

# Vitamin D and Prostate Cancer Risk—A Less Sunny Outlook?

Lorelei A. Mucci, Donna Spiegelman

Vitamin D insufficiency is an emerging public health concern. National survey data confirm that large proportions of the populations in the United States and Northern Europe have low vitamin D levels (1,2). The prevalence of low vitamin D levels looms particularly large among African Americans and others with dark skin (3), the elderly, the overweight (4) and physically inactive, and those with little sun exposure, such as those who live at higher latitudes where sun exposure in the winter does not induce vitamin D formation in skin (5). Interest in vitamin D levels stems from the growing recognition that the low vitamin D levels that are sufficient to avoid rickets, the classical deficiency disease, may be suboptimal for overall health. The associations with low vitamin D range from increases in total mortality (6), cardiovascular disease (7), hypertension (8), and various infectious diseases (7) to poorer bone health (ie, bone fractures and low bone mineral density) (9).

Nearly three decades ago, Garland and Garland (10) were among the first to hypothesize a link with cancer, specifically suggesting that inadequate vitamin D levels could represent an important risk factor for colorectal cancer. Since that time, an increasing spate of studies have emerged suggesting links between poor vitamin D status and cancer incidence and mortality, particularly for digestive cancers (11). For example, using prospectively collected samples in a nested case-control design, the risk of colon cancer among individuals with the lowest vitamin D levels were about two times higher than those with the highest intake among both men and women (12). Epidemiological evidence also points to a role of inadequate vitamin D status and risk of cancers of the breast and pancreas (12).

Findings for vitamin D and prostate cancer have been less consistent (12). Most studies have reported null associations (13,14); some have reported inverse associations in subgroups defined by tumor characteristics or by genetic variants (15), but these subgroup findings have not been consistent. The setting of research on risk factors for prostate cancer—that is, widespread prostate-specific antigen (PSA) screening and considerable biologic heterogeneity of the disease—poses several difficulties for contemporary epidemiology. The prevalence of prostate cancer among middle-aged and older men is high, to the extent that half of US men over age 60 likely harbor a prostate cancer, although many of the tumors are subclinical and will remain undetected throughout the man's life. As a corollary, risk factors for prostate cancer may vary substantially depending on the characteristics (stage and grade) of the tumor (16). The pattern of risk factors observed in studies carried out before the era of PSA screening is most similar to that observed in contemporary studies of advanced-stage disease. The lack of

association for incidence of total prostate cancer, which is dominated by early-stage, low-grade disease, could obscure an important association with lethal prostate cancer. A related difficulty in studies of prostate cancer is its highly variable natural history (17) and the unknown duration that a cancer may be present before diagnosis.

Ahn et al. (18) recognize these challenges in their well-designed and well-executed study of plasma vitamin D levels and prostate cancer risk in this issue of the *Journal*. One particularly notable feature is the focus on the relation with extraprostatic disease as a separate stratum to disentangle risk factors for indolent from those of lethal prostate cancer. In this most important category, the authors find no evidence of a lower risk with high plasma levels of vitamin D; to the contrary, there is a non-statistically significant suggestion of increased risk at the highest levels. The analyses outlined by Ahn et al. (18) provide an excellent example for other researchers to follow in providing data for the specific categories of prostate cancer of greatest concern. The findings for other case groupings that contribute to “aggressive disease” are also of interest, but are less compelling, because many prostate cancers with Gleason grade 7, especially those with the 3+4 pattern, have a lower potential to progress to lethal disease. Moreover, findings for total prostate cancer are therefore difficult to interpret.

By design, Ahn et al. (18) have studied a highly screened population, men in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial. The authors wisely excluded cases diagnosed in the first year as almost certainly prevalent at the time of the blood collection. However, many of the other cases diagnosed later may have also been prevalent, as suggested by the pattern of diagnoses across the duration of follow-up, which extended for up to 8 years. Of the 749 men with newly diagnosed prostate cancer in this analysis, 434 (58%) were diagnosed in the second year and likely represent prevalent disease.

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**Affiliations of authors:** Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (LAM); Departments of Epidemiology (LAM, DS) and Biostatistics (DS), Harvard School of Public Health, Boston, MA.

**Correspondence to:** Donna Spiegelman, ScD, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115 (e-mail: stdls@channing.harvard.edu).

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Exclusion of those cases from the analysis did not materially alter the relative risks, although the confidence intervals were broader. Although the study was restricted to the screening arm of PLCO, there is a potential for noncompliance with the screening protocol. Men with a less healthy lifestyle may be more likely to be noncompliant and as such may be less likely to spend time outdoors exercising, therefore inducing a spurious association between prostate cancer risk and vitamin D levels. The extent of this bias would depend on the extent of noncompliance in the PLCO screening arm, about which information is not provided.

A randomized trial of prostate cancer in relation to vitamin D would be free from screening bias as well as from bias due to confounding. Natural experiments may already be available to address this need by capitalizing on randomized studies of vitamin D supplementation in relation to other endpoints (19–21), in which prostate cancer incidence could be ascertained as well. The randomization is valid over all endpoints, regardless of which one has been designated the “primary” endpoint.

As the authors state, the results of this study are based on a single measurement, leaving some uncertainty in the findings due to bias induced by random within-person variability in 25-hydroxyvitamin D [25(OH)D]. Platz et al. (22) reported in a population of men in a similar age range as in this study an intraclass correlation of 0.70 for measurements taken, on average, 3 years apart, indicating that a single measure has good validity. If a linear trend in risk with 25(OH)D status had been evident in the study of Ahn et al. (18), the estimated relative risk could have been corrected for bias due to random within-person variation [eg, Rosner et al. (23)], but with the possible nonlinearity that the authors observed a more appropriate adjustment would have involved the estimation of a misclassification matrix from the repeated measures separated in time, which then could have been used to adjust the categorical relative risks and their confidence intervals for measurement error, with no assumptions of linearity imposed [eg, Drews et al. (24) and Hertzmark (25)]. Particularly if random within-person variation had been found to increase or decrease with increasing underlying 25(OH)D level, the adjusted dose–response relationship could be quite different from that presented and is difficult to predict in advance.

It would be of interest to view the graph of the dose–response curve over the entire range of 25(OH)D levels observed. The limitations of analyses based on quintiles or other broad groupings on power and validity are well known (26,27). Given the relatively large number of cases in this study, the full power of the continuous data could have been used to stabilize the apparent irregularity of pattern in the relative risks from one level to the next [see table 3 of Ahn et al. (18)], to obtain a significance test for nonlinearity, and to observe possible thresholds at the high or low end of the observed range of exposure through a graphical view of the relation. Restricted cubic splines are one option that could have been applied here (28–30).

Ahn et al. (18) provide a useful summary figure (ie, figure 2) of previous prostate cancer studies using blood levels of vitamin D from prospectively collected samples. Taken together, the data in this figure do not support the hypothesis that higher vitamin D status is associated with lower risk of total or aggressive prostate cancer. Reassuringly, the suggestive increase in risk observed in this

study is not generally observed in the other studies. The material in Fig. 2 could, however, have been summarized more concisely and conclusively using meta-analytic methods for dose–response (31,32), accompanied by a summary meta-graph perhaps smoothed nonparametrically using restricted cubic splines (28).

Should there still be enthusiasm for a potential role of vitamin D in prostate cancer? The evidence to date does not strongly support an association between plasma vitamin D status in adulthood and prostate cancer risk. Interestingly, prostate cancer cells may lose the ability of normal prostate epithelial cells to convert 25(OH)D, the more prevalent circulating form, to its more active form of 1,25-dihydroxyvitamin D (33). It is also feasible that vitamin D status many years earlier in life could play a role in prostate cancer initiation. Such a long time lag remains to be demonstrated in epidemiological studies. Moreover, endpoints such as prostate cancer mortality in relation to vitamin D status have not been evaluated in detail, although data from a recent trial suggest that high-dose calcitriol among men with androgen-independent prostate cancer may improve survival (34).

The absence of a link between vitamin D and prostate cancer risk, even if ultimately confirmed, should not be misinterpreted as evidence against other well-documented health benefits of vitamin D. The weight of evidence does suggest that increased vitamin D levels—from diet, supplementation, or sun exposure—are likely to have a modest beneficial effect on the overall burden of chronic disease in the United States and other epidemiologically similar countries.

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#### Note

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