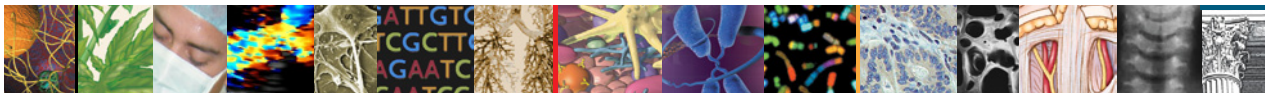

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Perspective

# Vitamin D and Prevention of Cancer — Ready for Prime Time?

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Given that the potential role of vitamin D in cancer prevention has been widely touted, many people were surprised that cancer-related considerations didn't figure prominently in the new Dietary Reference Intakes for vitamin D established by the Institute of Medicine (IOM).[1] An IOM committee on which we served, charged with determining the population needs for vitamin D in North America, reviewed the evidence linking vitamin D with both skeletal and nonskeletal health outcomes. The committee concluded that vitamin D plays an important role in bone health and that the evidence provides a sound basis for determining the population's needs. For outcomes beyond bone health, however, including cancer, cardiovascular disease, diabetes, and autoimmune disorders, the evidence was found to be inconsistent and inconclusive as to causality.

Based on vitamin D's importance to bone health, the recommended dietary allowances (RDAs) are 600 IU per day for persons 1 to 70 years of age and 800 IU per day for persons over 70 — intakes corresponding to a serum 25-hydroxyvitamin D level of at least 20 ng per milliliter (50 nmol per liter). Because of wide variation in skin synthesis of vitamin D and the known risks of skin cancer, we derived the RDAs under the assumption that sun exposure would be minimal. The committee also concluded that the prevalence of vitamin D inadequacy in North America has been overestimated. Most North Americans have serum 25-hydroxyvitamin D concentrations above 20 ng per milliliter, which is adequate for bone health in at least 97.5% of the population.[1]

The committee's comprehensive review of the evidence regarding vitamin D's role in preventing cancer, however, revealed that the research is inconsistent and doesn't establish a cause–effect relationship. Other recent reviews have reached similar conclusions.[2,3] No large-scale randomized clinical trial of vitamin D has been completed with cancer as the primary prespecified outcome. Most evidence is derived from laboratory studies, ecologic correlations, and observational investigations of serum 25-hydroxyvitamin D levels in association with cancer outcomes. Although this serum measure is a useful

**Vitamin D Supplementation and Total Cancer Incidence: Secondary Analyses from Randomized Clinical Trials.***

| Trial, Location | Population | Intervention Dose | Relative Risk (95% CI)† |
|---|---|---|---|
| Oxford, United Kingdom | 2686 men and women, 65–85 yr of age | Vitamin $D_3$, 100,000 IU every 4 mo (about 833 IU per day) vs. placebo | 1.09 (0.86–1.36) |
| Nebraska, United States | 1179 postmenopausal women, mean age 67 yr | Vitamin $D_3$, 1100 IU per day + calcium vs. calcium alone | 0.76 (0.38–1.55) |
| Women's Health Initiative, United States | 36,282 postmenopausal women, 50–79 yr of age | Vitamin $D_3$, 400 IU per day + calcium vs. placebo | 0.98 (0.91–1.05) |

* Adapted from the Institute of Medicine[1] and Chung et al.[2] CI denotes confidence interval.
† The numbers of incident cases of cancer in the treatment and control groups varied dramatically across the three studies: 188 and 173, respectively, for the study in the United Kingdom; 13 and 17 for the Nebraska study; and 1634 and 1655 for the Women's Health Initiative.

marker of current vitamin D exposure, associational studies have important limitations. Specifically, low serum 25-hydroxyvitamin D levels are also linked with confounding factors related to higher cancer risk, including obesity (vitamin D becomes sequestered in adipose tissue), lack of physical activity (correlated with less time outdoors and less solar exposure), dark skin pigmentation (less skin synthesis of vitamin D in response to sun), and diet or supplementation practices. Reverse-causation bias may also occur if poor health reduces participation in outdoor activities and sun exposure or adversely affects diet, resulting in lower vitamin D levels. Association therefore cannot prove causation. Many micronutrients that seemed promising in observational studies (e.g., beta carotene, vitamins C and E, folic acid, and selenium) were not found to reduce cancer risk in randomized clinical trials, and some were found to cause harm at high doses.[4]

The theory that vitamin D can help prevent cancer is biologically plausible. The vitamin D receptor is expressed in most tissues. Studies in cell culture and experimental models suggest that calcitriol promotes cell differentiation, inhibits cancer-cell proliferation, and exhibits antiinflammatory, proapoptotic, and antiangiogenic properties. Such findings suggest, but don't prove, that vitamin D has a role in preventing the development of cancer or slowing its progression.

Although several observational studies have linked low serum 25-hydroxyvitamin D levels with increased cancer incidence and mortality, randomized-trial evidence is sparse.[1,2] Three vitamin D trials, including one trial comparing a combination of vitamin D with calcium to calcium alone, have assessed the occurrence of newly diagnosed cancers or cancer mortality as secondary outcomes, but the results were null (see table).[1-3]

Regarding breast-cancer risk specifically, three observational cohort studies of plasma 25-hydroxyvitamin D levels had inconsistent results: one small study found an inverse association, one large study found no association, and one large study found no overall trend but an inverse association in one subgroup.[1,2] An inverse association observed in crude analyses in one study disappeared after adjustment for body-mass index and physical activity. Only one randomized trial (the Women's Health Initiative [WHI] trial) was large enough to assess breast cancer as a separate, although secondary, outcome; overall, it showed no significant effect of the intervention on breast-cancer incidence (hazard ratio, 0.96; 95% confidence interval [CI], 0.86 to 1.07) or related mortality (hazard ratio, 0.99). After stratifying the study population according to baseline vitamin D intake (diet plus supplements), the investigators found that women with the lowest baseline intakes had a reduced risk of breast cancer with the intervention (hazard ratio, 0.79; 95% CI, 0.65 to 0.97), whereas women with the highest baseline intakes (≥600 IU per day) actually had a significantly increased risk (hazard ratio, 1.34; 95% CI, 1.01 to 1.78; P for interaction = 0.003).

Observational studies of serum vitamin D levels and colorectal cancer generally support an inverse association.[1-3] According to a meta-analysis of prospective data from five studies, subjects with a serum 25-hydroxyvitamin D level of 33 ng per milliliter or higher had about half the risk of colorectal cancer of those with levels of 12 ng per milliliter or lower. The European Prospective Investigation into Cancer and Nutrition study recently reported a similarly strong inverse association. A prospective study from the Japan Public Health Center

did not find an inverse relation between plasma 25-hydroxyvitamin D levels and the occurrence of colon cancer, although an inverse association with rectal cancer was apparent. Randomized trial evidence is limited. In a British trial comparing vitamin $D_3$ with placebo, the intervention was not associated with a change in colorectal-cancer incidence (relative risk, 1.02; 95% CI, 0.60 to 1.74). Similarly, in the WHI trial, calcium plus vitamin $D_3$ did not reduce the incidence of colorectal cancer (relative risk, 1.08; 95% CI, 0.86 to 1.34) or related mortality (relative risk, 0.82; 95% CI, 0.52 to 1.29).

Although ecologic studies suggest that mortality due to prostate cancer is inversely related to sun exposure, observational analytic studies of serum 25-hydroxyvitamin D and prostate cancer haven't supported this conclusion.[1-3] Eight of 12 nested case–control studies showed no association between baseline serum 25-hydroxyvitamin D levels and prostate-cancer risk, and just 1 showed a significant inverse association; a more recent nested case–control analysis of data from the $\alpha$-Tocopherol, $\beta$-Carotene Cancer Prevention Study showed no association. Moreover, a meta-analysis of 45 observational studies of dairy-product intake and prostate-cancer risk showed no significant association with dietary intake of vitamin D. No relevant randomized clinical trials were identified.

The large-scale Cohort Consortium Vitamin D Pooling Project of Rarer Cancers showed no evidence linking higher serum 25-hydroxyvitamin D concentrations to reduced risk of less common cancers, including endometrial, esophageal, gastric, kidney, pancreatic, and ovarian cancers and non-Hodgkin's lymphoma[5] (which together account for approximately half of all cancers worldwide). Moreover, the report provided evidence suggestive of a significantly increased risk of pancreatic cancer at high 25-hydroxyvitamin D levels (≥40 ng per milliliter).[5] An increased risk of esophageal cancer at higher 25-hydroxyvitamin D levels has also been reported.

Despite biologic plausibility and widespread enthusiasm, the IOM committee found that the evidence that vitamin D reduces cancer incidence and related mortality was inconsistent and inconclusive as to causality. New trials assessing moderate-to-high-dose vitamin D supplementation for cancer prevention are in progress and should provide additional information within 5 to 6 years. Although future research may demonstrate clear benefits of vitamin D related to cancer and other nonskeletal health outcomes, and possibly support higher intake requirements, the existing evidence falls short.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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