Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Serum 25-Hydroxy Vitamin D and Prostate Cancer Risk in a Large Nested Case–Control Study

Demetrius Albanes[1], Alison M. Mondul[1], Kai Yu[2], Dominick Parisi[3], Ronald L. Horst[4], Jarmo Virtamo[5], and Stephanie J. Weinstein[1]

Abstract

Background: Vitamin D compounds inhibit prostate tumorigenesis experimentally, but epidemiologic data are inconsistent with respect to prostate cancer risk, with some studies suggesting nonsignificant positive associations.

Methods: The 25-hydroxy vitamin D [25(OH)D]–prostate cancer relation was examined in a nested case–control study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of 50- to 69-year-old Finnish men. We matched 1,000 controls to 1,000 cases diagnosed during up to 20 years of follow-up on the basis of age (±1 year) and fasting blood collection date (±30 days). Conditional multivariate logistic regression models estimated ORs and 95% CIs. All statistical significance testing was 2-sided.

Results: Cases had nonsignificantly 3% higher serum 25(OH)D levels ($P = 0.19$). ORs (95% CIs) for increasing season-specific quintiles of 25(OH)D concentrations were 1.00 (reference), 1.29 (0.95–1.74), 1.34 (1.00–1.80), 1.26 (0.93–1.72), and 1.56 (1.15–2.12), with $P_{trend} = 0.01$. Analyses based on prespecified clinical categories and season-adjusted values yielded similar results. These findings seemed stronger for aggressive disease [OR (95% CI) for fifth quintile of serum 25(OH)D [1.70 (1.05–2.76), $P_{trend} = 0.02$], among men with greater physical activity [1.85 (1.26–2.72), $P_{trend} = 0.002$], higher concentrations of serum total cholesterol [2.09 (1.36–3.21), $P_{trend} = 0.003$] or α-tocopherol [2.00 (1.30–3.07), $P_{trend} = 0.01$] and higher intakes of total calcium [1.82 (1.20–2.76), $P_{trend} = 0.01$] or vitamin D [1.69 (1.04–2.75), $P_{trend} = 0.08$], or among those who had received the trial α-tocopherol supplements [1.74 (1.15–2.64), $P_{trend} = 0.006$].

Conclusion: Our findings indicate that men with higher vitamin D blood levels are at increased risk of developing prostate cancer.

Impact: Greater caution is warranted with respect to recommendations for high-dose vitamin D supplementation and higher population target blood levels. *Cancer Epidemiol Biomarkers Prev; 20(9); 1850–60. ©2011 AACR.*

Introduction

Prostate cancer remains the most common male malignancy in the United States and many developed populations, yet few if any modifiable etiologic factors have been firmly established. For example, leads from basic, epidemiologic, and clinical research have implicated androgens, insulin, diabetes, vitamin E, and selenium, but cumulative data are inconclusive or conflicting, including those from large controlled trials (1, 2). Substantial recent interest in the potential health benefits of higher vitamin D intake and status has raised attention with respect to available human evidence for its relationship to cancer, including prostate cancer. A recent meta-analysis of cohort-based nested case–control studies of serum 25-hydroxy vitamin D [25(OH)D] and prostate cancer risk concluded that there was no protective association for higher vitamin D status and that a weak positive relation was possible (3). In contrast, most basic research supports a beneficial role for vitamin D compounds in prostate cell proliferation and differentiation, prostate cancer cell growth and invasion, and tumorigenesis (4–6). Combined with ecologic data suggesting correlations between prostate (and other organ site) cancer rates and latitude and other geographically-defined population exposures to solar radiation (7), the latter experimental findings, along with positive effects of vitamin D supplementation on bone health (8), have contributed to growing clinical and public trends toward broad use of higher-dose vitamin D supplementation. Given the clinical significance of

Authors' Affiliations: [1]Nutritional Epidemiology Branch and [2]Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda; [3]Information Management Services, Silver Spring, Maryland; [4]Heartland Assays Inc., Ames, Iowa; and [5]Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland

Corresponding Author: Demetrius Albanes, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Suite 320, Bethesda, MD 20982. Fax: 301-496-6829; E-mail: daa@nih.gov.

doi: 10.1158/1055-9965.EPI-11-0403

Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

prostate cancer, a more definitive understanding of the impact vitamin D status might have on its occurrence is needed.

To this end, we analyzed nested case–control data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort to examine whether circulating concentrations of 25(OH)D, a reliable biomarker of vitamin D status, is prospectively associated with prostate cancer risk during 20 years of follow-up. Special attention was paid to variation in solar ultraviolet B (UVB) exposure, a key predictor of vitamin D status, using information for date/season of blood collection.

Materials and Methods

Study population

Details of the ATBC Study design have been published (9, 10). In brief, the ATBC Study was a phase 3 controlled trial that tested daily supplementation of α-tocopherol (50 mg/d), β-carotene (20 mg/d), both, or placebo. The study enrolled 50- to 69-year-old male cigarette smokers from southwestern Finland between 1985 and 1988 (n = 29,133). Study supplementation and active follow-up continued for 5 to 8 years (median = 6.1 years) through April 30, 1993, and the study was approved by the Institutional Review Boards of the U.S. National Cancer Institute and the National Public Health Institute of Finland, with written informed consent obtained from all participants.

Selection of cases and controls

Prostate cancer cases (International Classification of Diseases 9, code 185) were identified through active follow-up and through linkage with the Finnish Cancer Registry, which provides nearly 100% complete incident cancer ascertainment in Finland (11). Medical records for cases diagnosed prior to July 2002 were reviewed by 1 or 2 study oncologists to confirm diagnosis and staging, whereas information for subsequent cases was based on Finnish Cancer Registry data. One thousand cases diagnosed through April 30, 2005, were selected from among 1,628 cases identified, including all aggressive prostate cancer cases. Among these were 193 stage 1 cases, 191 stage 2, 170 stage 3, and 252 stage 4 (194 cases did not have stage data; ref. 12). Gleason score was available for only 341 cases, 250 scored less than 8 and 91 scored 8 or more. Cases diagnosed in stage 3 or 4 or with Gleason score of 8 or more were categorized as having aggressive disease. There were 294 fatal prostate cancers. Controls were randomly selected from ATBC Study participants who were alive and cancer free at the time of the cancer case diagnosis and matched 1:1 to cases on the basis of age at randomization (±1 year) and date of baseline blood collection (±30 days).

Specimen and data collection

Serum was collected at the study baseline visit after an overnight fast and stored at −70°C. Smoking, physical activity, and self-reported illness questionnaire data were collected, height and weight were measured, and body mass index (BMI) calculated as [weight in kilograms/(height in meters)^2]; ref. 9). A validated food frequency questionnaire reflecting the previous 12 months was also completed at baseline that included 276 food and beverage items (13). Prostate cancer family history (father and brothers) was queried during follow-up (1991–1992) and was available for 76% of the cases and controls.

Laboratory assays

Serum 25(OH)D level was measured using the DiaSorin Liaison 25(OH)D TOTAL assay platform by a direct, competitive chemiluminescence immunoassay (Heartland Assays, Inc.; refs. 14, 15). Sample batches included matched case–control sets and 4 to 6 blinded quality control (QC) specimens from our study and from 2 concentrations of standard reference material provided by the National Institute of Standards and Technology (NIST). Inter- and intrabatch coefficients of variation were 12.3% and 10.5%, respectively, for the ATBC Study QC samples and ranged between 12.7%–13.6% and 9.3%–11.0%, respectively, for the 2 concentrations of NIST QC standard samples. Further details of the laboratory and QC methods are discussed elsewhere (14).

Statistical analysis

Wilcoxon rank-sum and χ^2 tests were used to compare characteristics of cancer cases and controls. The season-adjusted 25(OH)D values (see next paragraph) were used to create a smoothed plot of predicted 25(OH)D values by week of blood collection.

Logistic regression models conditioned on the matching factors and adjusted for age, family history of prostate cancer, and serum α-tocopherol were used to estimate ORs and 95% CIs for the serum 25(OH)D–prostate cancer association based on (i) commonly studied, predefined clinical categories (<25, 25 to <37.5, 37.5 to <50, 50 to <75, and ≥75 nmol/L; refs. 14, 16); (ii) season-specific 25(OH)D quintiles (based on the control subject distributions for darker and sunnier months); and (iii) season-standardized 25(OH)D values calculated from the regression of log-transformed 25(OH)D on calendar week of blood collection using a locally weighted polynomial regression method. Linear trends were tested through a category-based ordinal covariate (1–5). Variables tested for potential confounding included prostate cancer family history, history of diabetes, cigarettes per day, years of smoking, BMI, serum α-tocopherol, β-carotene, retinol, and total cholesterol, meat and alcohol consumption, and dietary fat, calcium, and selenium. Only family history of prostate cancer and serum α-tocopherol were retained as model covariables because they were statistically significant ($P < 0.05$) or led to a more than 10% change in the β-coefficient for 25(OH)D in the bivariate model. Direct determinants of 25(OH)D, including dietary vitamin D, vitamin D supplement use, and physical activity, were not tested for confounding.

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Unconditional logistic regression models that adjusted for the matching factors were used for subgroups of the following factors: age, BMI, number of cigarettes per day and years smoked, vitamin D, calcium, and selenium intake, alcohol consumption, and serum α-tocopherol, β-carotene, retinol, and total and high-density lipoprotein (HDL) cholesterol (stratified by medians); leisure physical activity (low vs. high), season of blood collection, disease aggressiveness, time to case diagnosis, history of diabetes, family history of prostate cancer, and α-tocopherol and β-carotene intervention groups. Season of blood collection was empirically defined as "darker" months (November–April) and "sunnier" months (May–October) on the basis of the monthly median 25 (OH)D concentrations among controls, and years from blood collection to case diagnosis were divided as 1–10 and 10–20 years. Effect modification was examined through subgroup analyses of predictors of vitamin D (e.g., vitamin D intake, season, and activity), prostate cancer risk factors (e.g., prostate cancer family history, vitamin E trial supplementation, and serum α-tocopherol), and other factors relevant to the clinical course of the disease or association assessment (e.g., disease aggressiveness and time from blood collection to diagnosis) and tested through log-likelihood ratio tests of models with and without the cross-product term of 25 (OH)D (categorical) and the stratification factor. Statistical analyses were carried out by using SAS software version 9.1.3 (SAS Institute, Inc.), and all P values were 2-sided.

Results

Prostate cancer cases were somewhat taller and more likely to have a family history of prostate cancer (by 80%), lower concentrations of baseline serum α-tocopherol (by 3%), and higher serum retinol (by 3%), than controls at study entry (Table 1). They also had nonsignificantly higher 25(OH)D levels (by 3%, $P = 0.19$). Median follow-up time to prostate cancer diagnosis was 12.6 years, with controls having a median observation time of 17.5 years. Cases and controls did not differ materially with respect to other characteristics at baseline, including history of diabetes and leisure time physical activity.

Table 1. Selected baseline characteristics of prostate cancer cases and controls, the ATBC Study

Characteristic	Median (25%–75%) or %	
	Cases ($n = 1{,}000$)	Controls ($n = 1{,}000$)
Age, y	57.0 (54.0–62.0)	57.0 (54.0–62.0)
Height, cm	174.0 (170.0–178.0)	173.0 (169.0–177.0)
Weight, kg	77.9 (70.9–86.9)	77.3 (70.0–85.3)
BMI, kg/m^2	26.0 (23.9–28.5)	25.8 (23.6–28.2)
Cigarettes per day	20.0 (15.0–25.0)	20.0 (15.0–25.0)
Years of smoking	36.5 (30.0–42.0)	37.0 (31.0–42.0)
History of BPH, %	5.2	4.0
History of diabetes, %	2.3	3.8
Family history of prostate cancer,[a] %	5.2	2.9[b]
Leisure activity, moderate and heavy (%)	60.4	59.1
Vitamin D supplement use, %	7.8	6.5
Calcium supplement use, %	11.6	10.7
Energy intake,[c] kcal/d	2,612 (2,178–3,156)	2,636 (2,156–3,090)
Dietary vitamin D intake,[c] μg/d	4.7 (3.2–6.8)	4.7 (3.4–6.5)
Dietary calcium intake,[c] mg/d	1,335 (1,003–1,725)	1,335 (989–1,708)
Dietary fat intake,[c] g/d	118 (96–147)	119 (95–146)
Ethanol consumption,[c] g/d	10.7 (2.3–24.3)	9.2 (1.7–22.9)
Serum α-tocopherol, mg/L	11.4 (9.8–13.4)	11.6 (10.1–13.6)[d]
Serum retinol, μg/L	589 (513–671)	570 (499–662)[d]
Serum β-carotene, μg/L	180 (121–270)	184 (123–286)
Serum total cholesterol, mmol/L	6.21 (5.43–6.93)	6.27 (5.53–7.07)
Serum 25(OH) vitamin D, nmol/L	34.5 (22.7–50.0)	33.6 (21.4–49.1)

Abbreviation: BPH, benign prostatic hyperplasia.
[a]Family history data available for 76% of cases and controls.
[b]$P \leq 0.01$ by χ^2 test. All statistical tests are 2-sided.
[c]Dietary data available for 93% of cases and controls.
[d]$P \leq 0.05$ by Wilcoxon rank-sum test.

Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

Only 7% of the subjects were taking a supplement containing vitamin D.

Controls in the higher quintiles of baseline 25(OH)D levels had greater intake of vitamin D from dietary and supplemental sources, greater calcium supplement use and consumption of vegetables and alcohol, higher serum α-tocopherol and retinol concentrations, and lower serum total cholesterol (Table 2). Corresponding correlation coefficients (r) for some of the characteristics in the table include age (0.04), height (0.04), BMI (0.01), cigarettes per day (–0.04), energy intake (–0.01), dietary calcium (–0.04), leisure physical activity ($r = 0.16$; $P < 0.0001$), dietary and total vitamin D intake (0.26 and 0.27; $P < 0.0001$), serum α-tocopherol (0.09; $P < 0.0001$), serum β-carotene (0.08; $P = 0.0002$), serum retinol (0.11; $P < 0.0001$), and serum total cholesterol (–0.08; $P = 0.0002$). Mean 25(OH)D concentrations among vitamin D supplement users were 45.6 nmol/L as compared with 38.0 nmol/L among nonusers ($P = 0.01$).

On the basis of date of baseline blood collection, we observed the expected strong seasonal variation in 25(OH)D concentrations (Fig. 1). A wide range of blood levels for any given week was evident throughout the year, however, indicating the likely substantial influence of other factors including diet, supplements, sun exposure and outdoor activity, and genetic variation.

Prostate cancer risk increased with higher 25(OH)D concentrations regardless of the categorization and modeling approach used to adjust for date/season of blood collection (Table 3). Moderately strong and significant associations were apparent for the higher quintiles of season-specific and the season-adjusted 25(OH)D (i.e., 36%–56% elevated risk for men with the highest serum levels), and the dose-risk trend tests were statistically significant. Although the magnitude of elevated risk for men with the highest vitamin D levels (≥75 nmol/L) compared with those in the predefined clinical category of 50 to 75 nmol/L that is considered in

Table 2. Selected baseline characteristics (medians or percents) of the 1,000 controls by quintile[a] of fasting serum 25(OH)D, the ATBC Study

Characteristic	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Age, y	58.0	57.0	57.0	58.0	58.0
Height, cm	173.0	173.0	173.0	174.0	173.0
Weight, kg	76.1	76.2	77.8	78.8	77.1
BMI, kg/m^2	25.7	25.3	26.0	26.1	25.9
Cigarettes per day	20	20	20	20	20
No. of years of smoking	38.0	37.0	36.0	36.0	37.0
History of diabetes, %	2.0	3.5	6.5	2.0	5.0
History of BPH, %	5.0	3.5	4.0	4.5	3.0
Family history of prostate cancer,[b] %	2.5	3.0	2.0	5.5	1.5
Leisure activity, moderate and heavy, %	50.8	51.5	64.5	63.5	65.3
Vitamin D supplement use, %	2.5	5.0	6.0	7.5	11.6
Calcium supplement use, %	6.5	8.0	12.5	11.0	15.6
Energy intake,[c] kcal/d	2,648	2,829	2,653	2,700	2,504
Dietary vitamin D intake,[c] μg/d	3.7	4.4	4.6	5.2	5.9
Dietary calcium intake,[c] mg/d	1,446	1,409	1,357	1,404	1,347
Dietary fat intake,[c] g/d	119	124	118	124	111
Fruit consumption,[c] g/d	100	98	120	124	123
Vegetable consumption,[c] g/d	87	94	103	104	117
Ethanol consumption,[c] g/d	7.7	6.9	8.6	9.7	11.9
Serum α-tocopherol, mg/L	11.3	11.6	11.5	12.0	11.7
Serum retinol, μg/L	544	552	583	580	592
Serum β-carotene, μg/L	180	186	168	190	192
Serum total cholesterol, mmol/L	6.45	6.32	6.25	6.33	5.98
Serum 25(OH) vitamin D, nmol/L	14.2	22.6	31.2	43.9	63.6

Abbreviation: BPH, benign prostatic hyperplasia.

[a]Cutoff points for season-specific quintiles were Q1 ≤16.3, Q2 >16.3 and ≤23.8, Q3 >23.8 and ≤33.3, Q4 >33.3 and ≤45.6, Q5 >45.6 nmol/L for the less sunny months; Q1 ≤25.9, Q2 >25.9 and ≤35.7, Q3 >35.7 and ≤48.3, Q4 >48.3 and ≤59.9, Q5 >59.9 nmol/L for sunnier months.

[b]Family history data available for 76% of cases and controls.

[c]Dietary data available for 93% of cases and controls

Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

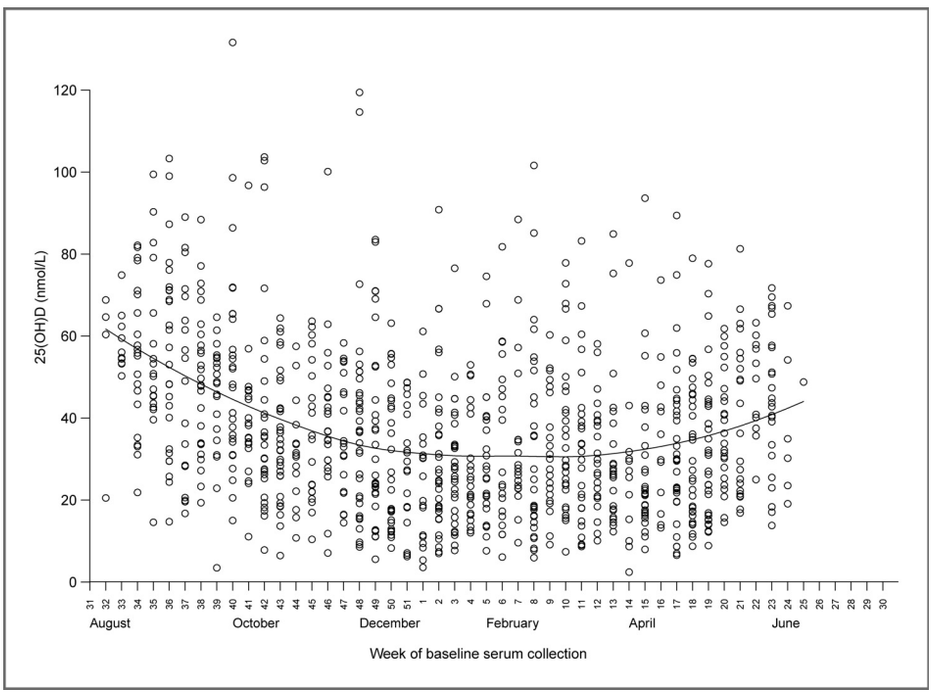

Figure 1. Individual serum 25(OH)D concentration plotted by week of blood collection in 1,000 controls in the ATBC Study (1985–2005). Smoothed line represents predicted 25(OH)D values calculated using a locally weighted polynomial regression.

the "sufficient" range is modest (e.g., OR = 1.16) and not significant, we observed an OR of 1.44 (95% CI = 0.91–2.30) for the highest category when the lowest, less than 25 nmol/L, category served as a reference. Further support of a dose–response association with prostate cancer risk at higher 25(OH)D concentrations was provided when we subdivided the top quintiles into 2 deciles on the basis of their median levels. This revealed ORs of 1.46 (95% CI = 1.02–2.10) and 1.67 (95% CI = 1.16–2.42) for deciles 9 and 10 in the season-specific

Table 3. Association between serum 25(OH)D categories and risk of prostate cancer, ATBC Study

	Quintiles of 25(OH)D[a]					P_{trend}
	1	2	3	4	5	
Season-specific						
Cases/controls, *n*	168/201	201/200	208/199	197/200	225/199	
OR[b] (95% CI)	1.00 (reference)	1.29 (0.95–1.74)	1.34 (1.00–1.80)	1.26 (0.93–1.72)	1.56 (1.15–2.12)	0.01
Season-adjusted						
Cases/controls, *n*	174/200	198/200	193/199	218/200	216/200	
OR[b] (95% CI)	1.00 (reference)	1.17 (0.87–1.57)	1.12 (0.84–1.51)	1.34 (0.99–1.82)	1.36 (1.01–1.82)	0.03
	Categories of 25(OH)D, nmol/L					
	<25	25 to <37.5	37.5 to <50	50 to <75	≥75	
Clinically predefined						
Cases/controls, *n*	299/327	255/241	195/190	194/195	56/46	
OR[b] (95% CI)	0.81 (0.60–1.08)	0.94 (0.71–1.26)	0.96 (0.71–1.31)	1.00 (reference)	1.16 (0.73–1.86)	0.07

[a]Cutoff -points for season-specific quintiles were Q1 ≤16.3, Q2 >16.3 and ≤23.8, Q3 >23.8 and ≤33.3, Q4 >33.3 and ≤45.6, Q5 >45.6 nmol/L for the less sunny months; Q1 ≤25.9, Q2 >25.9 and ≤35.7, Q3 >35.7 and ≤48.3, Q4 >48.3 and ≤59.9, Q5: >59.9 nmol/L for sunnier months. Cutoff points for season-adjusted quintiles were Q1 ≤3.00, Q2 >3.00 and ≤3.34, Q3 >3.34 and ≤3.63, Q4 >3.63 and ≤3.92, Q5 >3.92 residual units.

[b]ORs based on conditional logistic regression. Models conditioned on the matching factors and adjusted for age, family history of prostate cancer, and serum α-tocopherol.

Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

Table 4. Association between serum 25(OH)D and risk of prostate cancer, stratified by selected baseline and clinical characteristics, the ATBC Study

	Quintiles[a]					P_{trend}
	1	2	3	4	5	
Total vitamin D intake (diet + supplements)[b]						
Low (<5.0 μg/d)						
Cases/controls, *n*	121/137	107/103	88/99	87/82	60/56	
OR[c] (95% CI)	1.00 (reference)	1.22 (0.84–1.78)	1.04 (0.71–1.54)	1.28 (0.86–1.91)	1.24 (0.79–1.95)	0.30
High (≥5.0 μg/d)						
Cases/controls, *n*	41/52	84/86	108/94	106/112	153/132	
OR[c] (95% CI)	1.00 (reference)	1.34 (0.80–2.26)	1.65 (1.00–2.75)	1.32 (0.80–2.18)	1.69 (1.04–2.75)	0.08
					$P_{interaction}$	0.57
Total calcium intake (diet + supplements)[b]						
Low (<1,338 mg)						
Cases/controls, *n*	82/80	98/91	102/106	87/98	107/102	
OR[c] (95% CI)	1.00 (reference)	1.09 (0.71–1.67)	0.99 (0.65–1.51)	0.93 (0.60–1.43)	1.15 (0.75–1.75)	0.77
High (≥1,338 mg)						
Cases/controls, *n*	80/109	93/98	94/87	106/96	106/86	
OR[c] (95% CI)	1.00 (reference)	1.40 (0.92–2.12)	1.65 (1.08–2.52)	1.60 (1.06–2.42)	1.82 (1.20–2.76)	0.01
					$P_{interaction}$	0.06
Leisure activity						
Sedentary						
Cases/controls, *n*	94/99	100/97	82/71	54/73	65/69	
OR[c] (95% CI)	1.00 (reference)	1.21 (0.80–1.82)	1.35 (0.87–2.10)	0.79 (0.50–1.27)	1.12 (0.71–1.78)	0.81
Moderate/heavy						
Cases/controls, *n*	74/102	101/103	126/129	143/127	160/130	
OR[c] (95% CI)	1.00 (reference)	1.42 (0.94–2.15)	1.44 (0.97–2.14)	1.67 (1.13–2.46)	1.85 (1.26–2.72)	0.002
					$P_{interaction}$	0.03
Season of blood collection						
Less sunny months (November–April)						
Cases/controls, *n*	120/98	120/115	119/131	120/130	119/125	
OR[d] (95% CI)	1.00 (reference)	1.24 (0.83–1.86)	1.42 (0.96–2.10)	1.46 (0.97–2.21)	1.42 (0.95–2.12)	0.07
Sunnier months (May–October)						
Cases/controls, *n*	81/70	80/86	81/77	80/67	80/100	
OR[d] (95% CI)	1.00 (reference)	1.20 (0.72–1.98)	1.18 (0.72–1.94)	1.01 (0.60–1.69)	1.70 (1.01–2.85)	0.12
					$P_{interaction}$	0.78
Vitamin E supplementation						
No						
Cases/controls, *n*	90/94	112/100	116/95	91/100	118/108	
OR[c] (95% CI)	1.00 (reference)	1.29 (0.86–1.94)	1.49 (0.99–2.24)	1.05 (0.69–1.59)	1.29 (0.86–1.93)	0.56
Yes						
Cases/controls, *n*	78/107	89/100	92/105	106/100	107/91	
OR[c] (95% CI)	1.00 (reference)	1.29 (0.85–1.95)	1.23 (0.82–1.86)	1.54 (1.02–2.32)	1.74 (1.15–2.64)	0.006
					$P_{interaction}$	0.12
Serum α-tocopherol						
Low (<11.6 mg/L)						
Cases/controls, *n*	104/107	111/103	114/104	91/89	105/98	
OR[c] (95% CI)	1.00 (reference)	1.19 (0.80–1.76)	1.25 (0.84–1.85)	1.17 (0.78–1.77)	1.23 (0.82–1.84)	0.38
High (≥11.6 mg/L)						
Cases/controls, *n*	64/94	90/97	94/96	106/111	120/101	
OR[c] (95% CI)	1.00 (reference)	1.51 (0.97–2.34)	1.63 (1.05–2.52)	1.45 (0.95–2.23)	2.00 (1.30–3.07)	0.01
					$P_{interaction}$	0.15

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Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

Table 4. Association between serum 25(OH)D and risk of prostate cancer, stratified by selected baseline and clinical characteristics, the ATBC Study (Cont'd)

	Quintiles[a]					P_{trend}
	1	2	3	4	5	
Serum retinol						
Low (<570 μg/L)						
Cases/controls, *n*	81/120	95/112	91/93	81/93	93/83	
OR[c] (95% CI)	1.00 (reference)	1.39 (0.93–2.09)	1.67 (1.10–2.54)	1.43 (0.93–2.19)	1.80 (1.18–2.75)	0.01
High (≥570 μg/L)						
Cases/controls, *n*	87/81	106/88	117/107	116/107	132/116	
OR[c] (95% CI)	1.00 (reference)	1.19 (0.78–1.81)	1.10 (0.73–1.65)	1.09 (0.72–1.64)	1.22 (0.81–1.82)	0.51
					$P_{interaction}$	0.22
Serum total cholesterol						
Low (<6.27 mmol/L)						
Cases/controls, *n*	95/91	105/97	112/100	99/97	124/116	
OR[c] (95% CI)	1.00 (reference)	1.08 (0.72–1.62)	1.14 (0.76–1.70)	1.03 (0.69–1.56)	1.12 (0.75–1.66)	0.69
High (≥6.27 mmol/L)						
Cases/controls, *n*	73/110	96/103	96/100	98/103	101/83	
OR[c] (95% CI)	1.00 (reference)	1.53 (1.01–2.32)	1.61 (1.06–2.45)	1.56 (1.03–2.38)	2.09 (1.36–3.21)	0.003
					$P_{interaction}$	0.07
Case stage/Gleason score[e]						
Nonaggressive						
Cases/controls, *n*	57/61	77/88	80/68	78/86	52/81	
OR[d] (95% CI)	1.00 (reference)	0.99 (0.59–1.65)	1.34 (0.81–2.23)	1.00 (0.60–1.66)	1.31 (0.81–2.13)	0.29
Aggressive						
Cases/controls, *n*	84/103	81/79	84/85	82/71	90/84	
OR[d] (95% CI)	1.00 (reference)	1.28 (0.82–2.01)	1.34 (0.85–2.09)	1.59 (0.98–2.60)	1.70 (1.05–2.76)	0.02
					$P_{interaction}$	0.43
Follow-up period						
<10 y						
Cases/controls, *n*	61/75	65/62	67/57	64/66	65/63	
OR[d] (95% CI)	1.00 (reference)	1.16 (0.69–1.96)	1.42 (0.84–2.39)	1.06 (0.60–1.88)	1.51 (0.86–2.63)	0.21
≥10 y						
Cases/controls, *n*	107/126	136/138	141/143	133/134	160/136	
OR[d] (95% CI)	1.00 (reference)	1.27 (0.88–1.85)	1.30 (0.90–1.88)	1.30 (0.89–1.89)	1.59 (1.09–2.31)	0.03
					$P_{interaction}$	0.67

[a]Cutoff points for season-specific quintiles were Q1 ≤16.3, Q2 >16.3 and ≤23.8, Q3 >23.8 and ≤33.3, Q4 >33.3 and ≤45.6, Q5 >45.6 nmol/L for the less sunny months; Q1 ≤25.9, Q2 >25.9 and ≤35.7, Q3 >35.7 and ≤48.3, Q4 >48.3 and ≤59.9, Q5 >59.9 nmol/L for sunnier months.

[b]Dietary data available for 1,909 subjects.

[c]ORs based on unconditional logistic regression, adjusted for age, season of blood draw, family history of prostate cancer, and serum α-tocopherol.

[d]ORs based on conditional logistic regression, conditioned on the matching factors and adjusted for age, family history of prostate cancer, and serum α-tocopherol.

[e]Data for disease stage and Gleason score were available for 636 cases.

models, and 1.26 (95% CI = 0.89–1.79) and 1.47 (95% CI = 1.03–2.10) in the season-adjusted models. Given the more consistent distribution of cases and resulting higher precision across control-based quintiles than the predefined categories, season-specific quintiles were used for subsequent analyses, including exploratory subgroup analyses (season-adjusted models yielded similar findings). On the basis of 294 cases, risk of fatal prostate cancer across increasing season-specific quintiles of 25(OH)D was 1.0 (reference), 1.33 (95% CI = 0.77–2.31), 1.35 (0.79–2.30), 1.12 (0.61–2.05), and 1.40 (0.79–2.49), with P_{trend} of 0.40. (Our study was not, however, powered for a main effect test of prostate cancer mortality.)

Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

We observed stronger prostate cancer–serum 25(OH)D associations and trends among men with higher total vitamin D and calcium intake, greater leisure activity, higher serum α-tocopherol and total cholesterol, lower serum retinol, men receiving the ATBC Study vitamin E supplement, and for aggressive disease (Table 4). In contrast, the positive vitamin D–risk association was similar among men whose serum was obtained during both darker and sunnier months as well as for the earlier and later periods of follow-up (Table 4). All formal tests for interaction with these biologically based, *a priori* factors yielded $P > 0.05$, however, with the exception of leisure physical activity ($P = 0.03$), whereas the interactions with calcium intake ($P = 0.06$), vitamin E supplementation ($P = 0.12$), serum α-tocopherol ($P = 0.15$), and serum total cholesterol ($P = 0.07$) were marginally nonsignificant. There was no modification of the serum vitamin D–prostate cancer association by age, smoking intensity or duration, BMI, family history of prostate cancer, history of diabetes, serum HDL cholesterol or β-carotene, the trial β-carotene supplementation, alcohol consumption, or selenium intake (data not shown).

Discussion

On the basis of a large complement of prostate cancer cases and up to 20 years of follow-up, our findings indicate that men with higher vitamin D status, as determined by serum 25(OH)D concentrations, are at elevated risk of developing prostate cancer and provide no evidence of greater risk in men with low vitamin D status. We found approximately 40% to 60% increased risk in men with the highest serum vitamin D concentrations compared with men with low levels. The estimates of elevated risk were materially identical from the 3 currently accepted methods for controlling season of blood collection, and they appeared stronger for aggressive prostate cancer. Specific findings in our study that further support an etiologic basis for the positive association with vitamin D include the stable relation throughout the follow-up period and incrementally elevated risk within the highest serum 25(OH)D quintiles; for example, the OR of 1.56 for the highest season-specific vitamin D quintile was contributed by ORs of 1.46 and 1.67 for its lower and higher deciles, respectively. We also showed stronger associations for men with higher total vitamin D intake (Q5 OR = 1.69) and those with greater leisure physical activity (Q5 OR = 1.85), 2 factors related to higher vitamin D status (refs. 16, 17, and data in Table 2). This may be reflecting higher overall exposure to circulating vitamin D in those strata with a resulting greater impact on prostate cancer risk.

Our observation of a significant positive 25(OH)D–prostate cancer association is not consistent with most basic research and common prevailing expectations of a beneficial role for higher vitamin D status in several malignancies, including prostate cancer (18). It is, however, supported by several studies in the United States and Europe that suggest elevated prostate cancer risk among men with higher 25(OH)D concentrations (Fig. 2). The most recent of these nested case–control studies were from the Multiethnic Cohort (MEC) and European Prospective Investigation into Cancer and Nutrition (EPIC; refs. 19, 20). In the MEC study of 329 ethnically-diverse prostate cancer cases (19), men with plasma 25(OH)D concentrations of 50 ng/mL or more (or ≥125 nmol/L) appeared at increased risk compared with men in the 25(OH)D range from 30 to less than 50 ng/mL, but the finding was not statistically significant [OR (95% CI) = 1.52 (0.92–2.51); $P_{trend} = 0.32$]. A quartile-based analysis

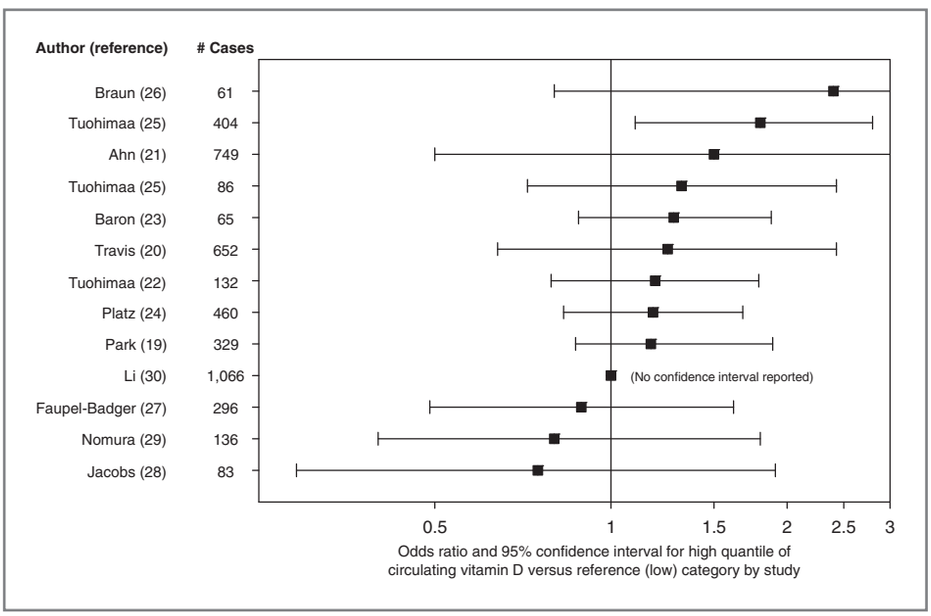

Figure 2. Published nested case–control studies of serum 25(OH)D and risk of developing prostate cancer.

Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

revealed a more attenuated risk estimate for the highest compared with lowest category (OR = 1.17; $P_{trend} = 0.60$). EPIC yielded similar data and conclusions based on 652 cases and an overall OR of 1.28 for high versus low quintile of 25(OH)D ($P_{trend} = 0.19$; ref. 20). In fact, as depicted in Figure 2, other studies suggesting elevated prostate cancer risk estimates for men in highest categories of serum (or plasma) 25(OH)D included the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (OR = 1.18; ref. 21), the Helsinki Heart Study (OR = 1.25; ref. 22), the Calcium Polyp Prevention Study (OR = 1.32; ref. 23), the Health Professionals Follow-Up Study (OR = 1.19; ref. 24), the Northern Sweden Health and Disease Cohort and Norwegian Janus Project (OR = 1.5 and 1.8, respectively; ref. 25), and the early Washington County, Maryland, cohort (OR = 2.4; ref. 26), for example. Most of these studies were included in a recent meta-analysis of 3,100 incident prostate cancer cases (3) that concluded an association with serum vitamin D was not present, based on the summary OR estimate of 1.03 (95% CI = 0.96–1.11) for every 25 nmol/L increase in 25(OH)D concentrations. The meta-analysis also calculated an OR for $1,25(OH)_2D$ in the 5 studies that measured it, which yielded 4% higher prostate cancer risk per 25 pmol/L increment (95% CI = −6% to 16%), consistent with the direction observed for the 25(OH)D relation. Some investigations included in the meta-analysis (27–29) and one not included (30), reported overall associations between 25(OH)D and prostate cancer risk at or near ORs of 1.0 for the high vitamin D categories, and a few suggested elevated risk (overall or for aggressive disease) for low vitamin D status (25, 30). These prior studies represent a range of population 25(OH)D concentrations (median levels, 60–100 nmol/L, average 70 nmol/L) that are generally higher than in the ATBC Study cohort, as well as a diverse spectrum of study methods and other population characteristics including lengths of follow-up (up to 5–18 years), blood collection procedures and approaches to adjustment for season, smoking exposure, vitamin D intake and prevalence of vitamin D deficiency, and cancer case characteristics (e.g., subsets based on disease aggressiveness), with no apparent consistent impact on resulting risk estimates across studies.

Without further basic or clinical research, we can only speculate with respect to how higher 25(OH)D status might promote the development of prostate cancer, especially given that experimental research to date shows that exposure to high concentrations of $1,25(OH)_2D$ inhibits cell proliferation and cell-cycle signaling, angiogenesis, inflammation, and LNCaP cell culture and *in vivo* tumor growth and upregulates apoptotic pathways (4–6). Earlier research found circulating and tissue concentrations of 25(OH)D and 1,25(OH)D to be similar (31), and nearly all tissues including the prostate express the vitamin D receptor (VDR; ref. 4). It is theoretically possible that 25(OH)D at higher concentrations displaces $1,25(OH)_2D$ from vitamin D binding protein, leading to reduced delivery of the latter to the prostate and other tissues. Potentially relevant to the issue of plausible causal mechanisms is the positive vitamin D–cancer association observed for the exocrine pancreas in both this cohort (32) and in a recent pooling project that investigated more than 800 cases from the United States, China, and Finland (33). This similarity could represent a common underlying biological action of vitamin D that may impact tumorigenesis at both sites; for example, $1,25(OH)_2D$ is known to stimulate the insulin receptor and increase insulin synthesis (34). In turn, higher fasting insulin has been associated with substantially elevated risks of developing pancreatic cancer (35) and prostate cancer (36). Higher vitamin D status could, therefore, promote cell proliferation and tumor growth in both organs through hyperinsulinemia. Our finding of a stronger vitamin D–prostate cancer association for aggressive disease would be consistent with a tumor growth stimulatory effect.

The randomized controlled trial component of the ATBC Study, collection of dietary and other data, and measurement of other serum nutrients at baseline for the entire cohort permitted exploration of several biologically relevant interactions potentially related to the development of prostate cancer. These analyses revealed strong serum vitamin D associations among men with higher calcium intake and those randomized to receive the trial α-tocopherol supplement (which was previously shown to lower prostate cancer incidence; ref. 37), men with high serum α-tocopherol or total cholesterol, and those with low serum retinol. Higher calcium intake has been associated with elevated prostate cancer risk (38, 39), which could explain a synergistic effect observed here. Consistency between the effect modification of the controlled α-tocopherol supplement and baseline serum α-tocopherol levels supports a biological basis for the observations. For example, if higher vitamin E exposure acts through tumor growth inhibition via slowed cell proliferation (40), it may be that vitamin D reverses the latter in a dose–response manner through VDR and possibly other nuclear receptor signaling, whereas in the setting of lower circulating vitamin E or nonsupplementation, tumor growth inhibition by vitamin E is minimal and vitamin D may not have as great an absolute influence to stimulate growth. The fact that in both the present findings for vitamin D, and prior research on vitamin E showing the effects (of supplements) and serum associations were stronger for aggressive or more advanced disease, further supports a biological basis for this interaction. Diminished competitive ligand binding of nuclear retinoid X receptor and retinoic acid receptor (RXR/RAR) by retinol with a consequent reduction in receptor dimerization and transcriptional activity through VDR (5), for example, is consistent with our finding regarding the influence of lower vitamin A status. These hypothesis-generating findings may be indicative of metabolic interactions and should be examined in other studies.

Our investigation is limited by its sole inclusion of smokers and Caucasians, although our data are

Published OnlineFirst July 22, 2011; DOI: 10.1158/1055-9965.EPI-11-0403

consistent with the aforementioned studies of wide-ranging smoking prevalence among primarily Caucasians. The relatively low vitamin D status of the population, contributed to by the high latitude location of the study and the paucity of summer blood collections (9), may have limited our ability to find a protective vitamin D–prostate cancer association at very high serum levels. Our sensitivity analysis of the highest 25(OH)D deciles, and recently reported beneficial association for bladder cancer (41), does not support this, however. On the basis of several recent studies showing good reliability and relatively low intraindividual variability of serum vitamin D (42, 43), our measurement of 25(OH)D from blood collected after an overnight fast at one point in time for each participant at study entry should have provided a reasonable estimation of long-term exposure during the years incident prostate cancers were diagnosed. A large sample size with 86% power to detect the observed association, high-quality laboratory measurements, and examination of serum 25(OH)D up to 20 years prior to prostate cancer diagnoses are key strengths of our investigation. Two decades of follow-up minimized bias from reverse causality, and the elevated vitamin D risks were evident for cancers diagnosed 10 to 20 years after their baseline fasting blood collection. Long follow-up was recently emphasized in a report on vitamin D and cancer by the International Agency for Research on Cancer, which concluded, "It is plausible that for prostate cancer, vitamin D level much longer before the time of diagnosis is most relevant" (ref. 44, p. 191–2). Prostate cancer ascertainment through the Finnish Cancer Registry was complete (11), so we were able to examine risk by disease stage, and because nearly all cases were clinically diagnosed, the potential for detection bias from any vitamin D–prostate-specific antigen (PSA) association was small. We also carefully controlled for the impact of sun-related UVB exposure on vitamin D levels through tight matching on date of blood collection (±30 days), use of multiple methods of adjustment for season (all of which showed the same positive vitamin D–prostate cancer association), and stratification of leisure activity level. Confounding is an unlikely explanation for our findings because of the large number of characteristics we were able to adjust for and the general pattern of healthier lifestyle exposures in the higher 25(OH)D categories (Table 2).

Although additional, sufficiently powered studies or consortium efforts confirming this association in other populations are needed, our findings show that the risk of developing prostate cancer is adversely impacted by higher vitamin D status, particularly for 25(OH)D levels above 50 nmol/L (or 46 and 60 nmol/L for serum concentrations measured from darker and sunnier months of blood collection, respectively). Reevaluation of the interactions between serum 25(OH)D and vitamin D and calcium intake, vitamin E supplementation, and serum cholesterol, α-tocopherol, and retinol observed here would be useful and likely contributory to our understanding of how vitamin D may modify prostate and other cancer risk. Genetic variants related to serum 25(OH)D levels that encode the vitamin D binding protein [something that should be measured in future studies to estimate free versus bound 25(OH)D] and other enzymes involved in vitamin D metabolism (45, 46) should be examined for association with prostate cancer risk as an alternative test of the causal nature of our findings and to assess genetic modification of the serum 25(OH)D association. To date, such studies have been based on relatively small samples, focused primarily on variants in the gene-encoding VDR, and inconsistent in their findings (47–49). Given the high incidence of prostate cancer in the United States and elsewhere and the growing popularity of vitamin D supplementation (e.g., nearly 40% of U.S. adults reporting vitamin D use; ref. 50), how higher vitamin D status might increase prostate cancer risk, and any impact of vitamin D status on prostate cancer survival, should be carefully examined.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

The ATBC Study was supported in part by U.S. Public Health Service (contract numbers N01-CN-45165, N01-RC-45035, N01-RC-37004, and HHSN261201000006C) from the National Cancer Institute, Department of Health and Human Services, and Intramural Research Program of the National Cancer Institute.

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Received April 27, 2011; revised June 24, 2011; accepted July 14, 2011; published OnlineFirst July 22, 2011.

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Serum 25-Hydroxy Vitamin D and Prostate Cancer Risk in a Large Nested Case–Control Study

Demetrius Albanes, Alison M. Mondul, Kai Yu, et al.

Cancer Epidemiol Biomarkers Prev 2011;20:1850-1860. Published OnlineFirst July 22, 2011.