Editorial

Pharmacogenomics

Can Vitamin D supplementation reduce prostate cancer disparities?

"Given that African–Americans are at higher risk for both aggressive prostate cancer and Vitamin D deficiency, African–Americans are a more appropriate group to investigate the effects of Vitamin D on prostate cancer."

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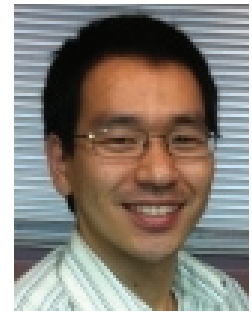

Ken Batai
Division of Urology, Department of Surgery, The University of Arizona, Tucson, AZ, USA

Rick A Kittles
Author for correspondence:
Division of Urology, Department of Surgery, The University of Arizona, Tucson, AZ, USA
Tel.: +1 520 626 8003
Fax: +1 520 626 3663
rkittles@email.arizona.edu

Vitamin D & prostate cancer in African–Americans

Vitamin D deficiency is prevalent among African–Americans (AAs) and higher incidences of aggressive prostate cancer (PCa) and higher mortality from PCa is also more common among AAs [1]. Vitamin D deficiency may partly explain PCa disparities, but the mechanism in which vitamin D impacts PCa pathogenesis and progression in AAs is not well understood [2]. *In vitro* and molecular studies have shown that the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D), have cancer preventive and therapeutic effects by regulating cell cycle and inducing apoptosis [3]. Vitamin D is also involved in PCa initiation and progression through regulation of immune response [4]. 1,25(OH)$_2$D binds to the vitamin D receptor (VDR), a transcription factor, and with co-activators VDR influences expression of genes that are involved in cell cycle, apoptosis and immune response.

Epidemiologic studies, on the other hand, provide limited supports. Low circulating levels of vitamin D, 25-hydroxyvitamin D (25[OH]D), are associated with increased risk of advanced PCa and mortality [5,6], but conflicting results have been reported for PCa incidence. Several studies show lack of association, and others even report increased risk of PCa in men with high serum 25(OH)D levels [7,8]. Most epidemiologic studies of vitamin D and PCa have been conducted among men of European ancestry. They have lighter skin pigmentation, higher vitamin D intake and more frequent dietary supplement use. Therefore, many of them have sufficient levels of circulating 25(OH)D levels, if not optimal.

Given that AAs are at higher risk for both aggressive PCa and vitamin D deficiency, AAs are a more appropriate group to investigate the effects of vitamin D on PCa. Recently, a cross-sectional study in a multiethnic population from Chicago (IL, USA) evaluated the relationship between vitamin D and PCa and provided evidence that vitamin D deficiency plays a role in PCa. In this study, 1,760 men who underwent prostate biopsy and healthy controls were recruited between 2009 and 2014. The study demonstrated that serum 25(OH)D levels predicted biopsy outcome in both vitamin D deficient AAs and European–Americans (EAs) [9]. Also among men who underwent radical prostatectomy (26.7% of them were AAs), low serum 25(OH)D levels were associated with higher odds of adverse pathology [10]. Compared to previous work, this biopsy study had the advantage of including a large number of AA study participants who were vitamin D defi-

cient. For darker skinned individuals who live in high latitude regions where sufficient levels of ultraviolet ray for cutaneous vitamin D synthesis are available only for limited times during year, such as AAs living in Chicago (IL, USA), diet and dietary supplement is the major source of vitamin D. However, the majority of AA patients did not consume the daily recommended amount of vitamin D.

Vitamin D supplementation in African–Americans

Vitamin D supplementation trials in AAs often demonstrate that even short term supplementation can effectively increase serum 25(OH)D levels. The present study by Hardiman *et al.* reveals that 4000 IU/day of vitamin D supplementation for 2 months eliminated disparities in serum vitamin D levels between AAs and EAs. More importantly, vitamin D supplementation may alter prostate tissue microenvironment. At the end of their 2-month trial, patients underwent radical prostatectomy, and gene expression profiles of nonmalignant prostate tissues were evaluated with RNA-sequencing. They found that genes involved in immune response and inflammation were differentially expressed between AA and EA men. This is consistent with findings from other studies that compared gene expression differences in AA and EA prostate tumors using microarray and found differentially expressed immune related genes between them [11–13].

> "Research suggests that vitamin D supplementation may improve prostate cancer clinical characteristics, however it is unclear if this improvement is by modulating immune response."

Hardiman *et al.* also showed that immune and inflammatory genes are differentially expressed between the supplemented and placebo-receiving AAs, but vitamin D supplementation did not have an effect among EA patients. Immune response and inflammatory genes have also been identified as vitamin D targets in microarray studies of vitamin D treated prostate tumor and normal cell-lines. For example, *PTGS2* (also known as *COX-2*) were downregulated in LNCaP human PCa cell treated with $1,25(OH)_2D_3$ for 24 hours [14]. In a similar trial in Canada among PCa patients of mostly European descent (83% White, 6% Black and 11% other) who were scheduled to undergo prostatectomy, short-term vitamin D supplementation increased both serum and prostatic 25(OH)D as well as $1,25(OH)_2D$ levels [15]. They also observed significantly lower expression of *PTGS2* in the PCa cells from patients in the highest tertile of prostatic $1,25(OH)_2D$ compared with the lowest tertile [16]. Taken together, the difference in prevalence of vitamin D deficiency may partly explain the gene expression difference in prostate tumors from AA and EA men.

Vitamin D supplementation may also improve clinical outcome in vitamin D deficient AA PCa patients. One trial that included 14 AA men (27% of participants) examined if vitamin D supplementation improved PCa clinical characteristics among men with low-risk PCa under active surveillance [17]. After 1 year of supplementation, more than half of the patients had improved clinical characteristics, and 55% of patients had decreased number of positive cores or lower Gleason score at repeat biopsy after 1 year. The Canadian trial showed that the prostatic $1,25(OH)_2D$ levels were inversely correlated with Ki67 intensity and percent positive nuclei in the PCa and nonmalignant tissues indicating reduced PCa cell proliferation with increasing prostatic vitamin D levels [15]. In this study, patients also had lower PSA levels after supplementation. Rising PSA levels after prostatectomy or radiation therapy indicates progression of disease. Although 3 months of vitamin D supplementation did not lower PSA levels among healthy AA men from Boston [18], other studies suggest that supplementation reduced PSA levels or rate of PSA rise among PCa patients who had prostatectomy or radiation [19,20].

Vitamin D supplementation for prostate cancer prevention & therapy

Evidence is increasing that higher serum 25(OH)D levels reduce the risk of aggressive PCa and likely increase survival rates for PCa. Research suggests that vitamin D supplementation may improve PCa clinical characteristics, however it is unclear if this improvement is by modulating immune response. To answer this question, we need to address several issues. First, many supplementation trials use low supplementation dosage and/or have short trial period. The immune and inflammatory genes that were differentially expressed genes between vitamin D supplement and placebo group in the Hardiman *et al.* study could be responding to changing prostatic vitamin D levels or changes in microenvironment related to increasing tissue vitamin D levels. Different sets of genes may be differentially expressed after higher dosage of or long-term supplementation. Second, PCa epithelium tissue may respond differently to vitamin D supplementation than nonmalignant tissue or stroma. Future studies need to characterize immune gene expression profile in prostate tumor, adjacent normal epithelial cells and also stroma.

There are many more unanswered questions. Patients included in the trials have low to intermediate risk. Does vitamin D supplementation affect immune gene expression and improves clinical characteristics among patients with aggressive PCa? How is the altered immune profile or microenvironment in the prostate by supplementation correlated to changes in clinical characteristics? Do changes in gene expression predict prognosis? Does vitamin D supplementation improve efficacy of other treatment regimens? What is dosage and supplement period necessary for significant improvement of clinical characteristics?

A well known and important feature in our understanding of PCa disparities is that more tumors from AAs have higher expression of immune response and inflammatory genes compared with tumors from EAs. This gene expression signature is now seen as a consequence of vitamin D deficiency. What we also now know is that short-term vitamin D supplementation can reduce the disparity in vitamin D deficiency between AAs and EAs, and most importantly reduce immune response and inflammatory gene expression in the prostate. This provides strong support and justification for using serum 25(OH)D as a biomarker to help guide biopsy decisions and treatment and for vitamin D supplementation as a therapeutic option for early-stage PCa, in particular for AAs.

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