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See related article by Murphy et al., p. 2289

Vitamin D Status: Ready for Guiding Prostate Cancer Diagnosis and Treatment?

William B. Grant

Vitamin D deficiency is associated with increased risk of prostate cancer for those with elevated prostate-specific antigen (PSA) level or abnormal digital rectal examination. Vitamin D deficiency is also associated with aggressive prostate cancer. Vitamin D level could be added as an additional factor to consider before ordering a biopsy. *Clin Cancer Res; 20(9); 2241–3. ©2014 AACR.*

In this issue of *Clinical Cancer Research*, Murphy and colleagues associate vitamin D deficiency with increased risk of prostate cancer diagnosis on biopsy (1). Men in this study had their first prostate biopsy after a finding of an elevated or abnormal prostate-specific antigen (PSA) level or abnormal digital rectal examination. For African American (AA) men, serum 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL were significantly associated with prostate cancer, whereas for European American (EA) men, an insignificant increased risk of prostate cancer existed for serum 25(OH)D level <20 ng/mL. For both AA and EA men, serum 25(OH)D level <12 ng/mL was associated with a significant risk of stage ≥T2b and Gleason score ≥4 + 4. Thus, these findings add vitamin D status to the biomarkers for prostate cancer for those with other indications of prostate cancer.

This study offers further evidence that vitamin D deficiency is a risk factor for aggressive prostate cancer. Gilbert and colleagues associated low 25(OH)D levels with a 2-fold increased risk of advanced versus localized prostate cancer or high-grade versus low-grade prostate cancer (2). As with most observational studies (2), this study also found no correlation of serum 25(OH)D level with overall prostate cancer risk.

These findings have important benefits in helping men decide what to do after learning they have an elevated PSA level or an abnormal digital rectal examination. The authors note, "Most men who are diagnosed with localized prostate cancer attempt curative therapy with surgery or radiation, although observation may be appropriate for men with low-risk cancers or limited life expectancy" (3). Biopsies are associated with inconveniences as well as risk factors such as bloodstream infections (4).

Author's Affiliation: Sunlight, Nutrition, and Health Research Center, San Francisco, California

Corresponding Author: William B. Grant, Sunlight, Nutrition, and Health Research Center, P.O. Box 641603, San Francisco, CA 94164-1603. Phone: 415-409-1980; E-mail: wbgrant@infionline.net

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For nonaggressive prostate cancer, watchful waiting or active surveillance is often a better option than invasive treatment, which can affect sexual function, urinary function, and fertility, and can slightly increase risk of colorectal cancer (5). The UK National Institute for Health and Care Excellence recently issued new guidelines for active surveillance, which involve a 5-year program of PSA testing followed by MRI if the PSA changes irregularly during this time (5). A recent study evaluated tools being developed and used to select and monitor patients on active surveillance for low-risk prostate cancer (6): MRI, serum markers, urinary markers, histopathology markers, and germline genetic markers. All have pros and cons, and no indications of long-term outcomes are yet apparent. Serum 25(OH)D levels seem to be another tool for this purpose.

These tools offer further evidence that vitamin D deficiency helps explain the black–white prostate cancer disparities. All-cause mortality rates for men with prostate cancer are 25% to 40% lower for those with low compared with those with high serum 25(OH)D levels, whereas prostate cancer–specific mortality rates are about 10% to 20% higher for AA men than white American men (WA) after consideration of socioeconomic status, stage at diagnosis, and treatment (7). In addition, a vitamin D_3 supplementation study of patients on active surveillance with early-stage, low-risk prostate cancer found that among men given 4,000 IU/d of vitamin D_3, half had fewer positive cores at repeat biopsy 1 year after enrollment in the study (8). The authors suggest that such vitamin D_3 supplementation could reduce prostate cancer–related health disparities in AA men. However, based on evidence from randomized controlled trials (RCT) published by 2010, the Institute of Medicine Committee on Dietary Reference Intakes for Calcium and Vitamin D stated that the evidence supported a role for vitamin D and calcium in bone health but not for extraskeletal outcomes (9).

A study of patients with prostate cancer in six Veterans Administration medical centers in the southeastern United States between 1999 and 2012 (84.6% WA) found lower survival rates for those vitamin D deficient [serum 25(OH)D levels <20 ng/mL] than those nondeficient. Of the 906 men initially deficient, the 5-year survival rate was 89%, whereas for the 1,731 men initially nondeficient, the 5-year

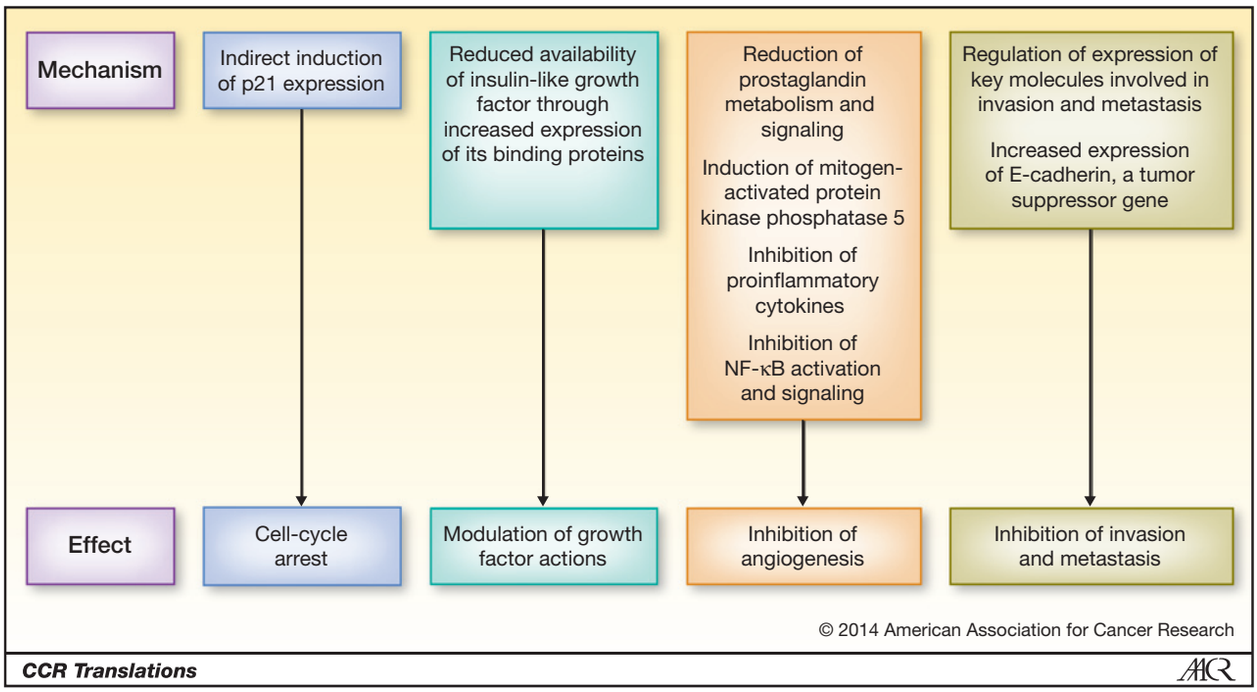

Figure 1. Mechanisms whereby vitamin D reduces the risk of prostate cancer incidence, progression, and metastasis.

survival rate was 95% ($P < 0.001$; ref. 10). Similar results emerged for survival rates with respect to vitamin D deficiency at follow-up.

The primary mechanisms whereby vitamin D reduces cancer risk include effects on cellular differentiation, proliferation, and survival; modulation of growth factor actions; anti-inflammatory effects; inhibition of angiogenesis; and inhibition of invasion and metastasis (Fig. 1; ref. 11). The mechanisms are driven by the hormonal metabolite of vitamin D, 1,25-dihydroxyvitamin D, which can control gene expression by binding to the vitamin D receptor. The cellular mechanisms help reduce the risk of cancer from DNA damage, whereas the others reduce tumor growth and spread into surrounding tissues. Organs in which cancer is developing convert circulating 25(OH)D to 1,25-dihydroxyvitamin D (11), which is why higher serum 25(OH)D levels are important.

We need additional RCTs to advance the use of vitamin D in clinical practice. The proper way to conduct such studies is to start with an understanding of the serum 25(OH)D level–health outcome of interest, enroll people in the study with baseline serum 25(OH)D levels near the low end of the range of the relation, supplement them with enough vitamin D_3 to raise 25(OH)D levels to the upper end of the range, and then remeasure serum 25(OH)D levels (12). Most vitamin D RCTs have enrolled healthy community-dwelling individuals with population average serum 25(OH)D levels and given them only 400 to 1,000 IU/d of vitamin D. Therefore, few of these studies found beneficial effects of vitamin D supplementation.

Evidence is mounting that higher serum 25(OH)D levels reduce risk of aggressive prostate cancer and increase survival rates for those diagnosed with prostate cancer, other types of cancer, and other diseases such as cardiovascular disease and diabetes mellitus (13). Thus, using serum 25(OH)D levels to guide biopsy decisions and treatment should receive strong consideration.

Disclosure of Potential Conflicts of Interest

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