

# Vitamin D Status and Cancer Incidence and Mortality: Something New Under the Sun

Gary G. Schwartz, William J. Blot

In this era of tumor genomics, proteomics, and metabolomics, the idea that fundamental insights about cancer could emerge from observations of the gross characteristics of individual persons (i.e., from classical epidemiology) seems almost anachronistic. Surely the era of discovery of common exposures with broad effects on cancer is over. Or is it?

In this issue of the Journal, Giovannucci et al. (1) report that estimates of vitamin D status derived from the Health Professionals Follow-up Study were associated with statistically significant reductions in total cancer incidence and mortality. Most of the protective effect for vitamin D status comes from an exposure that is common indeed—sunlight. Because many persons think of sunlight only as a cause of cancer (especially melanoma), that perspective may be helpful.

In 1941, Frank Apperly (2), a pathologist, demonstrated an inverse correlation between levels of ultraviolet radiation in North America and mortality rates from cancers in nonskin sites and proposed that sunlight somehow conferred “a relative cancer immunity” to nonskin cancers. Although Apperly’s paper attracted little attention in its day, epidemiologists rediscovered his fundamental insight half a century later. Many common cancers, such as cancers of the colon and prostate, display fascinating north–south gradients, with rates that increase systematically with increasing geographic latitude, and show an increased risk among African Americans (3). The increased risk with residence at northern latitudes and greater incidence and mortality in persons with dark pigmentation recall the descriptive epidemiology of rickets, the classic disease of vitamin D deficiency. These considerations led several epidemiologists, including Garland and Garland (4) for the colon in 1980, and Schwartz and Hulka (5) for the prostate in 1990, to propose that vitamin D deficiency increased the risk for these cancers. Similar claims later were made for cancers at other sites, e.g., breast, ovary, and pancreas, so that vitamin D has become a prime candidate for cancer prevention (6,7).

Understanding how vitamin D could influence cancer risk requires an understanding of vitamin D synthesis. The synthesis of vitamin D begins with the production of vitamin D<sub>3</sub> (cholecalciferol) after 7-dehydrocholesterol in the skin is exposed to ultraviolet B radiation (wavelength = 290–315 nm). Because melanin is an effective sunscreen, given the same ultraviolet exposure, blacks synthesize less vitamin D than whites, accounting for the far higher prevalence of vitamin D deficiency among blacks (8). Vitamin D can also be obtained from the diet, although the quantity of vitamin D in Western diets is generally small. To become biologically active, vitamin D undergoes two hydroxylations: The first occurs in the liver at the 25th carbon position, forming 25-hydroxyvitamin D [25(OH)D or calcidiol], the prohormone and major circulating form of vitamin D; the second occurs at the 1 $\alpha$  position, forming 1,25(OH)<sub>2</sub>D (calcitriol), the hormonal form of vitamin D. Most of the biological effects of 1,25(OH)<sub>2</sub>D are mediated by specific hormone receptors (vitamin D receptors, or VDRs) (9).

In 1979 VDRs were identified in normal cells that were not involved in mineral metabolism (10). In 1981, VDRs were found in malignant melanoma cells, and 1,25(OH)<sub>2</sub>D inhibited their proliferation (11); also, myeloid leukemia cells were induced to differentiate into macrophages by nanomolar concentrations of 1,25(OH)<sub>2</sub>D (12). These observations led to an explosion of interest in the role of 1,25(OH)<sub>2</sub>D in many cell types, where the pleiotropic anticancer effects of 1,25(OH)<sub>2</sub>D, including those on cell cycle, invasion, and metastasis, were widely confirmed. These findings have now led to the exploration of 1,25(OH)<sub>2</sub>D and its analogs as cancer therapeutic agents (13,14).

Although possible mechanisms for the anticancer effects of 1,25(OH)<sub>2</sub>D were becoming evident, how sunlight or vitamin D could influence cancer risk was not, because serum levels of 1,25(OH)<sub>2</sub>D are tightly controlled by the kidney and generally do not vary with geographic latitude or race. How, then, could vitamin D deficiency contribute to the north–south gradients and African American excess in cancer rates? This problem was solved by the demonstration that many nonrenal cells, such as prostate and colon cells, can also hydroxylate 25(OH)D at the 1 $\alpha$  position and synthesize 1,25(OH)<sub>2</sub>D locally. In these cells, 1,25(OH)<sub>2</sub>D promotes differentiation and inhibits proliferation in a microendocrine fashion (15). The implications of the extrarenal synthesis of 1,25(OH)<sub>2</sub>D by nonclassical cells are profound; they imply that sunlight exposure, which produces greater serum levels of 25(OH)D, could result in a decreased risk of cancer in the sites where 1,25(OH)<sub>2</sub>D is synthesized locally (16).

The knowledge that many factors—including skin pigmentation, geographic latitude, and outdoor exposure—contribute to plasma levels of 25(OH)D enabled Giovannucci et al. (1) to attempt an assessment of the contribution of these factors to cancer risk. They assayed plasma 25(OH)D among a subset of 1095 men in the Health Professionals Follow-Up Study and used a linear regression model incorporating six personal characteristics (dietary and supplemental vitamin D, race, adiposity, geographic residence, and leisure-time physical activity) as predictors of the plasma levels of 25(OH)D. They then used this statistical model to compute predicted 25(OH)D levels for all 47 800 men in the cohort and examined whether the 25(OH)D index was related to subsequent cancer risk. They report that an increment of 25 nmol/L (10 ng/ml) in predicted 25(OH)D was associated with a 17% reduction in total cancer incidence (relative risk [RR] = 0.83, 95% confidence interval [CI] = 0.73 to 0.94) and a 29%

*Affiliations of authors:* Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC (GGS); International Epidemiology Institute, Rockville, MD, and Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN (WJB).

*Correspondence to:* Gary G. Schwartz, MPH, PhD, Departments of Cancer Biology and Epidemiology, Wake Forest University, School of Medicine, Winston-Salem, NC 27157 (e-mail: gschwartz@wfubmc.edu).

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reduction in total cancer mortality (RR = 0.71, 95% CI = 0.60 to 0.83), with even stronger effects for digestive cancer. The findings from this cohort study are the latest of several (7,17,18) linking vitamin D status with reduced cancer risk and are some of the most compelling yet. The results, with lower risks of most (but not all) forms of cancer, are also some of the most broad based, and they indicate that vitamin D may have a role in most human tumors.

Although the cohort findings are likely to increase enthusiasm for the cancer prevention potential of vitamin D, inherent limitations of observational epidemiologic studies combined with a history of prior disappointments with other potential chemopreventive agents suggest caution in their interpretation. Two decades ago there was intense interest and hope that supplementation with  $\beta$ -carotene might reduce the risk of several cancers. Epidemiologic studies have consistently reported that men and women with the highest dietary intakes of  $\beta$ -carotene as well as with elevated blood levels experienced lower risks of respiratory, gastrointestinal, and other cancers. The zeal was crushed, however, when randomized trials in the United States and Finland showed increased rather than decreased risks of lung cancer among adults receiving  $\beta$ -carotene supplements (19,20). Vitamin E was similarly touted as an inhibitor of cancer, as well as of cardiovascular disease, but again the “gold standard” of randomized trials failed to confirm the preventive correlations noted in cohort and case-control studies (21). Epidemiologic studies also strongly indicated that hormone replacement therapy might not only relieve menopausal symptoms but also lower the risk of heart disease and breast and other cancers, but again, when clinical trials were conducted, no benefit with respect to these conditions accrued to women administered the therapy (22). In each of these examples, the agents may have demonstrated benefit with modification of the dose, formulation, or timing of the intervention or with longer follow-up, but the sobering lesson is that trends observed in non-experimental settings, including cohort studies, are not always confirmed experimentally when tested in randomized clinical trials. Science, after all, is a continual process of hypothesis formulation, testing, and refinement; ecologic (e.g., geographic correlations) and analytic (e.g., cohort and case-control) studies provide the evidence-based clues to cancer etiology, but randomized trials are generally needed to confirm these leads and develop effective disease prevention strategies.

Will a similar unrealized promise eventually befall vitamin D? We hope not. Although *ex post facto* mechanistic explanations can often be postulated to explain epidemiologic observations, for vitamin D the biologic evidence for inhibition of carcinogenesis is strong and, often, was predicted by the prior epidemiologic findings on sunlight exposure. Laboratory and observational epidemiologic research will continue to further elucidate and refine hypotheses on vitamin D's role, but the potential for cancer prevention by vitamin D (in pill form) must now proceed to the clinical trial testing arena. Several randomized trials have assessed the effects of vitamin D supplementation on bone fracture (23), but few have assessed its preventive effect on the risk of cancer or precancerous lesions [although small trials are evaluating 1,25(OH)<sub>2</sub>D or its analogs on the treatment of prostate and other cancers].

We close with the recognition that heavy sun exposure can cause harm. Because the ultraviolet radiation action spectra required for vitamin D synthesis and the spectra that induce DNA damage are essentially the same, there is an apparent conflict

between the advantages of sunlight exposure for vitamin D synthesis and its deleterious effects, the most serious being malignant melanoma. Although much has been made of it in the lay press, and by some in the dermatology community, the conflict may be more apparent than real (24). The amount of sun needed to produce adequate levels of vitamin D, at least for bone health, is modest and can be obtained in a light-skinned person by a brief afternoon summertime stroll. Although the dose-response relation between ultraviolet exposure and the development of melanoma is not well quantified, the limited exposure required for vitamin D synthesis is likely at the very low end of the curve.

Sunlight generally is an effective means of generating large amounts of vitamin D, but it may not be safe for all persons. For many individuals, including those who are darkly pigmented or who live at northern latitudes, sunlight exposure may also be insufficient to generate adequate vitamin D. Conversely, vitamin D supplements are widely available, inexpensive, and believed to be safe over a large dosing range. As is often pointed out, the present recommended allowance for vitamin D—400 IU—for individuals aged 50–70 years is inadequate even to maintain skeletal health and is probably too low for meaningful anticancer effects (25). A dose of 400 IU of vitamin D<sub>3</sub> will raise serum levels of 25(OH)D<sub>3</sub> only modestly, by about 7 nmol/L or less than 3 ng/mL. The use of this low dose, in conjunction with the relatively short duration of the trial, may explain the recent failure of vitamin D to reduce the incidence of colorectal cancer in the Women's Health Initiative (26).

In summary, a role for sunlight and vitamin D in cancer prevention is strongly suggested by epidemiologic observations, including the findings of Giovannucci et al. (1), and potential mechanisms have been identified by experimental studies. The promising results from both observational and laboratory studies should usher in a new era of intervention studies of vitamin D and cancer risk. Because many public health scientists are already clamoring for higher levels of vitamin D supplementation for bone and other health, randomized trials of vitamin D and cancer risk should be undertaken speedily (27). If the promise of vitamin D holds, a brief walk in the sun may turn out to be a step toward cancer prevention.

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