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Does an Inverse Correlation Exist between Vitamin D as Measured by 25-hydroxyvitamin D and PSA in Veterans with Prostate Cancer

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Abstract

Objective: Several observational and epidemiological studies have suggested that the incidence of prostate cancer seems to be lower in relation to ultraviolet light exposure and distance from the equator, which has led to theories that vitamin D may play a role in the prevention of cancer. This study seeks to determine if a correlation exists between vitamin D levels in the serum as measured by 25-hydroxyvitamin D and serum PSA in male veterans with prostate cancer.

Methods: Veterans with prostate cancer seen in the urology or oncology clinic at the Southeast Louisiana Veterans Affairs Healthcare system were identified using ICD 9 codes. After informed consent, serum 25-hydroxyvitamin D levels and PSA were drawn. 119 patients were enrolled on the study from 1/16/13 to 11/15/13. Demographic data such as age, ethnicity, cancer stage, use of vitamin D supplements, gleason score, and treatment were examined. Pearson's correlation analysis was performed.

Results: 91 patients self-identified as African American (61 of these had low 25-hydroxyvitamin D values and 30 had normal values), 27 self-identified as White, (15 low 25-hydroxyvitamin D, 12 normal), and one self-identified as other who had 25-hydroxyvitamin D in the normal range. The mean age of the veteran population was 66.27 years, and 38.66% (46) of them have undergone prostatectomy. There were 24 patients (20.17%) taking vitamin D supplements at the time of study. We conducted correlation analysis on both whole sample and multiple subgroups. We found the correlation coefficient for vitamin D and PSA in the subgroup of veterans with high PSAs and no prostatectomy was -0.38 (p=0.133).

Conclusion: There was no significant correlation between 25-hydroxyvitamin D and PSA in veterans with prostate cancer. There was a trend for correlation in the subgroup of veterans with high PSAs who did not undergo prostatectomy.

Keyword: Prostate; Vitamin D; 25-hydroxyvitamin D; Veterans; Chemotherapy

Introduction

Prostate cancer is the most common non skin cancer malignancy diagnosed in males in the United States, with an estimated 217,730 new cases in 2010. Major risk factors for the development of prostate cancer are age and family history. Ethnicity and geographic location also play a role. The highest incidence in the world is in African American men, who have a 9.8% lifetime risk of developing prostate cancer. In addition, risk increases at age 50 in White males but begins at age 40 in African American males. Worldwide, the risk of prostate cancer is higher in Scandinavian countries and lowest in Asia (22 vs. 5 per 100,000) [1]. Epidemiologic studies have suggested that sunlight exposure is linked to lower cancer risks [2]. The incidence of prostate cancer and other malignancies seem to be lower in relation to ultraviolet light exposure and distance from the equator, with the exception of the Jamaican population which has a higher incidence of prostate cancer but is located closer to the equator [1]. This observation has led to theories that vitamin D may be involved in the prevention of cancer. CF Garland was the first to publish an article in the Lancet in 1989 showing an inverse association between serum 25-hydroxyvitamin D and colorectal cancer [3].

Prostate cancer is the most common malignancy diagnosed at Southeast Louisiana Veterans Healthcare System, comprising 34% of all cancers. At SLVHCS, about 100 patients are diagnosed with prostate cancer each year. We designed this study to determine whether an inverse correlation exists between vitamin D as measured by serum 25-hydroxyvitamin D and PSA in male veterans with prostate cancer. Results from this study may lead to future interventions that aid in the prevention, treatment, or prognosis of veterans with prostate cancer.

Research Design and Methods

IRB and institutional approval were obtained per protocol. Patients with prostate cancer on their electronic medical record problem list were identified from appointment lists for oncology and urology clinics. All interested male patients at Southeast Louisiana Veterans Affairs Healthcare system who were capable of providing informed consent with a diagnosis of prostate cancer were eligible. After informed consent, serum 25-hydroxyvitamin D and PSA levels were obtained and processed in the Southeast Louisiana Veterans Healthcare System lab. Patients were informed of their results via mail, and advised to follow up with their treating physicians if abnormal results were obtained.

Chart review was performed to account for factors that may have an effect on vitamin D or PSA levels. Medication list was reviewed to account for those receiving vitamin D or calcium supplements. We also reviewed self- identified ethnicity, past medical history, and treatment history for prostate cancer including surgery, radiation, hormonal therapy, bisphosphonates, and chemotherapy.

The distribution of demographic characteristics and medication

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history were summarized for both low serum 25-hydroxyvitamin D and normal serum 25-hydroxyvitamin D groups. A frequency table was constructed to show the proportion of treatment received and pathology characteristics for the whole sample. To assess the magnitude of the correlations between vitamin D and PSA levels, we calculated the Pearson correlation coefficient on multiple subsamples (i.e., those without prostatectomy, and PSA normal group). T-tests were then performed to test the statistical significance for each correlation. We also constructed scatter plots for each correlation test for graphical information.

Results

119 male veterans enrolled on this study from 1/16/2013 to 11/15/2013. Demographics and serum 25-hydroxyvitamin D levels are summarized in (Table 1). The mean age of all subjects was 66 years. 64% of the veterans had low levels of serum 25-hydroxyvitamin D. Most were not on vitamin D or multivitamin supplements at the time of study enrollment, and only 1 subject reported sunscreen use. Ninety-one veterans self- identified as African American, 27 self-identified as Caucasion, and 1 veteran self- identified as other. 50% had a Gleason score of </= 6. Most patients had localized disease, with 13 patients diagnosed with stage IV disease (Table 1).

Treatment and pathology characteristics are summarized in (Table 2). 60 patients (50 percent) had a gleason score of less than or equal to 6, consistent with gleason 6 being the most common form of prostate cancer. 29 patients had gleason 7 (moderately differentiated cancers), and 30 or 35% had gleason scores of 8-10 (high grade cancers).

46 patients underwent prostatectomy. Of the patients who had undergone prostatectomy as their primary treatment (N=46, 38%), 13 (28%) had a detectable PSA of >0.1 post operatively. 45 were treated with radiation for localized disease. 43 patients (36%) received a GnRH agonist as part of their treatment.

Total N= 119		**Low serum 25-OH D**	**Normal 25-OH D**
		(<32 ng/ml) N=	**(32-100 ng/ml) N=**
Age			
Mean and 95%CI	66.27 (64.82, 67.73)	66.61 (64.62, 68.59)	65.67 (63.62, 67.73)
Ethnicity			
African American	91	61	30
Caucasion	27	15	12
Hispanic	0	0	0
Asian	0	0	0
Other	1	0	1
Cancer stage			
I	9	6	3
IIA	21	13	8
IIB	25	18	7
III	9	6	3
IV	13	9	4
Vitamin D supplements			
Yes	24	15	9
No	95	61	34
Multivitamin with D			
Yes	3	2	1
No	116	74	42
Sunscreen prescribed			
Yes	1	1	0
No	118	75	43

Table 1: Demographics and serum serum 25-hydroxyvitamin D levels.

Total Gleason score		
8-10	30	(25.21%)
7	29	(24.37%)
</=6	60	(50.42%)
Prostatectomy		
Yes	46	(38.66%)
No	73	(61.34%)
Radiation		
Yes	45	(37.82%)
No	74	(62.18%)
GnRH agonist		
Yes	43	(36.13%)
No	76	(63.87%)
Anti-androgen		
Yes	31	(26.05%)
No	88	(73.95%)
Chemotherapy		
Yes	3	(2.52%)
No	116	(97.48%)
Bisphosphonate		
Yes	6	(5.04%)
No	113	(94.96%)
Ketoconazole/prednisone		
Yes	7	(5.88%)
No	112	(94.12%)
Abiaraterone/prednisone		
Yes	4	(3.36%)
No	115	(96.64%)
PSA >0.1 after prostatectomy		
Yes	13	(28.26%)
No	33	(71.74%)

Table 2: Treatment and pathology characteristics.

Thirteen patients on study had metastatic or stage IV disease. Of these, 3 patients received chemotherapy, 6 had bisphosphonates as part of their therapy, 4 were treated with abiatarone, and 7 had been treated with ketoconazole (Table 2).

Correlation analysis was conducted on whole sample and subgroups (Figures 1a-2b and Tables 3-8). For the whole sample, there was no significant correlation between serum 25-hydroxyvitamin D and PSA (Figure 1a and Table 3). There was also no correlation in the group which did not undergo prostatectomy group as a whole or those with PSA less than 4 (Figure 1b and 1c) or in those patients with low serum 25-hydroxyvitamin D (Figure 2a) or those patients with normal serum 25-hydroxyvitamin D (Figure 2b).

In the group of patients who did not undergo prostatectomy, there was a trend for correlation in the subgroup of veterans with high PSAs (N=16) with p=0.1330, as shown in (Figure 1d and Table 6).

Discussion

Although there has been interest in screening for vitamin D deficiency in the general population, there is no current recommendation for routine screening of cancer patients for vitamin D deficiency. We found low levels of serum 25-hydroxyvitamin D to be prevalent in our

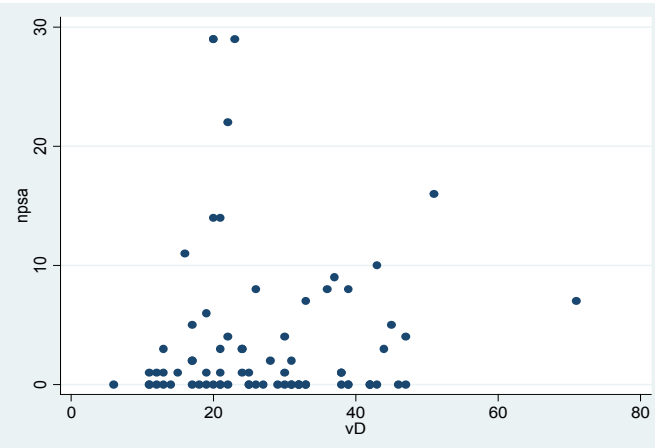

Figure 1a: Scatter plots between 25-hydroxyvitamin D and PSA, whole sample.

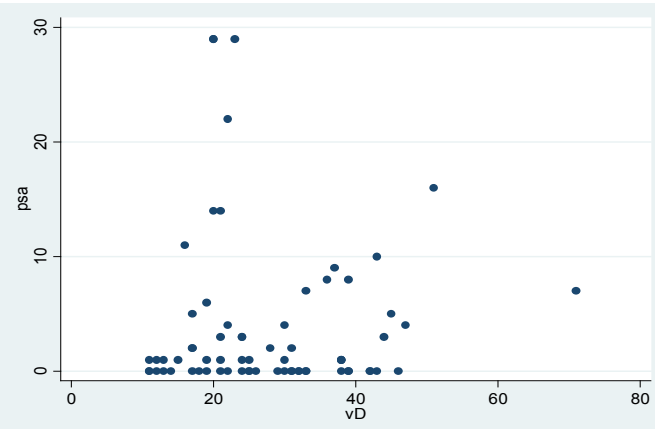

Figure 1b: Scatter plots between serum 25-hydroxyvitamin D and PSA, without prostatectomy.

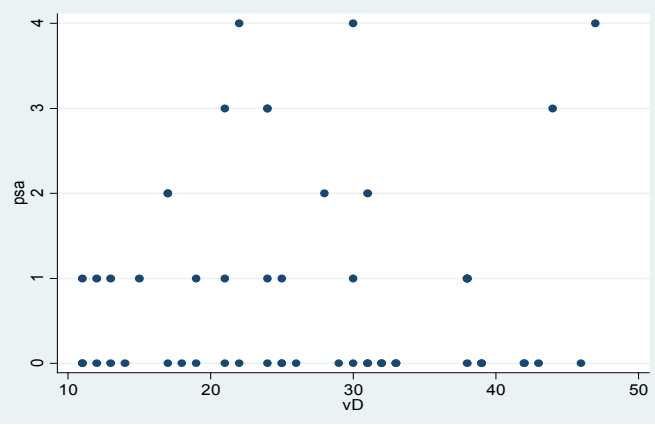

Figure 1c: Scatter plots between serum 25-hydroxyvitamin D and PSA, PSA normal group (PSA<=4) without prostatectomy.

study population. Most veterans diagnosed with prostate cancer are older males, with a mean of 66 years in our group. Because vitamin D is synthesized in the skin by exposure to ultraviolet light, the elderly or chronically ill may be vulnerable to developing vitamin D deficiency due to decreased mobility, less time spent outdoors, and limited exposure to sunlight.

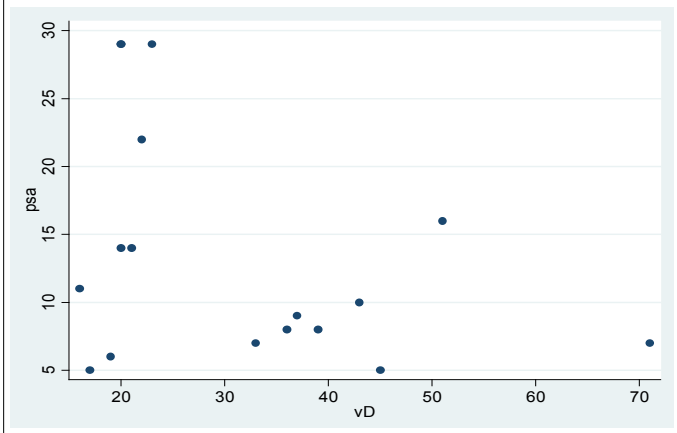

Figure 1d: Scatter plots between serum 25-hydroxyvitamin D and PSA, PSA high group (PSA>4) without prostatectomy.

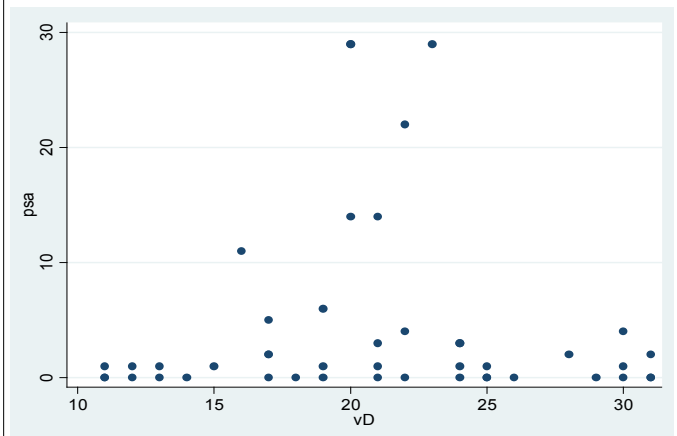

Figure 2a: Scatter plots between serum 25-hydroxyvitamin D and PSA, Low serum 25-hydroxyvitamin D (<32) group without prostatectomy.

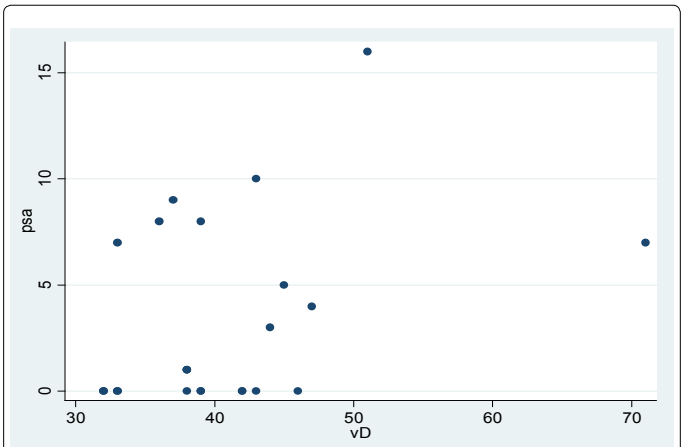

Figure 2b: Scatter plots between serum 25-hydroxyvitamin D and PSA, normal serum 25-hydroxyvitamin D (32-100) group without prostatectomy.

	PSA	25-OH D
PSA	1	
25-OH D	-0.002	1
p=0.9862		

Table 3: Correlation between serum 25-hydroxyvitamin D and PSA, whole sample.

	PSA	25-OH D
PSA	1	
25-OH D	0.0001	1
p=0.9994		

Table 4: Correlation between serum 25-hydroxyvitamin D and PSA, without prostatectomy.

	PSA	25-OH D
PSA	1	
25-OH D	0.0496	1
p=0.7272		

Table 5: Correlation between serum 25-hydroxyvitamin D and PSA,PSA normal group without prostatectomy.

	PSA	25-OH D
PSA	1	
25-OH D	-0.3795	1
p=0.1330		

Table 6: Correlation between serum 25-hydroxyvitamin D and PSA, PSA high group without prostatectomy N=16.

	PSA	25-OH D
PSA	1	
25-OH D	0.0001	1
p=0.9994		

Table 7: Correlation between serum 25-hydroxyvitamin D &PSA, low serum 25-hydroxyvitamin D (<32) group without prostatectomy.

	PSA	25-OH D
PSA	1	
25-OH D	0.3641	1
p=0.0803		

Table 8: Correlation between serum 25-hydroxyvitamin D and PSA, normal VD(32-100) group without prostatectomy.

The mechanism between vitamin D and cancer has not been clearly established. Some studies suggest that vitamin D may exert a role in the regulation of cell proliferation and differentiation as well as inhibit angiogenesis [4]. Several studies have focused on the risk for development of cancer and on the impact of vitamin D on mortality. A prospective cohort study of 257 patients with colorectal cancer showed that higher 25-hydroxyvitamin D levels were associated with better overall survival under multi-variate analysis (HR 0.91; 95% CI, 0.84-0.99, P= 0.027) [5]. Another study involving squamous cell carcinomas of the head and neck revealed that serum levels of serum 25-hydroxyvitamin D were significantly reduced in patients with these malignancies, and that disease free as well as overall survival were associated with serum 25-hydroxyvitamin D levels [6]. A large case control study of 7273 patients from the National Health and Nutrition Examination Surveys examined serum 25-hydroxyvitamin D levels in ovarian cancer patients compared to controls and found that patients with ovarian cancer were more than 3 times likely to have low levels (Odds ratio 3.68, 95% CI 1.03-13.21, p=0.04) [7].

A meta-analysis in 2009 reviewing 35 studies found an inverse relationship between serum 25- hydroxyvitamin D and colorectal cancer, but not in breast or prostate cancer. The authors did caution that levels were often drawn after patients were diagnosed with cancer, which could be a result of cancer causing low levels as opposed to low levels causing cancer [8]. The Third National Health and Nutrition Examination Survey reviewed 16,818 subjects from 1988 through 2000. Using Cox proportional hazard regression models, the authors found that total cancer mortality was unrelated to baseline vitamin D levels, although they did find an inverse relationship between serum 25-hydroxyvitamin D and colorectal cancer mortality with a 72% risk reduction in mortality [9]. Our study was observational only, and not designed to evaluate a relationship with mortality.

The general public has an avid interest in vitamin supplements and perceived natural therapies. Many patients believe vitamins are helpful, despite unproven efficacy. The Institute of Medicine recently reviewed recommendations for vitamin D supplementation. They concluded that vitamin D plays an important role in bone health and recommended increases in daily allowances to achieve a serum 25-hydroxyvitamin D level of at least 20 nanograms per milliliter. However, they concluded there was insufficient evidence to recommend supplementation to prevent cancer, cardiovascular disease, or autoimmune disorders [10,11]. We found that the majority of our patients were not taking multivitamin or vitamin D supplements at the time of study enrollment.

African Americans, who have an increased risk of prostate cancer, have also been found to have a higher prevalence of vitamin D deficiency. An analysis by Ashraf Zadshir et al. [12] reviewed data from the National Health and Nutrition Examination Survey (NHANES III) which evaluated serum levels of serum 25-hydroxyvitamin D among 15,390 adults from 1988-1994. They found that mean vitamin D levels were lower in minority populations with African Americans having the lowest levels followed by Hispanics with the second lowest levels compared to Whites [12]. We also found that the prevalence of low serum 25-hydroxyvitamin D was higher in the African American subjects at our facility.

Our study has several limitations, including small sample size, and a greater proportion of early stage disease. It is possible that the subset of patients with PSA >4 who did not undergo prostatectomy had more advanced disease at that time of diagnosis or comorbidities prohibiting surgery, and elected for a more conservative treatment approach.

Conclusion

There was no significant correlation between serum 25-hydroxyvitamin D and PSA in veterans with prostate cancer. There was a trend for correlation in the subgroup of veterans with high PSAs who did not undergo prostatectomy. Further studies with larger numbers of patients could explore this subgroup to identify a possible relationship.

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