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Plasma 25-hydroxyvitamin D and prostate cancer risk: The Multiethnic Cohort

Song-Yi Park [a,*], *Robert V. Cooney* [b], *Lynne R. Wilkens* [a], *Suzanne P. Murphy* [a], *Brian E. Henderson* [c], *Laurence N. Kolonel* [a]

[a] *Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813, USA*
[b] *Natural Products and Cancer Biology Program, Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813, USA*
[c] *Department of Preventive Medicine, Keck School of Medicine, University of Southern California, 1441 Eastlake Avenue, Los Angeles, CA 90033, USA*

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ABSTRACT

The purpose of this study was to examine the relationship of plasma 25-hydroxyvitamin D (25(OH)D) concentrations to prostate cancer within a large multiethnic cohort in Hawaii and California using a nested case-control design. The study included 329 incidents of prostate cancer of African American, Native Hawaiian, Japanese, Latino and White ancestry, and 656 controls matched on age, race/ethnicity, date/time of blood collection and fasting status. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI). No association with prostate cancer risk was found in an analysis based on quartiles of 25(OH)D. When clinically defined cutpoints were used, there was no increased risk for the lowest 25(OH)D concentration (OR for <20 versus 30–<50 ng/ml = 1.10, 95% CI = 0.68–1.78), while there was a suggestive increased risk for higher concentrations (OR for ⩾50 ng/ml = 1.52, 95% CI = 0.92–2.51). The findings from this prospective study of men in the Multiethnic Cohort do not support the hypothesis that vitamin D lowers the risk of prostate cancer. Further follow-up is warranted to determine whether the findings are consistent across ethnic groups.

1. Introduction

Ecological studies showing that regions with a higher exposure to ultraviolet radiation tend to have lower prostate cancer mortality rates have generated and supported the hypothesis that vitamin D protects against prostate cancer.[1–3] *In vitro* human cell studies have also demonstrated that vitamin D metabolites suppress the growth and stimulate the differentiation of prostate cancer cells.[4,5] To test this hypothesis in prospective epidemiologic studies, investigators have measured prediagnostic serum or plasma 25-hydroxyvitamin D (25(OH)D) concentrations, since circulating 25(OH)D is considered the best estimate of vitamin D status.[6] However, the associations with prostate cancer have been inconsistent.[7–16] Furthermore, an IARC Working Group that recently reviewed 11 publications on circulating 25(OH)D and prostate cancer risk reported that the findings in general do not offer clear support for the vitamin D hypothesis.[17]

To further address this hypothesis, we examined the association between plasma 25(OH)D concentration and prostate cancer risk in a nested case-control study within a large cohort in Hawaii and California. Since skin pigmentation

* *Corresponding author:* Tel.: +1 808 564 5947; fax: +1 808 586 2982.
E-mail address: spark@crch.hawaii.edu (S.-Y. Park).
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influences vitamin D status,[18] studying this association with multiple racial/ethnic groups provides a wide range of vitamin D concentrations; most previous studies on this exposure and prostate cancer have been conducted in ethnically homogeneous groups.

2. Materials and methods

2.1. Study population

The Multiethnic Cohort Study enrolled more than 215,000 adults (45–75 years) living in Hawaii and California who completed a 26-page mailed questionnaire in 1993–1996.[19] The study was approved by the review boards of the University of Hawaii and the University of Southern California. The study targeted five racial/ethnic groups: African Americans, Native Hawaiians, Japanese Americans, Latinos and Whites. A prospective biorepository was developed primarily between 2001 and 2006.[20] More than 67,000 participants who gave informed consent to participate provided blood and/or urine specimens as well as updated information on a few items from the baseline questionnaire.

2.2. Selection of cases and controls

Incidents of prostate cancer were identified through linkage to the tumour registries covering the states of Hawaii and California, which are part of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute. For this nested case-control study, cases were defined as men who were diagnosed with invasive prostate cancer after blood collection up to the 2006 tumour registry linkage. Advanced prostate cancers were defined as all cancers that were regional or metastatic (not in situ or localised) while high-grade cancers were based on the Gleason score $\geqslant 7$ (categorised as poorly differentiated). During the follow-up period, 467 eligible prostate cancer cases were identified. For each case, two controls were randomly selected from a pool of potential controls in the biorepository who were alive and free of prostate cancer at the age of the case's diagnosis and who matched the case on location (Hawaii or California), race/ethnicity, birth year (±1 year), date of blood draw (±6 months), time of blood draw (±2 h) and fasting hours (0–<6, 6–<8, 8–<10 and 10+h).

Of 467 cases, 329 had fasting blood samples available for analysis. Of their 658 matched controls with fasting blood, 656 had samples available for analysis. Therefore, our analysis included 329 matched sets: 327 with two controls and 2 with 1 control. There were 62 advanced or high-grade prostate cancer cases, 213 localised cases without a high-grade tumour, and 54 cases where this staging could not be determined due to missing values.

2.3. Plasma 25-hydroxyvitamin D assay

Plasma 25(OH)D was measured according to the manufacturer's directions utilising an immunoassay kit purchased from Immunodiagnostic Systems, Ltd. (Fountain Hills, AZ). Samples from matched cases and controls were analysed in the same analytical batch. One hundred and twenty-nine samples from 46 quality control plasma pools were analysed blindly with the study samples. The within-batch coefficient of variation was 2% and the across-batch coefficient of variation was 3%.

2.4. Statistical analyses

Selected characteristics were tested between cases and controls by the *t*-test for continuous variables and the chi-square test for categorical variables. Subjects were divided into quartiles determined by the overall distribution of plasma 25(OH)D in both cases and controls. Also, clinically defined cutpoints (<20, 20–<30, 30–<50, and $\geqslant 50$ ng/ml) were used in order to evaluate the risk of prostate cancer for vitamin D deficient (<20 ng/ml) or insufficient level (20–<30 ng/ml)[21] as well as higher level. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using conditional logistic regression where matched sets were the strata to account for the matching criteria given above. We entered age at blood draw, fasting hours, and season of blood draw (winter: December–February; spring: March–May; summer: June–August; and fall: September–November) to account for any possible systematic differences within matched sets, in addition to adjustment for family history of prostate cancer (yes/no), body mass index (BMI, <25, 25–<30, $\geqslant 30$ kg/m^2), education (years of schooling) and physical activity (hours spent in moderate or vigorous activity per day), as these variables were previously found to affect risk. Other potential confounders including calcium and vitamin D intake from foods and/or supplements were evaluated, but were not included in the models because they did not alter the association. Dose–response was tested using a trend variable assigned to the median of the appropriate quartile. The analyses were repeated separately by tumour stage/grade. Two-sided *P*-values less than 0.05 were considered significant. All analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

The matching characteristics, as well as years of education, physical activity level, and BMI, were similar between cases and controls but family history of prostate cancer differed (13% versus 8%, respectively, $P = 0.01$) (Table 1). Mean plasma 25(OH)D concentrations did not differ statistically between cases (34.0 ng/ml) and controls (33.1 ng/ml). However, mean concentrations were higher in participants living in Hawaii than those living in California. Mean concentrations were highest in cases in the summer (35.3 ng/ml) and in controls in the fall (36.7 ng/ml), but the differences were not great. Also, means of plasma 25(OH)D concentration with adjustment for age, BMI and physical activity were significantly different across racial/ethnic groups ($P < 0.001$); adjusted means amongst controls were 26.3 ng/ml in African Americans, 31.1 ng/ml in Latinos, 36.9 ng/ml in Japanese Americans, 37.7 ng/ml in Native Hawaiians and 45.6 ng/ml in Whites (data not shown).

No association was found between quartiles of plasma 25(OH)D and prostate cancer risk overall (Table 2). Adjusting

Table 1 – Characteristics of prostate cancer cases and controls in the Multiethnic Cohort Study.

	Cases	Controls	P-value[a]
n	329	656	
Age at blood draw, y	68.9 ± 7.1	68.7 ± 7.2	0.77
Fasting hours prior to blood draw	13.6 ± 2.5	13.8 ± 2.6	0.25
Education, y	14.0 ± 2.7	13.9 ± 2.9	0.53
Body mass index (kg/m^2)	26.1 ± 3.9	26.3 ± 4.0	0.52
Physical activity (h/d)[b]	1.33 ± 1.44	1.24 ± 1.34	0.32
Family history of prostate cancer (%)	13.1	8.1	0.01
Ethnicity, n (%)			
African Americans	136 (41.3)	272 (41.5)	1.00
Native Hawaiians	12 (3.7)	23 (3.5)	
Japanese Americans	74 (22.5)	148 (22.6)	
Latinos	52 (15.8)	104 (15.9)	
Whites	55 (16.7)	109 (16.6)	
Plasma 25-hydroxyvitamin D (ng/ml)	34.0 ± 15.1	33.1 ± 15.5	0.86
Study location			
Hawaii	43.2 ± 17.6	42.3 ± 17.4	0.65
California	28.7 ± 11.2	27.8 ± 10.4	0.30
Season of blood draw[c]			
Winter	32.1 ± 14.9	31.7 ± 14.0	0.84
Spring	33.5 ± 17.6	31.5 ± 15.7	0.34
Summer	35.3 ± 15.9	32.3 ± 12.2	0.14
Fall	34.9 ± 13.3	36.7 ± 17.2	0.36

Data shown as mean ± S.D. unless specified otherwise.

[a] Tested by *t*-test (means) and chi-square test (percentages).

[b] Hours spent in moderate or vigorous activity per day.

[c] The season categories were defined as winter: December–February; spring: March–May; summer: June–August; and fall: September–November.

Table 2 – ORs and 95% CIs for prostate cancer according to plasma 25(OH)D in the Multiethnic Cohort Study.[a]

	Plasma 25(OH)D (ng/ml)				P for trend
Range of 25(OH)D[b]	<22.9	22.9–<31.0	31.0–<39.9	⩾39.9	
No. of cases	82	84	72	91	
No. of controls	163	166	172	155	
OR (95% CI)[c]	1.00 (Referent)	0.98 (0.67–1.44)	0.80 (0.52–1.25)	1.19 (0.76–1.87)	0.47
OR (95% CI)[d]	1.00 (Referent)	1.05 (0.70–1.58)	0.81 (0.52–1.28)	1.17 (0.72–1.89)	0.60
Range of 25(OH)D[b]	<20	20–<30	30–<50	⩾50	
No. of cases	53	98	137	41	
No. of controls	106	204	287	59	
OR (95% CI)[c]	1.05 (0.67–1.65)	0.98 (0.70–1.38)	1.00 (Referent)	1.60 (0.98–2.61)	0.17
OR (95% CI)[d]	1.10 (0.68–1.78)	1.04 (0.73–1.48)	1.00 (Referent)	1.52 (0.92–2.51)	0.32

OR, odds ratio; CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D.

[a] Matching criteria were accounted for by conditional logistic regression: geographic location (Hawaii or California), race/ethnicity, birth year (±1 year), date of blood draw (±6 months), time of blood draw (± 2 h), and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, and 10 + h).

[b] The first set of cutpoints is based on quartiles of 25(OH)D; the second set is based on the clinical definition of deficiency (<20 ng/ml) and insufficiency (20–<30 ng/ml).

[c] Adjusted for age at blood draw, fasting hours prior to blood draw, and season of blood draw.

[d] Additionally adjusted for family history of prostate cancer, BMI, education, and physical activity.

for family history of prostate cancer, BMI, education and physical activity did not change the estimate substantially. When we used clinically defined cutpoints for plasma 25(OH)D and fixed the range of 30–<50 ng/ml as the reference group, there was no increased risk for deficient (OR for <20 ng/ml = 1.10, 95% CI = 0.68–1.78) or insufficient levels (OR for 20–<30 ng/ml = 1.04, 95% CI = 0.73–1.48) of plasma 25(OH)D, while there was a suggestive increased risk for the higher 25(OH)D concentration (OR for ⩾50 ng/ml = 1.52, 95% CI = 0.92–2.51). When we ran the models for localised and advanced or high-grade cases separately, we found no significant relation for either (data not shown).

4. Discussion

In this nested case-control study within the Multiethnic Cohort, we did not observe a significant association between plasma 25(OH)D levels and prostate cancer risk overall. Indeed, we observed a nonsignificant increased risk of total prostate cancer for high 25(OH)D concentration (⩾50 ng/ml). We found no significant associations with advanced or high-grade cancer.

An IARC Working Group conducted a meta-analysis of seven prospective studies, and found no association between circulating 25(OH)D and prostate cancer; the relative risk for an increase of l ng/ml unit of serum 25(OH)D was 0.998 (95% CI = 0.992–1.005).[17] Adding the present study, as well as other recent prospective studies showing no association between circulating 25(OH)D and prostate cancer in Finnish men[8] and in the European Prospective Investigation into Cancer and Nutrition[22] would clearly not alter the result of this meta-analysis. In fact, two studies observed an increased risk with higher 25(OH)D levels, especially for a more aggressive disease,[7,23] which was contrary to the hypothesis that vitamin D is protective against prostate cancer.

Plasma 25(OH)D concentrations in our study population (33.1 ng/ml in the controls) were higher than those reported for the US male population covering similar age groups: 24.8 ng/ml in men 50–69 years and 24.0 ng/ml in men ⩾ 70 -years.[24] Using the cutoff of 20 ng/ml,[21] 16.1% of our study subjects would be considered vitamin D deficient, which is lower than in the general US male population (27.0% of men 50–69 years and 26.6% of men ⩾ 70 years).[24] However, since methods for the assessment of blood 25(OH)D have not been standardised, such comparison between studies may not be reliable.[17] Nonetheless, since our subjects are residents of Hawaii and California (primarily Los Angeles County) where sunlight is abundant all year round, circulating vitamin D levels might be expected to be higher than in men living at higher latitudes. Thus, it is possible that we did not observe any association between 25(OH)D and prostate cancer because of the small number of participants with low plasma 25(OH)D concentrations. For instance, Ahonen and colleagues[12] found an elevated risk of prostate cancer only for men with 25(OH)D levels below 16 ng/ml, whereas only 6.9% of our subjects had such low levels.

Racial/ethnic differences in 25(OH)D concentrations amongst our study population are consistent with other reports for the US population; for example, non-Hispanic whites had higher concentrations than did Mexican Americans and non-Hispanic Blacks.[25] This is also consistent with the fact that people with more extensive skin pigmentation have lower plasma 25(OH)D concentrations.[18] When we examined African American men separately, who had the lowest mean values of 25(OH)D and the largest number of cases in our study (n = 136), we still did not observe any effect of low vitamin D status on prostate cancer development (OR for < 20 versus ⩾30 ng/ml = 1.03, 95% CI = 0.64–1.66). However, it is premature to draw any conclusions regarding race/ethnic-specific associations in this study due to the limited number of cases in each ethnic group for the different exposure levels. Few other studies examined circulating vitamin D levels related to prostate cancer risk amongst non-White populations. Another study of Japanese Americans living in Hawaii, in which the median concentration of 25(OH)D (41.6 ng/ml) was higher than in the Japanese men in our study (median = 34.4 ng/ml), found no association between vitamin D metabolites and prostate cancer risk.[13]

The study's strengths include a prospective design, which minimised the chance that the disease influenced health-related behaviours (such as dietary practices and screening for prostate cancer) in the cases, and participants with diverse racial/ethnic backgrounds. Nevertheless, there are several limitations to be considered. We measured 25(OH)D using only a one-time plasma sample and thus it may not reflect long-term circulating vitamin D status. However, a validation study has shown a relatively high correlation coefficient (0.70) for two measures of 25(OH)D over a three-year period.[10] The majority of the cases had early stage disease which limited our ability to detect an effect of circulating 25(OH)D on tumour progression. Also, statistical power was limited for race/ethnic-specific analyses, due to the limited number of cases. The time between blood draw and tumour diagnosis (mean = 1.9 years) was relatively short, and thus preclinical disease might have influenced circulating vitamin D status in some cases.

In conclusion, findings from this prospective study of men in the Multiethnic Cohort do not support the hypothesis that vitamin D protects against prostate cancer. Further follow-up is warranted to determine whether the findings are consistent across ethnic groups.

Conflict of interest statement

None declared.

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