Re: Dietary Supplements and Cancer Prevention: Balancing Potential Benefits Against Proven Harms

Martínez et al. (1) recommended against vitamin D supplements for reducing the risk of cancer. However, the evidence that vitamin D reduces the risk of cancer is very strong despite reports to the contrary.

There are several types of evidence: ecological, case–control, cohort, and randomized controlled trials. Each approach has its strengths and limitations. The strengths of the ecological approach include the large number of cases and the large number of data sets available for such studies. The limitations include assessing the role of confounding factors, but many cancer risk–modifying factors are included in most recent ecological studies. A recent review of ecological studies found strong support for solar ultraviolet-B in reducing the risk of 15 types of cancer, with weaker support for another nine types of cancer (2).

Case–control studies have the strength of determining serum 25-hydroxyvitamin D [25(OH)D] concentrations near the time of cancer diagnosis. Although there is a concern that the disease state may affect serum 25(OH)D concentration, there does not seem to be evidence to support this concern. Case–control studies have found the strongest inverse associations between serum 25(OH)D concentration and breast and colorectal cancer incidence (3).

Cohort studies are perceived to be the strongest observational approach. The advantage is that the risk-modifying factors are determined before disease outcome. However, a little-recognized disadvantage is that a single blood collection at the time of enrollment in the cohort study is used to determine serum 25(OH)D concentrations, and this value loses predictive ability with increasing follow-up time (3). A recent analysis of the regression coefficient for two serum 25(OH)D concentration measurements for a cohort as a function of interval found a decrease of −0.020/year for intervals ranging from 1 to 14 years (4).

In cohort studies of breast and colorectal cancer, the relative risks increased toward unity at a rate of 0.03/year to 0.05/year (3), whereas the hazard ratios for all-cause mortality rate increased at a rate of 0.017/year (4). In addition, only cohort studies that find direct relationships between serum 25(OH) D concentration and cancer incidence rates, such as for pancreatic and prostate cancer, are mentioned in References 66 and 68 (1).

Many randomized-controlled trials such as the Women’s Health Initiative used only 400 IU/day vitamin D3. However, a reanalysis of the Women’s Health Initiative restricted to women who had not taken vitamin D or calcium (CaD) supplements before enrollment found that “CaD statistically significantly decreased the risk of total cancer, total breast cancer, and invasive breast cancers by 14–20% and nonsignificantly reduced the risk of colorectal cancer by 17%.” (5). Marshall et al. recently reported that for those with low-risk prostate cancer, supplementing with 4000 IU/day vitamin D3 led to biopsy-assessed tumor regression in 55% of case patients (6).

When all the evidence regarding solar ultraviolet-B and vitamin D is evaluated using the criteria for causality in a biological system proposed by AB Hill, the evidence is found to be strong for several types of cancer (2,7).

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References


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Response

Dr Grant states that there is strong and sufficient evidence that vitamin D supplementation will reduce cancer risk. Although we acknowledge that there are potential health benefits associated with vitamin D supplements, and we respect the Hill criteria, we remain skeptical. A more thorough review of the literature than that conducted by Dr Grant shows that the evidence is mixed. Our conclusion is in agreement with the Institute of Medicine, which states, “Although data related to cancer risk and vitamin D are potentially of interest, a relationship between cancer incidence and vitamin D (or calcium) nutriture is not adequately and causally demonstrated at present; indeed, for some cancers, there appears to be an increase in incidence associated with higher serum 25-hydroxyvitamin D (25OHD) concentrations or higher vitamin D intake” (1).}

As noted in our Commentary, over the past 20 years, clinical trials have provided