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Prediagnostic circulating 25-hydroxyvitamin D and prostate cancer-specific survival: a collaborative pooled analysis of 13 prospective studies

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Abstract

Background Previous research suggests higher risk of prostate cancer diagnosis in men with high vitamin D serology, but there are limited data related to prostate cancer survival. In this study, we examine the associations between prediagnostic circulating levels of 25-hydroxyvitamin D [25(OH)D] with risk of prostate cancer-specific mortality, as well as mortality from other causes, in participants diagnosed with prostate cancer.

Methods We conducted a prospective multi-national collaborative analysis of pre-diagnostic circulating 25(OH)D, the major biochemical indicator of vitamin D status, with data for 12,635 incident prostate cancer cases from 13 cohorts. Multivariable-adjusted Cox proportional hazards regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between study-specific/season-standardized categories as well as clinically defined 25(OH)D categories (<30, 30-<50, 50-<75, and ≥75 nmol/L) and mortality from prostate cancer and other causes.

Results Analyses of circulating 25(OH)D and mortality were based on 3,445 deaths, of which 1,316 (38.2%) were due to prostate cancer. In fully adjusted models, men with high pre-diagnostic 25(OH)D concentrations experienced lower prostate cancer-specific mortality (HR for 80-percentile increase = 0.75, 95% CI: 0.64, 0.88; $P_{trend} < 0.001$) and slightly

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lower risk of mortality from other causes (HR = 0.85, 95% CI: 0.75, 0.96, P_{trend} = 0.009). In the subset of cases with complete stage and grade data (5,078 cases [40.2%] and 761 deaths from prostate cancer [57.8%]), the association between 25(OH)D and prostate cancer mortality was 0.81 (0.65, 0.99, P_{trend}=0.04).

Conclusions In this pooled analysis of 13 prospective cohorts, higher pre-diagnostic circulating vitamin D (25(OH)D) was associated with increased prostate cancer survival.

Keywords Circulating vitamin D, Prostate cancer survival, A prospective cohort study

Background

Prostate cancer is the second leading cause of cancer-related mortality in the U.S., and the sixth-most common cause of cancer mortality in men worldwide [1]. Despite such public health importance, well-established modifiable risk factors are lacking. Current known risk factors include age, height, a positive family history, African ancestry and low-penetrance genetic variants, none of which are modifiable [2, 3]. Furthermore, little is known regarding factors that influence prostate cancer survival with the exception of smoking and obesity at diagnosis which have been related to lower survival in several studies [4].

Vitamin D is a fat-soluble vitamin whose 1,25 dihydroxylated form is a hormone which plays a central role in calcium homeostasis, bone health, and other physiological processes. Determinants of vitamin D status include the well-recognized seasonal variation in epidermal ultraviolet B radiation exposure-related production, diet and dietary supplements [5]. Vitamin D (cholecalciferol) is hydroxylated to its major circulating metabolite, 25-hydroxyvitamin D (25(OH)D) in the liver which is a robust and reliable marker of vitamin D status [6], and then converted to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the hormonal form, primarily in the kidney and also in extra-renal tissues, including the prostate [7–9]. Extra-renal 1α-hydroxylase activity has also been described in prostate cells, supporting intraprostatic conversion of 25(OH)D to $1,25(OH)_2D$ [8, 9]. Experimental prostate cell studies further suggest that 25(OH)D may exert biological activity through the vitamin D receptor (VDR) in prostate cells beyond its role as a precursor of $1,25(OH)_2D$ [10, 11]. Because $1,25(OH)_2D$ production is regulated primarily by parathyroid hormone, which in turn is regulated by calcium and vitamin D in circulation, serum concentrations of $1,25(OH)_2D$ may not reflect the body's overall vitamin D stores as consistently as 25(OH)D. In addition, a higher circulating $1,25(OH)_2D$/25(OH)D molar ratio has been associated with lower odds of highly aggressive prostate cancer, particularly among African American men [12]. More broadly, laboratory studies from cell culture and animal models have shown that ligand-receptor binding between vitamin D metabolites and the vitamin D receptor regulates transcription of targeted genes through thousands of vitamin D response elements [5, 13] which may impact cancer-related biological mechanisms, including suppression of low-grade inflammation, cell cycle and proliferation control, and metastasis, as well as induction and sensitization of apoptosis and differentiation [5, 7, 13].

Although the epidemiological association between circulating vitamin D and risk of incident prostate cancer has been inconsistent [13–17], a recent large collaborative study of 19 prospective studies (partially the same dataset as used in the current study) reported that men with higher vitamin D concentrations had a higher risk of being diagnosed with non-aggressive prostate cancer, but not aggressive disease [14]. Beyond possible etiological differences between indolent and clinically relevant disease, detection bias could partially account for these findings, in that health-conscious men may be more likely to actively seek outdoor physical activity (which would increase sun exposure), have vitamin D-enriched diets and/or use supplements, to attend prostate cancer clinical screenings or health checks (i.e. prostate-specific antigen (PSA) testing and digital rectal examination (DRE)), and to promptly seek medical evaluation for symptoms at early stages [14]. The few observational studies investigating the association between circulating vitamin D and survival following a prostate cancer diagnosis have reported lower mortality among cases with higher prospective vitamin D levels [15, 18–22].

This study aimed to comprehensively examine the association between prediagnostic circulating concentrations of 25(OH)D and $1,25(OH)_2D$ and prostate cancer-specific mortality as well as mortality from other causes among men with a prostate cancer diagnosis by performing a collaborative analysis of individual participant data from 13 prospective cohort studies in the Endogenous Hormones, Nutritional Biomarkers and Prostate Cancer Collaborative Group (EHNBPCCG). This is the largest analysis to date to investigate the association of prediagnostic vitamin D biochemical status in relation to prostate cancer survival.

Methods

Study population, data collection and processing, and vitamin D measurement

Details of the EHNBPCCG have been described elsewhere [14, 23–29]. Further details on study identification,

data collection, study designs, and data processing are provided in Additional File 1: Supplementary methods [16, 17, 20, 30–53]. Published and unpublished prospective studies were identified by literature searches and correspondence, and invited to join this collaborative pooling analysis if they had prospective data on circulating 25(OH)D and/or $1,25(OH)_2D$ measurements from blood samples collected prior to prostate cancer diagnosis, as well as information on prostate cancer-specific death (underlying cause) or death from other causes.

Data items collected included individual-level data on circulating 25(OH)D and $1,25(OH)_2D$, months of blood draw, age and fasting status at sample draw, smoking status, alcohol consumption, height, weight, waist and hip circumference, ethnicity, family history of prostate cancer, marital status, educational attainment, vital status, as well as cancer stage, grade, and cause and date of death. All participant data were harmonized in a central database at Oxford University, UK.

This pooling project included 13 separate cohorts, with individual data on circulating 25(OH)D or $1,25(OH)_2D$ for 12,635 and 1,889 men with prostate cancer, respectively (Additional File 1: Tables S1–S6). Most of the studies were prospective studies that used a nested case-control design to investigate pre-diagnostic circulating vitamin D and prostate cancer risk. The PLCO study was conducted within a randomized controlled trial which screened for prostate cancer, and which excluded men with PSA blood values of >4 ng/ml or abnormal findings from DRE at study entry, with the majority of trial-period prostate cancer cases detected from annual PSA and DRE screening. Informed consent was provided by all participants in all studies, and each study was approved by the respective institutional review board.

"Early" stage of prostate cancer was defined as tumor-node-metastasis (TNM) stage T1 with no documented lymph node involvement or metastasis, or stage I; "other localized" stage was defined as TNM stage T2 with no documented lymph node involvement or metastasis, or stage II; "advanced" stage was defined as TNM stage T3 or T4 and/or N1 + and/or M1, or stage III or IV; or stage "unknown". Histologic grade was classified as low, intermediate, high, or unknown. Low grade was defined as Gleason score ≤ 6; intermediate grade as Gleason score 7; and high grade as Gleason score 8–10.

Missing values of categorical variables were handled by creating a missing data indicator for inclusion in the multivariable models whereas in stratified analyses, participants with missing data for the stratification variable were excluded.

Statistical analyses

Circulating concentrations of 25(OH)D and $1,25(OH)_2D$ were log-transformed to approximate a normal distribution and then standardized by season at blood collection to allow for the influence of month of blood draw on circulating concentrations. To allow for any systematic differences in the studies regarding measurement methods and blood sample types [54], men were categorized into fifths according to the cut points of study-specific season-standardized categories, and the trend in risk for an 80 percentile increase was calculated by assigning values of 0, 0.25, 0.5, 0.75 and 1 to the fifths.

We calculated person-time of follow-up for each case from the date of diagnosis to date of death or end of follow-up, whichever came first, in each participating study. The associations of season-standardized study-specific quintile categories of circulating 25(OH)D and $1,25(OH)_2D$ with prostate cancer-specific survival were calculated using Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The regression models were stratified by study and adjusted for potential confounders for aggressive prostate cancer or prostate-cancer specific mortality including age at blood collection (continuous), body mass index (BMI, as a categorical variable), height (as a categorical variable), marital status (married or cohabiting, not married or cohabiting, or not known), educational attainment (did not graduate from high school/secondary school/college, high school/secondary school/college graduates, university graduates, or not known) and cigarette smoking (never smoker, past smoker, current, or not known). Models were further additionally adjusted for prostate cancer stage, prostate cancer grade, and time between blood collection and cancer diagnosis (0 to <5 years, 5 to <10 years, or ≥10 years). To assess potential multicollinearity among covariates, we calculated generalized variance inflation factors (GVIF) where adjusted GVIF values [GVIF^(1/(2*df))] were examined to ensure that no variable inflated the variance of the regression coefficients substantially. All adjusted GVIF values were below 2, indicating no concern for multicollinearity.

In further analyses we used pre-defined categories of circulating 25(OH)D of < 30, 30-<50, 50-<75 and ≥ 75 nmol/L to estimate survival related to very low (deficiency), low (insufficiency), moderate (sufficiency) and high circulating vitamin D concentration, according to the Institute of Medicine recommendations [55]. Cox regression models were also conducted using death from other causes (i.e. excluding prostate cancer-specific death) as the endpoint of interest.

For the associations between circulating 25(OH)D, $1,25(OH)_2D$, and prostate cancer-specific mortality, tests for heterogeneity across the studies in linear trends were assessed through likelihood ratio tests by comparing Cox regression models with and without the cross-product terms between study factor and the linear trend

variable. We performed stratified analyses by age at diagnosis (<65, or ≥65 years), years from blood collection to diagnosis (< 5 or ≥ 5 years), years of diagnosis (pre-1989, 1990–1994, 1995–1999 or 2000 onwards), grade of prostate cancer (low, intermediate or high), stage of prostate cancer (early, other localized, or advanced), age at blood draw (<60, or ≥60 years), PSA at baseline blood draw (< 4, or ≥ 4 ng/mL), university or other higher education (no, or yes), White ethnicity (yes, or no), BMI (<25, or ≥25 kg/m^2), cigarette smoking (never/past smoker, or current smoker), usual alcohol consumption (<10, or ≥10 g/d), family history of prostate cancer (yes, or no).

Since not all studies had information regarding stage and/or grade of prostate cancer at diagnosis and due to the importance of these clinical factors on prostate cancer survival, the following sensitivity analyses were performed: (a) multivariable-adjusted model restricted to cases with information on either stage or grade; (b) model adjusted for stage of prostate cancer; (c) model (a) was further adjusted for grade of prostate cancer; (d) multivariable-adjusted model restricted to participants with information on both stage and grade, and further adjustment for these factors; (e) competing risk analyses using the Fine-Gray sub-distribution hazard model to assess death from prostate cancer and other causes; (f) lag-time analyses restricted to 0–2 years (short lag) and 2–4 years (mid lag) of follow-up to evaluate the potential impact of regression dilution.

All statistical analyses were conducted using Stata Statistical Software, Release 14 (StataCorp, LP, College Station, Texas). All reported P values are two-sided, and we used the Bonferroni correction threshold to control for multiple tests, and the statistical significance threshold was 0.013 (0.05/4 for primary analysis [2 tests for 25(OH)D and $1,25(OH)_2D$ and for 2 survival end points]), and 0.0033 (0.05/15 for the population subgroup interaction tests).

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The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

The median survival time from prostate cancer diagnosis to the end of follow-up (either death or censoring) for the cohort was 5.6 years (interquartile range [IQR]: 2.7–10.4). Specifically, among the participants who died during follow-up, the median time from diagnosis to prostate cancer-specific death was 4.0 years (IQR: 2.0-7.3), and 7.3 years (IQR: 3.9–11.9) for death from other causes. At enrollment, 11% of cases were categorized as vitamin D deficient (i.e. < 30 nmol/L of 25(OH)D). Compared with men in the lowest fifth of circulating 25(OH)D, men in the higher categories were less likely to be current smokers and more likely to be married or cohabiting and to have lower BMI and educational attainment (Table 1). Baseline characteristics of each of the 13 participating studies are presented in Additional File 1: Tables S1–S6. The mean age at recruitment across the cohorts ranged from 54.1 (SD = 4.8) to 76.4 (SD = 3.7), and geometric mean concentrations of 25(OH)D ranged from 33.0 nmol/L (95% CI: 31.8, 34.3 nmol/L) in Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC, Finland), to 82.2 nmol/L (95% CI: 76.2, 88.6 nmol/L) in CLUE I (USA). Data on $1,25(OH)_2D$ concentrations are available for 1,889 cases from 3 participating studies, and geometric mean concentrations of $1,25(OH)_2D$ ranged from 78.6 pmol/L (95% CI: 77.0, 80.4 pmol/L) in PHS (USA), to 95.9 pmol/L (88.3, 104.2 pmol/L) in CLUE I (USA) (Additional File 1: Table S2).

In a multivariable-adjusted model that included age at blood collection, smoking, marital status, education,

Table 1 Baseline characteristics by study-specific 25(OH)D categories in men diagnosed with prostate cancer[a]

Characteristic	Fifths of season-standardized circulating 25(OH)D				
	1	2	3	4	5
Number of men with prostate cancer	2,532	2,525	2,526	2,530	2,522
Age at recruitment, years	61.3 (7.4)	61.4 (7.2)	61.6 (7.0)	61.8 (6.9)	62.0 (6.9)
Age at diagnosis, years	67.0 (6.9)	67.1 (6.7)	67.4 (6.6)	67.7 (6.3)	67.9 (6.5)
Time between blood draw and diagnosis, years	5.7 (4.2)	5.7 (4.3)	5.8 (4.3)	6.0 (4.4)	5.9 (4.4)
BMI (kg/m^2)*	27.4 (4.1)	27.3 (3.8)	27.0 (3.7)	26.7 (3.4)	26.4 (3.3)
Height (cm)	174.8 (7.2)	175.3 (7.1)	175.2 (6.8)	175.1 (6.8)	175.0 (6.9)
Married or cohabiting (%)*	84.5	87.1	86.6	89.1	89.6
Higher education (%)*	46.3	47.1	44.7	43.8	42.6
Current smoker (%)*	21.5	18.1	16.6	15.0	15.3
Alcohol consumption (g/d)*	19.5 (26.0)	18.6 (22.1)	18.1 (21.9)	18.3 (21.1)	18.4 (20.0)
Family history of prostate cancer (%)*	17.4	18.3	17.8	17.3	18.2

[a]Values are mean (SD) unless otherwise indicated

*Unknown for some cases

BMI, and height, we found an inverse association between circulating, season-standardized study-specific 25(OH)D and prostate cancer-specific mortality, with a 20% lower prostate cancer mortality risk in the top fifth compared with the lowest fifth (HRs for 5th versus 1st quintile category [95% CI]: 0.80 [0.67, 0.95]; P_{trend} < 0.001); the HR for an 80-percentile increase in 25(OH)D was 0.74 (95% CI: 0.63, 0.87; Table 2). Further adjustment for prostate cancer stage and grade, and time between blood collection and cancer diagnosis, did not materially change the inverse associations (HRs for 5th versus 1st quintile category [95% CI]: 0.79 [0.67, 0.94]; P_{trend} < 0.001; HR = 0.75 (95% CI: 0.64, 0.88) for 80-percentile increase; Table 2).

In the fully adjusted model, we also found an inverse association between pre-defined clinical categories of circulating 25(OH)D and prostate cancer-specific mortality in a dose-response manner, with a 34% mortality risk reduction in the highest category (sufficiency, ≥75 nmol/L) as compared with the very low category (deficiency, <30 nmol/L), with HRs [95% CI] for insufficiency [30-<50 nmol/L], moderate sufficiency [50-<75 nmol/L] and sufficiency categories versus deficiency being 0.83 [0.70, 0.99], 0.78 [0.65, 0.93] and 0.66 [0.54, 0.82]; P_{trend} < 0.001; Table 2). Circulating $1,25(OH)_2D$ was not associated with prostate cancer-specific mortality after multivariable adjustment (HR [95% CI] per 80 percentile increase: 1.09 (0.75, 1.57); P_{trend} = 0.65; Table 2).

We also observed that men with higher 25(OH)D concentrations had a lower risk of dying from causes other than prostate cancer (HR for 80-percentile increase = 0.85, 95% CI: 0.75, 0.96, P_{trend} = 0.009; Table 3). Season-standardized study-specific circulating $1,25(OH)_2D$ was not associated with mortality from other causes (P_{trend} = 0.29; Table 3).

In sensitivity analyses restricted to the 5,078 participants with complete data on stage and grade of prostate cancer at cancer diagnosis (40.2%), we found that there was attenuation but still significance in the HRs for prostate cancer mortality (based on 761 of the prostate cancer deaths, or 57.8%) when the model was adjusted for these clinical factors (HR for 80-percentile increase = 0.76, 95% CI: 0.62, 0.93, P_{trend} = 0.009 compared to HR = 0.81, 95% CI: 0.65, 0.99, P_{trend} = 0.04 with additional adjustment for stage and grade) (Table 4). Vitamin D was not associated with risk of death from other causes in this subset

Table 2 Hazard ratios (HRs) for prostate cancer-specific death by categories of circulating season-standardized 25(OH)D and $1,25(OH)_2D$ in men diagnosed with prostate cancer in 13 prospective studies

	Fifths of season-standardized circulating 25(OH)D					**Per 80 Percentile increase**	P_{trend}[e]
	1	**2**	**3**	**4**	**5**		
Person-years	16,927	17,241	17,394	17,897	17,467		
Cases/deaths	2,532/302	2,525/290	2,526/250	2,530/233	2,522/241	12,635/1,316	
HR (95% CI)[a]	1.00	0.96 (0.81, 1.13)	0.78 (0.66, 0.93)	0.70 (0.59, 0.83)	0.75 (0.63, 0.89)	0.69 (0.59, 0.81)	< 0.001
HR (95% CI)[b]	1.00	1.01 (0.85, 1.18)	0.83 (0.70, 0.98)	0.75 (0.63, 0.89)	0.80 (0.67, 0.95)	0.74 (0.63, 0.87)	< 0.001
HR (95% CI)[c]	1.00	1.02 (0.87, 1.20)	0.87 (0.73, 1.03)	0.79 (0.67, 0.94)	0.80 (0.67, 0.95)	0.75 (0.65, 0.88)	< 0.001
HR (95% CI)[d]	1.00	1.02 (0.87, 1.21)	0.86 (0.73, 1.03)	0.79 (0.66, 0.94)	0.79 (0.67, 0.94)	0.75 (0.64, 0.88)	< 0.001
	Fifths of season-standardized circulating $1,25(OH)_2D$					**Per 80 Percentile increase**	
	1	**2**	**3**	**4**	**5**		
Person-years	4,687	4,910	5,131	4,945	4,668		
Cases/deaths	378/51	378/63	376/44	379/54	378/46	1,889/258	
HR (95% CI)[a]	1.00	1.28 (0.88, 1.85)	0.86 (0.57, 1.29)	1.08 (0.73, 1.58)	0.94 (0.63, 1.41)	0.89 (0.63, 1.26)	0.51
HR (95% CI)[b]	1.00	1.27 (0.87, 1.85)	0.92 (0.61, 1.39)	1.17 (0.79, 1.72)	1.01 (0.67, 1.51)	0.97 (0.68, 1.38)	0.88
HR (95% CI)[c]	1.00	1.02 (0.69, 1.49)	0.87 (0.58, 1.32)	1.18 (0.80, 1.75)	1.00 (0.66, 1.50)	1.06 (0.74, 1.52)	0.74
HR (95% CI)[d]	1.00	0.96 (0.66, 1.41)	0.86 (0.56, 1.30)	1.15 (0.78, 1.71)	1.01 (0.67, 1.53)	1.09 (0.75, 1.57)	0.65
	Pre-defined categories of circulating 25(OH)D (nmol/L)					**Per 50 nmol/L increase**	
	<30	**30 to <50**	**50 to <75**	**≥75**	**-**		
Person-years	7,063	22,196	34,537	23,130	-		
Cases/deaths	1,424/218	3,773/365	4,805/472	2,633/261	-	12,635/1,316	
HR (95% CI)[a]	1.00	0.82 (0.69, 0.98)	0.77 (0.64, 0.92)	0.62 (0.50, 0.76)	-	0.71 (0.61, 0.83)	<0.001
HR (95% CI)[b]	1.00	0.85 (0.71, 1.01)	0.80 (0.67, 0.96)	0.68 (0.55, 0.84)	-	0.76 (0.66, 0.89)	0.001
HR (95% CI)[c]	1.00	0.83 (0.70, 1.00)	0.78 (0.65, 0.93)	0.67 (0.54, 0.82)	-	0.75 (0.65, 0.88)	<0.001
HR (95% CI)[d]	1.00	0.83 (0.70, 0.99)	0.78 (0.65, 0.93)	0.66 (0.54, 0.82)	-	0.75 (0.64, 0.87)	<0.001

[a]Unadjusted Cox proportional hazard regression models, stratified by study

[b]Cox proportional hazard regression models stratified by study and adjusted for age at blood collection, marital status, smoking status, education, BMI, and height

[c]Models further adjusted for prostate cancer stage (localized, advanced, unknown) and prostate cancer grade (low-intermediate, high, unknown)

[d]Models further adjusted for time between blood collection and cancer diagnosis (0 to <5 years, 5 to <10 years, or ≥10 years)

[e]P_{trend} was calculated by assigning the quintile categorical variable with a continuous variable of 0, 0.25, 0.5, 0.75 and 1

Table 3 Hazard ratios (HRs) for death from other causes by categories of circulating season-standardized 25(OH)D and $1,25(OH)_2D$ in men diagnosed with prostate cancer in 13 prospective studies

	Fifths of season-standardized circulating 25(OH)D					Per 80 Percentile increase	P_{trend}[e]
	1	2	3	4	5		
Person-years	16,927	17,241	17,394	17,897	17,467		
Cases/deaths	2,532/465	2,525/434	2,526/418	2,530/383	2,522/429	12,635/2,129	
HR (95% CI)[a]	1.00	0.93 (0.81, 1.06)	0.90 (0.79, 1.03)	0.72 (0.63, 0.82)	0.86 (0.75, 0.98)	0.80 (0.71, 0.90)	<0.001
HR (95% CI)[b]	1.00	0.96 (0.84, 1.10)	0.94 (0.82, 1.08)	0.76 (0.67, 0.88)	0.92 (0.80, 1.05)	0.85 (0.75, 0.96)	0.01
HR (95% CI)[c]	1.00	0.96 (0.84, 1.09)	0.94 (0.83, 1.08)	0.76 (0.66, 0.88)	0.91 (0.80, 1.04)	0.85 (0.75, 0.96)	0.009
HR (95% CI)[d]	1.00	0.96 (0.84, 1.09)	0.94 (0.82, 1.08)	0.76 (0.66, 0.87)	0.91 (0.80, 1.05)	0.85 (0.75, 0.96)	0.009
	Fifths of season-standardized circulating 1, $25(OH)_2D$					Per 80 Percentile increase	
	1	2	3	4	5		
Person-years	4,687	4,910	5,131	4,945	4,668		
Cases/deaths	378/174	378/161	376/153	379/155	378/168	1,889/811	
HR (95% CI)[a]	1.00	0.91 (0.73, 1.13)	1.02 (0.82, 1.26)	0.96 (0.77, 1.19)	1.18 (0.96, 1.47)	1.17 (0.96, 1.42)	0.13
HR (95% CI)[b]	1.00	0.87 (0.70, 1.08)	1.02 (0.82, 1.27)	0.95 (0.76, 1.18)	1.19 (0.96, 1.47)	1.18 (0.97, 1.44)	0.11
HR (95% CI)[c]	1.00	0.89 (0.72, 1.11)	1.05 (0.84, 1.31)	0.94 (0.76, 1.18)	1.13 (0.91, 1.41)	1.12 (0.92, 1.37)	0.25
HR (95% CI)[d]	1.00	0.88 (0.71, 1.10)	1.03 (0.83, 1.29)	0.92 (0.73, 1.14)	1.13 (0.91, 1.41)	1.11 (0.91, 1.36)	0.29
	Pre-defined categories of circulating 25(OH)D (nmol/L)					Per 50 nmol/L increase	
	< 30	30 to < 50	50 to < 75	≥ 75	-		
Person-years	7,063	22,196	34,537	23,130	-		
Cases/deaths	1,424/228	3,773/515	4,805/768	2,633/618	-	12,635/2,129	
HR (95% CI)[a]	1.00	0.89 (0.75, 1.05)	0.75 (0.64, 0.88)	0.74 (0.62, 0.88)	-	0.81 (0.72, 0.91)	<0.001
HR (95% CI)[b]	1.00	0.91 (0.77, 1.07)	0.80 (0.68, 0.94)	0.79 (0.66, 0.94)	-	0.85 (0.76, 0.96)	0.007
HR (95% CI)[c]	1.00	0.91 (0.77, 1.08)	0.80 (0.68, 0.94)	0.79 (0.66, 0.94)	-	0.85 (0.75, 0.95)	0.006
HR (95% CI)[d]	1.00	0.91 (0.77, 1.07)	0.79 (0.67, 0.94)	0.79 (0.66, 0.94)	-	0.85 (0.75, 0.95)	0.006

[a]Unadjusted Cox proportional hazard regression models, stratified by study

[b]Cox proportional hazard regression models stratified by study, and adjusted for age at blood collection, marital status, smoking status, education, BMI, and height

[c]Models further adjusted for prostate cancer stage (localized, advanced, unknown) and prostate cancer grade (low-intermediate, high, unknown)

[d]Models further adjusted for time between blood collection and cancer diagnosis (0 to < 5 years, 5 to < 10 years, or ≥ 10 years)

[e]P_{trend} was calculated by assigning the quintile categorical variable with a continuous variable of 0, 0.25, 0.5, 0.75 and 1

Table 4 Hazard ratios (HRs) for prostate cancer death by categories of circulating season-standardized 25(OH)D in men diagnosed with prostate cancer with complete information on both stage and grade from 8 studies

		Fifths of season-standardized circulating 25(OH)D					Per 80 Percentile increase	P_{trend}[e]
	Cases/deaths	1	2	3	4	5		
HR (95% CI)[a]	5078/761	1.00	1.15 (0.92, 1.42)	0.90 (0.72, 1.13)	0.79 (0.63, 1.00)	0.85 (0.67, 1.07)	0.76 (0.62, 0.93)	0.009
HR (95% CI)[b]	5078/761	1.00	1.16 (0.93, 1.44)	0.95 (0.76, 1.19)	0.86 (0.68, 1.08)	0.84 (0.67, 1.07)	0.78 (0.63, 0.96)	0.02
HR (95% CI)[c]	5078/761	1.00	1.20 (0.96, 1.49)	0.91 (0.73, 1.14)	0.80 (0.64, 1.01)	0.87 (0.69, 1.09)	0.76 (0.62, 0.94)	0.01
HR (95% CI)[d]	5078/761	1.00	1.19 (0.96, 1.48)	0.96 (0.77, 1.21)	0.88 (0.70, 1.11)	0.88 (0.69, 1.11)	0.81 (0.65, 0.99)	0.04

All Cox proportional hazard regression models were stratified by study, and adjusted for age at blood collection, marital status, smoking status, education, BMI, and height and are restricted to participants with complete information on both stage and grade

[a]Multivariable-adjusted model, with additional adjustment for time from blood collection to diagnosis

[b]Model (a) was further adjusted for stage of prostate cancer

[c]Model (a) was further adjusted for grade of prostate cancer

[d]Model (a) was further adjusted for both stage and grade of prostate cancer

[e]P_{trend} was calculated by assigning the quintile categorical variable with a continuous variable of 0, 0.25, 0.5, 0.75 and 1

(HR for 80-percentile increase = 0.97, 95% CI: 0.83, 1.12, P_{trend} = 0.66, Additional File 1: Table S7). In the subgroup of men with unknown tumor grade or stage, the inverse association between circulating 25(OH)D and risk of prostate cancer death did not differ materially (HR for 80-percentile increase = 0.72, 95% CI: 0.56, 0.91, P_{trend} = 0.007, Additional File 1: Table S8). In sensitivity analyses accounting for competing risks of death using the Fine-Gray model, the inverse association between circulating 25(OH)D and prostate cancer mortality remained consistent with the primary analysis (sub-distribution HR [SHR] for the 80-percentile increase = 0.81, 95% CI: 0.70, 0.94, P_{trend} = 0.007, Additional File 1: Table S9). In contrast, no significant associations were observed for other cause mortality when prostate cancer death was treated as a competing risk (SHR = 0.92, 95% CI: 0.82, 1.03, P_{trend}

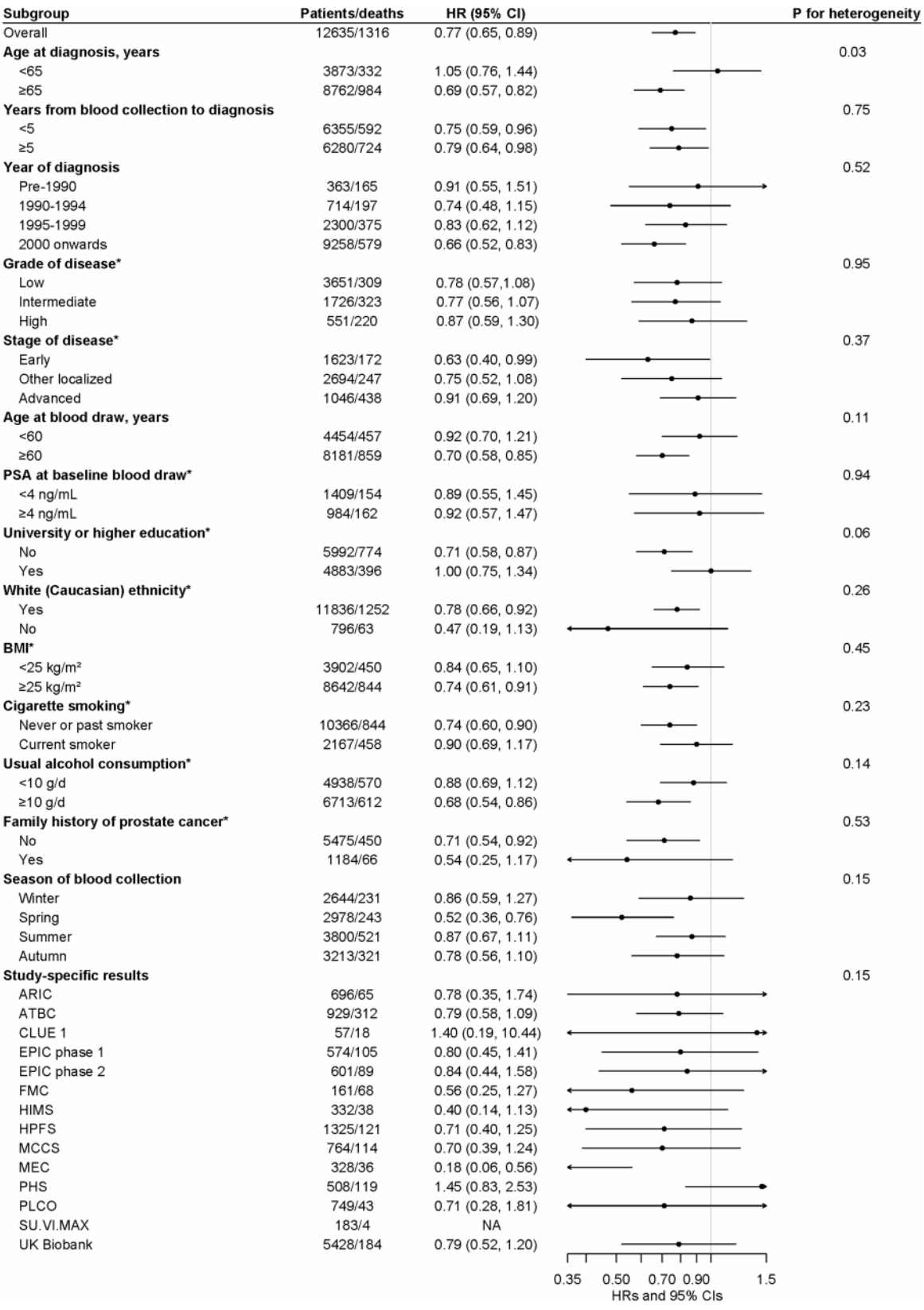


Fig. 1 (See legend on next page.)

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Fig. 1 Hazard ratios (HRs) of prostate cancer-specific mortality for a study-specific 80-percentile increase in season-standardized 25(OH)D according to selected factors in men diagnosed with prostate cancer. [a]Cox proportional hazard regression models stratified by study, and adjusted for age at blood collection, marital status, smoking status, education, BMI, and height. *Unknown for some cases and excluded from the stratified analysis. [#]Obtained by comparing models with and without a season-standardized 25(OH)D by study interaction term. All other tests of heterogeneity use the inverse variance method, assuming independence of risk between the categories

= 0.14, Additional File 1: Table S10). The inverse association with prostate cancer-specific mortality remained robust during the first 0–2 years of follow-up (short lag; HR per 80-percentile increase = 0.74, 95% CI: 0.54, 0.996, P_{trend} = 0.047) and 2–4 years of follow-up (mid lag; HR per 80-percentile increase = 0.71, 95% CI: 0.52, 0.99, P_{trend} = 0.04, Additional File 1: Table S11). Similarly, the inverse association with mortality from other causes remained stable during 0–2 years of follow-up (HR per 80-percentile increase = 0.69, 95% CI: 0.49, 0.98, P_{trend} = 0.04) and 2–4 years of follow-up (HR per 80-percentile increase = 0.72, 95% CI: 0.52, 0.996; P_{trend} = 0.047, Additional File 1: Table S12).

Stratified analyses showed generally similar associations of circulating 25(OH)D (and 1,25$(OH)_2$D status) with prostate cancer-specific mortality across key population subgroups (Fig. 1 and Additional File 1: Fig. S1), with no statistical evidence for heterogeneity including by PSA, stage and grade with the exception of significant heterogeneity for circulating 25(OH)D by age at diagnosis (P = 0.03), with HRs (95% CI) of 1.05 (0.76–1.44) in men diagnosed before age 65 and 0.69 (0.57–0.82) in men diagnosed aged 65 and above, and possibly education (P = 0.06; HRs of 1.00 (0.75–1.34) and 0.71 (0.58–0.87) in men with and without a university or higher education, respectively). However, none of these associations achieved the formal threshold of statistical significance for subgroup interaction tests (all P for interaction > 0.0033). There was no evidence of heterogeneity in the associations across the contributing studies, and no significant effect modification by tumour characteristics, time from blood collection to diagnosis, or other case-specific characteristics (Fig. 1 and Additional File 1: Fig. S1).

Discussion

In this international collaborative pooling analysis of men diagnosed with prostate cancer, we found significant inverse associations between circulating 25(OH)D concentrations and both prostate cancer-specific mortality and, to a lesser extent, mortality from other causes. The association with prostate cancer-specific death was similar across a range of risk factor subgroups.

We also evaluated clinical categories of vitamin D status which resulted in stronger inverse dose-dependent associations when using < 30 nmol/L as the reference limit, which has been associated with poorer treatment outcomes in other malignancies [56]. While the vitamin D association appeared to be stronger for prostate cancer-specific mortality than for other causes of death—and hence might be interpreted as suggesting that vitamin D could be involved in limiting cancer progression—both associations may be affected by residual confounding, although a recent methodological study using data from the ATBC cohort (included in current analysis), did not support a role for biases in the association with prostate cancer mortality [57]. In terms of the temporality of the association, all blood samples in our collaborating studies were collected at least one year before cancer diagnosis, and therefore vitamin D biochemical status should not be influenced by cancer treatment—which has been shown in some previous studies to reduce vitamin D concentration; [58] however, it is unclear whether early stage tumours may affect vitamin D concentrations. Furthermore, the inverse associations remained essentially unchanged in analyses adjusting for (or stratified by) time interval from blood collection to cancer diagnosis.

Although there was no statistically significant effect modification by disease stage or grade, the 25(OH)D-prostate cancer mortality association appeared stronger among cases diagnosed with earlier stage disease, which might be interpreted as suggesting a suppressive role for vitamin D in early tumor growth/cell proliferation rather than in invasion or metastasis; however, due to the lack of effect modification by tumour grade this finding should be interpreted carefully. Alternatively, the finding may be influenced by detection bias if "health conscious" men with higher vitamin D concentrations are also more likely to be detected at an earlier stage and therefore less likely to die from the disease. We previously found positive associations of circulating 25(OH)D concentration with risks for overall and nonaggressive prostate cancer risk in our prospective analyses of circulating 25(OH)D concentrations and risk of prostate cancer in this pooling project [14], with no association for aggressive disease, which supports the possibility of this detection bias hypothesis.

Few prospective studies have examined whether vitamin D is related to prostate cancer-specific death among men diagnosed with prostate cancer. The present collaborative analysis is the largest to examine the association, and our findings are concordant with most previous studies showing inverse associations [15, 19–22, 59], though a few other studies did not detect an association [18, 60]. For example, a recent meta-analysis of six studies, which included > 7,000 cases, reported lower

prostate cancer-specific mortality in prostate cancer patients with higher 25(OH)D concentrations, with a 9% risk reduction per 20 nmol/L 25(OH)D increment [19]. However, three of the six studies were conducted using post-diagnostic 25(OH)D concentrations which may bias the findings through reverse causality or other factors. In fact, a recent study documented the high prevalence of vitamin deficiencies in cancer patients, including especially vitamin D (i.e. 89% of patients being clinically deficient) [61]. Relevant to cohort follow-up time, the ATBC Study of 1,294 cancer cases with a 28-years of follow-up (of which a subset is included in the current pooled analysis) observed that men in the highest category of pre-diagnostic serum 25(OH)D experienced a 23% lower risk of prostate cancer mortality compared with those with the lowest concentrations (P trend = 0.02) [22]. One clinical cross-sectional study showed that concentrations of vitamin D in the insufficiency or deficiency range were related to higher odds of adverse pathology among patients who underwent radical prostatectomy, indicating a prognostic role for vitamin D status [59]. Similarly, greater prostate tumor tissue expression of the VDR protein was associated with lower subsequent risk of progression to lethal prostate cancer and improved clinical characteristics, including lower Gleason score and locally confined tumors, supporting the involvement of the vitamin D pathway in prostate cancer progression [62].

There is some evidence to suggest that vitamin D may inhibit carcinogenesis, including tumor progression, however, the significance of this for prostate cancer is still unclear [5]. A dose-response meta-analysis of prospective studies indicated that higher circulating 25(OH)D concentration was associated with an elevated risk of incident prostate cancer [63]. The vitamin D–calcium pathway may also be relevant, as the principal function of vitamin D in calcium homeostasis is to increase calcium absorption from the intestine [64]. In addition, a systematic review and meta-analysis of cohort studies reported that high intakes of dairy products and total, dietary, and dairy calcium may increase total prostate cancer risk [65]. Some in vitro studies suggest that vitamin D may interact with multiple pathways known to be involved in prostate cancer development and progression. In particular, vitamin D may interact with androgens in part through VDR activation, to down-regulate androgen receptor expression and inhibit androgen signaling [5, 58, 66], as well as induce cell-cycle arrest and regulate genes that control androgen catabolism [5, 67, 68].

The major strengths of this study include the prospective design of the contributing studies (i.e. the use of pre-diagnostic concentrations of 25(OH)D and $1,25(OH)_2D$), and the large multi-cohort sample size, which provides power to both detect moderate 25(OH)D associations with mortality from prostate cancer and other causes and assess effect modification by other risk factors. However, our subgroup analyses for $1,25(OH)_2D$ should be interpreted carefully given the small number of studies and cases and the limited usefulness of this biomarker to reflect overall vitamin D status [69]. Several study limitations should also be noted. The use of a single vitamin D measurement may be associated with measurement error as it might not reflect long-term concentrations; although data from the Women's Health Initiative study has shown moderate correlations of 0.42 to 0.70 between multiple vitamin 25(OH)D measurements taken 3 and 14 years apart [70], it is likely that an individual's vitamin D biochemical status will have changed during follow-up (for example, following cancer treatment). The shorter median time to death from prostate cancer (4.0 years) compared with other causes (7.3 years) underscores the presence of competing risks in this population. While the median follow-up of 5.6 years captured early-to-mid-term mortality events, future studies with long-term follow-up are warranted to re-examine these associations. Most of the participants in this collaborative analysis were of White European ancestry (and we did not adjust for race and ethnicity in the multivariable models), which might limit generalization of our findings to other races and ethnicities (although we believe it unlikely that the association would vary markedly by ethnicity). Nevertheless, our findings should be re-examined in more diverse populations. Notably, 17.8% of participants in our pooled dataset reported a positive family history of prostate cancer, exceeding the ~ 7% prevalence typically observed in unscreened populations [71, 72]. This likely reflects our case-only design and the resulting overrepresentation of higher-risk individuals. Consequently, the generalizability of our findings to the general population may be somewhat limited. Nevertheless, this design enhances relevance to "at-high-risk" men and provides supportive evidence that maintaining adequate circulating 25(OH)D concentrations may be particularly important in this subgroup. Also, we cannot preclude the possibility of residual confounding, such as by sunlight exposure, outdoor physical activity, concomitant D-vitamin supplementation, and/or renal failure, even though we adjusted for several known potential confounders. Finally, although discrepancies between registry-based and expert-committee-based cause of death may exist, previous validation studies have demonstrated high concordance (agreement 97.7% for 305 out of 311 cases, kappa coefficient of 0.95; sensitivity of 96.1%) [73]. Fall et al. also reported an 86% overall agreement between official death certificates and reviewed medical records in a population-based study of 5,675 Swedish prostate cancer patients, with an approximately 3% higher registration of prostate cancer deaths in official death certificates [74]. Registry linkage therefore remains

an appropriate approach for large-scale epidemiological studies, although residual misclassification cannot be fully excluded.

Conclusions

In this prospective pooled analysis using multi-national data for over 12,000 men diagnosed with prostate cancer, we found that higher pre-diagnostic circulating vitamin D (i.e. 25(OH)D) concentrations are associated with longer survival, particularly in older men. This inverse association was stronger for prostate cancer-specific death than for deaths from other causes combined, and it appeared to be stronger for cases diagnosed in an earlier stage of disease. Further research is required to establish whether the association may be contributed to by biases such as the earlier detection of disease and thus better survival in men with higher vitamin D in these populations, as well as to investigate possible biological impacts of vitamin D on prostate cancer progression.

Abbreviations

1,25(OH)2D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
ARIC	Atherosclerosis Risk in Communities Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BMI	body mass index
CI	confidence interval
CLUE	Campaign Against Cancer and Stroke ("Give Us a Clue to Cancer") Study
DRE	digital rectal examination
EHNBPCCG	Endogenous Hormones, Nutritional Biomarkers and Prostate Cancer Collaborative Group
EPIC	European Prospective Investigation into Cancer and Nutrition
FMC	Finnish Mobile Clinic Health Examination Survey
GVIF	generalized variance inflation factor
HIMS	Health In Men Study
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
IQR	interquartile range
MCCS	Melbourne Collaborative Cohort Study
MEC	Multiethnic Cohort
PHS	Physicians' Health Study
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PSA	prostate-specific antigen
SD	standard deviation
SHR	sub-distribution hazard ratio
SU.VI.MAX	SUpplémentation en VItamines et Minéraux AntioXydants
TNM	tumor-node-metastasis
VDR	vitamin D receptor

Supplementary Information

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Supplementary Material 1: Supplementary methods, Tables S1–S13, and Fig. S1.

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Author contributions

JH, APC, DA, and NA contributed to concept and study design. JH, APC, DA, and NA prepared the manuscript. DA and JH supervised the project. All authors (JH, APC, RT, PA, DC, MP, UN, SW, NF, AJ, IJ, EP, CJ, BY, LF, LM, KT, PK, PL, AM, KV, KH, GG, MBS, MD, MT, JMH, LL, MS, TK, DA, and NA) provided input on statistical analysis and interpretation of results. All authors (JH, APC, RT, PA, DC, MP, UN, SW, NF, AJ, IJ, EP, CJ, BY, LF, LM, KT, PK, PL, AM, KV, KH, GG, MBS, MD, MT, JMH, LL, MS, TK, DA, and NA) revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Data availability

Because of previously enacted EU General Data Protection Regulation privacy rules and an existing data use agreement between Oxford University (UK) and the US National Cancer Institute, the EHNBPCCG Study data and materials described in the article may not be made publicly available for the purpose of reproducing the findings. Data requests are subject to approval by the study review committees. To minimize the possibility of unintentionally sharing information that can be used to identify private information, a subset of the data generated for this study will be made available first on reasonable request.

Declarations

Ethics approval and consent to participate

Each individual study obtained ethical approval, and written informed consent was obtained from all participants. Details of the ethics review bodies and ethics approval/reference numbers for each cohort are provided in Additional File 1: Table S13.

Consent for publication

Not applicable.

Competing interests

Dr. Huang is a member of the BMC Medicine Editorial Board. She was not involved in handling this manuscript during the submission and the review processes for the journal. The remaining authors declare that they have no competing interests.

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References

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020;77(1):38–52.
2. Conti DV, Darst BF, Moss LC, Saunders EJ, Sheng X, Chou A, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. Nat Genet. 2021;53(1):65–75.
3. Attard G, Parker C, Eeles RA, Schroder F, Tomlins SA, Tannock I, et al. Prostate cancer. Lancet. 2016;387(10013):70–82.
4. Darcey E, Pereira G, Salter A, Fritschi L, Leavy J, Ambrosini GL, et al. The Impact of Lifestyle-related Factors on Survival After a Prostate Cancer Diagnosis. Eur Urol. 2019;75(5):884–5.
5. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. 2014;14(5):342–57.
6. Cashman KD, van den Heuvel EG, Schoemaker RJ, Preveraud DP, Macdonald HM, Arcot J. 25-Hydroxyvitamin D as a Biomarker of Vitamin D Status and Its Modeling to Inform Strategies for Prevention of Vitamin D Deficiency within the Population. Adv Nutr. 2017;8(6):947–57.
7. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control. 2005;16(2):83–95.
8. Townsend K, Evans KN, Campbell MJ, Colston KW, Adams JS, Hewison M. Biological actions of extra-renal 25-hydroxyvitamin D-1alpha-hydroxylase and implications for chemoprevention and treatment. J Steroid Biochem Mol Biol. 2005;97(1–2):103–9.
9. Richards Z, Batai K, Farhat R, Shah E, Makowski A, Gann PH, et al. Prostatic compensation of the vitamin D axis in African American men. JCI Insight. 2017;2(2):e91054.
10. Munetsuna E, Kawanami R, Nishikawa M, Ikeda S, Nakabayashi S, Yasuda K, et al. Anti-proliferative activity of 25-hydroxyvitamin D3 in human prostate cells. Mol Cell Endocrinol. 2014;382(2):960–70.
11. Susa T, Iizuka M, Okinaga H, Tamamori-Adachi M, Okazaki T. Without 1α-hydroxylation, the gene expression profile of 25(OH)D(3) treatment overlaps deeply with that of 1,25(OH)(2)D(3) in prostate cancer cells. Sci Rep. 2018;8(1):9024.
12. Ramakrishnan S, Steck SE, Arab L, Zhang H, Bensen JT, Fontham ETH, et al. Association among plasma 1,25(OH)(2) D, ratio of 1,25(OH)(2) D to 25(OH)D, and prostate cancer aggressiveness. Prostate. 2019;79(10):1117–24.
13. Carlberg C, Munoz A. An update on vitamin D signaling and cancer. Semin Cancer Biol. 2022;79:217–30.
14. Travis RC, Perez-Cornago A, Appleby PN, Albanes D, Joshu CE, Lutsey PL, et al. A Collaborative Analysis of Individual Participant Data from 19 Prospective Studies Assesses Circulating Vitamin D and Prostate Cancer Risk. Cancer Res. 2019;79(1):274–85.
15. Mondul AM, Weinstein SJ, Moy KA, Mannisto S, Albanes D. Circulating 25-Hydroxyvitamin D and Prostate Cancer Survival. Cancer Epidemiol Biomarkers Prev. 2016;25(4):665–9.
16. Albanes D, Mondul AM, Yu K, Parisi D, Horst RL, Virtamo J, et al. Serum 25-hydroxy vitamin D and prostate cancer risk in a large nested case-control study. Cancer Epidemiol Biomarkers Prev. 2011;20(9):1850–60.
17. Travis RC, Crowe FL, Allen NE, Appleby PN, Roddam AW, Tjonneland A, et al. Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Epidemiol. 2009;169(10):1223–32.
18. Shui IM, Mondul AM, Lindstrom S, Tsilidis KK, Travis RC, Gerke T, et al. Circulating vitamin D, vitamin D-related genetic variation, and risk of fatal prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer. 2015;121(12):1949–56.
19. Song ZY, Yao Q, Zhuo Z, Ma Z, Chen G. Circulating vitamin D level and mortality in prostate cancer patients: a dose-response meta-analysis. Endocr Connect. 2018;7(12):R294–303.
20. Shui IM, Mucci LA, Kraft P, Tamimi RM, Lindstrom S, Penney KL, et al. Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer: a prospective nested case-control study. J Natl Cancer Inst. 2012;104(9):690–9.
21. Tretli S, Hernes E, Berg JP, Hestvik UE, Robsahm TE. Association between serum 25(OH)D and death from prostate cancer. Br J Cancer. 2009;100(3):450–4.
22. Weinstein SJ, Mondul AM, Yu K, Layne TM, Abnet CC, Freedman ND, et al. Circulating 25-hydroxyvitamin D up to 3 decades prior to diagnosis in relation to overall and organ-specific cancer survival. Eur J Epidemiol. 2018;33(11):1087–99.
23. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst. 2008;100(3):170–83.
24. Roddam AW, Allen NE, Appleby P, Key TJ, Ferrucci L, Carter HB, et al. Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. Ann Intern Med. 2008;149(7):461–71,W83–8.
25. Travis RC, Appleby PN, Martin RM, Holly JMP, Albanes D, Black A, et al. A Meta-analysis of Individual Participant Data Reveals an Association between Circulating Levels of IGF-I and Prostate Cancer Risk. Cancer Res. 2016;76(8):2288–300.

26. Crowe FL, Appleby PN, Travis RC, Barnett M, Brasky TM, et al. Circulating fatty acids and prostate cancer risk: individual participant meta-analysis of prospective studies. J Natl Cancer Inst. 2014;106(9):dju240.
27. Allen NE, Travis RC, Appleby PN, Albanes D, Barnett MJ, Black A, et al. Selenium and Prostate Cancer: Analysis of Individual Participant Data From Fifteen Prospective Studies. J Natl Cancer Inst. 2016;108(11):djw153.
28. Key TJ, Appleby PN, Allen NE, Travis RC, Roddam AW, Jenab M, et al. Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. Am J Clin Nutr. 2007;86(3):672–81.
29. Price AJ, Travis RC, Appleby PN, Albanes D, Barricarte Gurrea A, Bjorge T, et al. Circulating Folate and Vitamin B12 and Risk of Prostate Cancer: A Collaborative Analysis of Individual Participant Data from Six Cohorts Including 6875 Cases and 8104 Controls. Eur Urol. 2016;70(6):941–51.
30. Joshu CE, Barber JR, Coresh J, Couper DJ, Mosley TH, Vitolins MZ, et al. Enhancing the Infrastructure of the Atherosclerosis Risk in Communities (ARIC) Study for Cancer Epidemiology Research: ARIC Cancer. Cancer Epidemiol Biomarkers Prev. 2018;27(3):295–305.
31. Braun MM, Helzlsouer KJ, Hollis BW, Comstock GW. Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). Cancer Causes Control. 1995;6(3):235–9.
32. Knekt P, Laaksonen M, Mattila C, Harkanen T, Marniemi J, Heliovaara M, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology. 2008;19(5):666–71.
33. Wong YY, Hyde Z, McCaul KA, Yeap BB, Golledge J, Hankey GJ, et al. In older men, lower plasma 25-hydroxyvitamin D is associated with reduced incidence of prostate, but not colorectal or lung cancer. PLoS ONE. 2014;9(6):e99954.
34. Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci E. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. Cancer Causes Control. 2004;15(3):255–65.
35. Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Hollis BW, Giovannucci E. Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and prostate cancer risk. Prostate. 2007;67(9):911–23.
36. Milne RL, Fletcher AS, MacInnis RJ, Hodge AM, Hopkins AH, Bassett JK, et al. Cohort Profile: The Melbourne Collaborative Cohort Study (Health 2020). Int J Epidemiol. 2017;46(6):1757–i1757.
37. Park SY, Cooney RV, Wilkens LR, Murphy SP, Henderson BE, Kolonel LN. Plasma 25-hydroxyvitamin D and prostate cancer risk: the multiethnic cohort. Eur J Cancer. 2010;46(5):932–6.
38. Gann PH, Ma J, Hennekens CH, Hollis BW, Haddad JG, Stampfer MJ. Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. Cancer Epidemiol Biomarkers Prev. 1996;5(2):121–6.
39. Li H, Stampfer MJ, Hollis JB, Mucci LA, Gaziano JM, Hunter D, et al. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. PLoS Med. 2007;4(3):e103.
40. Ma J, Stampfer MJ, Gann PH, Hough HL, Giovannucci E, Kelsey KT, et al. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. Cancer Epidemiol Biomarkers Prev. 1998;7(5):385–90.
41. Ahn J, Albanes D, Berndt SI, Peters U, Chatterjee N, Freedman ND, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. Carcinogenesis. 2009;30(5):769–76.
42. Deschasaux M, Souberbielle JC, Latino-Martel P, Sutton A, Charnaux N, Druesne-Pecollo N, et al. A prospective study of plasma 25-hydroxyvitamin D concentration and prostate cancer risk. Br J Nutr. 2016;115(2):305–14.
43. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
44. Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer. 2004;108(1):104–8.
45. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control. 2000;11(9):847–52.
46. Nomura AM, Stemmermann GN, Lee J, Kolonel LN, Chen TC, Turner A, et al. Serum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States). Cancer Causes Control. 1998;9(4):425–32.
47. Corder EH, Friedman GD, Vogelman JH, Orentreich N. Seasonal variation in vitamin D, vitamin D-binding protein, and dehydroepiandrosterone: risk of prostate cancer in black and white men. Cancer Epidemiol Biomarkers Prev. 1995;4(6):655–9.
48. Corder EH, Guess HA, Hulka BS, Friedman GD, Sadler M, Vollmer RT, et al. Vitamin D and prostate cancer: a prediagnostic study with stored sera. Cancer Epidemiol Biomarkers Prev. 1993;2(5):467–72.
49. Barnett CM, Nielson CM, Shannon J, Chan JM, Shikany JM, Bauer DC, et al. Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men. Cancer Causes Control. 2010;21(8):1297–303.
50. Jacobs ET, Giuliano AR, Martínez ME, Hollis BW, Reid ME, Marshall JR. Plasma levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and the risk of prostate cancer. J Steroid Biochem Mol Biol. 2004;89–90(1–5):533–7.
51. Ordóñez-Mena JM, Schöttker B, Fedirko V, Jenab M, Olsen A, Halkjær J, et al. Pre-diagnostic vitamin D concentrations and cancer risks in older individuals: an analysis of cohorts participating in the CHANCES consortium. Eur J Epidemiol. 2016;31(3):311–23.
52. Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, Chatterjee N, et al. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. J Natl Cancer Inst. 2008;100(11):796–804.
53. Heath AK, Williamson EJ, Ebeling PR, Kvaskoff D, Eyles DW, English DR. Measurements of 25-hydroxyvitamin D concentrations in archived dried blood spots are reliable and accurately reflect those in plasma. J Clin Endocrinol Metab. 2014;99(9):3319–24.
54. Key TJ, Appleby PN, Allen NE, Reeves GK. Pooling biomarker data from different studies of disease risk, with a focus on endogenous hormones. Cancer Epidemiol Biomarkers Prev. 2010;19(4):960–5.
55. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Dietary reference intakes for calcium and vitamin D. Washington (DC): National Academies Press; 2011.
56. Borchmann S, Cirillo M, Goergen H, Meder L, Sasse S, Kreissl S, et al. Pretreatment Vitamin D Deficiency Is Associated With Impaired Progression-Free and Overall Survival in Hodgkin Lymphoma. J Clin Oncol. 2019;37(36):3528–37.
57. Etievant L, Gail MH, Albanes D. Disentangling discordant vitamin D associations with prostate cancer incidence and fatality in a large, nested case-control study. Int J Epidemiol. 2024;53(5):dyae110.
58. Duncan A, Talwar D, McMillan DC, Stefanowicz F, O'Reilly DS. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. Am J Clin Nutr. 2012;95(1):64–71.
59. Nyame YA, Murphy AB, Bowen DK, Jordan G, Batai K, Dixon M, et al. Associations Between Serum Vitamin D and Adverse Pathology in Men Undergoing Radical Prostatectomy. J Clin Oncol. 2016;34(12):1345–9.
60. Holt SK, Kolb S, Fu R, Horst R, Feng Z, Stanford JL. Circulating levels of 25-hydroxyvitamin D and prostate cancer prognosis. Cancer Epidemiol. 2013;37(5):666–70.
61. Zhu W, Liu C, Yao K, Zhang X, Huang J, Cheng M, et al. Micronutrient deficiency detected by liquid chromatography-tandem mass spectrometry and its association with clinical outcome of cancer patients-a prospective cohort study. BMC Med. 2025;23(1):539.
62. Hendrickson WK, Flavin R, Kasperzyk JL, Fiorentino M, Fang F, Lis R, et al. Vitamin D receptor protein expression in tumor tissue and prostate cancer progression. J Clin Oncol. 2011;29(17):2378–85.
63. Gao J, Wei W, Wang G, Zhou H, Fu Y, Liu N. Circulating vitamin D concentration and risk of prostate cancer: a dose-response meta-analysis of prospective studies. Ther Clin Risk Manag. 2018;14:95–104.
64. Christakos S, Dhawan P, Porta A, Mady LJ, Seth T. Vitamin D and intestinal calcium absorption. Mol Cell Endocrinol. 2011;347(1–2):25–9.
65. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr. 2015;101(1):87–117.
66. Sun WJ, Liang F, Zhao H, Wang YM, Zhou ZY, Xu H, et al. Androgen induces 3′UTR shortening of de novo lipogenesis genes by alternative polyadenylation in prostate cancer cells. Sci China Life Sci. 2025;68(11):3217–30.
67. Maund SL, Barclay WW, Hover LD, Axanova LS, Sui G, Hipp JD, et al. Interleukin-1alpha mediates the antiproliferative effects of 1,25-dihydroxyvitamin D3 in prostate progenitor/stem cells. Cancer Res. 2011;71(15):5276–86.
68. Zhao XY, Peehl DM, Navone NM, Feldman D. 1alpha,25-dihydroxyvitamin D3 inhibits prostate cancer cell growth by androgen-dependent and androgen-independent mechanisms. Endocrinology. 2000;141(7):2548–56.
69. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency:

an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
70. Meng JE, Hovey KM, Wactawski-Wende J, Andrews CA, Lamonte MJ, Horst RL, et al. Intraindividual variation in plasma 25-hydroxyvitamin D measures 5 years apart among postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2012;21(6):916–24.
71. Abdel-Rahman O. Prostate Cancer Incidence and Mortality in Relationship to Family History of Prostate Cancer; Findings From The PLCO Trial. Clin Genitourin Cancer. 2019;17(4):e837–44.
72. Roemeling S, Roobol MJ, de Vries SH, Gosselaar C, van der Kwast TH, Schröder FH. Prevalence, treatment modalities and prognosis of familial prostate cancer in a screened population. J Urol. 2006;175(4):1332–6.
73. Mäkinen T, Karhunen P, Aro J, Lahtela J, Määttänen L, Auvinen A. Assessment of causes of death in a prostate cancer screening trial. Int J Cancer. 2008;122(2):413–7.
74. Fall K, Strömberg F, Rosell J, Andrèn O, Varenhorst E. Reliability of death certificates in prostate cancer patients. Scand J Urol Nephrol. 2008;42(4):352–7.

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