Genetic Variation in the Vitamin D Pathway in Relation to Risk of Prostate Cancer—Results from the Breast and Prostate Cancer Cohort Consortium


Abstract

Background: Studies suggest that vitamin D status may be associated with prostate cancer risk although the direction and strength of this association differs between experimental and observational studies. Genome-wide association studies have identified genetic variants associated with 25-hydroxyvitamin D [25(OH)D] status. We examined prostate cancer risk in relation to single-nucleotide polymorphisms (SNP) in four genes shown to predict circulating levels of 25(OH)D.

Methods: SNP markers localized to each of four genes (GC, CYP24A1, CYP2R1, and DHCR7) previously associated with 25(OH)D were genotyped in 10,018 cases and 11,052 controls from the National Cancer Institute (NCI) Breast and Prostate Cancer Cohort Consortium. Logistic regression was used to estimate the individual and cumulative association between genetic variants and risk of overall and aggressive prostate cancer.

Results: We observed a decreased risk of aggressive prostate cancer among men with the allele in rs6013897 near CYP24A1 associated with lower serum 25(OH)D [per A allele, OR, 0.86; 95% confidence interval (CI), 0.80–0.93; P_trend = 0.0002] but an increased risk for nonaggressive disease [per A allele: OR, 1.10; 95% CI, 1.04–1.17; P_trend = 0.002]. Examination of a polygenic score of the four SNPs revealed statistically significantly lower risk of aggressive prostate cancer among men with a greater number of low vitamin D alleles (OR for 6–8 vs. 0–1 alleles, 0.66; 95% CI, 0.44–0.98; P_trend = 0.003).

Conclusions: In this large, pooled analysis, genetic variants related to lower 25(OH)D levels were associated with a decreased risk of aggressive prostate cancer.

Impact: Our genetic findings do not support a protective association between loci known to influence vitamin D levels and prostate cancer risk. Cancer Epidemiol Biomarkers Prev; 22(4); 688–96. ©2013 AACR.

Introduction

There is evidence that vitamin D compounds promote prostate cell differentiation and inhibit prostate cancer cell growth and invasion (1–3). In contrast to this basic research, a meta-analysis of epidemiologic studies including a total of 3,124 cases and 4,682 controls concluded...
there was no evidence that higher vitamin D status assessed by circulating 25-hydroxyvitamin D (25(OH)D) levels is associated with a reduced risk of prostate cancer (4). Furthermore, men with higher circulating 25(OH)D were recently reported to have a statistically significantly elevated risk of prostate cancer in one nested case–control analysis of 1,000 cases and 1,000 controls (5).

Two recent genome-wide association studies (GWAS) identified single-nucleotide polymorphisms (SNP; including 2 not previously known) in or near 4 genes related to circulating 25(OH)D (6, 7), the primary circulating form of vitamin D. Considered the best indicator of vitamin D status (8), 25(OH)D is converted to its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], in the kidney and other organs (8). The 4 genes identified in the GWAS were: GC, which encodes vitamin D-binding protein (DBP), the major carrier of vitamin D compounds in circulation; CYP24A1, which encodes the cytochrome p450 (CYP) 24-hydroxylase that initiates intracellular metabolism of 25(OH)D and 1,25(OH)2D to less bioactive species; CYP2R1, which encodes a key 25-hydroxylase responsible for conversion of vitamin D to 25(OH)D in the liver; and DHCR7, which encodes the enzyme that catalyzes the conversion of 7-dehydrocholesterol, a vitamin D3 precursor, to cholester (6, 7).

To further elucidate the vitamin D–prostate cancer association, we examined prostate cancer risk in relation to genetic variants associated with 25(OH)D status identified in GWAS in a pooled analysis of 10,000 cases and 11,000 controls within the Breast and Prostate Cancer Cohort Consortium (BPC3).

Materials and Methods

Study sample

Details of the BPC3 have been reported previously (9). Briefly, the BPC3 is a consortium effort encompassing nested case–control sets from the following cohort studies: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, the American Cancer Society Cancer Prevention Study II (CPS-II), the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC)—includes cohorts from Denmark, Great Britain, Germany, Greece, Italy, the Netherlands, Spain, and Sweden, the Health Professionals Follow-up Study (HPFS), the Multiethnic Cohort (MEC), the Physicians’ Health Study (PHS), and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Within each cohort, controls were matched to cases based on age, race/ethnicity, and region of recruitment, depending on the study. Because of the small number of non-White participants, the present analysis was restricted to men who reported being of Caucasian ancestry.

Written informed consent was obtained for all participants and each study was approved by its respective Institutional Review Board (IRB). The IRBs for each study were: U.S. National Cancer Institute (NCI, Bethesda, MD) and Finnish National Institute for Health and Welfare (ATBC Study), the Emory University School of Medicine (Atlanta, GA) IRB (CPS-II), Ethikkommission—Medizinische Fakultät Heidelberg and Imperial College Research Ethics Committee (EPIC), the IRB of Harvard School of Public Health (Boston, MA; HPFS), the IRB at the University of Southern California (Los Angeles, CA) and the IRB at the University of Hawaii (Honolulu, HI; MEC), The Human Subjects Committee at Brigham and Women’s Hospital (PHS) and NCI Special Studies IRB (PLCO).

SNP selection and genotyping

We chose SNPs that were identified from GWAS of circulating 25(OH)D levels (6, 7): rs2282679 (GC), rs10741657 (CYP2R1), rs12785878 (DHCR7), and rs6013897 (CYP24A1). A recent article reported that, collectively, these 4 SNPs explained a greater degree of the variation in circulating vitamin D levels (i.e., 5.2%) than a polygenic score that included 9,000 SNPs and explained only 0.16% of the variation (10). TaqMan genotyping was conducted at the Core Genotyping Research Laboratory of the U.S. NCI, DKFZ (Heidelberg, Germany) and the University of Southern California for 8,881 cases and 9,265 controls from all 7 cohorts. An additional 1,137 cases and 1,787 controls with previous BPC3 data for these genes from GWAS analyses were included. Details of the genome-wide scans have been described previously (11). Of the 4 primary SNPs, only rs2282679 was available from GWAS data, and surrogate SNPs with r2 values of 1.0 were selected for each of the other 3 SNPs: rs17217119 for rs6013897, rs2060793 or rs1993116 for rs10741657, and rs3794060, rs12800438, or rs7944926 for rs12785878. Because the primary findings were unchanged when the GWAS participants were excluded, the latter were retained in the final analysis.

Outcome assessment

Cases of prostate cancer were identified through cohort linkage with a population-based registry or from self-reports verified through medical records and pathology reports. Genotype data were available for 10,018 prostate cancer cases and 11,052 controls. Information on cancer stage was available for 86% of the cases and information on tumor grade was available for 88%. High stage cancer was defined as stage C or D at diagnosis (n = 1,834) and high grade was defined as cases with Gleason sum >7 or cases that were histologically diagnosed as poorly differentiated or undifferentiated (n = 1,843). Aggressive prostate cancer (n = 3,066) was defined as a case that was either of high stage or high grade at diagnosis.

Collection and harmonization of nongenetic data

Each cohort collected self-reported information on baseline (prediagnostic) medical and lifestyle characteristics. These data were assembled by the data coordinating center using a common protocol for variable formatting aimed to retain the most detailed data without resulting in missing data for any study. The data collected and variable formats agreed upon were: age at diagnosis or...
selection as a control (except for MEC which provided the age at blood draw for controls; years, continuous), height (cm, continuous), body mass index (BMI; kg/m², continuous), history of diabetes (yes, no), smoking status (never, current, and former), and family history of prostate cancer (yes no). Previously measured serum or plasma 25(OH)D concentrations were available for 6,030 participants included in this analysis. Any inconsistencies in the data were resolved through discussion between the data coordinating center and the individual cohorts. All data elements have been used in analyses published by the individual cohorts (as well as in prior BPC3 publications), and details of their collection and quality control can be found in these previous reports.

Statistical methods

Unconditional logistic regression was used to estimate the association between each SNP and risk of prostate cancer. The SNPs were coded on the basis of the number of alleles (0, 1, 2) associated with lower circulating 25(OH)D levels (i.e., low vitamin D alleles) in the published GWAS studies (6, 7), rather than on the number of minor alleles. The mean circulating 25(OH)D levels by genotype of each individual SNP for the 6,030 individuals with previously measured plasma or serum 25(OH)D are as follows (in nmol/L): rs2282679: GG = 56.6, TT = 64.6; rs6013897: AA = 59.8, TT = 62.2; rs10741657: GG = 58.6, AA = 64.2; rs12785878: GG = 56.1, TT = 65.3. Circulating 25(OH)D was statistically significantly linearly associated with genotype for each of the SNPs examined with the exception of rs12785878. The test statistic for heterogeneity across studies for the prostate cancer—SNP associations with the exception of rs6013897 showed a borderline decrease in prostate cancer risk (GG vs. AA: OR, 0.97; 95% CI, 0.85–1.00; P = 0.05; uncorrected for multiple testing; Table 2). There was no observed heterogeneity across studies for the prostate cancer association using the likelihood ratio test to compare a logistic regression model that included all 4 SNPs (AT vs. TT: OR, 1.09; 95% CI, 1.02–1.17; AA vs. TT: OR, 1.01; 95% CI, 0.87–1.16; additive OR, 1.05; 95% CI, 1.00–1.11; P_{interaction} = 0.19). Assuming no directionality in the vitamin D–prostate cancer association using the likelihood ratio test to compare a logistic regression model that included all 4 SNPs with one that included none, we did not observe a statistically significant association with overall risk (P = 0.15).

The estimated magnitude of the association for rs10741657 was greater for nonaggressive disease (GG vs. AA: OR, 0.88; 95% CI, 0.80–0.98; P = 0.03) than for aggressive disease (GG vs. AA: OR, 0.97; 95% CI, 0.85–1.10; P = 0.61; Table 3). Our findings for the other SNPs in relation to aggressive disease were similar to those for overall prostate cancer with the exception of rs6013897, which showed an additive per-allele positive association with nonaggressive disease and an inverse relation with aggressive disease (per A allele: nonaggressive OR, 1.10; 95% CI, 1.04–1.17; P_{trend} = 0.002; aggressive OR, 0.86; 95% CI, 0.80–0.93; P_{trend} = 0.0002; Table 3). Exploratory subgroup analyses showed no statistically significant (i.e., P < 0.002) interactions between the vitamin D genetic variants, prostate cancer, and any of the factors examined, including age, family history of prostate cancer, and BMI (data not shown). Overall prostate cancer risk was nonstatistically significantly lower among men with a greater number of low
<table>
<thead>
<tr>
<th>Table 1. Characteristics of the study populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATBC</strong></td>
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<td><strong>Cases</strong></td>
</tr>
<tr>
<td><strong>N</strong></td>
</tr>
<tr>
<td><strong>Age</strong>&lt;sup&gt;a&lt;/sup&gt; Mean (SD)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
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<td><strong>BMI</strong> Mean (SD)</td>
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<td><strong>Smoking, %</strong></td>
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<td><strong>Diabetes, %</strong></td>
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<td><strong>High grade</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>High stage</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
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<td><strong>Aggressive</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td><strong>Missing</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup>Age is calculated at age of diagnosis/selection as control except for MEC (at blood draw for controls).
<sup>b</sup>Defined as Gleason sum 8–10 or WHO grade 3. Percentages calculated on the basis of participants without missing information.
<sup>c</sup>Defined as stage C or D. Percentages calculated on the basis of participants without missing information.
<sup>d</sup>Defined as either high stage or high grade. Percentages calculated on the basis of participants without missing information.
vitamin D alleles (OR for 6–8 vs. 0–1 alleles, 0.84; 95% CI, 0.66–1.07; per-allele OR, 0.98; 95% CI, 0.96–1.01; 
$P_{\text{trend}} = 0.17$; Fig. 1), an association that was similar across cohorts 
($P_{\text{trend for heterogeneity}} = 0.11$). The magnitude of the 
association was greater, however, and the association was 
statistically suggestive for aggressive disease (OR for 6–8 
vs. 0–1 alleles, 0.66; 95% CI, 0.44–0.98; per-allele OR, 0.95; 
95% CI, 0.92–0.98; $P_{\text{trend}} = 0.003$; Fig. 2). In a sensitivity 
analysis, men with 6 low vitamin D alleles had a statis-
tically significantly decreased risk of prostate cancer com-
pared with men with 0–1 alleles (OR, 0.72; 95% CI, 0.55–
0.94), and those with 7–8 alleles had an increased risk (OR, 
1.91; 95% CI, 1.02–3.58); the latter category included only 
44 men (29 prostate cancer cases) however. We observed a 
similar pattern between the vitamin D genetic score and 
aggressive prostate cancer (6 vs. 0–1: OR, 0.51; 95% CI, 
0.32–0.81; 7–8 vs. 0–1: OR, 2.17; 95% CI, 0.94–5.03). Exclud-
ing rs6013897 from the score resulted in an attenuated 
association with aggressive disease (6 vs. 0–1 alleles: OR, 
0.88; 95% CI, 0.63–1.22; $P_{\text{trend}} = 0.39$), and a statistically 
significant inverse relation with overall prostate cancer (6 
vs. 0–1 alleles: OR, 0.78; 95% CI, 0.62–0.96), although the 
trend test was marginally not statistically significant ($P = 
0.06$). The results in Figs. 1 and 2 were not altered by the

**Table 2. Individual SNP associations with risk of overall prostate cancer**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Low vitamin D allele frequency</th>
<th># Low vitamin D alleles</th>
<th>Mean serum 25(OH)Dc</th>
<th># Cases</th>
<th># Controls</th>
<th>OR (95% CI)a</th>
<th>$P_{\text{value}}$b</th>
<th>$P_{\text{heterogeneity across studies}}$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>GC</td>
<td>0.27</td>
<td>0</td>
<td>64.6</td>
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<td>1</td>
<td>59.4</td>
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<td></td>
<td></td>
<td>2</td>
<td>56.6</td>
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<td>774</td>
<td>0.98 (0.88–1.10)</td>
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<tr>
<td>rs6013897</td>
<td>CYP24A1</td>
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<td>0</td>
<td>62.2</td>
<td>6,026</td>
<td>6,433</td>
<td>1.0 (ref)</td>
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<td>1</td>
<td>63.0</td>
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<td>58.9</td>
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<td>rs10741657</td>
<td>CYP2R1</td>
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<td>64.2</td>
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<td>2</td>
<td>58.6</td>
<td>3,481</td>
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<td>rs12785878</td>
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</table>

aAdjusted for age (5-year groups) and study cohort.
bFor categorical analyses of genotype this is a 2 degree of freedom test comparing a model containing indicator variables for genotype 
with a model containing only the covariates. For the per allele analyses, this is a 1 degree of freedom test comparing a model containing 
the ordinal genotype variable to a model containing only the covariates.
cIn nmol/L; among the 6,030 participants who had measured serum 25(OH)D available.

**Discussion**

In this large, pooled analysis, we found evidence that genetic variants previously related to lower vitamin D 
status are associated with a decreased risk of prostate cancer. A SNP near CYP2R1 was marginally associated 
with risk of overall prostate cancer, whereas one near CYP24A1 was associated with aggressive disease. The 4- 
SNP polygenic score was related to both overall and 
aggressive prostate cancer. These genetic findings indi-
rectly support a role for vitamin D in the etiology of 
prostate cancer.

We observed a borderline, nominally statistically sig-
ificant association for rs10741657 near CYP2R1, the gene 
encoding a key vitamin D 25-hydroxylation enzyme, such 
that men with alleles conferring lower vitamin D status 
were at decreased risk of overall prostate cancer. Similarly, 
the low vitamin D allele in rs6013897 near CYP24A1, the gene encoding the 24-hydroxylase that initiates 
intracellular catabolism of 25(OH)D and 1,25(OH)2D, was 
associated with a reduced risk of aggressive, but not 
nonaggressive, disease. Study heterogeneity in our

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Mondul et al.

Cancer Epidemiol Biomarkers Prev; 22(4) April 2013

Cancer Epidemiology, Biomarkers & Prevention
findings for rs6013897 could be explained by the differences in the proportion of aggressive disease diagnosed across cohorts, a conclusion supported by the disappearance of heterogeneity following exclusion of the one study with substantially more aggressive prostate cancers having been diagnosed (i.e., EPIC).

Our study also examined the relation between vitamin D and prostate cancer risk using a genetic score proxy for vitamin D that was based on the number of alleles across the 4 SNPs in or near GC, CYP24A1, CYP2R1, and DHCR7 previously associated with 25(OH)D levels in GWAS. We found an association with overall prostate cancer risk that was stronger and statistically significant for aggressive disease wherein men with a greater number of low vitamin D alleles were at decreased risk compared with men with only 0 or 1 low vitamin D alleles. The stronger association with all prostate cancer, and the weaker association with aggressive disease, for the 3 SNP score that

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th># Controls</th>
<th># Cases</th>
<th>OR (95% CI)</th>
<th>P value</th>
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<td>1.01 (0.95–1.06)</td>
<td>0.86</td>
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*Adjusted for age (5-year groups) and study cohort.

*For categorical analyses of genotype this is a 2 degree of freedom test comparing a model containing indicator variables for genotype with a model containing only the covariates. For the per allele analyses, this is a 1 degree of freedom test comparing a model containing the ordinal genotype variable to a model containing only the covariates.
excluded rs6013897 near CYP24A1 is consistent with the latter being the only examined SNP contributing to lower risk of aggressive disease. A nonlinear relation similar to that reported in a previous serologic study of vitamin D and risk of prostate cancer (12) was suggested, with low risk among men with 6 low vitamin D alleles but substantially elevated risk among men with 7 or 8 low vitamin D alleles; however, the latter category was sparsely populated (0.2% of the study sample), and the finding may be due to chance. Examination of this and other vitamin D risk scores in relation to prostate cancer in other studies will be informative.

Most studies of prostate cancer risk and genetic variants in the vitamin D pathway focused on the vitamin D receptor (VDR) gene (13, 14), with few investigations of other relevant loci (15, 16). Five studies examined variants in CYP24A1 and found either no association (15–19) or a statistically significant association in Hispanic Caucasians (20), and 3 studies of GC variants were null (15, 17, 21). CYP2R1 and DHCR7, genes newly identified in the aforementioned GWAS of circulating 25(OH)D levels (6, 7), have only been examined in relation to prostate cancer risk in 2 recent studies that found no association with overall (15, 16) or fatal prostate cancer (15). However, the number of cases was relatively small in both studies (overall prostate cancer \( n = 1,260 \) and 375; fatal prostate cancer \( n = 114 \)). Collectively, these studies have provided little evidence in support of a vitamin D–cancer association, and to our knowledge, no SNPs in vitamin D pathway genes have been associated with prostate cancer at the genome-wide level of significance in GWAS analyses (22, 23).

Our findings for vitamin D genetic variants are consistent with our recent investigation showing an increased risk of prostate cancer for men with higher serum 25(OH)D status (5). A meta-analysis published before that study concluded that there was no association between serum 25(OH)D and risk of prostate cancer; however, when we calculated a summary point estimate that included the studies from the meta-analysis by Yin and colleagues and our data using inverse variance weighting, the summary OR for a 10 ng/mL increase in serum 25(OH)D was borderline statistically significant (OR, 1.05; 95% CI, 1.00–1.10; \( P = 0.058 \)). The positive associations observed between circulating vitamin D and prostate cancer, as well as the inverse associations for genetic variants that promote lower 25(OH)D levels, are contrary to experimental evidence and do not support the notion that higher vitamin D status should have a preventive role in this malignancy (1–3). Although it remains unclear why lower vitamin D status might be related to decreased risk of prostate cancer, it is known that 1,25(OH)_{2}D stimulates...
the insulin receptor and increases insulin synthesis (24), and that elevated circulating insulin has been associated with higher prostate cancer risk (25). Alternatively, the fact that the strongest signals we found were for 2 mixed-function oxidases (i.e., CYP2R1 and CYP24A1) leaves open the possibility that some of the genetic associations observed here may be reflecting effects on the metabolism of other molecular species relevant to prostate cancer risk and progression unrelated to vitamin D (e.g., androgens). In support of this, a recent study found higher 25(OH)D levels to be associated with increased levels of total and free testosterone in men (26). Additional mechanistic studies of these findings in humans are needed.

The present investigation is the largest to examine prostate cancer risk in relation to a score of genetic variants that have been associated with vitamin D status from GWAS (16). Our analysis is based on a large, multicohort sample, which enabled us to detect more modest risk associations. Studying vitamin D–related genes mitigates some of the limitations of serologic analyses of circulating 25(OH)D, which include interlaboratory differences, variable season of blood collection, and fasting status, and genetic association studies do not suffer from the effects of reverse causation or residual confounding that are of concern in biomarker studies. Furthermore, the variants in these genes may better represent the potential for higher or lower vitamin D status over the life course than measurement of circulating vitamin D at one point in time. It should be noted, however, that the GWAS reports identifying these genes as predicting 25(OH)D levels estimated that they only explain between 4% and 5% of the variation in 25(OH)D concentration (6, 7, 10). These genes may, therefore, have pleiotropic effects on prostate cancer that do not operate through vitamin D–related mechanisms. For example, serum transport of vitamin D metabolites has been historically considered the primary function of the vitamin D–binding protein (Gc globulin), but there is now evidence that its other biologic activities include a role in inflammation and immunity (27, 28). Thus, the observed genetic associations may be acting through biologic mechanisms independent of an association with circulating vitamin D.

Conclusions

In this large, pooled analysis of men of European ancestry, we found that genetic variants near CYP24A1 related to lower vitamin D status could be associated with a decreased risk of aggressive prostate cancer, and a polygenic vitamin D score was similarly related to both overall and aggressive prostate cancer. Our findings do not support a protective association between higher vitamin D status and lower risk of prostate cancer, and point to the possibility of a positive association.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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