findings on digital rectal examination (Table 4). 25-OH D as a continuous variable did not have a significant association with adverse pathology for all men in the model. On stratified analysis, serum 25-OH D level (OR, 0.92; 95% CI, 0.86-0.98; $P = .01$) and serum 25-OH D less than 30 ng/mL (OR, 3.62; 95% CI, 1.15 to 11.46; $P = .03$) were significantly associated with adverse pathology in men with NCCN intermediate PCa at diagnosis. There were no significant contributions to the models with race or season of blood draw added. Additionally, no significant associations were observed on multivariate analyses stratified by race/ethnicity with vitamin D.

Table 1. Demographic and Clinical Characteristics of Patients After Radical Prostatectomy

Characteristic	Adverse Pathology (n = 87)	Nonadverse Pathology (n = 103)	*P*
Continuous, median (IQR)			
Age, years	65.0 (60.0-69.0)	62.0 (58.0-66.0)	.005*
Body mass index, kg/m^2†	28.9 (26.2-32.0)	27.7 (25.0-29.8)	.04*
Serum PSA	6.8 (5.0-11.8)	4.5 (3.8-6.0)	< .001*
25-OH D serum level, ng/mL	22.7 (15.9-29.0)	27.0 (20.0-34.0)	.007*
Categorical, %			
First-degree family history of PCa (n = 184)	24.1	14.9	.57
Abnormal findings on DRE (n = 189)	44.2	18.5	< .001*
Race/ethnicity			
Black (n = 45)	32.2	16.5	
White (n = 128)	56.3	76.7	
Other (n = 17)	11.5	6.7	.03*
High school diploma or equivalent	96.6	99.0	.24
25-OH D level, ng/mL			
< 30	80.5	57.3	.001*
< 20	33.3	23.3	.12
< 12	16.1	7.8	.07
Vitamin D supplement use	16.1	22.3	.28
Married	75.9	76.7	.89
Obesity (n = 188)‡	36.8	24.8	.07
Tobacco use, current	35.6	43.7	.26
5-ARI use (n = 187)	2.4	3.9	.54

NOTE. *P* values for continuous variables were derived from Wilcoxon rank-sum testing. *P* values for categorical variables were derived from χ^2 analysis.
Abbreviations: 5-ARI, 5 alpha reductase inhibitor; 25-OH D, serum 25 hydroxyvitamin D; DRE, digital rectal examination; PCa, prostate cancer; PSA, prostate specific antigen.
*Denotes statistic significance.
†BMI information was missing for one patient in this cohort.
‡Obesity was defined as a BMI ≥ 30 ng/mL.

DISCUSSION

Serum 25-OH D was consistently associated with adverse pathology on univariate and multivariate analysis in our cohort. Men with adverse pathology had a 15.9% lower serum 25-OH D level than did their counterparts. A 25-OH D level less than 30 ng/mL was associated with increased odds of adverse pathology, even after controlling for well-known preoperative risk factors of adverse pathology, such as PSA level and disease palpable on digital rectal examination.[6] This relationship seemed to be most pronounced among men with intermediate risk disease on stratified analysis; however, there was a nonsignificant association observed in men with low and low NCCN risk disease preoperatively.

Table 2. Pretreatment Characteristics of Patients in the Cohort (N = 190)

Characteristic	No. (%)
Clinical TNM stage, N0/x, M0/x	
cT1c	130 (68.4)
cT2a	32 (16.8)
cT2b	5 (2.6)
cT2c	23 (12.1)
Gleason score at initial biopsy	
G3 + 3	78 (41.1)
G3 + 4	52 (27.3)
G4 + 3	28 (14.7)
≥ G4 + 4	32 (16.8)
Serum PSA level (ng/mL)	
≤ 10.0	158 (83.2)
10.1-20.0	24 (12.6)
> 20.0	8 (4.2)
NCCN risk criteria	
Very low	21 (11.1)
Low	45 (23.7)
Intermediate	85 (44.7)
High	39 (20.5)

Abbreviations: NCCN, National Comprehensive Cancer Network; PSA, prostate specific antigen; TNM, tumor, node, metastasis staging system.

There is sparse literature on the association of circulating serum 25-OH D and adverse pathology at the time of radical prostatectomy. To our knowledge, there is only one other study evaluating this relationship. Berg et al[10] reviewed 100 consecutive men undergoing radical prostatectomy and did not find any correlation between Gleason score, pathologic staging, or positive margin status and vitamin D on multiple logistic regressions. The study, however, is limited by a small sample size. Given our sample size, we had 87% power to detect an OR greater than 2.5 for 25-OH D levels less than 30 ng/mL and the presence of adverse pathology at radical prostatectomy, assuming a 35% rate of adverse pathology.[12] The Berg et al[10] study would have been underpowered to assess for this association, especially in adjusted analyses.

The correlation between vitamin D and PCa is being evaluated among men in a variety of basic science and translation research endeavors. Studies have demonstrated that PCa cells express the vitamin D receptor, which acts as a substrate in the activation and deactivation of many important cellular pathways.[14-16] Specifically, vitamin D has been found to have an inhibitory effect on cellular proliferation,[17,18] differentiation,[17-20] and apoptosis.[21-23]

We have previously demonstrated an association of an increased overall risk of PCa in blacks and aggressive/high-risk disease both whites and blacks at the time of prostate biopsy among men with low vitamin D levels.[3] Kristal et al[1] demonstrated a U-shaped

Table 3. Surgical Pathologic Characteristics

Characteristic	No. (%)
Pathologic TNM stage (N = 190)	
pT2a	22 (11.6)
pT2b	4 (2.1)
pT2c	104 (54.7)
pT3a	41 (21.6)
pT3b	19 (10.0)
pNx	3 (1.6)
pN0	88 (46.6)
pN1	0 (0.0)
Pathologic Gleason score (N = 190)	
G3 + 3	48 (25.4)
G3 + 4	75 (39.7)
G4 + 3	43 (22.8)
≥ G4 + 4	41 (21.7)
Unknown	1 (0.01)
Adverse pathology by NCCN criteria (n = 87)	
Very low/low risk	11 (12.7)
Intermediate risk	43 (49.4)
High risk	33 (37.9)

Abbreviations: NCCN, National Comprehensive Cancer Network; TNM, tumor, node, metastasis staging system.

relationship between vitamin D and PCa risk on the basis of prospective, multi-institutional data collected in the Selenium and Vitamin E Cancer Prevention Trial. Similarly, Schenck et al[2] showed an increased risk of aggressive PCa among men with low vitamin D. Additionally, Steck et al[24] showed that low 25-OH D levels were associated with aggressive PCa among black men in the North Carolina-Louisiana Prostate Cancer Project, and this relationship was modified negatively by low calcium intake. However, there are a couple of methodological differences—such as timing of blood draw, which was several months after PCa diagnosis in their cohort, and different risk strata definitions—that may explain disparities in some of the results from our respective cohorts. Nonetheless, our findings at the time of radical prostatectomy are consistent with the observations from these studies because vitamin D deficiency was associated with more aggressive disease findings at the time of radical prostatectomy in men with localized PCa. Unfortunately, Chicago, Illinois, is an ultraviolet-poor location, and elevated levels of vitamin D did not occur in this cohort.

The initial assessment of our Chicago cohort demonstrated a significant disparity regarding low vitamin D levels and black race compared with white men in both univariate and multivariate analyses. In fact, greater than 90% of black men in that study had vitamin D levels less than 30 ng/mL.[4] Interestingly, black men show a higher likelihood of progression and mortality on active surveillance for PCa.[25] Data from the Johns Hopkins Hospital group suggest that failure on surveillance for black men may result from adverse pathologic features, as demonstrated in low-risk black men at the time of radical prostatectomy.[9] Unfortunately, we could not verify any relationship between low serum vitamin D levels and adverse pathology on race-stratified univariate or multivariate analysis. Wes feel these analyses were significantly limited by a lack of power due to the relatively small size of each subgroup analyzed.

In addition, studies show a decrease in PSA velocity in men with advanced PCa receiving supplementation with calcitriol and closely related vitamin D analogs.[27,28] The relationship between serum 25-OH D and PSA levels may be due to the effect of vitamin D on PCa cell proliferation and differentiation. Our findings showed that the largest association of low serum vitamin D was among men with intermediate NCCN risk disease at diagnosis. On the basis of the aforementioned data, this group may benefit most from normalization of their vitamin D levels with regard to their disease. Future studies should evaluate the effect of vitamin D levels and supplementation on PCa pathologic aggressiveness with regard to NCCN risk stratification, especially for men being considered for active surveillance, because vitamin D levels may be a useful biomarker in this population.

In a clinical setting, men with insufficient or deficient levels of 25-OH D at the time of PCa diagnosis may benefit from supplementation, with a goal of increasing serum 25-OH D levels to a range of 30 to 55 ng/mL. This could be achieved by assessing the serum vitamin D level at PCa diagnosis in all men with clinically localized disease prior to supplementation. An open-label trial of 4,000 IU of oral vitamin D3 in men undergoing active surveillance for favorable risk PCa demonstrated a 55% decrease in the number of positive biopsies or Gleason grade at 1 year, with no adverse events among men in the study.[26] However, we note that our recommendation needs to be substantiated with a large, randomized trial that would evaluate the impact of long-term vitamin D supplementation in men diagnosed with localized PCa.

The limitations of this study include its cross-sectional study design, which can lead to selection, observer, and analytical biases. The authors recognized these limitations as part of nested, retrospective analyses and adjusted for them by including all relevant

Table 4. Regressions for the Association of Adverse Pathology and Serum 25-OH D Less Than 30 ng/mL

	Adverse Pathology: All Men * (n = 189) OR (95% CI)	Adverse Pathology: NCCN Very Low/Low Risk (n = 65) OR (95% CI)	Adverse Pathology: NCCN Intermediate Risk (n = 85) OR (95% CI)	Adverse Pathology: NCCN High Risk (n = 39) OR (95% CI)
Serum 25-OH D < 30 ng/mL	2.64 (1.25 to 5.59)*	2.83 (0.54 to 14.89)	3.63 (1.15 to 11.46)*	5.73 (0.82 to 40.03)
Age	1.08 (1.02 to 1.15)†	1.03 (0.92 to 1.15)	1.08 (0.99 to 1.20)	1.02 (0.81 to 1.29)
Serum PSA level	1.23 (1.11 to 1.37)†	0.93 (0.67 to 1.30)	1.26 (1.08 to 1.46)†	1.16 (0.86 to 1.55)
Suspicious DRE	4.09 (1.91 to 8.75)†	1.88 (0.28 to 12.51)	3.14 (1.06 to 9.26)§	—‡

Abbreviations: DRE, digital rectal examination; NCCN, National Comprehensive Cancer Network; 25-OH D, 25-hydroxyvitamin D; OR, odds ratio; PSA prostate specific antigen.
*One patient was removed from analysis for incomplete data for multivariate analysis.
†$P < .01$.
‡Abnormal DRE perfectly predicted adverse pathology in men with NCCN high-risk disease.
§$P < .05$.

confounders. In addition, the sample size of the cohort diminished the power of many of the stratified analyses. A one-time measurement of serum 25-OH D has some limits as a proxy for overall vitamin D status in patients. In addition, adjustment for season of blood draw, which could confound associations with vitamin D levels, did not change our results. Lastly, men treated with radical prostatectomy at large, tertiary medical institutions may have limited generalizability to men treated in other settings. Nonetheless, our findings present new data that corroborate recent associations between PCa aggressiveness and low vitamin D levels demonstrated in a diverse population of men from a cohort in a large urban city.

In conclusion, insufficiency/deficiency of 25-OH D is associated with increased odds of adverse pathology in men with localized disease undergoing radical prostatectomy. Men with intermediate risk disease demonstrated the largest association between serum vitamin D levels and adverse pathologic findings at prostatectomy. Vitamin D could serve as an important biomarker of adverse pathology in men with PCa, and the associations between PCa aggressiveness and vitamin D deserve continued exploration.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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