Cancer Epidemiology, Biomarkers & Prevention

Null Results in Brief

Null Association between Vitamin D and PSA Levels among Black Men in a Vitamin D Supplementation Trial

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Abstract

Background: Black men exhibit a high prevalence of vitamin D deficiency as well as a higher incidence of prostate cancer and higher mortality rates from prostate cancer than Whites. There are few data about the effect of vitamin D3 (cholecalciferol) supplementation on prostate-specific antigen (PSA) in healthy Black men.

Methods: During three winters from 2007 to 2010, 105 Black men (median age, 48.9 years) of Boston, MA were randomized into a four-arm, double-blind trial for 3 months of placebo, 1,000, 2,000, or 4,000 U of vitamin D3. At baseline and 3 months, free and total PSA was measured.

Results: With vitamin D supplementation, no significant differences in free and total PSA were observed; free PSA, −0.0004 ng/mL ($P = 0.94$) and total PSA, −0.004 ng/mL ($P = 0.92$) for each additional 1,000 U/d of vitamin D3.

Conclusion: Within an unselected population of healthy Black men without a cancer diagnosis, we found no effect of vitamin D supplementation on free or total PSA.

Impact: These findings support prior findings of no change in PSA with vitamin D supplementation and emphasize the need for new methods to assess the influence of vitamin D supplementation on prostate cancer prevention. *Cancer Epidemiol Biomarkers Prev; 23(9); 1944–7. ©2014 AACR.*

Introduction

A number of studies have suggested that low levels of vitamin D may account for higher prostate cancer mortality in Blacks (1). The major risk factors for prostate cancer—older age, black race, and residence at northern latitudes—are all associated with lower synthesis of vitamin D (1). Prostate cancer cells have vitamin D receptors that convert 25(OH)D to 1,25$(OH)_2$D via 1-α-hydroxylase (1). Some studies have found that administration of 1,25$(OH)_2$D can slow or moderate the rate of prostate-specific antigen (PSA) increase in patients with advanced prostate cancer (2–4). Other studies have observed no effect of vitamin D supplementation on PSA (5, 6). To summarize, findings about the effects of vitamin D on PSA are mixed (7–10). Most studies, however, have assessed this association among small (11), nonminority patient populations, and when supplementation has been studied, the administration period has been relatively short (i.e., days or weeks; ref. 12). To our knowledge, this is the first study to examine the preventive benefits of vitamin D intake on PSA levels among men without a cancer diagnosis.

Materials and Methods

This study was conducted as part of a prospective, randomized, double blind, placebo-controlled clinical trial of vitamin D3 in a healthy Black population. The main aim of the study was to examine the effect of daily supplementation (placebo, 1,000 U, 2,000 U, and 4,000 U) of vitamin D3 on plasma 25(OH)D levels. All capsules also contained 200 mg of calcium. Details of study procedures are presented elsewhere. Participants received supplementation during early winter (November or December) and were taken orally once daily for 3 months (completed in February or March).

The primary endpoints of the study were changes in total and free PSA from baseline to 3-month follow-up (after supplementation). Total and free PSA was measured separately by a sandwich electrochemiluminescence immunoassay on the 2010 Elecsys autoanalyzer

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(Roche Diagnostics). The lowest detection limit of the total PSA assay is 0.002 ng/mL and the day-to-day imprecision values at concentrations of 0.30, 4.76, and 51.1 ng/mL are 2.4%, 2.9%, and 3.8%, respectively. The lowest detection limit of the free PSA assay is 0.01 ng/mL and the day-to-day imprecision at concentrations of 0.17, 1.36, and 24.30 ng/mL are 4.5%, 4.9%, and 4.2%, respectively.

Statistical power and analysis

Statistical power for this trial was based on the intent-to-treat population of 80 subjects per arm. Using a two-sided *t* test at the 0.05 significance level, the minimum detectable difference in 25(OH)D between treatment arms was 5.3 with 80% power. All statistical analyses were performed using SAS 9.2 (SAS Institute). Differences in the baseline characteristics of participants across the four treatment groups were compared using the Kruskal–Wallis test for continuous variables and χ^2 test for categorical comparisons. The primary endpoints were 3-month change in total and free PSA at the end of treatment. For our primary analysis, we used linear regression with the dose of vitamin D3 (per 1,000 U/d) as the independent variable and the 3-month change in total PSA (or 3-month change in free PSA) as the dependent variables. This targeted population of healthy vitamin D–deficient Black males allows for small sample size with adequate power to test the hypothesis that vitamin D supplementation lowers PSA.

All participants provided written informed consent. The project was approved by the Institutional Review Boards of Harvard School of Public Health and Dana-Farber Cancer Institute. All procedures were followed in accordance with institutional guidelines.

Table 1. Baseline characteristics

	Vitamin D dose, IU/d				
Characteristics	**Placebo**	**1,000**	**2,000**	**4,000**	***P***
Age, y, *N*	27	21	28	29	0.67
Median (IQR)	51.6 (40.0–59.6)	45.7 (51.8–58.3)	42.4 (46.1–55.8)	39.9 (46.3–57.3)	
BMI, kg/m^2					0.45
Median (IQR)	25.68 (28.03–35.31)	25.86 (29.42–34.26)	23.75 (28.06–32.95)	27.32 (30.11–35.71)	
Total PSA, ng/mL					
Mean (SD)	1.02 (1.35)	1.16 (0.84)	1.09 (0.91)	2.15 (3.22)	0.30
Free PSA, ng/mL					
Mean (SD)	0.28 (0.29)	0.28 (0.14)	0.28 (0.22)	0.32 (0.21)	0.46
Enlarged prostate, *n* (%)					0.12
No	25 (92.59)	21(100)	(27) 96.43	5 (82.76)	
Yes	2 (7.41)	-	(1) 3.5	5 (17.24)	
PSA test, *n* (%)					0.55
No	9 (33.33)	7 (33.33)	13 (46.43)	15 (51.72)	
Yes	15 (55.56)	14 (66.67)	15 (53.57)	14 (48.28)	
Abnormal DRE, *n* (%)					0.54
No	19 (70.37)	17 (80.95)	15 (53.57)	18 (62.07)	
Yes	1 (3.70)	1 (4.76)	2 (7.14)	-	
Family history of prostate cancer, *n* (%)					0.28
No	25 (92.59)	15 (71.43)	25 (89.29)	26 (89.66)	
Yes	2 (7.41)	5 (23. 81)	3 (10.71)	3 (10.34)	
Smoked in life, *n* (%)					0.13
No	8 (29.63)	11 (52.38)	8 (28.57)	15 (51.72)	
Yes	19 (70.37)	10 (47.62)	20 (71.43)	14 (48.28)	
Current smokers, *n* (%)					0.32
No	14 (51.85)	14 (66.67)	17 (60.71)	22 (75.86)	
Yes	13 (48.15)	7 (33.33)	11 (39.29)	7 (24.14)	
Type of insurance, *n* (%)					0.85
No	26 (96.30)	21 (100)	28 (100)	28 (96.55)	
Yes	1 (3.70)	-	-	1 (3.45)	
Marital status, *n* (%)					0.77
No	18 (66.67)	12 (57.14)	15 (53.57)	16 (55.17)	
Yes	9 (33.33)	9 (42.86)	13 (46.43)	13 (44.83)	

Table 2. Effect of vitamin D supplementation on PSA (ng/mL) during the treatment (baseline to 3 months)

	Vitamin D dose, IU/d					
Parameter, mean (SE)	**Placebo**	**1,000**	**2,000**	**4,000**	**3-Month change[a] (SE) (95% CI)**	***P***
n (at baseline)	27	21	28	29		
Total PSA, ng/mL						
Baseline PSA, mean (SE)	1.024 (0.26)	1.158 (0.18)	1.091 (0.17)	2.152 (0.60)	−0.0004 (0.005)	0.94
3 mo PSA, mean (SE)	1.035 (0.31)	1.204 (0.24)	0.987 (0.15)	2.207 (0.73)	(−0.003–0.011)	
Difference PSA (3 − 0), mean (SE)	−0.045 (0.10)	0.006 (0.05)	−0.113 (0.07)	−0.042 (0.16)		
Free PSA, ng/mL						
Baseline PSA	0.278 (0.06)	0.281 (0.03)	0.279 (0.04)	0.316 (0.04)	−0.004	0.92
3 mo PSA	0.276 (0.06)	0.273 (0.04)	0.296 (0.05)	0.330 (0.05)	(0.038)	
Difference PSA (3 − 0)	0.017 (0.02)	0.002 (0.01)	0.012 (0.01)	0.011 (0.02)	(−0.0006–0.001)	
25(OH)D, ng/mL						
Baseline 25(OH)D	17.07 (1.03)	17.33 (1.00)	16.12 (0.98)	17.79 (0.98)	7.88 (0.75) (6.39–9.37)	<0.0001
3 mo. 25(OH)D	14.23 (0.96)	28.12(1.11)	35.48 (1.21)	47.30 (1.22)		
Difference 25(OH)D (3 − 0)	−2.58 (0.66)	11.01(1.22)	19.21 (1.21)	29.79 (1.29)		

NOTE: Difference PSA (3 − 0) = month 3 PSA ng/mL − month 0 PSA level ng/mL: mean (SE).

[a]0–3-month change in PSA per 1,000 IU/d of vitamin D supplementation; 0–3-month change in 25(OH)D per 1,000 IU/d of vitamin D supplementation.

Results

Subject characteristics according to supplementation arm

Among the 105 eligible participants, no significant differences in baseline characteristics between dose groups was observed with an overall median age [interquartile (IQR)] of 48.9 (42.0–57.8) years and a median body mass index (BMI; IQR) of 29.2 (25.7–35.3) kg/m^2 (Table 1).

Oral vitamin D supplementation produced no change in the plasma levels of PSA (Table 2). We examined the influence of 25(OH)D level at 3 months on the free and total PSA levels. No significant effect of 25(OH)D level at 3 months on free and total PSA ($P > 0.05$) was observed. Narrow confidence intervals for the differences in the means (month 3 − month 0 for free and total PSA) suggest adequate precision to reject the null hypothesis. An interaction between baseline 25(OH)D and vitamin D supplementation was assessed with free and total PSA as the outcomes and no significant association ($P > 0.05$) was found.

Discussion

To our knowledge, this is among the first randomized placebo-controlled trials to examine the impact of oral vitamin D3 supplementation on PSA in a healthy Black male cohort. Vitamin D3 supplementation did not alter PSA levels in this relatively young cohort despite a clear trend in the change of follow-up serum 25(OH)D concentrations with increasing doses of supplemental vitamin D3. Vitamin D promotes the differentiation of prostate cancer cells, highlighting the possibility that vitamin D deficiency over time may contribute to the progression from subclinical prostate cancer to clinical disease (13). Prior research has shown that vitamin D deficiency is an indicator of aggressive prostate cancer and spread of the disease in men who underwent their first prostate biopsy because of an abnormal PSA test (14). Furthermore, a dose–response relationship between tumor grade and vitamin D levels was observed (14). In a study of patients with prostate cancer (Gleason 6 or 7), oral vitamin D3 (400, 10,000, or 40,000 U/d) administered before prostatectomy, raised prostate calcitriol levels and lowered PSA (12). In a study of early-stage low-risk prostate cancer patients given vitamin D3 4,000 U/d for 1 year, a decrease in the number of positive cores at repeat biopsy was observed in more than half of the participants without a change in PSA (15).

Strengths of this study include the use of healthy Black men without prior prostate cancer. Our multiple doses of vitamin D3 allowed us to examine whether vitamin D supplementation is associated with plasma levels of PSA, and whether a threshold effect exists within this association. The narrow confidence intervals for the outcome values highlight the adequate sample size for testing the hypothesis that vitamin D supplementation reduces PSA in Blacks in a dose-dependent manner. The time frame during which vitamin D protects against prostate cancer is unknown. Limitations of our study include the fact that PSA is not an ideal endpoint for assessment of prostate cancer risk, as it

may also be indicative of a number of other noncancerous outcomes. Given the high prostate cancer incidence and mortality in Black men combined with vitamin D deficiency, future trials of vitamin D3 supplementation for longer duration are needed to evaluate the possible clinical benefit of vitamin D3 supplementation for prostate cancer prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funding sources had no role in the conception or conduct of the study, took no part in the data collection or analysis, and had no role in the drafting, review, or approval of the article.

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