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

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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

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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