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ORIGINAL PAPER

Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men

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Abstract
Objective Multiple studies have shown clear evidence of vitamin D's anti-tumor effects on prostate cancer cells in laboratory experiments, but the evidence has not been consistent in humans. We sought to examine the association between vitamin D and prostate cancer risk in a cohort of older men.
Methods We conducted a prospective case-cohort study nested within the multicenter Osteoporotic Fractures in Men (MrOS) study. Baseline serum 25-OH vitamin D was measured in a randomly selected sub-cohort of 1,433 men ≥65 years old without a history of prostate cancer and from all participants with an incident diagnosis of prostate cancer ($n = 297$). Cox proportional hazards models were used to evaluate the associations between quartiles of total 25-OH vitamin D and incident prostate cancer, as well as Gleason score.
Results In comparison with the lowest quartile of 25-OH vitamin D, the hazard ratio for the highest quartile of 25-OH vitamin D was 1.22 (CI 0.50–1.72, $p = 0.25$), no trend across quartiles ($p = 0.94$) or association with Gleason score was observed. Adjustment for covariates did not alter the results.
Conclusions In this prospective cohort of older men, we found no association between serum 25-OH vitamin D levels and subsequent risk of prostate cancer.

Keywords Vitamin D · Prostate cancer

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Introduction

Early epidemiologic studies have driven investigations of the hypothesis that vitamin D signaling plays a role in the physiology of cancers [1, 2]. Population studies have shown a fairly consistent link between low levels of vitamin D and increased risk of some malignancies, for example adenocarcinoma of the colon. While data from animal models and cell lines have shown an effect of vitamin D on prostate cancer biology [3–8], a direct association between vitamin D levels and prostate cancer risk in humans has not been consistently demonstrated [9–21], necessitating additional high-quality studies.

Our study adds analysis of older men to the growing body of reports on the relationship between serum vitamin D status and prostate cancer risk. Our study includes men 65 years old or above, who usually have a greater risk of prostate cancer compared to younger men. Also, our study includes a large number of participants from areas of the United States where vitamin D deficiency is common. With this population at high risk of both prostate cancer and vitamin D deficiency, our study aims to clarify this relationship between serum vitamin D status and prostate cancer risk. In addition, our study has a fair number of high-grade prostate cancers, allowing for analysis of the relationship between vitamin D status and prostate cancer aggressiveness.

Materials and methods

Subjects and design

We present analyses from a case-cohort study nested within a cohort of 5,995 men aged 65 and older who participated in the Osteoporotic Fractures in Men (MrOS) study [22]; a longitudinal study conducted at multiple centers in the United States (Birmingham, Alabama; Palo Alto, California; San Diego, California; Minneapolis, Minnesota; Portland, Oregon; Pittsburgh, Pennsylvania). The MrOS study was designed to evaluate risk factors for fractures in older men, with active follow-up for incident prostate cancer as a secondary endpoint. The participants were recruited from March 2000 through April 2002. Exclusion criteria were (1) inability to walk without assistance from another person, (2) bilateral hip replacements, (3) inability to provide self-reported data, (4) residence not near a study site, (5) judged by an investigator to have a medical condition that would result in imminent death, (6) or inability to understand and sign informed consent. Initial enrollment included completion of a self-administered questionnaire and a clinic visit with blood draw and anthropometric measurements. Physical activity was assessed using the Physical Activity Score for the Elderly (PASE) [23]. Details of the assessment have been previously described [24].

Data and laboratory measurements

Tri-annual follow-up questionnaires were sent to all participants in the study to ascertain incident prostate cancer. If a patient reported being diagnosed with prostate cancer, medical records were obtained and centrally adjudicated for stage and Gleason score of the cancer, treatment, serum PSA, pathology, and biopsy results. Men without prostate cancer were censored at death or withdrawal from the study.

Serum vitamin D was analyzed in a sample of 1,433 men with no history of prostate cancer at baseline. In this group, 82 cases of prostate cancer arose and the remaining 1,351 men were non-cases. At the end of a mean 5.3-year follow-up period, all additional 215 incident prostate cancer cases that had occurred outside of the random sample were identified and included in the serum vitamin D analyses. This case-cohort design allows for time-to-event analysis while making efficient use of resources [25].

Serum 25-OH vitamin D was measured in blood specimens that were obtained at baseline from both the cases and the non-cases. Archived serum specimens were stored at −70°C. Following incubation for 15 min with stable isotope 25-OHD3-d6 and precipitation with acetonitrile, the supernatant was injected onto Cohesive Turbo Flow Cyclone extraction columns followed by chromatography on a Supelco LC-18 column and analysis for 25-OH vitamin D by tandem mass spectrometry (Mayo Clinic Reference Laboratories, Dr. Ravinder Singh) [26]. Aliquots of a single serum pool were included in alternate assay runs. Using the pooled serum, the interassay coefficient of variation for 25-OH vitamin D was 4.4%, and the intraassay coefficient of variation was 4.9% [24].

Statistical analysis

Baseline characteristics for men with incident prostate cancer were compared to those with no prostate cancer diagnosis. Total 25-OH vitamin D was categorized into quartiles based on the distribution of 25-OH vitamin D in the randomly sampled sub-cohort. The decision to categorize into quartiles was made prior to the analyses, and quartile cut points coincided with clinical categories of deficiency (<20 ng/ml in the lowest quartile) and sufficiency (>30 ng/ml in the highest quartile). We also examined 15 ng/ml as an additional cut point for deficiency, as a dichotomous variable. Cox proportional hazards models were used to evaluate the association between

total 25-OH vitamin D and incident prostate cancer, with men in the lowest quartile of serum vitamin D considered as the reference group. To account for potential differences by disease severity, we also present analyses stratified by Gleason score. Consistent with clinical practice, a Gleason score of less than seven was considered less aggressive while a Gleason score of greater than or equal to seven was considered representative of more aggressive disease. In Cox proportional hazards models, Prentice weights were used to account for the case-cohort design [27]. Factors that differed between men with incident prostate cancer and those without, with a p-value < 0.10, were considered as potential confounders (including those in Table 1). Variables were maintained in the final hazard ratio models

Table 1 Comparison of baseline characteristics (n (%), mean ± SD, or median (IQR)) by incident prostate cancer, the MrOS study[a]

	No prostate cancer (non-cases) (n = 1,351)	Incident prostate cancer (n = 297)	Incident prostate cancer Gleason <7 (n = 141)	Incident prostate cancer Gleason ≥7 (n = 151)
Demographics				
Age	73.6 ± 5.9	72.5 ± 5.1	71.4 ± 4.3	73.4 ± 5.6
***p* for t test**		**0.001**	**<0.0001**	**0.65**
Race				
White, non-hispanic	1,217 (90.1)	269 (90.6)	131 (92.9)	133 (88.1)
African-American	42 (3.1)	13 (4.4)	4 (2.8)	9 (6.0)
Asian	37 (2.7)	7 (2.4)	3 (2.1)	4 (2.7)
Hispanic	38 (2.8)	5 (1.7)	1 (0.7)	4 (2.7)
Other	17 (1.3)	3 (1.0)	2 (1.4)	1 (0.7)
***p* for χ2**		**0.62**	**0.64**	**0.44**
Study site				
Birmingham	232 (17.2)	32 (10.8)	14 (9.9)	17 (11.3)
Minneapolis	200 (14.8)	69 (23.2)	41 (29.1)	27 (17.9)
Palo Alto	222 (16.4)	56 (18.9)	25 (17.7)	31 (20.5)
Pittsburgh	227 (16.8)	50 (16.8)	21 (14.9)	27 (17.9)
Portland	232 (17.2)	41 (13.8)	15 (10.6)	25 (16.6)
San Diego	238 (17.6)	49 (16.5)	25 (17.7)	24 (15.9)
***p* for χ2**		**0.002**	**0.0002**	**0.37**
Family history of prostate cancer				
First degree	142 (12.8)	50 (20.0)	32 (25.6)	17 (14.2)
***p* for χ2**		**0.003**	**<0.0001**	**0.67**
Lifestyle/diet				
Smoking—Never	498 (36.9)	126 (42.4)	62 (44.0)	63 (41.7)
Past	801 (59.3)	163 (54.9)	74 (52.5)	85 (56.3)
Current	52 (3.9)	8 (2.7)	5 (3.6)	3 (2.0)
***p* for χ2**		**0.16**	**0.25**	**0.31**
Physical activity score (PASE)	146.8 ± 69.3	157.5 ± 71.3	166.4 ± 77.0	150.8 ± 64.5
***p* for t test**		**0.02**	**0.002**	**0.47**
BMI (kg/m^2)	27.4 ± 3.7	27.2 ± 3.6	27.1 ± 3.5	27.4 ± 3.6
***p* for t test**		**0.60**	**0.39**	**0.94**
Medication use				
Statins	351 (32.3)	88 (37.6)	39 (35.8)	46 (38.3)
***p* for χ2**		**0.12**	**0.46**	**0.18**
NSAIDS	106 (9.8)	19 (8.1)	13 (11.9)	6 (5.0)
***p* for χ2**		**0.44**	**0.47**	**0.10**
Vitamin D measures				
Total serum vitamin D (ng/ml)	25.1 ± 8.1	25.5 ± 7.5	26.0 ± 7.8	25.1 ± 7.3
***p* for t test**		**0.42**	**0.20**	**0.95**

[a] Statistical tests are for comparisons of each prostate cancer group to the non-case group

if they altered the hazard ratio for any of the 25-OH vitamin D quartiles by >5% in the unstratified models or in the models stratified by Gleason score. These included age, site, reported physical activity, first degree relative with a history of prostate cancer, statin use, and non-steroidal anti-inflammatory drug use. Season of blood draw has been a significant confounder in prior studies, given the potential variation in vitamin D status, but adjusting for differences in season of blood draw did not significantly alter the hazard ratios in our analysis. In addition, very few cases occurred in racial or ethnic minority participants. Adjusting for race either as a dichotomous white/non-white variable or as a five-category variable did not alter the hazard ratios.

Results

In comparison with the subjects without prostate cancer (non-cases in Table 1), cases had a similar smoking history and race distribution, but were slightly younger and had a significantly higher percent reporting a first degree relative with prostate cancer (20% compared to 12.8%). The mean serum 25-OH vitamin D levels were similar in the cases and the non-cases (25.5 ± 7.5 and 25.1 ± 8.1 ng/mL, respectively, $p = 0.42$). The proportions of men with vitamin D deficiency (defined as <20 ng/mL) were similar (24% of cases, 25% of non-cases).

For each increasing quartile of 25-OH vitamin D, there was no significant association with risk of prostate cancer. In comparison with the lowest quartile of 25-OH vitamin D (<20 ng/mL), the hazard ratio for the highest quartile of 25-OH vitamin D (>30 ng/mL) was 1.22 (CI 0.50–1.72, $p = 0.25$), and no linear trend across quartiles was observed (p for trend = 0.94). No increased risk of prostate cancer was observed, even with very severe deficiency defined as 25-OH vitamin D level less than 15 ng/mL (HR 0.61, CI 0.36–1.02) (Table 2).

There was no difference in these findings between less aggressive (Gleason <7) and more aggressive (Gleason ≥7) prostate cancers. The hazard ratios did not change after adjustment for age, area of residence, physical activity level, family history of prostate cancer, and other covariates.

In this prospective case-cohort study of older men, we found no association between serum 25-OH vitamin D levels and prostate cancer risk, with or without stratification by Gleason score. Further, even men with the very lowest levels of 25-OH vitamin D (<15 ng/mL) did not appear to be at elevated risk of prostate cancer.

Table 2 Results of Cox regression models for adjudicated incident prostate cancer: adjusted relative risks (95% CI) related to serum vitamin D, adjusted for confounders as appropriate

	Serum vitamin D			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Range (ng/ml)	3.1–19.9	20.0–24.9	25.0–29.9	30–75.6
Mean (ng/ml)	15.5	22.6	27.3	35.2
N at risk (events)	411 (68)	415 (91)	406 (53)	416 (85)
HR (95% CI)	Ref	1.35 (0.96–1.89)	0.73 (0.50–1.07)	1.22 (0.50–1.72)
p for trend = 0.94		$p = 0.09$	$p = 0.11$	$p = 0.25$
Adjusted HR* (95% CI)	Ref	1.35 (0.91–2.01)	0.64 (0.41–1.00)	1.20 (0.81–1.78)
p for trend = 0.76		$p = 0.13$	$p = 0.05$	$p = 0.37$
Gleason <7	376 (33)	364 (40)	378 (25)	374 (43)
HR (95% CI)	Ref	1.37 (0.83–2.26)	0.79 (0.45–1.38)	1.52 (0.93–2.47)
p for trend = 0.32				
Adjusted HR* (95% CI)	Ref	1.26 (0.69–2.31)	0.65 (0.33–1.28)	1.43 (0.81–2.52)
p for trend = 0.54				
Gleason ≥7	377 (34)	372 (48)	381 (28)	372 (41)
HR (95% CI)	Ref	1.33 (0.83–2.16)	0.74 (0.43–1.27)	1.07 (0.65–1.75)
p for trend = 0.62				
Adjusted HR* (95% CI)		1.42 (0.82–2.45)	0.75 (0.41–1.39)	1.11 (0.64–1.91)
p for trend = 0.64				

Comparison group for all three outcomes is men without prostate cancer

* adjusted for age, site, PASE score, first degree relative with a history of prostate cancer, statin use, and NSAIDS use

Discussion

In the early 1990s, studies reported an association between cancer-mortality and geographic region, with the greatest mortality in northern regions where there is less UV light exposure [28]. This observation led to the hypothesis that vitamin D may play a role in cancer development and progression. The geographic distribution of mortality was consistent with an inverse relationship between prostate cancer risk and UV exposure, and presumably, serum vitamin D levels [29]. This relationship between low UV exposure and increased risk of prostate cancer has been confirmed by several other investigators [30–33].

This association of low UV exposure and increased cancer risk has also been demonstrated in seasonal studies, where patients who were diagnosed with cancer in the summer and fall had increased survival compared to patients diagnosed in the winter [34–36]. For example, Robsahm et al. found that being diagnosed with prostate cancer in the summer conferred a 20–30% reduction in the risk of death. This was supported by Lagunova et al. who showed that patients diagnosed with prostate cancer in the summer and autumn had a better prognosis than those patients diagnosed in winter or spring with a relative risk of death of 0.80.

Prior to this study, there have been 12 studies that have examined the association between vitamin D levels and prostate cancer risk (Table 3). Four of these studies have suggested an association between increased prostate cancer risk and low serum levels of vitamin D [9–12]. Two demonstrated an inverse association between 1,25-OH_2 vitamin D levels and prostate cancer risk [10, 11]. The two other studies demonstrated a link between low 25-OH vitamin D levels and increased risk of prostate cancer [9, 12]. Tuohimaa et al. showed an increased risk of prostate cancer with extreme 25-OH vitamin D deficiency (<7.6 ng/mL), and they also showed an increased risk of prostate cancer in those with the highest 25-OH vitamin D levels suggesting a U-shaped relationship between vitamin D status and prostate cancer risk [12]. In a 2007 study by

Table 3 Studies correlating serum vitamin D and prostate cancer risk

Study	Population	Number of subjects	% Vitamin D deficient	Conclusions
Corder 1993 [10]	African-American and Caucasian men in CA	181 cases, 181 controls	~50%	Decreased risk of prostate cancer in men older than 57yo with higher levels of 1,25-OH_2, especially in those men with low 25-OH levels.
Braun 1995 [14]	Caucasians in MD	61 cases, 122 controls	~10%	Null (measured both 25-OH and 1,25-OH_2 levels)
Gann 1996 [16]	US physicians	232 cases, 414 controls	~20%	High 1,25-OH_2 associated with non-significant reduction in prostate cancer risk
Nomura 1998 [19]	Japanese Americans in HI	136 cases, 136 controls	None	Null (measured both 25-OH and 1,25-OH_2 levels)
Ahohen, 2000 [9]	Finnish men	149 cases, 566 controls	>60%	Low levels of 25-OH are associated with increased risk of earlier and more aggressive prostate cancer in men less than 52yo
Tuohimaa 2004 [12]	Scandinavian men	622 cases, 1,451 controls	~50%	Both high and low levels of 25-OH are associated with an increased risk of prostate cancer
Platz 2004 [18]	US health professionals	460 cases, 460 controls	~20%	Null (measured both 25-OH and 1,25-OH_2 levels)
Jacobs 2004 [17]	Eastern US Caucasians	83 cases, 166 controls	20%	Null (measured both 25-OH and 1,25-OH_2 levels)
Li et al. 2007 [11]	US Physicians	492 cases, 644 controls	19%	Higher levels of 1,25-OH_2 were associated with decreased risk of aggressive prostate cancer in older (>65yo) men. Also, low 1,25-OH_2 in combination with low 25-OH was associated with highest risk of aggressive prostate cancer.
Faupel-Badger et al. 2007 [15]	Finnish men	296 cases, 297 controls	~50%	Null (measured 25-OH levels only)
Ahn et al. 2008 [13]	Caucasian Americans	749 cases, 781 controls	<15%	No association with low levels of 25-OH vitamin D and risk of prostate cancer, possible increased risk of aggressive prostate cancer with higher 25-OH vitamin D levels
Travis et al. 2009 [21]	Europeans	652 cases, 752 controls	~25%	Null (measured 25-OH levels only)

Li et al., there was an increased risk of aggressive prostate cancer when both 1,25-OH_2 vitamin D and 25-OH vitamin D levels were low, but no increased risk was found in patients with low 25-OH vitamin D levels, but normal 1,25-OH_2 vitamin D levels. This additive risk of low levels of both forms of vitamin D was also shown by Corder et al. suggesting that perhaps low 25-OH vitamin D levels may only be associated with increased prostate cancer risk when they are low enough to effect 1,25-OH_2 vitamin D levels. However, eight other epidemiologic studies have shown no significant relationship between measured serum vitamin D levels and prostate cancer risk [13–19, 21].

Additionally, a recent study examined the role of vitamin D on mortality in patients with known prostate cancer [20]. Tretli et al. found that higher levels of 25-OH vitamin D were associated with a better prognosis with a relative risk of mortality of 0.33 compared with patients who had lower levels of 25-OH vitamin D.

In the laboratory, prostate carcinoma cell lines and human specimens have been shown to express vitamin D receptors [3, 37–39]. Normal prostate cells express alpha-1-hydroxylase [40, 41] and this activity can be lost when cancer develops [40, 42], although the incidence of this loss in patients has not been fully characterized. Extrarenal alpha-1-hydroxylase, that is responsible for autocrine and paracrine, but not endocrine vitamin D activation, is thought to be constitutively active [43, 44] and not down-regulated by its downstream product, 1,25-OH_2 vitamin D [45]. If this model for the role of vitamin D in prostate carcinogenesis is correct, one would expect little effect of 25-OH deficiency unless it is severe enough to reduce autocrine 1,25-OH_2 vitamin D production. We did not detect a relationship between severe vitamin D deficiency and prostate cancer risk, but our ability to do so was limited by the modest number of subjects (both cases and non-cases) with severe deficiency ($n = 148$). Unfortunately, we were unable to measure prostatic tissue vitamin D status, which would clearly be of interest.

While this study had many strengths including relatively large numbers of cases, a representation of multiple populations across the US where vitamin D deficiency is common (Portland, OR, and Minneapolis, MN, for example), a population of older men who are usually at the greatest risk of prostate cancer, and a relatively large number of high-grade prostate cancers, the results were not consistent with the hypothesis that low serum levels of 25-OH vitamin D increase the risk for prostate cancer. 1,25-OH_2 vitamin D, while of interest, was outside the scope of this study and only 25-OH vitamin D was measured. When compared to other similar studies (Table 3), our study had a large, geographically diverse population, common to less than half the prior studies [11, 13, 16, 18]. Also, our study had an acceptable number of highly aggressive prostate cancers (Gleason $\geq$7) compared to other studies.

In general, the studies that were done in locations with a high prevalence of vitamin D deficiency have more frequently shown a relationship between low vitamin D levels and prostate cancer risk. Even though our population came from at least two sites with a high prevalence of vitamin D deficiency (Portland, OR, and Minneapolis, MN), there was still no association with 25-OH vitamin D levels and prostate cancer risk. Despite this, only 24% of participants in this analysis had vitamin D deficiency (<20 ng/mL), and only 9% had 25-OH vitamin D levels <15 ng/mL. Similarly, as illustrated by only the top quartile having normal vitamin D levels (>30 ng/mL), our subjects were largely clustered in around and just below the normal range of vitamin D. Thus, it is possible that our cohort did not include enough patients with severe vitamin D deficiency to demonstrate an effect. It is also possible that the study did not have a sufficient number of high-grade cancers. Some recent data and hypotheses suggest a link between vitamin D status and prostate cancer aggressiveness rather than incidence [13, 46]. It is also possible that measurement of vitamin D status in men age 65 or older, as reported here, occurs too late in life to detect an effect on an oncogenic process that is thought to be initiated earlier in life [47].

The compelling biologic links between vitamin D and prostate cancer cell growth has motivated the search for such a link in patients. For this reason, it is worthwhile to contemplate possible explanation of how our analysis may have missed an effect. Nevertheless, the most obvious explanation for our findings is that an association between prostate cancer risk and vitamin D status does not exist. While we cannot rule out the existence of such an association in this study, our findings indicate that the vitamin D status, measured by 25-OH vitamin D, in men age 65 or older, does not predict for the subsequent development of prostate cancer.

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