has been proposed to explain the correlation with or effect of UVB doses on cancer risk in well-conducted ecological studies.

Further support for the beneficial role of vitamin D in reducing the risk of cancer is that an individual and group index of high solar UVB irradiance and incidence or mortality rate of non-melanoma skin cancer is often inversely correlated with the incidence or mortality rates for other forms of cancer. In an ecological study in Spain, the mortality rate of non-melanoma skin cancer inversely correlated with mortality rates for 15 types of cancer after adjusting for the smoking index.[6]

A comprehensive method to evaluate the evidence for a natural compound such as vitamin D is by applying Hill's criteria for causality in a biological system. The primary criteria are strength of association, consistency, biological gradient, plausibility (mechanisms), experimental verification (eg, RCTs), and accounting for confounding factors. These criteria were evaluated for cancer and found to apply well for breast and colorectal cancer and reasonably well for 9 other types of cancer.[7]

Although additional evaluation linking UVB irradiation, vitamin D, and cancer risk is warranted, evidence is sufficient to recommend increasing serum 25(OH)D levels to reduce the risk of cancer incidence and death.

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In reply: We agree with Dr Grant that evidence from ecological studies suggests that vitamin D may reduce cancer risk. Increasing distance from the equator is associated with increased risk of several cancers at a population level. However, one of the major limitations of ecological studies is referred to as the *ecological fallacy*, which is the error of making inferences at an individual level on the basis of aggregate population level data. It is entirely possible that a disease association found by comparing populations is absent, or even in the opposite direction, when individual level data are examined. Individuals in the population who develop cancer may not be those with low vitamin D status. In the case of ecological studies involving international cancer registries, many low-income countries are close to the equator and their cancer registries may be limited by the fact that many cancers are undiagnosed and underreported, resulting in a high likelihood of an ascertainment bias.[1] Ecological studies are useful for generating hypotheses, but experimental studies and individual level data are necessary to ascertain causality.

The association of reduced sunlight exposure at higher latitudes with increased cancer risk does not indicate that low vitamin D status causes increased cancer risk. Many confounding environmental and population variables are associated with both latitude and vitamin D exposure that can affect disease risk. For example, income, industrialization, temperature, water consumption, meat and fat intake, outdoor activity, obesity, and affective disorders are all associated with latitude and could be hypothesized to affect cancer risk apart from vitamin D status. Although vitamin D deficiency may be identified as a major risk factor for certain types of cancer or other diseases, experimental studies are needed to confirm this, in part because RCTs have failed to demonstrate the benefit of vitamin D supplementation for the prevention of breast and colon cancer.[2,3] A large 5-year RCT of vitamin D supplementation currently under way may clarify the nonskeletal benefits of vitamin D, but the duration may be too short to establish its effect in long-latency diseases like cancer.[4]

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