

Review

Current Impediments to Acceptance of the Ultraviolet-B-Vitamin D-Cancer Hypothesis

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Abstract. *The ultraviolet-B (UVB)-vitamin D-cancer hypothesis was proposed in 1980. There have been numerous ecological, observational and other studies of the hypothesis. There are about 14 types of cancer for which it seems to apply: bladder, breast, colon, endometrial, esophageal, gallbladder, gastric, ovarian, pancreatic, rectal, renal and vulvar cancer and both Hodgkin's and non-Hodgkin's lymphoma. Nonetheless, the hypothesis has not yet been accepted by public health agencies. Some of the reasons for this include a distrust of ecological studies, some mistrust of observational studies, and the existence of just one positive randomized controlled trial, an analysis of a vitamin D and calcium supplementation study involving post-menopausal women in Nebraska. Paradigm shifts such as this generally take time, in part due to opposition from those content with the status quo. In this paper, results of ecological studies in the United States using summertime solar UVB as the index of vitamin D production, which is highly asymmetrical with respect to latitude, and indices for other cancer risk-modifying factors (air pollution, alcohol consumption, dietary iron and zinc, ethnic background, socioeconomic status, smoking and urban/rural residence) are discussed in terms of supporting the hypothesis. These studies were not considered while other ecological studies were examined in recent critiques of the hypothesis. While additional randomized controlled trials would, of course, be helpful, the current evidence seems to satisfy the criteria for causality as outlined by A. Bradford Hill.*

The understanding of vitamin D as a risk factor in the epidemiology of cancer incidence and mortality as well of the mechanisms whereby vitamin D can affect cancer initiation, progression and metastasis has progressed considerably since the ultraviolet B (UVB)-vitamin D-cancer hypothesis was hypothesized by Cedric and Frank Garland in 1980 to explain the geographical variation of colon cancer mortality rates in the United States (1). Many of the epidemiological studies are ecological in nature, relating cancer incidence or mortality rates with indices of local solar UVB to represent vitamin D production (2-4). There are also numbers of case-control and a few cohort studies (2); some based on pre-diagnostic serum 25-dihydroxyvitamin D [25(OH)D] concentrations (5-7), dietary vitamin D intake (8), a measure of integrated lifetime solar UV irradiance or a combination of oral intake and production (9). There are to date two randomized controlled trials of vitamin D supplementation and cancer incidence (10, 11), which are discussed later. There are several reviews of the epidemiological literature (2, 12, 13) and also of relevant mechanisms (14). The evidence for vitamin D reducing cancer risks satisfies the criteria for causality in a biological system as laid down by A. Bradford Hill (15, 16). As of April 24 2009, there were 1,818 papers listed at www.pubmed.gov with both 'vitamin D' and 'cancer' in their title and/or abstract.

Despite the increasing body of evidence that better vitamin D status is associated with reduced cancer risk, there has been little official recognition of the evidence whilst a number of recent papers and reports criticize this hypothesis (17-19). This mini-review explores this and aims to answer the question of why the UVB-vitamin D-cancer hypothesis is not yet generally accepted either as a basis for urgent interventional trials or even for improving minimal vitamin D intakes in populations where deficiency and insufficiency are widespread and recognized to reduce bone health.

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Paradigm Shifts

Paradigm shifts involve initial discovery/hypothesis followed by scientific investigations leading to acceptance by the scientific community or, for healthcare advances, by the appropriate health organizations and agencies. During this process there can be many stumbling blocks including reluctance of those involved to accept a change to a paradigm to which they have contributed, which challenges their systems of work, or where working within the existing paradigm has economic benefits for those working within the status quo, as explored by Thomas Kuhn in his classic book "The Structure of Scientific Revolutions" (20).

How do changes in health policy occur and why do they take so long? A useful review of changes in health practices with particular reference to preserving chordal-papillary muscle integrity in mitral valve replacement is given by Lillehei (21). He points out with examples from history that

"Most 'new ideas' have been surrounded by controversy and opposition before wide acceptance. Some of the basic reasons for this inevitable opposition are: an innate skepticism over anything 'new.' Simplicity is often resented, as well as any need to change patterns of behavior/habits. Determination, persistence, stubbornness are the most important components for successful research. In addition, the successful innovator must learn to expect opposition and not be deterred by it, but rather must learn to take sustenance from it, and 'learn to thrive upon opposition'."

Impediments to Accepting Vitamin D as a Risk Reduction Factor for Cancer

The slow acceptance of and resistance to the idea that vitamin D is a risk reduction factor for cancer by the health systems of the world seem to have several causes. They are discussed in this section.

Perceived quality of the evidence. One impediment is that health systems have accepted the randomized controlled trial (RCT) as the gold standard for accepting drugs and other substances for the treatment or prevention of disease. For example, while it appeared that high-dose dietary beta-carotene was associated with reduced risk of lung cancer, two RCTs found supplementation with beta-carotene to increase risk (22, 23). It has, however, been pointed out that the effects of restoration of normal supplies of nutrients in deficiency must be distinguished from those of supplementation at pharmacological dosages (24). Likewise for hormone replacement therapy (HRT): the observational evidence supported a benefit in reducing the risk of coronary heart disease in 1991 (25). However, at least as early as 1988 it was suspected that HRT use could be a risk factor for breast cancer (26). In 2002, the results of two RCTs were published, one

finding no benefit in reducing the risk of CHD (27), the other reporting that treatment for 6.8 years with estrogen plus progestin in older women with coronary heart disease (CHD) increased the rates of venous thromboembolism and biliary tract surgery (28). Trends in other disease outcomes including cancer were not favorable and should be assessed in larger trials and in broader populations (28). It was later realized that the earlier benefit was likely due to the selection bias of health-conscious women using HRT in that period (29). A recent comment in *The Lancet* reviewed the controversy over HRT use and CHD and breast cancer outcomes (30). It was pointed out that discrepancies between observational and RCT studies arose from differences in timing of HRT use. For CHD, risk increases for HRT with increasing age. For breast cancer, the increase due to HRT use is higher the nearer to menopause. This finding points out the importance of not relying solely on RCTs but considering other epidemiological approaches as well, then trying to resolve the differences between them. For cancer, this has implications for timing and whether vitamin D affects incidence, progression, and/or survival.

Ecological Studies

Ecological studies, which have provided much of the support for the UVB/vitamin D/cancer hypothesis are viewed with general distrust by the health community. It is not clear why, but one source of distrust may be the difficulty that observational approaches such as case-control and cohort studies have in confirming that the consumption of animal fat is an important risk factor for breast cancer, as repeatedly shown in ecological studies (31-33). The term 'ecological fallacy' was coined to suggest that ecological studies might find apparent correlations between suspected risk-modifying factors and disease outcome that were in reality explained by unaccounted for etiological factors acting as confounders. In the past few years, however, it has been appreciated that ecological studies encompass dietary animal fat throughout life, and that risk of breast cancer is strongly linked to diet early in life as well as to lifetime endogenous estrogen production (34, 35).

Ecological studies of solar UVB and cancer incidence and mortality rates, when properly conducted, can be extremely valuable in assessing the role of vitamin D in affecting the risk of cancer as in the study where the UVB-vitamin D-cancer hypothesis was proposed (1); additional ecological studies have now extended the hypothesis to pancreatic (36), breast (37), prostate (38), ovarian (39) cancer, and then to another ten types of cancer (40). However, in all such studies up to and through 2002, the only risk-modifying factor included in the analysis was solar UVB. For pancreatic and prostate cancer, latitude was used as the index, while for the other types of cancer, either annual sunlight (1, 37, 39) or July solar UVB (40-43) was used as the index of vitamin D production. The

study by Grant (40) was criticized both for omitting several states from analysis and also for not including other risk-modifying factors. In response, indices for several additional risk-modifying factors were assessed in a revised analysis (alcohol consumption, Hispanic heritage for white Americans, level of poverty, smoking, and urban/rural residence) and the data were averaged at the state level rather than the state economic area as in the 2002 study. After extensive reviews and revisions, the revised findings were published in 2006 (43), showing the effects of solar UVB/vitamin D status to be unchanged. A paper using both incidence and mortality rate data from a more recent period in the United States was also published in 2006, with similar findings (44). Subsequently, additional risk-modifying factors have been added to the analysis (dietary sources of iron and zinc (45) and air pollution as acid rain (an index of black carbon and polycyclic aromatic hydrocarbons) (46). These recent studies suggest that there are at least 14 types of cancer for which solar UVB appears to be protective: bladder, breast, colon, endometrial, esophageal, gallbladder, gastric, ovarian, pancreatic, rectal, renal and vulvar cancer and both Hodgkin's and non-Hodgkin's lymphoma. Other more rare types of cancer may also be vitamin D sensitive but their low frequency in the United States makes this impossible to assess.

One of the important criticisms of ecological studies linking solar UVB to reduced risk of cancer is that latitude is not a good index of vitamin D production (19, 47), a credible assessment. Indeed, in the United States, cancer mortality rates are inversely correlated with summertime solar UVB doses in particular; these doses being distinctly asymmetrical with respect to latitude and longitude (41) due to higher surface elevation over the Rocky Mountains to the west and thinner stratospheric ozone layer due to the westerly winds elevating the tropopause as the air masses rise before crossing the Rocky Mountains. In multi-country ecological studies, however, dietary factors are often more important than solar UVB or vitamin D in determining cancer rates as shown in several ecological studies (18, 40, 43). Furthermore, most European countries lie at latitudes above 40° and, based on ecological studies of cancer mortality rates in the United States, vitamin D production at those latitudes is likely to be insufficient for it to have a significant impact on cancer incidence and mortality rates for countries other than the lower-latitude countries such as France, Italy and Spain (48), even though there appear to be survival benefits (49).

Further evidence that the ecological approach used with solar UVB doses in the United States to determine the role of vitamin D in disease outcome is valid is supplied in a study of septicemia, where the epidemiology of septicemia (highest rate in the Northeast, lowest in the West, more frequent in winter, and with black-Americans at greater risk than white-Americans) led to the hypothesis that vitamin D, through induction of human cathelicidin, LL-37, reduced the risk of

septicemia (50). The researchers who unwittingly supplied the epidemiological data then tested this hypothesis on 24 patients with septicemia in comparison with 21 health persons in Atlanta, Georgia and found that both serum 25(OH)D and LL-37 were significantly lower in those with septicemia (51). A mechanistic basis for this association exists since vitamin D has now been shown to enhance cathelicidin formation in human tissue (52, 53). Other recent reviews support the ecological approach for UVB and cancer (2-4).

Observational Studies

Observational studies include both case-control and cohort studies. For vitamin D and cancer, some measure of vitamin D intake or production or serum 25(OH)D data is compared with cancer incidence or mortality rate. The results of observational studies can also be combined using meta-analyses.

An analysis of cancer incidence in the Health Professionals Follow-Up Study with respect to a vitamin D index based on both oral intake and vitamin D production for men followed up to 14 years found significantly reduced relative risks for six types of cancer, colorectal, esophageal, oral/pharyngeal, and pancreatic cancer and leukemia, and insignificantly reduced relative risks for six additional ones (9).

Meta-analyses of observational studies of breast and colon cancer incidence as a function of prediagnostic serum 25(OH)D levels have been used to estimate the 25(OH)D dose/cancer incidence relations (5, 6). A meta-analysis of ten case-control studies from Australia, Europe, and the USA found that the composite measure of increasing recreational sun exposure had a pooled odds ratio of 0.76 (95% CI 0.63-0.91) for the highest exposure category (p for trend, 0.01) (54). "The protective effect of recreational sun exposure was statistically significant at 18-40 years of age and in the 10 years before diagnosis, and for B cell, but not T cell, lymphomas."

Non-melanoma skin cancer incidence can also be used as a measure of solar UVB dose. The findings for second solid tumors after diagnosis of basal cell carcinoma and squamous cell carcinoma in sunny countries (Australia, Singapore and Spain), standardized incidence ratio = 0.86 (95% CI, 0.80-0.92) and 0.79 (95% CI, 0.68-0.91) respectively (55) supports the UVB/vitamin D/cancer hypothesis (56). However, in the less sunny countries (latitude >45°), second tumors were more frequent than for controls (55), which can be attributed to too small a skin surface area being exposed for sufficient vitamin D to be generated for reduction in risk of such tumors (57, 58). The dividing line appears to be around 35°-40°.

Prostate Cancer

One cancer that is often considered vitamin D sensitive, prostate cancer, appears under more careful scrutiny not to be so. Firstly, the geographical variation of prostate cancer

mortality rates in the United States differs from that of the 14 vitamin D-sensitive cancers in that it exhibits a strong increase with latitude rather than being highest in the northeast and lowest in the southwest. A chance finding of the map of highest ancestry by county (*i.e.* each county is assigned a color representing the country with the largest number of inhabitants with roots in that country) for the United States in 2000 (59) led to the finding that ethnic background appears to play an important role in risk of prostate cancer. There are many features common to both the map of ancestry and the map of prostate cancer mortality rate (60). For example, Utah has a high prostate cancer rate and those with English ancestry are more numerous than from any other country; likewise, a region near the far north of Michigan has a relatively low prostate cancer rate and those with Finnish ancestry comprise the group with largest ancestry. Prostate cancer mortality rates are low along the U.S.-Mexican border, a region where those from Mexico have the largest ancestral group. The ancestral pattern seems, therefore, to explain much of the variation in prostate cancer mortality rate. However, vitamin D does seem to have a benefit in reducing the risk of metastasis (61) and increasing survival once diagnosed with prostate cancer (62).

Randomized Controlled Trials

There have been two important RCTs evaluated for cancer risk reduction. The first was the Women's Health Initiative Study in which women were assigned 400 IU/day of vitamin D₃ and 1,000 mg/day of calcium and evaluated for a variety of disease outcomes. There were no significant differences for colorectal cancer between those taking the vitamin D and calcium and those taking the placebo (10). As indicated from two reviews of vitamin D and colorectal cancer risk reduction, 400 IU/day is insufficient to produce a significant effect, especially when there is considerable non-compliance with the protocol (6, 63). The second was a post-hoc analysis of cancer incidence for post-menopausal women living in Nebraska. One third of the women took 1,100 IU/day of vitamin D₃ and 1,500 mg/day calcium, one third just the calcium and one third a placebo. When the cancer incidence rates between the ends of the first and fourth years were compared, there was a 77% reduction in all-cancer incidence rate for those taking vitamin D plus calcium, and 40% for those taking calcium alone (11). The fact that vitamin D supplementation had a profound effect over a short time period is consistent with the effects of vitamin D being important, even at the more advanced stages of cancer development and also with the fact that those diagnosed with cancer in Norway in summer or fall have longer survival times than those diagnosed in winter or spring (49). However, the Lappe study has been criticized in a report (19) claiming, for example, that the incidence rate for those taking the placebo was much lower than expected. However, careful analysis of

the number of expected cases for that age group and location yielded a number very close to that observed (64). The Authors note that the Lappe research group has recently received funding from the National Institute of Health to extend their study (J. Lappe, personal communication, 2009).

There are about 22 clinical trials in progress or planned on vitamin D and cancer prevention and more than 200 clinical trials apparently investigating the use of vitamin D to treat cancer. This is strong evidence of an established belief among clinical researchers that vitamin D is likely to have benefits because researchers do not undertake these arduous studies unless they believe that the study is likely to demonstrate benefit; furthermore, grants are not usually awarded unless felt to be justified after rigorous peer review. These trials are listed www.clinicaltrials.gov (accessed April 27, 2009).

As pointed out recently, "Perhaps clinical trials cannot be the only 'gold standard' for cancer prevention research. Their size and duration, along with their inherent problems in long-term adherence, make them unfeasible for addressing many important questions, especially those related to behavior change. Admittedly, the effect of some cancer prevention trials has been profound, but in general, we have learned more from trials about cancer biology and epidemiology than about effective policies for cancer control." (65).

The call for positive results from vitamin D supplementation RCTs as the sole condition for future acceptance of the UVB/vitamin D/cancer hypothesis (19, 66) may itself lead to delays in work seeking to establish the validity or otherwise of the hypothesis.

It is noted that there are also calls for RCTs for other diseases including type 2 diabetes mellitus (67, 68), coronary heart disease (69), and respiratory infections (70).

Power of entrenched health systems. Changes in health policy are generally made at governmental or large organizational levels. For example, the U.S. Surgeon General C. Everett Koop issued a report in 1982 declaring smoking to be an important risk factor for lung cancer (71), which set in motion measures to encourage people not to smoke and led to reduced lung cancer rates in the United States (72) as in many other countries (73).

Cancer policies seem to be largely set by such agencies as the U.S. National Cancer Institute (NCI) and organizations such as the American Cancer Society (ACS), Canadian Cancer Society (CCS), Cancer Research UK (CRUK), and the Cancer Council Victoria (CCV) (Australia). The NCI is following the progress of the UVB-vitamin D-cancer hypothesis although also recommending more research (66) and recently funding a second RCT by Joan Lappe and colleagues at Creighton University (J. Lappe, personal communication, 2009). The ACS, CRUK, and CCV have long been concerned about reducing the incidence and mortality rates from melanoma and non-melanoma skin cancer (73-76). There is some evidence

that melanoma incidence rate trends are leveling off in Australia (77) but apparently still rising in the United States (78) and in the UK (79), although much of the increase occurred for those over the age of 50 years. Part of the reason for these continued increases is reliance on sunscreen that does not effectively block the UVA (320-400 nm) radiation most likely involved in risk of melanoma (80).

However, an unintended consequence of the emphasis on reducing UV irradiance in order to reduce the risk of melanoma and non-melanoma skin cancer appears to be reduced serum 25(OH)D concentrations in both Australia (81) and the United States (82), although people interviewed in Queensland, Australia, were beginning to realize that they need more vitamin D (83). Part of the reason may be that dermatologists still assume that approximately 200-600 IU/day of vitamin D is sufficient for optimal health (84) despite recent recommendations (85). Interestingly, Australian dermatologists themselves have below average serum 25(OH)D concentrations (86) which may lead to changes in the advice on vitamin D supplementation they provide.

There have been some reasoned reviews suggesting that moderate solar UVB irradiance can provide the benefits of vitamin D production without undue risk of skin cancer and melanoma (87-89) but education achieving ideal modulation of sun exposure across whole populations would be much less easy to achieve than either improved food fortification or simple supplementation.

The International Agency for Research on Cancer (IARC) issued Working Group Report 5, Vitamin D and Cancer in November 2008 (19). The report concluded that there was sufficient evidence for a protective role of vitamin D against only one type of cancer, colon cancer. In responding to this Report it has been made clear that there were a number of errors and omissions in the procedures followed by the Working Group in order to reach their very limited conclusion (64). It was also noted that panel members had special interests in UV irradiance in the causation of skin cancer, only one having a particular and long standing interest in vitamin D. Whilst the Working Group rightly excluded anyone associated with the indoor tanning industry, most members had devoted their careers to trying to reduce the risk of skin cancer and melanoma (64). Importantly, the Working Group did not adopt a set of criteria by which to evaluate evidence in journal papers *a priori*, instead excluding the findings from any paper with perceived problems when discussed (64). Whilst noting that many papers were excluded as not examining other risk factors than vitamin D or UVB, the Working Group also excluded data from multi-factor ecological studies in the United States (43, 45) that used July UVB doses (41) as the index of solar UVB and also included many cancer risk-modifying factors in the analysis, in contradiction to the claim in the Report that ecological studies use of latitude had not allowed for other risk modifying factors. Thus, it is unclear why data from the Grant

and Garland (43) paper (which has been widely-cited [n = 55 on April 10, 2009]) was excluded.

Arising from concern that the IARC Report might be used by others as the basis to block further consideration of the UVB-vitamin D-cancer hypothesis until a large-scale RCT returns convincing evidence, fourteen leading vitamin D researchers from the United States and Europe wrote an open letter to the new director of the IARC, Christopher P. Wild, Ph.D., pointing out the above problems with the Report and asking him to consider rescinding the Report or preparing an update (90). In his reply Dr Wild described the Report as a "balanced presentation of the current state of the evidence" and said that it "remains an important document to place in the public domain" whilst declining to reopen the review without substantial new evidence (C. P. Wild, personal communication).

Future Outlook

The UVB-vitamin D-cancer hypothesis is likely to be modified as additional focused research continues. Based on consideration of how paradigm shifts occur in science in general, and in health policy in particular, it appears likely that the hypothesis will become widely accepted in the next 5-10 years provided that, during this period, there are additional research results supporting the hypothesis. Continued advocacy to convince both the general public and decision makers that measures to improve vitamin D status are justified where vitamin D inadequacy is common amongst the general population would, if it led to sustained supplementation, itself be likely to provide a valuable test of the role of vitamin D in reducing cancer risks.

There appears, additionally, to be an important role for non-governmental and non-profit organizations to play in hastening the time when vitamin D status will be improved nationally; The Canadian Cancer Society recently recommended supplementation with 1000 IU/day of vitamin D year round (www.cancer.ca). Carole Baggerly formed Grassrootshealth Organization after learning about vitamin D and cancer following diagnosis and treatment for breast cancer. One of the important activities of this organization was the preparation and dissemination of the position statement of the Scientists' Call to Action; 16 leading vitamin D researchers calling for a standard vitamin D intake of 2,000 IU/day and the achievement of a serum level of 40-60 ng/ml (91), and this document was successful in persuading both the American Medical Association and the American Public Health Association to adopt resolutions in support of vitamin D supplementation (92, 93).

In response to the growing evidence of health benefits of vitamin D, the National Academy of Sciences Institute of Medicine has established an ad hoc committee to review the scientific literature on vitamin D (94). This committee is expected to release its report in May 2010. While the panel has

many experts on the effects of nutrition on human health, those who have advocated most strongly for increasing the vitamin D recommendations recently are not on the panel. However, given the many health benefits and limited risks of having serum 25(OH)D levels in the 40-60 ng/ml range (95-98), it is very likely that the recommended daily requirement of vitamin D will be increased.

In closing, it is fitting to recall Schopenhauer's observation on paradigm changes: "All truth passes through three stages; First, it is ridiculed; Second, it is violently opposed; Third, it is accepted as being self-evident."

Based on the increasing number of critical attacks lately, it appears that the UVB-vitamin D-cancer hypothesis is in Stage Two.

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