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Commentary: Sunlight, vitamin D, and the cancer connection revisited

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This discussion commemorates the 25th anniversary of the publication in this journal of the report by Cedric and Frank Garland that first raised the hypothesis that vitamin D—the so-called ‘sunlight vitamin’—might have a protective influence on colon cancer. As research in this area has accelerated, most rapidly in only the last few years, the Garlands’ insights can now be fully recognized. Experimental, clinical, and epidemiological data is pointing to a beneficial role of vitamin D, not only for colorectal malignancy but also potentially for many of the most common and lethal forms of cancer in temperate climates. Garland notes that high vitamin D levels are found in populations from many parts of the world who historically have consumed certain foods and have had relatively low skin exposure to UV light. Since the data is pointing to a ‘solar’ role for vitamin D, it is important to recognize the importance of sunlight in the development of the human immune system and its role in cancer prevention. The Garlands observed that widespread use of sunbeds is likely to decrease the overall vitamin D content of a country’s population, and this will have a direct impact on cancer risk. The importance of sunlight in cancer prevention is also evident in studies on the relationship between sun exposure and the risk of several different cancers, including melanoma, skin cancer, breast cancer, prostate cancer, and colorectal cancer. The Garlands also noted that the use of vitamin D supplements is likely to increase the risk of toxicity, which may be due to the high doses of vitamin D that are currently being used. However, in vivo studies have shown that vitamin D is capable of reducing the risk of cancer in vitro, and this suggests that it may be possible to use vitamin D as a preventive measure for cancer. The Garlands’ insights can now be fully recognized, as experimental, clinical, and epidemiological data is pointing to a beneficial role of vitamin D, not only for colorectal malignancy but also potentially for many of the most common and lethal forms of cancer in temperate climates. Garland notes that high vitamin D levels are found in populations from many parts of the world who historically have consumed certain foods and have had relatively low skin exposure to UV light. Since the data is pointing to a ‘solar’ role for vitamin D, it is important to recognize the importance of sunlight in the development of the human immune system and its role in cancer prevention.
D3 (cholecalciferol). This form undergoes further modifications (hydroxyxations) in the liver and kidneys, which culminate in the production of the biologically active form, 1,25-dihydroxyvitamin D3 \([1,25(\text{OH})_2\text{D}_3]\); calcitriol. Large segments of the world’s population outside the tropics are at risk for vitamin D deficiency. At higher latitudes, particularly in winter months, the amount of UVR reaching the Earth’s surface may be inadequate to trigger endogenous vitamin D production. Persons of African ancestry living outside the tropics are at especially high risk because melanin in the skin attenuates the photochemical reactions that stimulate vitamin D production. High rates of vitamin D deficiency are observed in US blacks, a group that is also burdened by higher rates of many of the cancers that have been linked to inadequate vitamin D. Thus, the implications for cancer prevention may be very substantial. If vitamin D turns out to be a major risk reduction factor in cancer, hiding in plain sight of us, the Garlands will be credited with a remarkable hunch given how little was known at the time about this versatile ‘nutrient’.

The unfolding story of vitamin D and health begins less than a century ago. Rickets, the hallmark of vitamin D deficiency, had been described as early as the 17th century and was recognized to occur in situations of inadequate sunlight. However, it was not until the 1920s that progress was made in understanding the root cause of the disease. In the early 1920s, Sir Edward Mellanby demonstrated in experiments with dogs that rickets could be prevented by administration of cod liver oil. The modern era for vitamin D began only in 1965–70 with the discovery and chemical characterization of the active hormonal form of vitamin D \([1,25(\text{OH})_2\text{D}_3]\), and its nuclear receptor, the VDR (vitamin D receptor). In 1980, the year in which the Garlands’ report was published, evidence was just emerging that vitamin D might have other functions besides its role in calcium homeostasis. The first hint of any specific action of vitamin D in cancer had been published only the year before with the demonstration that cancer cells express the nuclear receptor for vitamin D. The year following the Garlands’ report, Suda and co-workers reported for the first time that active vitamin D promotes differentiation and inhibits proliferation of tumour cells.

The Garlands based their inferences about vitamin D and colon cancer on one simple observation: that like rickets prior to milk fortification, colon cancer is more likely to occur under conditions of limited sunlight. Using ground level radiation values obtained through the US Weather Service, the Garlands developed an isoline map of the contiguous 48 US states that displayed bands of constant levels of ground level solar radiation. They then applied this information to published colon cancer mortality data in the US (spanning the period 1950–69), and found a clear inverse association between mortality rates and annual radiation values. Because penetration of UV through the atmosphere is attenuated by various factors, including altitude, cloud cover, depth of atmospheric ozone, and even smog, their analyses based on ground level measures would have provided a more accurate picture than latitude alone of regional differences in vitamin D status. However, even ignoring these influences, a pronounced North–South trend is still evident for colon cancer in the eastern half of the US. As Grant and Holick point out, the North–South pattern may be less evident in the Western US owing to the higher surface elevation and lower stratospheric ozone layer for states west of the Rocky Mountains (http://toms.gsfc.nasa.gov/ery_uv/dna_exp.gif). The Garlands were not the first to report an apparently protective influence of solar radiation on cancer: 40 years earlier, Appley had demonstrated an inverse relationship of UVR levels with total cancer mortality in the US and suggested that solar radiation is responsible for a ‘relative cancer immunity’ in exposed populations.

An important modifier of residential sunlight—as recognized by the Garlands—is urbanization. The authors cited data showing that rickets had been a problem even in cities in the tropics, presumably because city dwellers are more likely to work indoors and may be shaded from sunlight by tall buildings. To address the problem (misclassification) the Garlands examined colon cancer mortality patterns separately, in less and more urbanized states (defined as %/80% of the population residing in a metropolitan area), and found, if anything, stronger correlations among the more urbanized areas of the US. If not due to chance, this result could indicate that residence provides a better single measure of sun exposure in urban populations, whereas in more rural localities, individual factors (outdoor occupations and other activities) contribute more to individual and hence group-level variation. Dietary intake of vitamin D would also contribute to misclassification of geographical exposure. The major natural dietary source, certain types of fish (sardines, mackerel, etc.) are not a mainstay of the US diet. However, a more widely consumed food item—liquid milk—had been fortified with vitamin D in the US since the 1930s. Milk fortification was very effective in reducing rickets incidence in the US and elsewhere, so the Garlands must have speculated that doses available in milk are insufficient to block colon carcinogenesis. Only relatively small amounts of vitamin D are added to milk in the US: one glass contains ~100 IU or 25% of the current adult Recommended Daily Intake. In contrast, large quantities of vitamin D can be obtained from only minor doses of sunlight: it has been estimated that only 20 min of direct exposure can create as much as 10 000 IUs of vitamin D. The minimal dose required (and upper threshold) for colon cancer prevention is by no means established. However, the persistence of strong regional patterns 2–3 decades after milk fortification is consistent with the idea that the higher doses attainable by sunlight may be optimal for cancer prevention.

The report also considered the possibility of ecological fallacy, or confounding at the group level, by two potential covariates: regional differences in the consumption of red meat, which was assumed to increase rates, and fruit and vegetables (as sources of fibre) assumed to reduce rates, of colon cancer. The Garlands examined per capita consumption of these foods in several regions of the US (North-east, North Central, South, and West) but found that consumption patterns did not track in expected ways assuming confounding by these factors. Mean pounds of red meat, and poultry and fish consumed per week showed little variation across the regions. Larger regional differences were found in fruit (though not vegetable) consumption; however, lower—not higher—consumption of fruits was found in the low-incidence South. As Willett has pointed out, ecological analysis of food consumption data can be misleading, as ‘consumption’ data reflects the sum of both food ingestion and food ‘disappearance’, the latter largely a function of food wastage, thus, ecological associations involving food consumption data may be
confounded by SES, even potentially within the US, limiting conclusions that can be drawn from these data. The author’s stratification on urban/rural locality would have helped to dampen confounding by these factors (and other potential risk factors) that correlate with urbanization.

Results were presented for white males; the Garlands did not perform (or report) analyses in other subgroups. Fewer women in that era worked outside the home, and women’s access to, and patterns of, sun exposure would have differed appreciably from men’s (melanoma rates are higher in males than females in Caucasian populations worldwide). Thus, a separate analysis in women would have provided a useful further check on the hypothesis. Blacks have a higher prevalence of frank vitamin D deficiency in the US and elsewhere (cases of rickets are still reported in breastfed African American infants), and differences from whites in North–South patterns in SES and other potential confounders would have made for an especially informative analysis. However, the lower prevalence of blacks relative to whites, particularly outside of urban areas, would have made geographical patterns more difficult to discern (though an intriguing hint can still be seen).

What is the mechanism for the anticancer benefit of vitamin D? The Garlands proposed a mechanism for vitamin D in colon cancer secondary to its function in calcium absorption from the gut (calcium is still considered a potentially important nutrient in colon cancer prevention). However, vitamin D has since been shown to have diverse primary biological effects in epithelial cells relevant to cancer prevention. Active vitamin D \([1,25(OH)_{2}D_{3}]\) binds with high affinity to the VDR, and is a well-known potent regulator of cell growth and differentiation in diverse tissues and cell types. The demonstration of 1alpha-hydroxylase, the enzyme catalysing the final step in the activation of vitamin D, in diverse tissue types, suggests a role for 1,25(OH)_{2}D_{3} in normal tissue maintenance. Local production of active vitamin D is dependent on circulating precursor levels, providing a potential explanation for the association of vitamin D deficiency with various systemic diseases including cancer. Vitamin D at physiological concentrations has been found to protect cell proteins and membranes against oxidative damage, and there is evidence that it may stabilize chromosomal structure and enhance repair of double strand breaks. Finally, effects of vitamin D on the immune system may also be relevant to the emergence and spread of malignant cells. A number of suspected influences of vitamin D—including effects on angiogenesis, apoptosis, and cancer cell extravasation—are consistent with the concept that adequate vitamin D stores could increase cancer survival. Well-done epidemiological studies showing a benefit among cancers diagnosed in the summer and fall, when serum concentrations of vitamin D are at their highest levels, support this view.

Since publication of their report, the Garlands and their associates have remained active in research on vitamin D’s role in cancer. In 1985, they provided the first prospective dietary analysis, which demonstrated a lower rate of colon cancer in persons with a higher intake of calcium/vitamin D. In 1989, they published the first seroepidemiological study, which showed an apparent protective association for colon cancer in persons with a history of chronic sun exposure may have a lower mortality from the disease when compared with their less sun exposed counterparts. Dietary studies are also supportive of a benefit for vitamin D in melanoma incidence. Despite emerging work in these other areas, the strongest evidence still prevails for colon cancer, as recently reviewed by Cedric Garland and associates.

Grant has demonstrated ecological patterns in the US similar to those for colon cancer for 13 other cancer sites, including breast, bladder, corpus uteri, oesophageal, kidney, lung, ovary, pancreas, prostate, rectum, stomach, multiple myeloma, and non-Hodgkins lymphoma. In a recent major review of the evidence, Giovannucci observed that vitamin D offers a coherent explanation for these geographical trends, as no other agent correlated with UV/latitude could plausibly be associated with such an aetiologically diverse group of cancers. Adding weight to the hypothesis, as also noted by Giovannucci, obesity is associated with lower serum vitamin D (body fat reduces bioavailability of the fat-soluble prohormone), and obesity is also a risk factor for a majority of the vitamin D-linked cancers. Finally, as noted, African Americans have higher incidence and/or mortality for many of these same cancers. Thus, though still circumstantial, the weight of the evidence seems to be pointing to a potentially important role for vitamin D in reducing the burden of cancer. Cedric Garland and associates, William Grant and Michael Holick, have estimated that 50 000–63 000 Americans die prematurely from cancer annually due to insufficient vitamin D, and 19 000–25 000 in the UK. These figures do not take into account the additional morbidity and mortality related to other chronic diseases—including hypertension, type I diabetes, multiple sclerosis and osteoporosis—that are linked to vitamin D insufficiency. The Garlands deserve great credit for stimulating research on the ‘sunlight vitamin’ and its potential role in cancer. If the vitamin D–cancer hypothesis is supported, their 1980 report may one day be seen as a milestone in the contribution of epidemiology to the understanding and prevention of human malignancy.

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