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Research Article

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Plasma Vitamin D and Prostate Cancer Risk: Results from the Selenium and Vitamin E Cancer Prevention Trial

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Abstract

Background: *In vitro*, animal, and ecological studies suggest that inadequate vitamin D intake could increase prostate cancer risk, but results of biomarker-based longitudinal studies are inconsistent.

Methods: Data for this case ($n = 1{,}731$) and cohort ($n = 3{,}203$) analysis are from the Selenium and Vitamin E Cancer Prevention Trial. Cox proportional hazard models were used to test whether baseline plasma vitamin D (25-hydroxy) concentration, adjusted for season of blood collection, was associated with the risk of total and Gleason score 2–6, 7–10, and 8–10 prostate cancer.

Results: There were U-shaped associations of vitamin D with total cancer risk: compared with the first quintile, HRs were 0.83 [95% confidence interval (CI), 0.66–1.03; $P = 0.092$], 0.74 (95% CI, 0.59–0.92; $P = 0.008$), 0.86 (95% CI, 0.69–1.07; $P = 0.181$), and 0.98 (95% CI, 0.78–1.21; $P = 0.823$), for the second through fifth quintiles, respectively. For Gleason 7–10 cancer, corresponding HRs were 0.63 (95% CI, 0.45–0.90; $P = 0.010$), 0.66 (95% CI, 0.47–0.92; $P = 0.016$), 0.79 (95% CI, 0.56–1.10; $P = 0.165$), and 0.88 (95% CI, 0.63–1.22; $P = 0.436$). Among African American men ($n = 250$ cases), higher vitamin D was associated with reduced risk of Gleason 7–10 cancer only: in the *a posteriori* contrast of quintiles 1–2 versus 3–5, the HR was 0.55 (95% CI, 0.31–0.97; $P = 0.037$), with no evidence of dose–response or a U-shaped association.

Conclusions: Both low and high vitamin D concentrations were associated with increased risk of prostate cancer, and more strongly for high-grade disease.

Impact: The optimal range of circulating vitamin D for prostate cancer prevention may be narrow. Supplementation of men with adequate levels may be harmful. *Cancer Epidemiol Biomarkers Prev; 23(8); 1494–504. ©2014 AACR.*

Introduction

The role of vitamin D in prostate cancer risk remains controversial. There is a large body of evidence based on *in vitro*, animal experimental, and ecological studies, which suggests that inadequate vitamin D could increase prostate cancer risk (1); however, the results of longitudinal studies based on prediagnostic serum concentrations of vitamin D (25-hydroxy vitamin D) are mixed. With the exception of small studies ($n < 200$ cases), no longitudinal study has reported a significant inverse association of vitamin D with prostate cancer, most have reported no association of serum vitamin D with risk (2–7), and others have reported statistically significant associations that are U-shaped (8), inverted U-shaped (9, 10), and positive (11–13). The reasons for inconsistency across studies are unclear.

Here, we give results on vitamin D and prostate cancer risk from the Selenium and Vitamin E Cancer Prevention Trial (SELECT). This is one of the largest studies to date examining blood vitamin D and prostate cancer incidence, with 1,731 total and 502 high-grade (Gleason 7–10) cases. There are also a sufficient number of cases ($n = 250$) among African American men to support a stratified analysis, which is of considerable interest because, compared with Caucasian men, African American men have both a higher risk of prostate cancer (14) and lower blood vitamin D concentrations (15). Results of this study can help resolve the question of whether or not circulating concentrations of vitamin D are associated with prostate cancer risk.

Materials and Methods

Data and blood samples for this study are from the SELECT, which was a randomized, placebo-controlled

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trial that tested whether selenium and vitamin E, either alone or combined, reduced prostate cancer risk (16). Briefly, in 427 participating sites across the United States, Canada, and Puerto Rico, men ≥50 years (African American) or ≥55 years (all other men) of age, who had no history of prostate cancer, and who had a serum PSA of ≤4 ng/mL and nonsuspicious digital rectal exam (DRE) were eligible to participate. Between July 2001 and May 2004, 35,533 men were block-randomized by study site to one of 4 groups: selenium + vitamin E; vitamin E + placebo; selenium + placebo; or placebo + placebo. On September 15, 2008, the Data and Safety Monitoring Committee recommended the discontinuation of the trial supplements due to no observed evidence of a protective effect and no likelihood of an effect given current rates of cancer in each arm. All men provided written informed consent, and study procedures were approved by local institutional review boards for each participating study center.

The present study is a case–cohort design nested within SELECT. Cases included in these analyses were men with baseline blood samples available for analysis who were diagnosed with incident, primary prostate cancers before July 31, 2009. Most cases (95.0%) were detected by PSA and/or DRE screening, which was suggested annually but not required. At each annual visit, participants reported screening procedures during the preceding year and, at each quarterly study contact, participants reported new cancer diagnoses. Study staff obtained pathology reports and, when possible, pathology slides. Most cases included in these analyses (85.1%; 1,473 of 1,731) were reviewed centrally for pathologic confirmation and grading using the Gleason system. For 43 cases from whom slides were not available, Gleason scores were abstracted from local pathology reports. For the main analyses, high-grade tumors were defined as Gleason scores 7–10 and more conservatively as Gleason scores 8–10, and low-grade tumors were Gleason scores 2–6. Grade was unknown for 215 cases.

A subcohort representative of SELECT participants was created *a priori* as the comparison group for this and other biomarker studies, using the following approach. Men randomized into the study who had baseline blood samples available were stratified into 9 age/race cohorts: <55 for African Americans, and 55 to 59, 60 to 64, 65 to 69, ≥70 years for both African Americans and others. For each case, men were selected for the subcohort at random from the same age/race group, using a ratio of 1:3 for African Americans and 1:1.5 for others. There were 3,203 men in the subcohort, of whom 201 were also cases.

Data on demographic and health-related characteristics were collected at baseline by self-administered questionnaire. Study staff measured height and weight, which were used to calculate body mass index (BMI; kg/m^2). Venous blood samples, collected after a minimum 4-hour fast, were collected at baseline, refrigerated, and shipped overnight to the specimen repository where the samples were centrifuged, aliquoted, and stored at −70°C until analysis. Vitamin D (25-OH) concentration in plasma was measured using the LIAISON 25 OH Vitamin D TOTAL Assay (DiaSorin Inc.), which is a chemiluminescent immunoassay, following the manufacturer's instructions. The limit of quantitation of this assay was 4 ng/mL. Each batch of samples was bracketed by both a low (pooled plasma) and high (BioRad Liquichek Level 3) quality control sample; their interbatch coefficients of variation were 12.1% and 6.9%, respectively. Starting in 2005 and continuing annually through 2009, samples from cases and the subcohort members selected due to each case were analyzed in the same batch, and laboratory personnel were blinded to the status of the samples. Two or three separate aliquots from 376 men were analyzed in batches completed in different years; from these samples, the weighted average of the coefficients of variation for vitamin D was 15.5%, and there was a small assay drift of approximately −3 nmol/L per year.

Cox proportional hazards models were used to estimate HR and 95% confidence interval (CI) for the association between plasma vitamin D and risk of prostate cancer. Separate models were fit for total, Gleason 2–6, and Gleason 7–10 cancers. Models for Gleason 8–10 cancer were completed only for the analyses not stratified by race, due to small number of these cases. Cases not occurring in the subcohort enter the proportional hazards model just before diagnosis and remain in the model until diagnosis. Noncases in the subcohort enter the model at randomization and continue until they are censored. Cases in the subcohort seem in the model twice: once treated as noncases in the subcohort (entering at randomization, censored just before diagnosis), and once treated as cases outside the subcohort (entering just before diagnosis, continuing until diagnosis). Because the sampling scheme used in creating the subcohort was stratified, all analyses were stratified by nine age–race groups and each stratum was weighted based on the inverse of its selection probability. We used the method proposed by Prentice (17) to assign weights for calculating the pseudo-likelihood function because it was found to be least biased based on a simulation study.

Blood vitamin D concentrations vary by season, because exposure to UV radiation stimulates the synthesis of vitamin D_3 in skin. We examined two approaches to adjust plasma vitamin D concentration for season of blood collection. The first calculated month-adjusted vitamin D values by first generating residuals from a multiple regression model that predicted vitamin D concentration by month and then adding these residuals to the overall mean vitamin D value. Lacking any standard approach to categorizing adequacy of vitamin D, these month-adjusted values were categorized using both a set of *a priori* cutpoints for deficient (<37.5 nmol/L), low (37.5 to <50 nmol/L), adequate (50 to <75 nmol/L), and high (≥75 nmol/L), and by quintiles defined by the distribution in the subcohort. The second approach was based on month-specific quintiles: within strata defined by month of blood collection, vitamin D values were categorized into quintiles and these quintile assignments were used in

subsequent analyses of the entire dataset. Results based on this second approach were almost identical to those based on month-adjusted vitamin D values and are therefore not presented. In analyses stratified by race (African American and non–African American), month-adjusted vitamin D values were generated using data from each race group separately, and quintiles were defined by both the distribution of vitamin D in the race-specific subcohort and the total subcohort.

Additional covariates in multivariable regression models included BMI, history of diabetes, family history of prostate cancer, and SELECT intervention assignment. Results are also age- and race-adjusted, because all models were stratified by race–age groups before being weighted and combined to generate summary statistics. Additional control for total calcium intake and serum cholesterol concentration did not affect results and these are therefore not included in final models. Statistical analyses were performed using SAS version 9.2 software (SAS Institute). All statistical tests are two-sided, and $P < 0.05$ was considered statistically significant.

Results

Table 1 gives demographic characteristics and other study-related variables in prostate cancer cases and in the subcohort. Almost 41% of cases were ≥65 years old and 14.4% were African American. Because of matching, the age distribution of the subcohort was similar to that of cases and, due to the sampling scheme, the ratio of cases to subcohort members was 1.0:1.6 for Caucasians and 1.0:3.2 for African Americans. The percentages of total cases that were diagnosed with Gleason 7–10 cancer (33.1% and 31.9%) and the percentages of men who were obese (30.1% and 33.8%) were similar in cases and the subcohort. A substantially larger percentage of cases had a family history of prostate cancer (28.9%) compared with men in the subcohort (14.8%).

Table 2 gives raw and covariate-adjusted mean vitamin D concentrations, along with the percentages of men that are classified as deficient (<37.5 nmol/L) and low (37.5–<50 nmol/L) in vitamin D. The mean vitamin D concentration was 69.2 nmol/L, and after adjustment for covariates 12.2% and 14.7% of men were classified as deficient or low. Mean, covariate-adjusted vitamin D concentration was 9.8% higher in men ages ≥70 years compared with those ages 50 to 54 years, and 13.6% lower in men with BMI ≥30 kg/m^2 compared with those with BMI < 25 kg/m^2 (both $p_{trend} < 0.001$). Vitamin D concentration was 40.8% higher in Caucasian compared with African American men, and only 5.9% of Caucasian compared with 29.1% of African American men were classified as vitamin D deficient. As expected, there was substantial variation in covariate-adjusted vitamin D concentrations by month of blood draw, ranging from a high of 82.8 nmol/L in August to 59.4 nmol/L in February, with corresponding percentages of men classified as deficient ranging from 3.4% to 19.9%.

Table 1. Demographic and health-related characteristics of SELECT case–cohort sample

	Prostate cancer cases ($n = 1,731$)	Cohort[a] ($n = 3,203$)
Age, y		
Mean ± SD	63.5 ± 6.1	63.3 ± 6.5
50–54	44 (2.5)	128 (4.0)
55–59	461 (26.6)	856 (26.7)
60–64	520 (30.0)	935 (29.2)
65–69	408 (23.6)	750 (23.4)
≥70	298 (17.2)	534 (16.7)
Race		
White	1,394 (80.5)	2,213 (69.1)
African American	250 (14.4)	802 (25.0)
Other/unknown	87 (5.0)	188 (5.9)
BMI, kg/m^2		
Mean ± SD	28.5 ± 4.3	28.8 ± 4.6
<25	335 (19.4)	615 (19.2)
25–<30	875 (50.5)	1,506 (47.0)
≥30	521 (30.1)	1,082 (33.8)
Gleason grade		
2–6	1,014 (58.6)	128 (63.7)[b]
7–10	502 (28.9)	60 (29.9)
8–10	104 (6.0)	12 (6.0)
Family history of prostate cancer		
No	1,231 (71.1)	2,729 (85.2)
Yes	500 (28.9)	474 (14.8)
Trial arm		
Placebo	407 (23.5)	790 (24.7)
Vitamin E	474 (27.4)	813 (25.4)
Selenium	431 (24.9)	800 (25.0)
Vitamin E + selenium	419 (24.2)	800 (25.0)

[a]201 men are both cases and in the cohort.
[b]Number (%) of total cases.

Table 3 gives associations of vitamin D concentrations with risks of total, and Gleason 2–6, 7–10, and 8–10 cancers. In models categorizing exposure based on the criteria for vitamin D adequacy, neither unadjusted (Model 1) nor month-adjusted (Model 2) vitamin D concentrations were associated with total, Gleason 2–6, or Gleason 7–10 cancer. There was a 59% ($P = 0.013$) reduced risk for Gleason 8–10 cancer among men classified as "adequate" in vitamin D when plasma concentrations were not adjusted for month of blood sampling: after adjustment for month of sampling, this association was attenuated to a 45% reduced risk and no longer statistically significant. When month-adjusted vitamin D was categorized into quintiles based on the distribution in the subcohort (Model 3), there were U-shaped associations of vitamin D with risks of total and Gleason 2–6, 7–10, and 8–10 cancers. Compared with the first quintile, the risk of total prostate

Table 2. Associations of age, race, BMI, and month of blood sample with plasma vitamin D concentration: SELECT

	Unadjusted vitamin D concentrations				Adjusted vitamin D concentrations[a]			
	Mean (SD)	P^b	<37.5 N (%)[c]	37.5–<50 N (%)[c]	Mean (SD)	P^b	<37.5 N (%)[c]	37.5–<50 N (%)[c]
Total	69.2 (29.7)		635 (13.4)	697 (14.7)	69.2 (28.8)		578 (12.2)	697 (14.7)
Age, y		<0.001				<0.001		
50–54	46.6 (25.2)		72 (43.6)	36 (21.8)	65.5 (24.6)		10 (6.1)	30 (18.2)
55–59	66.1 (28.9)		202 (15.9)	210 (16.5)	66.5 (25.4)		125 (9.8)	234 (18.4)
60–64	70.6 (29.6)		161 (11.5)	209 (15)	69.9 (27.6)		126 (9)	206 (14.8)
65–69	71.2 (29.1)		125 (11.4)	140 (12.7)	70.1 (26.7)		92 (8.4)	167 (15.2)
≥70	73.8 (30)		75 (9.3)	102 (12.7)	71.9 (28.4)		66 (8.2)	100 (12.5)
Race								
White	74.4 (28.3)		249 (7.2)	434 (12.5)	73.9 (27.1)		204 (5.9)	441 (12.7)
African American	50.3 (25.3)	<0.001	349 (35)	234 (23.4)	52.5 (24.6)	<0.001	290 (29.1)	244 (24.4)
Other/unknown	72 (33.3)	0.025	37 (13.8)	29 (10.8)	71.2 (31.9)	0.015	34 (12.7)	28 (10.4)
BMI, kg/m^2		<0.001				<0.001		
<25	75.5 (31.7)		99 (10.8)	104 (11.4)	74.4 (29.7)		74 (8.1)	119 (13)
25–<30	70.8 (29.8)		250 (10.9)	331 (14.5)	70.4 (27.1)		177 (7.7)	363 (15.9)
≥30	63.1 (27.1)		286 (18.6)	262 (17.1)	64.3 (24.6)		168 (10.9)	295 (19.2)
Month of blood draw		<0.001				<0.001		
January	65.3 (30)		76 (18.6)	60 (14.7)	64.8 (28.3)		64 (15.6)	77 (18.8)
February	59.1 (27.3)		85 (20.8)	89 (21.8)	59.4 (26.1)		81 (19.9)	74 (18.1)
March	62.3 (27.2)		79 (18.8)	75 (17.8)	63.1 (25.4)		65 (15.4)	76 (18.1)
April	63.2 (26.2)		67 (17)	72 (18.2)	63.3 (25.3)		56 (14.2)	71 (18)
May	65.7 (28.2)		68 (17.2)	60 (15.2)	66.9 (25.5)		40 (10.1)	62 (15.7)
June	71 (27.3)		46 (9.7)	68 (14.3)	71.4 (24.7)		20 (4.2)	72 (15.2)
July	74.8 (27.1)		18 (8)	23 (10.3)	76.8 (24.4)		10 (4.5)	18 (8)
August	83.9 (28.3)		6 (2.5)	19 (8.1)	82.8 (27.5)		8 (3.4)	12 (5.1)
September	80.6 (33)		18 (5.4)	40 (12)	79.4 (30.7)		15 (4.5)	29 (8.7)
October	77.1 (30.2)		37 (7)	59 (11.2)	76 (28.2)		27 (5.1)	57 (10.8)
November	71.3 (32.1)		69 (13.4)	69 (13.4)	70.7 (29.9)		55 (10.7)	82 (15.9)
December	63.8 (27)		66 (16.8)	63 (16)	64.1 (24.5)		50 (12.7)	64 (16.3)

[a]Vitamin D values are mutually adjusted for all other variables in table before calculating categories, except for the "Total" row, which is adjusted for month only.

[b]*P* values are for trend, except for race, where values are for contrast with White.

[c]All percentages are row percentages, except for the "Total" row, which is percentage of total.

cancer was lower by 26% ($P = 0.008$) in the third, 17% ($P = 0.092$) in the second, and 14% ($P = 0.181$) in fourth quintiles, and almost the same in the fifth quintile. This U-shaped association was similar for Gleason 2–6 cancer, but considerably stronger for Gleason 7–10 and 8–10 cancers. Most strikingly, the reduction in risk contrasting the third to first quintile was 64% ($P = 0.010$) for Gleason 8–10 and 24% ($P = 0.048$) for Gleason 2–6 cancer.

Table 4 gives results in the subset of African American men. Note that in some cells in these analyses the numbers of cases are very small (<10), confidence limits are very large, and interpretations of dose response are complicated by the imprecision of HR point estimates. In addition, very few African American men had vitamin D levels that would be classified as high (≥75 nmol/L) using our criterion, so that if there was a U-shaped association it would be difficult to detect. For all models examined, there were trends for lower risk of Gleason 7–10 cancer with increasing vitamin D levels, which reached statistical significance ($P_{trend} = 0.048$) only for Model 2. We conducted several *a posteriori* contrasts to test associations of Gleason 7–10 cancer with risk above and below model-specific cutpoints for vitamin D of ≥50 nmol/L (Model 2), ≥52.9 nmol/L (Model 3), and ≥58.2 nmol/L (Model 4). Corresponding HRs were 0.51 (0.30–0.89; $P = 0.016$), 0.55 (0.32–0.94; $P = 0.03$), and 0.55 (0.31–0.97; $P = 0.037$, data not shown).

Results for the subset of non–African American men were similar to those of the entire study sample (Table 5). There were U-shaped associations of plasma vitamin D with risk only when categories of exposure were defined by the distribution of vitamin D in the total subcohort

Table 3. Association of plasma vitamin D concentration with prostate cancer risk: SELECT

Model	Vitamin D (nmol/L)	*N* (case)	*N* (cohort)	HR	95% CI	*P*
Overall prostate cancer						
Model 1[a]	<37.5	199	464	1.00		
	37.5–<50	259	470	1.08	0.83–1.41	0.572
	50–<75	550	1,070	0.89	0.70–1.12	0.328
	≥75	723	1,199	0.98	0.78–1.24	0.897
Model 2[a,b]	<37.5	183	426	1.00		
	37.5–<50	239	475	0.90	0.68–1.18	0.444
	50–<75	588	1,123	0.85	0.67–1.09	0.200
	≥75	721	1,179	0.96	0.75–1.23	0.763
Model 3[a,b,c]	<44.1	308	639	1.00		
	44.1–<58.2	318	645	0.83	0.66–1.03	0.092
	58.2–<72.9	320	638	0.74	0.59–0.92	0.008
	72.9–<90.7	363	641	0.86	0.69–1.07	0.181
	≥90.7	422	640	0.98	0.78–1.21	0.823
Gleason 2–6 prostate cancer						
Model 1[a]	<37.5	107	464	1.00		
	37.5–<50	157	470	1.20	0.87–1.65	0.269
	50–<75	309	1,070	0.90	0.67–1.20	0.454
	≥75	441	1,199	1.05	0.79–1.40	0.738
Model 2[a,b]	<37.5	97	426	1.00		
	37.5–<50	137	475	0.94	0.67–1.32	0.732
	50–<75	345	1,123	0.89	0.66–1.21	0.467
	≥75	435	1,179	1.01	0.75–1.37	0.943
Model 3[a,b,c]	<44.1	167	639	1.00		
	44.1–<58.2	190	645	0.87	0.66–1.14	0.302
	58.2–<72.9	190	638	0.76	0.58–1.00	0.048
	72.9–<90.7	210	641	0.86	0.66–1.13	0.276
	≥90.7	257	640	1.01	0.77–1.31	0.957
Gleason 7–10 prostate cancer						
Model 1[a]	<37.5	67	464	1.00		
	37.5–<50	72	470	0.85	0.56–1.28	0.435
	50–<75	157	1,070	0.75	0.52–1.07	0.107
	≥75	206	1,199	0.86	0.60–1.22	0.402
Model 2[a,b]	<37.5	60	426	1.00		
	37.5–<50	73	475	0.86	0.56–1.31	0.477
	50–<75	163	1,123	0.75	0.51–1.09	0.132
	≥75	206	1,179	0.91	0.63–1.33	0.642
Model 3[a,b,c]	<44.1	104	639	1.00		
	44.1–<58.2	81	645	0.63	0.45–0.90	0.010
	58.2–<72.9	91	638	0.66	0.47–0.92	0.016
	72.9–<90.7	107	641	0.79	0.56–1.10	0.165
	≥90.7	119	640	0.88	0.63–1.22	0.436
Gleason 8–10 prostate cancer						
Model 1[a]	<37.5	16	464	1.00		
	37.5–<50	14	470	0.71	0.32–1.58	0.406
	50–<75	27	1,070	0.41	0.20–0.83	0.013
	≥75	47	1,199	0.70	0.36–1.36	0.288
Model 2[a,b]	<37.5	12	426	1.00		
	37.5–<50	15	475	0.96	0.41–2.25	0.926
	50–<75	29	1,123	0.55	0.25–1.20	0.131
	≥75	48	1,179	0.95	0.45–2.02	0.894

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Table 3. Association of plasma vitamin D concentration with prostate cancer risk: SELECT (Cont'd)

Model	Vitamin D (nmol/L)	*N* (case)	*N* (cohort)	HR	95% CI	*P*
Model 3[a,b,c]	<44.1	20	639	1.00		
	44.1–<58.2	20	645	0.68	0.34–1.34	0.267
	58.2–<72.9	13	638	0.36	0.16–0.78	0.010
	72.9–<90.7	27	641	0.85	0.44–1.65	0.630
	≥90.7	24	640	0.78	0.40–1.54	0.477

[a]HRs adjusted for age and race (though matching) and family history of prostate cancer, BMI, baseline diabetes, and SELECT treatment arm (as covariates).
[b]Vitamin D values adjusted for month of serum sample.
[c]Quintiles are calculated based on the distribution among the cohort.

(Model 4). Comparing men in third with first quintile, reductions in risk were 26% ($P = 0.015$), 27% ($P = 0.039$), and 33% ($P = 0.039$) for total, Gleason 2–6, and Gleason 7–10 cancers, respectively.

Discussion

In this large study of prediagnostic plasma (25-hydroxy) vitamin D and prostate cancer risk, we found significantly reduced risks among men with moderate concentrations (approximately 45–70 nmol/L) compared with men with lower or higher values. This U-shaped association was most pronounced for Gleason 7–10 and 8–10 cancers. Findings were similar among non–African Americans; however, among African American men there were no associations of plasma vitamin D with Gleason 2–6 cancer and a significant decrease in risk of Gleason 7–10 cancer at concentrations above approximately 50 nmol/L.

It is notable that not a single, large (n cases > 200) prospective study has reported a linear, inverse association between blood vitamin D concentrations and prostate cancer risk. Our results are similar to those from a study in European Nordic countries (18), which reported the lowest risk of prostate cancer among men with vitamin D concentrations of 40 to 60 nmol/L, with higher risk among men with lower and higher values. Given that there was little prostate cancer screening in these countries during the study period, most of these cases were clinically detected and likely advanced stage and/or high grade. This is in contrast to inverted U-shaped associations in two other large cohorts. In the Prostate Lung Colorectal and Ovarian Cancer Screening Trial, the risk of high-grade and/or aggressive disease was highest among men with vitamin D concentrations of approximately 50 to 70 nmol/L (19), and in the Malmo Diet and Cancer Study, risk was highest among men with vitamin D concentrations of 91 to 106 nmol/L (10). In a 2007 publication from the Health Professionals Follow-up Study based on 684 cases, men deficient in vitamin D (blood concentration <37 nmol/L) had a significant 68% lower risk of high-grade prostate cancer compared with those not deficient (12); however, in the latest publication based on 1,260 men, there were no associations with total, high-grade, or advanced-stage cancer (20). In the Alpha-Tocopherol Beta-Carotene Prevention Study, there was a significant linear increase across quintiles of serum vitamin D (21), and in the Janus Serum Bank cohort, there was a significant linear increase in the risk of advanced disease, but only among men with blood samples collected in summer and autumn months (13). Other large studies (2–7, 22) found no associations of blood vitamin D with prostate cancer risk. The reason for this inconsistency across studies is unclear. Studies in the United States tended to have a larger range of blood vitamin D concentrations than those in European studies, perhaps reflecting the more common use of multivitamins and fortification of milk; however, there was no pattern of results associated with study country. Studies used a variety of approaches to adjust blood vitamin D values for season of blood collection, but all approaches were statistically sound and there were no relationships between the approach used for adjustment and study findings. It is possible that findings on vitamin D and cancer risk are sensitive to the approach used to classify vitamin D exposure. We found that analyses using our definitions of deficient, low, adequate, and high, or contrasts across quintiles that were based on the race-specific distributions of vitamin D, showed no significant differences in risk across categories; only contrasts across quintiles based on the distribution of vitamin D in the entire subcohort reached statistical significance. Park and colleagues (6) and Branstedt and colleagues (10) also reported findings that differed by the approach used to define categories of exposure, suggesting that there may be an optimal range of serum vitamin D concentration for prostate cancer prevention that is both narrow and specific. It is also possible that genetic characteristics (12), calcium intake (23), and concentrations of metabolites such as vitamin D binding protein (24) modify associations of vitamin D with risk, which could also contribute to the inconsistency across studies. On the basis of studies published to date, there is at best only moderate evidence that very low vitamin D levels are associated with

Table 4. Association of serum vitamin D concentration with prostate cancer risk: SELECT African Americans only

Model	Vitamin D (nmol/L)	*N* (case)	*N* (cohort)	HR	95% CI	*P*
Overall prostate cancer						
Model 1[a]	<37.5	90	276	1.00		
	37.5–<50	70	180	1.24	0.81–1.88	0.319
	50–<75	58	218	0.85	0.56–1.28	0.437
	≥75	32	128	0.84	0.50–1.40	0.509
Model 2[a,b]	<37.5	92	274	1.00		
	37.5–<50	66	180	1.16	0.76–1.77	0.498
	50–<75	61	228	0.81	0.54–1.22	0.317
	≥75	31	120	0.86	0.51–1.44	0.555
Model 3[a,b,c]	<30.1	51	161	1.00		
	30.1–<40.4	58	159	1.27	0.79–2.05	0.330
	40.4–<52.9	61	161	1.33	0.81–2.18	0.256
	52.9–<69.1	40	160	0.76	0.45–1.29	0.316
	≥69.1	40	161	0.89	0.53–1.49	0.658
Model 4[a,b,d]	<44.1	126	362	1.00		
	44.1–<58.2	55	183	0.90	0.59–1.38	0.636
	58.2–<72.9	33	112	0.83	0.51–1.34	0.440
	72.9–<90.7	16	77	0.69	0.37–1.28	0.242
	≥90.7	20	68	0.84	0.47–1.53	0.574
Gleason 2–6 prostate cancer						
Model 1[a]	<37.5	46	276	1.00		
	37.5–<50	37	180	1.27	0.74–2.17	0.387
	50–<75	32	218	0.95	0.55–1.63	0.839
	≥75	17	128	0.96	0.48–1.92	0.900
Model 2[a,b]	<37.5	45	274	1.00		
	37.5–<50	32	180	1.11	0.64–1.93	0.717
	50–<75	38	228	1.07	0.64–1.78	0.800
	≥75	17	120	1.04	0.52–2.10	0.910
Model 3[a,b,c]	<30.0	24	161	1.00		
	30.0–<40.4	30	159	1.45	0.77–2.76	0.252
	40.4–<52.9	33	161	1.57	0.82–3.01	0.170
	52.9–<69.1	24	160	1.01	0.51–2.01	0.971
	≥69.1	21	161	1.10	0.54–2.22	0.800
Model 4[a,b,d]	<44.1	60	362	1.00		
	44.1–<58.2	33	183	1.11	0.64–1.94	0.712
	58.2–<72.9	20	112	1.11	0.61–2.03	0.730
	72.9–<90.7	7	77	0.71	0.29–1.77	0.467
	≥90.7	12	68	1.14	0.53–2.48	0.733
Gleason 7–10 prostate cancer						
Model 1[a]	<37.5	29	276	1.00		
	37.5–<50	23	180	1.18	0.62–2.25	0.617
	50–<75	19	218	0.90	0.47–1.70	0.737
	≥75	7	128	0.52	0.22–1.24	0.142
Model 2[a,b,e]	<37.5	31	274	1.00		
	37.5–<50	25	180	1.39	0.73–2.63	0.316
	50–<75	16	227	0.65	0.33–1.27	0.206
	≥75	6	120	0.47	0.19–1.18	0.106
Model 3[a,b,c]	<30.0	17	161	1.00		
	30.0–<40.4	19	159	1.31	0.62–2.75	0.480

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Table 4. Association of serum vitamin D concentration with prostate cancer risk: SELECT African Americans only (Cont'd)

Model	Vitamin D (nmol/L)	*N* (case)	*N* (cohort)	HR	95% CI	*P*
	40.4–<52.9	21	161	1.49	0.69–3.23	0.313
	52.9–<69.0	10	160	0.64	0.27–1.53	0.313
	≥69.0	11	161	0.76	0.33–1.76	0.516
Model 4[a,b,d,f]	<44.1	45	362	1.00		
	44.1–<58.2	16	183	0.89	0.46–1.72	0.729
	58.2–<72.9	8	112	0.54	0.24–1.21	0.133
	72.9–<90.7	4	77	0.46	0.16–1.34	0.154
	≥90.7	5	68	0.58	0.22–1.53	0.142

[a]HRs adjusted for age (through matching) and family history of prostate cancer, BMI, baseline diabetes, and SELECT treatment arm (as covariates).
[b]Vitamin D values adjusted for month of serum sample.
[c]Quintiles are calculated based on the distribution among African American cohort.
[d]Quintiles are calculated based on the distribution among the entire cohort.
[e]$P_{trend} = 0.048$.
[f]$P_{trend} = 0.056$.

increased prostate cancer risk, but there is agreement across many studies that very high vitamin D levels are associated with increased rather than decreased prostate cancer risk.

A series of recent studies have reported that low concentration of serum vitamin D is associated with increased risk of lethal prostate cancer (20, 25, 26). There are several methodological concerns that make interpretation of these studies difficult. One important consideration is that serum vitamin D is an acute phase reactant, whose concentration in the blood is substantially decreased in persons with even moderately elevated concentrations of C-reactive protein (27). Thus, if blood is collected either at or following cancer diagnosis, it is likely that the severity of disease is influencing the concentration of vitamin D. This most likely explains the study by Tretli and colleagues (25) and it may also explain the findings reported by Fang and colleagues (26) in which there was an association of vitamin D with increased lethal cancer only among men whose bloods were collected within 5 years of diagnosis. In the study by Shui and colleagues (20), there were strong inverse associations of vitamin D with lethal cancer. In this study and the study by Fang and colleagues (26), the definition of a lethal cancer is one that causes mortality after diagnosis regardless of its stage or grade at time of diagnosis, and it is thus heavily dependent upon competitive mortality and the length of follow-up after diagnosis. The biases due to this approach are difficult to predict, but using prostate cancer death as the study endpoint seems to us a more straightforward approach to testing hypotheses on "lethal" cancer.

Although our analyses of risk within African American men were based on a much larger sample size than in any previous study, the sample size was still modest and must be interpreted cautiously. It is also notable that the distribution of plasma vitamin D among African American men was skewed far to the left of the distribution among other races, such that quintiles 1 to 3 in African Americans corresponded roughly to quintile 1 in other races. Associations of plasma vitamin D were significant for high-grade cancer only, and rather than a U-shaped association, risk seemed to be approximately 50% lower, with no dose response, among men with concentrations greater than approximately 50 nmol/L. Given the small number of African American cases with very high plasma vitamin D concentrations, it is uncertain whether there are increases in risk associated with high concentrations that are similar to those for non–African Americans. Clearly, larger cohort studies of African American men are warranted.

The strengths of this study include its large size and careful follow-up for incident prostate cancer. There are several important limitations that deserve comment. SELECT participants were offered a free, specially formulated multivitamin, which in the early years of the study contained 200 IU and later contained 400 IU of vitamin D_3. Thus, baseline plasma vitamin D concentrations may not accurately reflect concentrations after randomization if men changed their intake of supplemental vitamin D. In secondary analyses, which included a time-dependent covariate to indicate whether use of supplemental vitamin D decreased, stayed about the same, or increased from baseline during each year of the trial, the findings given here were essentially unchanged. Another limitation is that the use of PSA screening, or the decision to follow-up an elevated PSA test, may differ between men with low and high vitamin D levels. In a secondary analysis, we limited the study sample to men who reported PSA screening within 2 years of diagnosis or censor, and

Table 5. Association of serum vitamin D concentration with prostate cancer risk: SELECT non–African Americans

Model	Vitamin D (nmol/L)	*N* (case)	*N* (cohort)	HR	95% CI	*P*
Overall prostate cancer						
Model 1[a]	<37.5	109	188	1.00		
	37.5–<50	189	290	1.08	0.79–1.48	0.640
	50–<75	492	852	0.91	0.69–1.19	0.476
	≥75	691	1,071	1.00	0.76–1.31	0.999
Model 2[a,b]	<37.5	97	154	1.00		
	37.5–<50	169	299	0.79	0.57–1.10	0.166
	50–<75	516	881	0.81	0.61–1.08	0.152
	≥75	699	1,067	0.90	0.68–1.20	0.462
Model 3[a,b,c]	<50.6	279	481	1.00		
	50.6–<64.2	273	480	0.96	0.77–1.20	0.729
	64.2–<77.9	299	480	0.95	0.77–1.18	0.670
	77.9–<94.0	282	480	0.97	0.78–1.21	0.794
	≥94.0	348	480	1.18	0.96–1.46	0.125
Model 4[a,b,d]	<44.1	182	277	1.00		
	44.1–<58.2	263	462	0.83	0.64–1.07	0.147
	58.2–<72.9	287	526	0.74	0.57–0.94	0.015
	72.9–<90.7	347	564	0.87	0.68–1.11	0.254
	≥90.7	402	572	0.98	0.77–1.25	0.881
Gleason 2–6 prostate cancer						
Model 1[a]	<37.5	61	188	1.00		
	37.5–<50	120	290	1.21	0.83–1.77	0.313
	50–<75	277	852	0.90	0.65–1.26	0.551
	≥75	424	1,071	1.06	0.76–1.47	0.726
Model 2[a,b]	<37.5	57	154	1.00		
	37.5–<50	101	299	0.80	0.54–1.19	0.274
	50–<75	303	881	0.81	0.57–1.14	0.230
	≥75	421	1,067	0.89	0.64–1.26	0.520
Model 3[a,b,c]	<50.6	167	481	1.00		
	50.6–<64.2	149	480	0.89	0.68–1.16	0.394
	64.2–<77.9	186	480	0.98	0.76–1.27	0.880
	77.9–<94.0	162	480	0.90	0.69–1.17	0.446
	≥94.0	218	480	1.20	0.94–1.54	0.151
Model 4[a,b,d]	<44.1	107	277	1.00		
	44.1–<58.2	157	462	0.84	0.63–1.14	0.271
	58.2–<72.9	170	526	0.73	0.55–0.99	0.039
	72.9–<90.7	203	564	0.84	0.63–1.13	0.257
	≥90.7	245	572	0.98	0.74–1.30	0.902
Gleason 7–10 prostate cancer						
Model 1[a]	<37.5	38	188	1.00		
	37.5–<50	49	290	0.81	0.50–1.31	0.386
	50–<75	138	852	0.74	0.49–1.11	0.143
	≥75	199	1,071	0.86	0.58–1.28	0.456
Model 2[a,b]	<37.5	30	154	1.00		
	37.5–<50	48	299	0.74	0.44–1.24	0.254
	50–<75	144	881	0.73	0.47–1.14	0.164
	≥75	202	1,067	0.88	0.57–1.36	0.555
Model 3[a,b,c]	<50.6	80	481	1.00		
	50.6–<64.2	84	480	0.99	0.71–1.39	0.962

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Table 5. Association of serum vitamin D concentration with prostate cancer risk: SELECT non–African Americans (Cont'd)

Model	Vitamin D (nmol/L)	*N* (case)	*N* (cohort)	HR	95% CI	*P*
	64.2–<77.9	76	480	0.85	0.60–1.20	0.354
	77.9–<94.0	85	480	1.06	0.76–1.49	0.726
	≥94.0	99	480	1.20	0.87–1.68	0.270
Model 4[a,b,d]	<44.1	59	277	1.00		
	44.1–<58.2	65	462	0.63	0.42–0.93	0.020
	58.2–<72.9	83	526	0.67	0.46–0.98	0.039
	72.9–<90.7	103	564	0.81	0.56–1.17	0.259
	≥90.7	114	572	0.90	0.63–1.28	0.556

[a]HRs adjusted for age (through matching) and family history of prostate cancer, BMI, baseline diabetes, and SELECT treatment arm (as covariates).
[b]Vitamin D values adjusted for month of serum sample.
[c]Quintiles are calculated based on the distribution among non–African American cohort.
[d]Quintiles are calculated based on the distribution among the entire cohort.

results reported here were also essentially unchanged. We did not have information about whether men with elevated PSA tests elected to undergo prostate biopsy, and thus the possibility of detection bias as an explanation of our findings cannot be ruled out. Another limitation in this and all other studies of blood vitamin D and prostate cancer risk is that exposure was based on a single blood measure that had to be adjusted for month of blood draw. Measurements of plasma vitamin D separated by 5 years are reasonably reliable when measures are taken at the same time of year (interclass correlation coefficient, ICC = 0.64), but less so when samples are from different seasons (ICC = 0.48; ref. 28), which suggests that, within a study population, the rank order of blood vitamin D concentrations is not highly consistent across seasons. It is also likely that the association of season with vitamin D concentration varies by geographic region, use of dietary supplements, age, and time spent out of doors, which would result in some misclassification when values are adjusted for season-specific trends in the population overall. Another limitation is that even though the SELECT study included over 35,000 men, there were still too few cases to support stratified analyses and, in particular, we had no power to test whether the results given here differed across SELECT treatment arms. Finally, as in all observational studies, it is possible that there is confounding by unknown factors; however, we controlled for all known risk factors for prostate cancer making this possibility less likely.

In summary, we found that optimal level of plasma vitamin D for prostate cancer prevention, adjusted for month of blood sampling, was between approximately 45 and 70 nmol/L. Vitamin D concentrations that were both lower and higher were associated with increased risk of total prostate cancer, and more strongly so for high-grade prostate cancer. However, the existing literature on vitamin D and prostate cancer risk is not consistent, and any clinical recommendations for vitamin D and prostate cancer prevention should await further research. Our findings are consistent with emerging evidence for an optimal range of blood vitamin D concentrations for other health outcomes, including cardiovascular disease, vascular disease, falls, frailty, pancreatic cancer, and all-cause mortality, as noted by the 2011 Institute of Medicine report on Dietary Reference Intakes for calcium and vitamin D (29). It will be important that the currently ongoing randomized trial examining the effects of vitamin D supplementation on cardiovascular diseases and cancers (30) measures the postsupplementation concentrations of vitamin D, and then uses these data in secondary analyses to examine whether specific ranges of serum vitamin D are associated both with total mortality and the risks of a broad range of chronic diseases. It is likely that vitamin D supplementation differentially affects the risks of many diseases, and the balance of benefit and harm will need to be understood more fully to formulate public health recommendations. Lacking such data, we believe it prudent to recommend that men over age 50 who are using supplemental vitamin D should limit their dose to levels that do not result in plasma concentrations above 70 nmol/L.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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