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Letter to the Editor

RE: "OVERVIEW OF THE COHORT CONSORTIUM VITAMIN D POOLING PROJECT OF RARER CANCERS"

The Cohort Consortium Vitamin D Pooling Project of Rarer Cancers failed to find a reduced risk of cancer incidence associated with higher levels (>75 nmol/L) of serum 25-hydroxyvitamin D (25(OH)D) for 7 types of cancer: endometrial, esophageal, gastric, kidney, ovarian, and pancreatic, as well as non-Hodgkin's lymphoma (1). These results are in stark contrast to those of many ecologic studies, which almost invariably found strong inverse correlations for ultraviolet B doses for these cancers even after accounting for confounding factors (2–7). In addition, a cohort study found significant inverse correlations with an index of serum 25(OH)D level for 5 types of cancer, including pancreatic and esophageal, and nonsignificant inverse correlations for 6 types of cancer, including gastric, kidney, and non-Hodgkin's lymphoma (8) (also refer to Bao et al. (9)).

A review of the evidence that solar ultraviolet B and vitamin D reduce the risk of many types of cancer, according to the criteria for causality in a biologic system that A. Bradford Hill established (strength of association, consistency, temporality, biologic gradient, plausibility (mechanisms), experiment, and analogy), concluded that the evidence was very strong for breast and colon cancer and that the evidence for 10 other cancer types was reasonably strong (10). For both breast and colorectal cancer, meta-analyses find significant inverse correlations between prediagnostic serum 25(OH)D level and cancer incidence (11).

Assuming that the risk reduction for many types of cancer that solar ultraviolet B irradiance affords is due to vitamin D production, because no other mechanism has been proposed, at least 3 possible explanations exist for the discrepancy for rarer cancers between observational studies of serum 25(OH)D levels and ecologic studies: greater impact of vitamin D on cancer survival than on cancer incidence, a longer time horizon than observational studies normally cover, and failure of a single serum 25(OH)D level measurement to capture relevant vitamin D history. In an ecologic study of cancer rates with respect to annual solar ultraviolet B doses in the United States, relative risks were much higher for mortality rates than for incidence rates of bladder, colon, other biliary, and rectal cancer and were higher for breast, esophageal, gallbladder, and kidney cancer and for non-Hodgkin's lymphoma (3). An ecologic study of cancer in China found solar ultraviolet B to be inversely correlated with several more types of cancers when mortality rate versus incidence rate was considered (7). These results are reasonable since more cancer risk factors exist than natural factors that reduce the risk of angiogenesis around tumors and metastasis (12).

As to the longer time horizon, the finding that nonmelanoma skin cancer is inversely correlated with internal cancers in sunnier countries such as Australia, Singapore, and Spain (4, 13) supports the long-term perspective.

Regarding the representativeness of a single serum 25(OH)D level measurement, 2 factors give rise to changes in serum 25(OH)D levels. One is concern about skin cancer, probably leading to lower serum 25(OH)D levels (14). The other is increased vitamin D supplementation due to widespread publicity in the past decade about the health benefits of vitamin D. Two studies found that serum 25(OH)D levels can vary significantly over time (15, 16). A randomized, controlled trial of vitamin D and calcium supplementation found a 35% reduction in all-cancer incidence between the ends of the first and fourth years, which was attributed to 1,100 IU/day of vitamin D (17). Thus, recent serum 25(OH)D levels can significantly affect cancer incidence rates.

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