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ORIGINAL ARTICLE

Vitamin D levels and the risk of prostate cancer and prostate cancer mortality

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ABSTRACT

Background: Vitamin D has a role in bone turnover and potentially bone-metastatic spread of prostate cancer (PCa). The aim of this observational study was to address the association between levels of serum vitamin D, diagnosis of PCa and subsequent mortality in men who underwent a biopsy of the prostate.

Methods: All men who underwent prostatic biopsy in the Danish PCa Registry (DaPCaR) and who had a serum vitamin D measurement during the period 2004 to 2010 ($n = 4{,}065$) were identified. Men were categorized by clinical cut-offs based on seasonally adjusted serum vitamin D levels in <25 (deficient), 25–50 (insufficient), 50–75 (sufficient) and >75 nmol/L (high) serum vitamin D. Logistic regression model for association between vitamin D and risk of PCa diagnosis and multivariate survival analyses were applied.

Results: No association between serum vitamin D and risk of PCa was found. Overall survival was lowest for serum vitamin D deficiency and a significantly higher PCa specific mortality (HR: 2.37, 95%CI: 1.45–3.90, $p < .001$) and other cause mortality (HR: 2.08, 95%CI: 1.33–3.24, $p = .001$) was found for PCa patients with serum vitamin D deficiency compared to serum vitamin D sufficiency.

Conclusion: No association was found between serum vitamin D categories and risk of PCa in men who underwent biopsy of the prostate. Men with PCa and serum vitamin D deficiency had a higher overall and PCa specific mortality compared to men with a sufficient level of serum vitamin D.

Abbreviations: Vitamin D: 25OH vitamin D_3; Calcidiol: 25-hydroxy vitamin D; Calcitriol: 1,25-hydroxy vitamin D; PCa: Prostate Cancer; DaPCaR: Danish prostate cancer registry; PSA: Prostate specific antigen; T: T-category; N: Lymph node status; M: Metastatic status; SRE: Skeletal related events; IQR: Interquartile range; CSC: Cause-specific Cox proportional hazard model; HR: Hazard ratio; 95%CI: 95% confidence intervals; ROC: Receiver operating characteristics; AUC: Area under the curve

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KEYWORDS
Prostatic neoplasms; Vitamin D; mortality; epidemiology; risk

Background

25OH vitamin D_3 (vitamin D) has a vital role in maintenance of calcium and bone homeostasis [1]. Vitamin D is available in some natural dietary products, fortified foods, and dietary supplements, but the main source of vitamin D is endogenous synthesis from 7-dehydrocholesterol in the human skin after sun exposure. Vitamin D acts as a metabolic hormone precursor for 25-hydroxy vitamin D (calcidiol) in the liver, which is metabolized to 1,25-hydroxy vitamin D (calcitriol) in the kidney [2]. It is hypothesized that high vitamin D levels could inhibit indolent prostate cancer (PCa) from progression into advanced stages, as African Americans have lower vitamin D levels and a higher risk of advanced PCa [3]. Also, PCa incidence is high in countries with varying sun-light exposure, whereas increased sun exposure has been suggested to decrease the risk of advanced PCa by roughly 50% [3–5]. The vitamin D receptor has been shown to be present in PCa tissue and cell lines, and calcitriol has been shown to have anti-proliferative effect in short term culture of normal prostate epithelial cells [6]. Furthermore, mean serum calcitriol levels were lower in PCa patients compared to matched controls, and risk of PCa diagnosis decreased with increasing serum calcitriol levels at baseline for men >57 years of age [7]. In biopsy-naïve men, low levels of both plasma and serum vitamin D is associated with 26% increased risk of PCa diagnosis with a 64% and 92% increased risk of being diagnosed with Gleason ≥8 and ≥7, respectively, compared to high levels of vitamin D [8,9].

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Supplemental data for this article can be accessed here.

A meta-analysis of seven studies pooling plasma vitamin D levels measured pre- and post-diagnosis found that an increase of 20 nmol/L plasma vitamin D decreased the overall and PCa specific mortality by 9% [10]. In the present study we used information from the nation-wide Danish PCa Registry (DaPCaR), holding information on men undergoing prostatic biopsies combined with serum vitamin D levels measured at the Copenhagen General Practitioners Laboratory [11]. We analyzed the association between serum vitamin D levels in biopsy-naïve men and their risk of PCa diagnosis compared to men in which no cancer was found in a case control design. Secondly, we addressed the prognostic impact of vitamin D levels in the men diagnosed with PCa.

Methods

Population

DaPCaR holds information on all Danish men ($n = 77,402$) who underwent histopathological evaluation of prostate tissue in the period 1995 to 2011. DaPCaR further holds data on stage, prostate specific antigen (PSA) and vital status [11]. We identified all men in DaPCaR who also had serum vitamin D analyses performed by the Copenhagen General Practitioners Laboratory in the Copenhagen Municipality and the former Copenhagen County between 2004 and 2010 [12].

The study was approved by the Danish Health and Medicines Authority (file number: 3-3013-858/1/) and the ethical committee of The Capital Region of Denmark (protocol number: H4-2014-FSP). No informed consent was needed, which was approved by The Ethical Committee. The two cohorts were merged using an anonymized code and stored on secure servers, following the approval and instructions provided by the Danish National Data Protection Agency (file number: 2012-41-0390).

Statistics

Serum vitamin D levels were categorized by clinical cut-off of <25 nmol/L (deficiency), 25-50 nmol/L (insufficient), 50-75 nmol/L (sufficient), and >75 nmol/L (high), after adjustment by month of measurement (January to March, April to June, July to September and October to December). PCa patients were classified according to PSA, Gleason score on biopsy, clinical T-category, lymph node- and metastatic status (i.e., TNM-classification). Subgroup analysis was performed for patients with clinical T3 or above, a group at risk of skeletal related events (SRE). Descriptive analyses of quantitative variables were reported as medians with interquartile ranges (IQR) and categorical variables as numbers and percentages (%). Logistic regression was used to calculate the odds ratio for PCa risk in a case control design. The control group consisted of men who underwent a transrectal ultrasound guided biopsy for suspicion of PCa with benign histology. Cases are not further matched on other characteristics than undergoing transrectal ultrasound guided biopsies of the prostate. Survival was analyzed with a delayed entry Kaplan-Meier method and univariate Cox proportional hazards. For the Kaplan-Meier analysis, starting point of follow-up was the date of biopsy until event or end of follow-up (28 April 2015). If vitamin D measurement was performed after diagnostic biopsy the subject entered the analysis when the measurement was taken. Median time to event or end of follow-up was calculated using reverse Kaplan-Meier. The association between serum vitamin D categories and cause-specific survival was estimated using a multivariate cause-specific Cox proportional hazards model (CSC) for PCa patients only. Time from PCa biopsy to the time of death or end of follow-up was the underlying time scale. PCa specific death and other cause death were competing events. For validation, a Cox proportional hazard regression model for PCa specific death with delayed entry (entry time at the time of serum vitamin D measurement when measured after PCa biopsy) was compared with the hazards of PCa mortality in the CSC model. Associations are presented as hazard ratios (HRs) with 95% confidence intervals (95%CI) adjusted for known PCa risk predictors PSA, age at biopsy, Gleason score and TNM and for time from biopsy to serum vitamin D measurement. The mortality for patients with PSA of 5, Gleason score $\geq$8, age of 60, cT1, M1, and serum vitamin D measurement at PCa diagnostic biopsy was predicted stratified for serum vitamin D category and was visualized using a prediction graph. With receiver operating characteristics (ROC) curves quantified by area under the curve (AUC) for selected time points the sensitivity and specificity of prediction with or without serum vitamin D categories were compared. The assumption of proportional hazards for all variables in the Cox regression analysis were evaluated graphically using Schoenfeld residual plots for proportionality. P-values were considered statistically significant if less than 0.05. The statistical analyses were performed with R v3.4.1 (R Development Core Team, Vienna, Austria).

Results

Patient characteristics

4,065 men in DaPCaR were identified with serum vitamin D measurement. Of the 4,065 men, 2,316 men (57%) were diagnosed with PCa. A total of 2,667 men (66%) had serum vitamin D measured pre-biopsy. Of these 1,570 (59%) men were diagnosed with PCa. A total of 1,398 men (34%) had serum vitamin D measured post-biopsy. Of these 746 (53%) were diagnosed with PCa, Figure 1. Patient characteristics are demonstrated in Table 1. Clinical T-category was also noted for men in which biopsies turned out to be benign.

Vitamin D levels and risk of prostate cancer

In adjusted logistic regression models no association was found between the level of serum vitamin D and neither the overall risk of PCa diagnosis nor Gleason score at diagnosis (Table 2). A non-significantly increased risk of Gleason score $\geq$8 PCa was found in men with deficient or insufficient

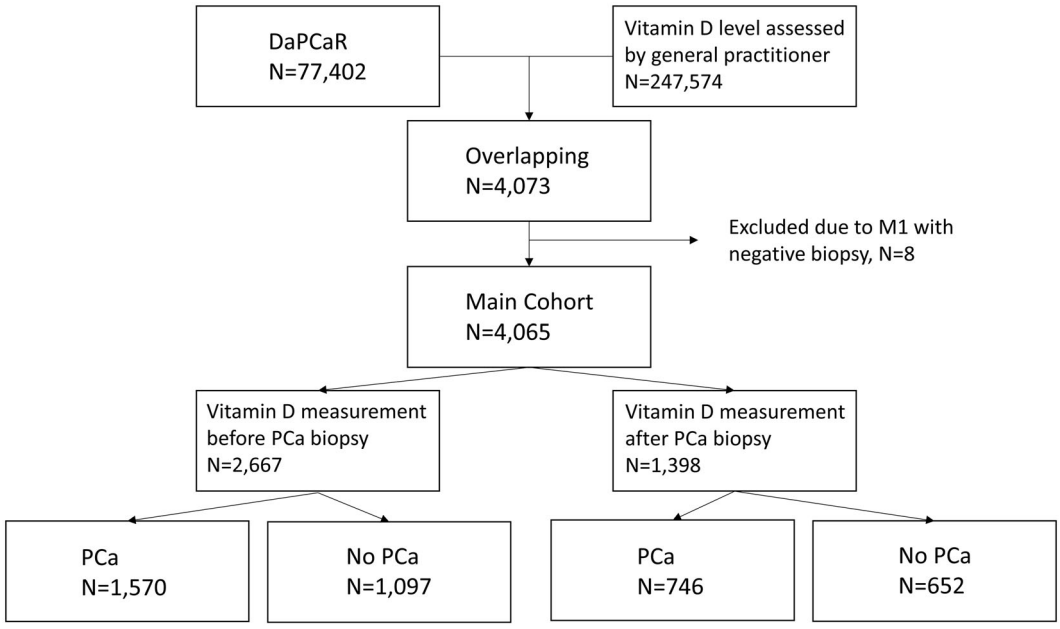

Figure 1. Flow chart of included subjects in the study. DaPCaR: Danish Prostate Cancer Registry; PCa: Prostate Cancer.

Table 1. Basic characteristics of men undergoing biopsy for suspicion of prostate cancer, stratified for a prostate cancer and benign biopsy.

Variable	Prostate cancer ($n = 2,316$)	Benign ($n = 1,749$)	Total ($n = 4,065$)
Adjusted vitamin D level (nmol/L, IQR)	49.0 [34.0–67.0]	48.0 [33.0–65.0]	49.0 [34.0–66.0]
Time from biopsy to vitamin D measurement (Years, IQR)	0.9 [−1.0 to 4.2]	0.7 [−1.5 to 4.0]	0.8 [−1.2 to 4.2]
PSA at biopsy (µg/L, IQR)	10.0 [6.4–26.0]	7.9 [5.5–13.6]	9.0 [5.9–19.0]
Missing	671	575	1246
Age at biopsy (Years, IQR)	70.0 [64.4–76.3]	65.5 [60.4–70.1]	68.0 [62.6–73.8]
Biopsy Gleason score			
≤6	606 (26.7)	0 (0.0)	606 (26.7)
7	909 (40.0)	0 (0.0)	909 (40.0)
≥8	758 (33.3)	0 (0.0)	758 (33.3)
Missing	43	1749	1792
Clinical T-category			
T1	788 (50.0)	136 (66.7)	924 (51.9)
T2	429 (27.2)	52 (25.0)	480 (27.0)
T3 + 4	358 (22.7)	17 (8.3)	375 (21.1)
Missing	741	1545	2286
M-category			
M0	1406 (89.3)	204 (100)	1610 (90.5)
M1	169 (10.7)	0 (0)	169 (9.5)
Missing	741	1545	2286

Characteristics of men with variables shown on the left together with units behind in brackets. For continuous variables median with inter quartile range shown and for categorical values number of patients and percentage of total.

Table 2. Risk of prostate cancer (PCa) diagnosis and risk of specific gleason score for clinical cut-off groups of vitamin D analyzed by logistic regression.

	Vitamin D measurement category (nmol/L, adjusted for time of year)				
	<25	25–50	50–75	>75	*P* trend
PCa risk					
Case patient/control subjects	100/80	248/252	245/205	153/115	
OR (95%CI)	1.01 [0.64–1.59]	1.24 [0.89–1.74]	Reference	0.97 [0.65–1.45]	0.27
Gleason 6 or below PCa risk					
Case patient/control subjects	23/80	78/252	82/205	48/115	
OR (95%CI)	1.56 [0.79–3.08]	1.12 [0.72–1.75]	Reference	0.98 [0.57–1.67]	0.27
Gleason 7 PCa risk					
Case patient/control subjects	41/80	78/252	80/205	52/115	
OR (95%CI)	0.89 [0.50–1.61]	1.56 [0.96–2.53] *	Reference	1.14 [0.65–2.02]	0.93
Gleason 8 or above PCa risk					
Case patient/control subjects	33/80	82/252	77/205	45/115	
OR (95%CI)	1.06 [0.54–2.11]	1.04 [0.64–1.69]	Reference	0.78 [0.44–1.38]	0.09

Divisions made for specific Gleason scores to see incidence for specific cancer aggressiveness. Model adjusted for age, PSA and time from serum vitamin D measurement to study entry. *$p = .07$.

serum vitamin D compared to men with sufficient serum Vitamin D ($p = .09$).

Vitamin D levels and survival

Median follow-up time in the entire cohort is 6.1 years (IQR: 4.6–7.8 years). Overall survival at 10 years was 51.8% (95%CI 43.1–60.6), 66.0% (95%CI 61.4–70.6), 63.8% (95%CI 58.7–68.9) and 60.9% (95%CI 54.1–67.7) for men with vitamin D deficiency, insufficiency, sufficient and high, respectively (Figure 2). Men with deficient serum vitamin D levels are associated with a significantly higher risk of dying compared to men with sufficient serum vitamin D levels in the whole cohort (HR 1.58; 95%CI 1.27–1.96; $p < .001$, Figure 2(A)) and in PCa patients deficient compared to sufficient vitamin D (HR 1.67; 95%CI 1.30–2.15; $p < .001$, Figure 2(B)) and insufficient compared to sufficient vitamin D is associated with a significantly higher risk of dying (HR 1.30; 95%CI 1.06–1.59; $p = .01$, Figure 2(B)).

Vitamin D levels and cause-specific mortality

Univariate and multivariate competing risk analysis demonstrated that Gleason score and tumor stage were significantly associated with PCa specific mortality (Table 3, Supplementary table 3). Furthermore, men with deficient serum vitamin D had a both higher PCa specific (HR 2.37; 95%CI 1.45–2.89; $p < .001$) and other-cause mortality (HR 2.08; 95%CI 1.33–3.24; $p = .001$) compared to men with sufficient serum vitamin D (Table 3). To elucidate the influence of vitamin D timing, a delayed entry was applied to the model which demonstrated a similar difference in PCa specific mortality (HR 2.28; 95%CI 1.39–3.74; $p = .001$, Supplementary table 1). No association with PCa mortality for time from serum vitamin D measurement to biopsy was found (HR 0.93; 95%CI 0.84–1.03; $p = .18$, Supplementary table 1).

In sub-analysis of PCa patients with cT3 or higher, men with serum vitamin D deficiency had higher PCa specific mortality compared to men with sufficient serum vitamin D multivariate analysis (HR 6.03; 95%CI 2.61–13.90; $p < .001$, Supplementary table 2). Furthermore, there was a trend toward increased PCa specific mortality for men with insufficient (HR 1.92; 95%CI 0.94–3.94; $p = .075$) or high vitamin D (HR 2.28; 95%CI 0.98–5.34; $p = .056$) compared to men with sufficient serum vitamin D. By contrast, other cause mortality in cT3 patients was not significantly affected between serum vitamin D categories (HR 1.62; 95%CI 0.62–4.26; $p = .33$).

Predicted outcomes and model validation

The predicted PCa specific mortality was highest among men with serum vitamin D deficiency (Figure 3(A)) which was validated by both odds and Fine Gray model (Supplementary Fig. S1). However, having a high serum vitamin D level was also associated with a higher predicted PCa specific mortality than an insufficient or sufficient serum vitamin D level. A spline curve showed a strong association with serum vitamin D levels below 25 nmol/L and PCa specific mortality and a weak association with the levels above 75 nmol/L, compared to 50 nmol/L serum vitamin D (Figure 3(D)). Other cause mortality was also affected by the level of serum vitamin D but to a lesser extent (Figure 3(B)). The prediction model demonstrated an accuracy (c-index) at 8 years of 81.4% without the serum vitamin D categories in the model and 82.3% with serum vitamin D categories in the predictive model. The ROC analysis showed only a modest increase in the AUC from

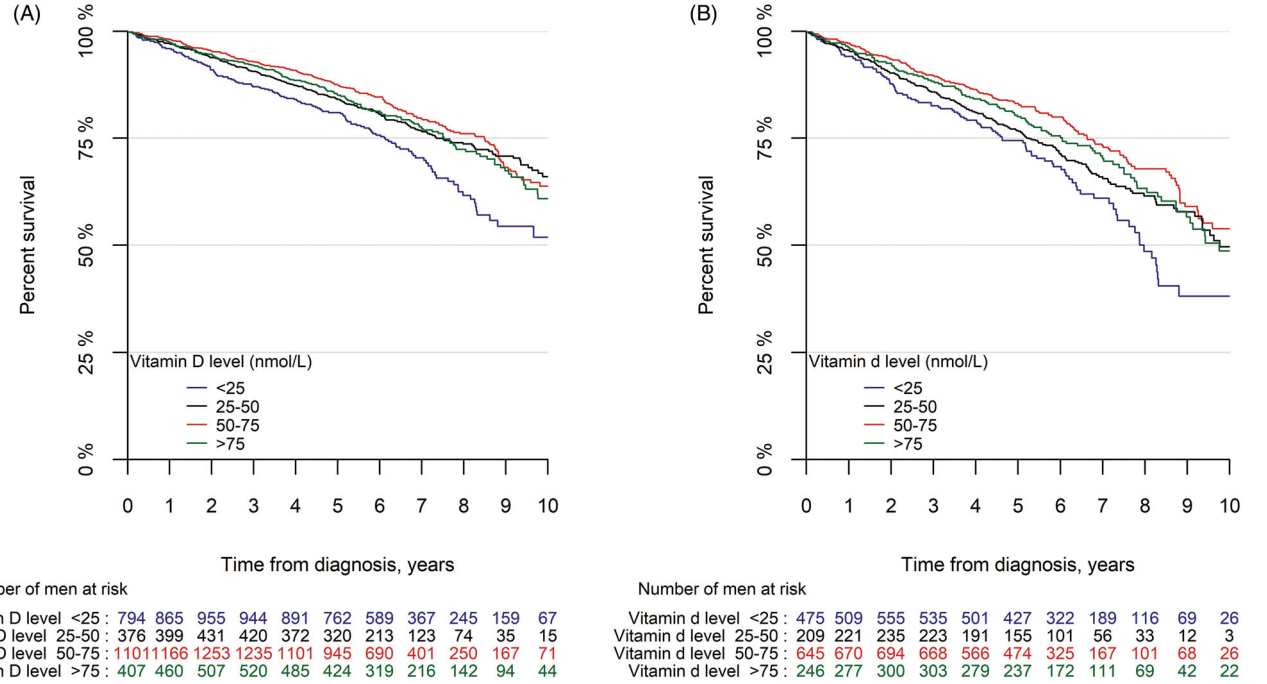

Figure 2. Delayed entry Kaplan-Meier curves for overall survival after diagnostic biopsy for prostate cancer (PCa) stratified for vitamin D clinical cut-off. Delayed Kaplan-Meier for all men undergoing biopsy for suspicion of Pca (A) and for men with PCa found in diagnostic biopsy (B), men with vitamin D measurement after diagnostic biopsy enter the analysis at time of vitamin D measurement. Below the graphs the number of subjects at risk at the specific time points are shown.

Table 3. Multivariate cause specific cox hazards of death after PCa diagnosis by competing risk, with prostate cancer specific and other cause mortality as competing events.

	Prostate cancer specific mortality		Other cause mortality	
Variable	Hazard [95%CI]	*p*-value	Hazard [95%CI]	*p*-value
Vitamin D (nmol/L)				
<25 (deficient)	2.37 [1.45–3.89]	<.001	2.08 [1.33–3.24]	.001
25–50 (insufficient)	1.18 [0.77–1.80]	.45	1.25 [0.89–1.76]	.20
50–75 (sufficient)	Reference			
>75 (high)	1.43 [0.87–2.32]	.14	0.89 [0.57–1.39]	.61
Age (Years)				
PSA (Log2)	1.05 [1.03–1.07]	<.001	1.10 [1.08–1.11]	<.001
Biopsy Gleason score	0.97 [0.89–1.06]	.51	1.02 [0.95–1.09]	.57
≤6	Reference			
7	2.76 [1.32–5.77]	.007	0.92 [0.62–1.36]	.67
≥8	7.75 [3.77–15.93]	<.001	1.43 [0.96–2.13]	.08
Clinical T category				
T1	Reference			
T2	1.04 [0.69–1.59]	.84	1.18 [0.84–1.68]	.34
T3 + 4	1.46 [0.96–2.22]	.075	1.63 [1.13–2.37]	.010
M category				
M0	Reference			
M1	4.41 [3.10–6.27]	<.001	1.37 [0.89–2.11]	.15
Time from biopsy to vitamin D measurement (Years)	1.10 [1.01–1.19]	.023	1.16 [1.08–1.25]	<.001

Multivariate analysis of all variables with their adjusted hazard ratio's (HR) Categorical values represented with reference values for each specified. Numerical values are per unit increase, units are represented within brackets behind variable. CI: Confidence interval.

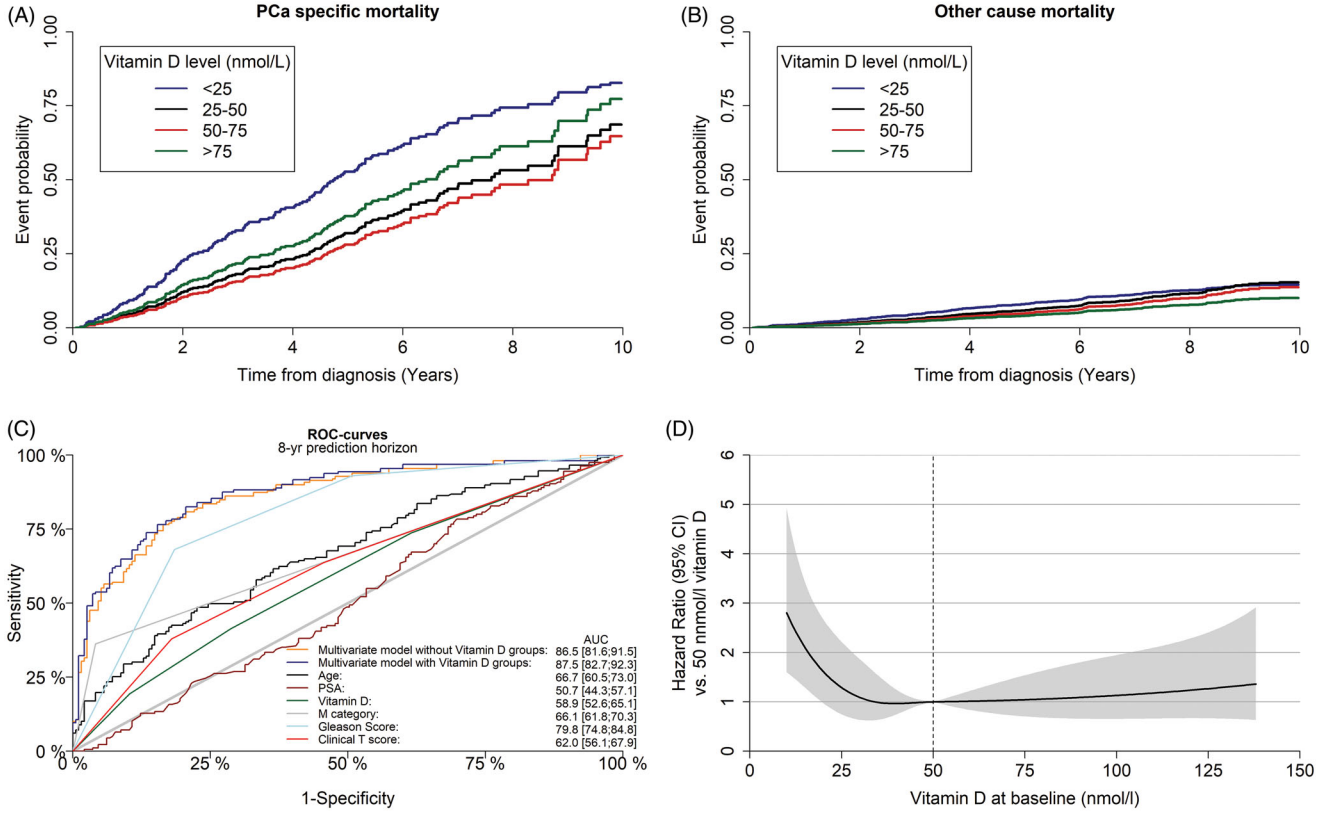

Figure 3. Predicted risk of event and predictability. (A) The predicted risk of dying of prostate cancer (PCa) per clinical cut-off category for a patient with baseline age 60, gleason ≥ 8, PSA 10, Clinical T-category cat T1, M category M1 and serum vitamin D measured at biopsy. (B) The predicted risk of dying of other causes than PCa per clinical cut-off category for a patient with baseline age 60, gleason ≥ 8, PSA 10, Clinical T-category cat T1, M category M1 and serum vitamin D measured at biopsy. (C) The ROC-curves at 8 years showing sensitivity and specificity for being able to predict if a patient will have an event based on the model and on individual measurements. (D) Spline curve showing hazards related to vitamin D level with nods: 10, 25, 50, 75 and 100. Dotted line represents reference point. CI: Confidence interval.

86.5 (81.6–91.5) to 87.5 (82.7–92.3) at 8 years ($p = .08$, Figure 3(C)) by adding vitamin D levels to the clinical parameters in the prediction model. Similar tendencies were found at 2, 5 and 10 years (Supplementary Fig. S2).

Discussion

Vitamin D levels and the risk of developing PCa has been debated over the years. The high incidence of PCa in the Nordic countries has sparked the interest for an association

between vitamin D and PCa due to the fluctuating sun exposure [13–15]. In this study, we did not find that clinical categories of serum vitamin D levels had an association with the risk of being diagnosed with PCa in groups of biopsy-naïve men who were referred for prostate biopsy due to elevated PSA. However, in men who received a PCa diagnosis, our data point to the fact that serum vitamin D deficiency is associated with a poorer survival both in terms of PCa- and other cause mortality compared to men with sufficient vitamin D levels.

The present Danish cohort is unique as it holds information on a large number of men from the same geographical area who were referred for biopsy due to a suspicion of PCa, where both benign and malignant diagnosis was available and where serum vitamin D levels were taken. This is an optimal setting for a case-control design. However, an important limitation to the study is that the timing of serum vitamin D measurements varied from before to after diagnostic biopsy. To adjust for this, we performed a delayed entry analysis, reducing the bias of men being alive until measurement taken [16]. The analysis demonstrated that the association between vitamin D levels and PCa mortality was not affected by the fact that the vitamin D measurement was taken before or after the diagnostic biopsy. However, we acknowledge that vitamin D levels may change over time in the individual patient which we cannot completely account for and as consequence this limits the interpretability of our findings. Another limitation is that the serum vitamin D measurements were performed by general practitioners and we do not have information on the indication for which the measurement was taken. Also, we did not have information on comorbidity and it is possible that the most comorbid patients are likely to get screened with a number of blood samples at their general practitioner and thus this study could deal with a group of men with lower overall survival than the background population. However, this bias would be expected to be similar across all vitamin D groups in this cohort and then have limited impact on the conclusions here. Furthermore, the cohort was restricted to the Copenhagen area and the follow-up was limited with the endpoint in April 2015, due to the long process of updating the sizeable original database. Lastly, lack of data such as treatment strategy, factors related to death such as smoking and weight, and supplementations taken by the specific patients could potentially affect both the serum vitamin D levels and the outcome.

Previous research has found mean plasma calcitriol levels in PCa patients to be lower compared to matched controls and has shown a higher risk of aggressive PCa in prostatectomy specimens in men with higher levels of plasma vitamin D, but also that low levels of serum vitamin D were associated with an increased risk of aggressive PCa [7–9]. We did not find an association between vitamin D and risk of aggressive PCa in men referred for prostate biopsy due to elevated PSA. Our findings are supported by a recent collaborative analysis that showed an increasing risk in non-aggressive PCa diagnosis with increasing circulating vitamin D levels but no association with aggressive disease [17]. Further, a recent large nationwide randomized placebo-controlled trial investigating supplementation of vitamin D and cancer risk that could not prove a significant change in PCa incidence by supplementing with vitamin D, indicating that the previously found increased risk of PCa show an association with prostate issues in general and not with PCa [18].

A meta-analysis has recently showed a 9% decrease in overall and PCa specific mortality with every 20 nmol/L increase in plasma vitamin D in PCa patients [10]. This meta-analysis is limited by inadequate adjustment for predictors of PCa specific mortality such as Gleason score, which was present in only three studies [10]. Of those three studies, only one found a significant association between vitamin D and PCa specific mortality and only one of the studies used predefined cut-off points for vitamin D categories, whereas else vitamin D quartiles based on the study population were used, limiting clinical extrapolation of the results [19–21]. Our study showed a strong association with higher PCa and other cause mortality in men with serum vitamin D levels below 25 nmol/L compared to 50–75 nmol/L serum vitamin D (Figure 3(D)). Although serum vitamin D was an independent predictor for mortality, the contribution of serum vitamin D to the risk prediction model was small, i.e., AUC only increased from 86.5 to 87.5%. Parameters such as Gleason score had a larger impact on prediction modeling than the biomarker itself, which is known from several studies [22–24]. Our study and the meta-analysis raise the question whether there is a true biological association between vitamin D and PCa. The similarity in overall and PCa specific mortality risk seem to point at a higher *a priori* risk of dying, which is likely to be caused by other characteristics of men with low serum vitamin D such as increased comorbidities, ethnicity or previously found associations of vitamin D with immune system functions that could partly explain this relation to the general health [25,26]. It seems unlikely, that serum vitamin D will become a reference biomarker for mortality after PCa diagnosis.

Currently, vitamin D supplementation with calcium is recommended when starting on castration-based therapy but evidence behind this recommendation is limited. It is known that therapy protecting against bone resorption decreases the risk of SRE but the recommendation for vitamin D and calcium supplementation is largely based on an empirical dogma. Our sub-analysis looking at men with locally advanced PCa (cT3 or higher, Supplementary table 2) shows that vitamin D deficiency was significantly related to higher PCa specific mortality. Also, we found a trend toward higher PCa specific mortality in men with high vitamin D, but interestingly, not for other cause mortality. These results should be interpreted with caution due to the low number of patients.

Conclusions

In summary, no clear relations between serum vitamin D and PCa risk were found despite being one of the largest PCa single case-control studies to date. We did show that serum vitamin D deficiency was related to PCa- and other cause mortality in PCa patients, but this is likely due to a higher *a*

priori risk of death for men with vitamin D deficiency. Further studies in a larger geographical area with focus on vitamin D supplementation, immunomarkers and other health related markers are warranted.

Ethics approval and consent to participate

The study was approved by the Danish Health and Medicines Authority (file number: 3-3013-858/1/) and the ethical committee of The Capital Region of Denmark (protocol number: H4-2014-FSP). No informed consent was needed, which was approved by The Ethical Committee. Merging of data was done using an anonymized code and stored on secure servers, following the approval and instructions provided by the Danish National Data Protection Agency (file number: 2012-41-0390).

Consent for publication

Not applicable.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

All authors contributed to the study conception and design. Data collection was performed by FJV, CMM, JTH, PS, BSL, HLJ, KB and MAR. Material preparation was performed by HVS, FJV, KB, HLJ and MAR. The statistical analysis was performed by HVS. The first draft of the manuscript was written by HVS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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