Cancer Epidemiology, Biomarkers & Prevention

Hypothesis/Commentary

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Vitamin D in Blood and Risk of Prostate Cancer: Lessons from the Selenium and Vitamin E Cancer Prevention Trial and the Prostate Cancer Prevention Trial

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Abstract

The effects of blood levels of 25-hydroxyvitamin D (25-OHD) on the risk of total, low-, and high-grade prostate cancer were examined in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) and the Prostate Cancer Prevention Trial (PCPT). In the SELECT study, plasma 25-OHD levels were associated with a linear decrease in prostate cancer risk for high-grade cancers in African American men and an apparent "U"-shaped effect in other men. The "U-shaped" curve may reflect detection bias. In the PCPT study, in which detection bias was minimized, serum 25-OHD levels were associated with a linear decrease in the risk of high-grade prostate cancers. The results from these large prevention trials support the hypothesis that circulating levels of 25-OHD decrease the risk of clinically relevant prostate cancers. *Cancer Epidemiol Biomarkers Prev; 23(8); 1447–9. ©2014 AACR.*

The hypothesis that vitamin D, or its major source, sunlight, inhibits prostate cancer has gone from a "dark horse" to a front-runner in the race to understand the epidemiology of prostate cancer. Clinically relevant prostate cancer preferentially afflicts the elderly, Blacks, and residents in northern latitudes (1). Conversely, the prevalence of subclinical prostate cancer (cancer detected in asymptomatic men) increases with age but does not vary by race or geography. In 1990, Schwartz and Hulka noted that the major descriptive risk factors for clinical prostate cancer (age, race, and northern latitudes) are associated with vitamin D deficiency and hypothesized that vitamin D inhibits the development of clinical prostate cancer from the ubiquitous subclinical cancers (2). Bolstered by maps showing that the geographic distribution of prostate cancer mortality is inversely correlated with the geographic distribution of sunlight (3), the hypothesis that vitamin D inhibits prostate cancer galvanized research in many fields. In the laboratory, it ceased to be a hypothesis, as we learned that prostate cells possess the receptor for the vitamin D hormone, 1,25-dihydroxyvitamin D (discovered in 1992; ref. 4), and the enzyme 1α-hydroxylase, which converts the vitamin D pro-hormone, 25-hydroxyvitamin D (25-OHD), into the vitamin D hormone (discovered in 1998; ref. 5). Both the hormone and pro-hormone exert prodifferentiating, antiproliferative, and antimetastatic effects on prostate cells (for reviews see refs. 6–8).

Although the results of experimental studies of vitamin D and prostate cancer have been uniformly positive, the results of observational studies have been mixed. Numerous ecologic studies replicated the inverse correlation of prostate cancer rates with sunlight (9–11). Analytic studies support a protective effect of sunlight exposure in individual men, including an effect for exposure during early life (12–14). However, results from serologic studies of 25-OHD and prostate cancer risk have been inconsistent, with articles reporting negative, null, and positive associations (for review see ref. 15). This inconsistency has several causes. First, if some of the protective effect of 25-OHD is due to a prodifferentiating effect on prostate cells during early life, then studies that measure 25-OHD during later life may not detect it. Second, part of the inconsistency may be due to differences in what is considered prostate "cancer." For example, consider a car; when it is new, it has no dents. However, virtually all cars accumulate minor dents with time but most do not threaten the working of the car. The prostate also accumulates subclinical lesions with age. Histologically, these lesions are classified as "cancer" yet most are not life-threatening. At diagnosis, approximately half of all newly diagnosed patients with prostate cancer have cancer with a Gleason score ≤ 6 ("low-grade cancer"; ref. 16). For men with low-grade prostate cancers (Gleason 2–6), the risk of death from prostate cancer during 15 years of follow-up is low: 6 to 30 deaths per 1,000 person-years. Conversely, the risk of death from prostate cancer for men with high-grade cancers (Gleason 8–10) is high: 121 deaths per 1,000 person-years. Men with a Gleason 7 cancer have an intermediate risk of death (17).

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These concepts are pertinent to two articles in the current issue of *Cancer Epidemiology, Biomarkers & Prevention*. The article by Kristal and colleagues examines plasma 25-OHD levels in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized, placebo-controlled trial of selenium and vitamin E on prostate cancer risk (18). Data for this case–cohort analyses included 1,731 cases and 3,203 controls. Kristal and colleagues examined the effects of baseline 25-OHD levels with risk of total, low-, and high-grade prostate cancer. Using quintiles of 25-OHD based on the distribution of 25-OHD in the cohort, the risk of total prostate cancer for non-African American men was U-shaped: compared with the first quintile, the reductions in prostate cancer risk in the second to fifth quintiles were 17%, 26%, 14%, and 2%. Similar findings were observed for Gleason 2–6 cancer and Gleason 7–10 and 8–10 cancer, but were strongest for Gleason 8–10 cancers. Conversely, among the 250 African American cases, the risk of high-grade prostate cancer decreased linearly with increasing levels of 25-OHD.

An important limitation of the SELECT study is that the use of PSA screening and prostate biopsy was not controlled. The use of PSA screening, or the decision to follow-up an elevated PSA with biopsy, may differ between men with low and high vitamin D levels. For example, in the NIH-AARP Diet and Health Study, which studied >295,000 men, high users of multivitamins were more likely to undergo prostate cancer screening by PSA (19). If men in the SELECT study behaved similarly, then men with higher levels of circulating vitamin D would be more likely to undergo biopsy and to be diagnosed with prostate cancer. A related bias may have occurred in the SELECT study. In population-based studies, mean blood levels of 25-OHD decline with age (20, 21). Yet, mean plasma 25-OHD levels in the SELECT study *increased* with age and were significantly higher among men of ages $\geq$70 years than among men of ages 50 to 54 years ($P < 0.001$; see Table 2; ref. 18). If the anomalously high 25-OHD levels in older men resulted from recent vitamin D supplementation (which seems likely), then the (pre-supplementation) association between plasma 25-OHD and prostate cancer risk would be distorted upwards.

In a second study in this issue, Schenk and colleagues examined associations between serum 25-OHD and prostate cancer risk in a case–control trial nested with the Prostate Cancer Prevention Trial (PCPT), a double-blind placebo-controlled trial of finasteride for the primary prevention of prostate cancer (22). This study included 1,695 men with prostate cancer and 1,682 controls. An important advantage of the PCPT study was its ability to minimize detection bias. All men had annual PSA and digital rectal examinations and the absence or presence of prostate cancer was confirmed by biopsy either during (for cases) or at the end of the trial (for all men). The key finding was that among combined treatment arms of this trial, comparing the highest with lowest quartile of serum 25-OHD, 25-OHD levels were associated with a linear decrease in the risk of Gleason 8–10 prostate cancer [OR, 0.55; 95% confidence interval (CI), 0.32–0.94]. There was no evidence of a preventive effect for Gleason 2–6 cancers, which were nonsignificantly increased, or of a "U"-shaped curve.

What is the "take-home" message from these studies? First, both studies support a protective role for circulating 25-OHD on prostate cancer risk. The effect was clearer in the PCPT study, which found that 25-OHD levels were associated with a linear decrease in risk of Gleason 8–10 prostate cancer, than in the SELECT study, which found that 25-OHD was associated with a linear decrease in the risk of high-grade cancers in African Americans and an apparent "U"-shaped curve in other men. Because a "U"-shaped curve was observed in the SELECT study, which was vulnerable to detection bias, but was not observed in the PCPT study, which was largely free from this bias, the "U"-shaped curve in the SELECT study may reflect such bias. Second, both studies show that the protective effect of 25-OHD was associated more strongly with high-grade than with low-grade prostate cancers. This finding is consistent with the hypothesis that vitamin D inhibits the development of clinically relevant, but not subclinical prostate cancer (2). To return to our automotive example, seat belts prevent serious injury and death from automobile collisions; they do not prevent whiplash, a common but non–life-threatening injury (23). Thus, if fatal and nonfatal automobile injuries were combined into the single category, "injuries," the life-saving effect of seat belts could be missed. This may be relevant to some of the inconsistency in previous reports of circulating 25-OHD and risk of (predominantly low grade) prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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