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Review

How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer?

An examination using Hill's criteria for causality

William B. Grant

Sunlight Nutrition and Health Research Center (SUNARC); San Francisco, California USA

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The ultraviolet-B (UVB)—vitamin D—cancer hypothesis was proposed in 1980. Since then, several ecological and observational studies have examined the hypothesis, in addition to one good randomized, controlled trial. Also, the mechanisms whereby vitamin D reduces the risk of cancer have been elucidated. This report aims to examine the evidence to date with respect to the criteria for causality in a biological system first proposed by Robert Koch and later systematized by A. Bradford Hill. The criteria of most relevance are strength of association, consistency, biological gradient, plausibility/mechanisms and experimental verification. Results for several cancers generally satisfy these criteria. Results for breast and colorectal cancer satisfy the criteria best, but there is also good evidence that other cancers do as well, including bladder, esophageal, gallbladder, gastric, ovarian, rectal, renal and uterine corpus cancer, as well as Hodgkin's and non-Hodgkin's lymphoma. Several cancers have mixed findings with respect to UVB and/or vitamin D, including pancreatic and prostate cancer and melanoma. Even for these, the benefit of vitamin D seems reasonably strong. Although ecological and observational studies are not generally regarded as able to provide convincing evidence of causality, the fact that humanity has always existed with vitamin D from solar UVB irradiance means that there is a wealth of evidence to be harvested using the ecological and observational approaches. Nonetheless, additional randomized, controlled trials are warranted to further examine the link between vitamin D and cancer incidence, survival and mortality.

Introduction

The solar ultraviolet-B (UVB)—vitamin D—cancer hypothesis was first proposed in 1980 by Cedric and Frank Garland to explain the geographical variation of colon cancer mortality rates in the United States for 1950–1969, highest in the Northeast and lowest in the Southwest.[1] They showed a rough correlation for the cancer mortality rates with annual hours of sunshine. They later showed that dietary vitamin D and calcium were inversely correlated with colorectal cancer risk[2] as well as prediagnostic serum 25-hydroxyvitamin D [25(OH)D].[3] They also linked solar UVB and vitamin D to reduced risk of breast[4] and ovarian[5] cancer. Gary Schwartz added prostate cancer in 1990.[6] After the publication of the *Atlas of Cancer Mortality in the United States, 1950–94*,[7] William Grant determined that 14 types of cancer had mortality rates inversely correlated with solar UVB levels for July.[8,9]

Much of this pioneering work was accomplished using the ecologic approach, in which populations and risk-modifying factors are averaged for geographically defined populations. The ecologic approach is particularly well suited for this particular task for several reasons: solar UVB is the primary source of vitamin D for most people on Earth; the amount of vitamin D generated from casual solar UVB irradiance in summer, sufficient to raise serum 25(OH)D by 10–15 ng/mL,[10,11] is sufficient to reduce the risk of many types of cancer by 10%–40%; and vitamin D seems to play an important role in fighting cancer in the disease's later stages.[12,13]

As convincing as the ecologic studies are to those intimately involved therewith, they have not met with universal acceptance. Even their having been would still not be sufficient to establish a causal relation between solar UVB, vitamin D production and cancer risk reduction. However, an approach exists that one can use to evaluate whether the association can be considered causal: apply the criteria for causality, originally postulated by Robert Koch to show that tuberculosis was caused by a bacterium,[14] and codified in recent times by A. Bradford Hill.[15] Others have also discussed applying these criteria.[16,17] Although these criteria were developed with respect to "causal" rather than to "preventive" agents, there is no a priori reason why most, if not all, criteria would not also apply to preventive agents.

The Hill criteria are as follows:

(1) Strength of association
(2) Consistency (repeated observation)
(3) Specificity (one agent, one result)
(4) Temporality (exposure precedes effect)
(5) Biological gradient (dose-response relation)
(6) Plausibility (e.g., mechanisms)
(7) Coherency (no serious conflict with the generally known facts of the natural history and biology of the disease)

Correspondence to: William B. Grant; Sunlight, Nutrition and Health Research Center (SUNARC); P.O. Box 641603; San Francisco, California 94164-1603 USA; Tel.: 1.415.409.1980; Email: wbgrant@infionline.net

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Table 1 **Sixteen vitamin D-sensitive cancers determined by ecologic and cohort studies by geopolitical region**

Cancer	North america	North america cohort	Europe	Asia	Multicontinent
Esophageal	22, 23, 10, 24	25	26	27, 28	
Gastric	22, 23, 10, 24	25*	26	27, 28	29*
Colon	1, 22, 30, 23, 10, 24	25	31, 32, 26	27, 28*	33, 29*
Rectal	22, 23, 10, 24	25	31, 26	27, 28*	29*
Gallbladder	10, 24		26	27	
Pancreatic	22, 10, 24	25	31, 26	34, 27, 35	29*
Lung	22, 23	36, 25*	37, 38	28*	29, 39
Breast	4, 22, 30, 23, 10, 24		9, 31, 32, 26, 40		
Uterine corpus	22, 10, 24				41
Ovarian	5, 22, 30, 10, 24		31, 26		33, 42, 29*
Vulvar	24, 43				
Prostate	6, 22, 30, 10, 24	25*	31, 32		29
Bladder	22, 10, 24	25*			29*
Renal	22, 10, 24	25*			33, 44, 29*
Hodgkin's lymphoma	10, 24		45, 46, 26		
NHL	22, 47, 10, 24	25*	31, 48, 26		33

*Marginally insignificant. References are indicated by numbers.

(8) Experimental verification (randomized, controlled trial)
(9) Analogy with other causal relationships

A link need not satisfy all of these to be considered causal; however, the more that are, the better the case that is made. As Poitschman and Weed[16] and Weed[17] have indicated, some of these criteria are not particularly relevant, such as specificity, which applies more to a microorganism that causes a particular disease.

This work aims to evaluate the extant literature on UV irradiance, vitamin D and cancer risk reduction for the 16 types of cancer for which the most evidence has been obtained.

Approach

Using the National Institutes of Health and National Library of Medicine's PubMed database (http://www.pubmed.gov), we searched the journal literature for reports of correlations with indices for solar UVB and/or vitamin D. Those selected for inclusion in this review generally found a significant correlation with UVB or vitamin D, whether direct or inverse. Those with insignificant correlations generally did not have enough values in the beneficial range to find a significant result, often because until the past several years, 400 IU/day was thought to be an adequate intake of vitamin D for many health benefits. After many such randomized, controlled trials before 2004 failed[18]—most notably the Women's Health Initiative, which generally found no benefit of vitamin D and calcium supplementation for hip fractures,[19] colon cancer[20] or diabetes[21]—it was realized that an intake level of 400 IU/day has one primary benefit: reduced risk of rickets. Some studies, which we discuss as well, reported increased risk of several types of cancer with respect to higher solar UV doses or serum 25(OH)D levels.

Findings

Table 1 lists the types of cancer for which a reasonable number of ecologic or observational studies have reported a benefit from UVB or vitamin D.

In general, the cancers fall under the categories of digestive tract, female organs, urogenital organs and hematopoietic cancers. These cancers are generally those that are common in Western developed countries. Smoking is an important risk factor for many of these types of cancer,[48] as are diets high in animal products.[9,49,50] Among other factors, smoking reduces serum 25(OH)D levels.[51] Because many of these cancers are related to diets high in animal products, insulin-like growth factor I is a likely risk factor.[52] Vitamin D compounds can affect the growth-promoting pathways of insulin-like growth factor I.[53] Because these cancers have reasonably high incidence and mortality rates, they are easy to study.

Evaluation using Hill's Criteria for Causality

Strength of association. Satisfying strength of association requires a strong correlation between a measure of vitamin D and reduced risk of cancer. One index of serum 25(OH)D level is solar UVB dose. Solar UVB is the primary source of vitamin D for most people on Earth, and in summer in the United States and Europe, casual solar UVB irradiance is sufficient to increase serum 25(OH)D levels by 5–15 ng/mL depending on such factors as amount of body surface area exposed, skin pigmentation, age and body mass.[11,23] Reducing the risk of breast and colorectal cancer by about 50% requires a vitamin D level of 10–15 ng/mL.[54,55] Thus, summertime solar UVB is sufficient to significantly reduce the risk of cancer. Also, those diagnosed in summer or fall in Norway have significantly increased survival rates,[13,32] and vitamin D also reduces the risk of cancer with a 1-year lag time after starting supplementation,[12] indicating that vitamin D is important in reducing the risk of cancer in the later disease stages. Thus, one can use ecological studies of cancer incidence and mortality rates to look for a beneficial effect of vitamin D. Cancer data in the United States are particularly useful in this regard because the solar UVB dose for July[8] is asymmetrical, much higher in the western states than in the eastern states at the same latitude. The

reasons are twofold: the surface elevation is generally higher in the western states, and the stratospheric ozone layer is thinner because the prevailing westerly winds push the tropopause higher as the air masses prepare to cross the Rocky Mountains.

One can use several ecological studies to examine strength of association for many types of cancer: studies using an index for solar UVB for cancer mortality rates[22] or incidence and mortality rates[24] and multifactorial studies of cancer mortality rates.[10,33,43] Grant and Garland's[10] multifactorial study included additional indices for alcohol consumption, ethnic background, poverty, smoking and urban/rural residence. The associations with solar UVB remained similar to those in the original study.[22] The associations with the other risk-modifying factors were in general agreement with the literature. However, when the study added an index for air pollution, acid rain for 1985, solar UVB was no longer a significant risk reduction factor for the respiratory cancers.[56]

A related study used annual average erythemal UV doses measured by a NASA satellite with cancer incidence and mortality rates in the United States for 1998–2002.[24] Cancers with the strongest correlations with UV were bladder, colon, esophageal, gallbladder, other biliary, prostate, rectal and vulva cancer, as well as Hodgkin's lymphoma and multiple myeloma. Cancers with weaker correlations were breast, kidney, small intestine and thyroid cancer, as well as leukemia and non-Hodgkin's lymphoma (NHL).

For two reasons, the cancers best satisfying this criterion are colorectal and breast cancer. First, the statistics are robust because of the high incidence and mortality rates; second, the other risk-modifying factors, such as smoking for colon cancer and alcohol consumption for breast cancer, are less important.

Meta-analyses of observational studies have established dose-response relations for serum 25(OH)D and reduced risk of cancer incidence for both colorectal[54] and breast[54,57] cancers.

Also, in a meta-analysis of 10 case-control studies covering a total of 8,243 cases and 9,697 control subjects in the United States, Europe and Australia, risk of NHL fell significantly. The composite measure of increasing recreational sun exposure (pooled odds ratio) was 0.76 (95% confidence interval [CI], 0.63–0.91) for the highest exposure category (p_{trend} = 0.01).[58]

Consistency (repeated observation). For consistency (repeated observation), we examined ecologic studies because several looked at many cancer types. In addition to the studies listed in the previous section, an ecologic study of cancer mortality rates in Spain used nonmelanoma skin cancer (NMSC) mortality rates and latitude as the indices of solar UVB irradiance and dose.[26,59] The cancers with large significant inverse correlations with UVB indices in all four studies if iron, zinc and air pollution were also risk-modifying factors are breast, colon, esophageal, gallbladder, gastric, ovarian and rectal cancer, as well as Hodgkin's lymphoma and NHL. Renal and uterine corpus cancers were inversely correlated with UVB in the United States but not in Spain. Also, vulvar cancer, which Grant and Garland[10] did not include, was significantly inversely correlated with UVB in the iron and zinc study,[43] as well as in Boscoe and Schymura's[24] ecologic study of cancer incidence and mortality rates for 1998–2002. Also, evidence that vitamin D reduces the risk of melanoma is mounting. Thus, there are 12 types of cancer for which ecologic studies of cancer mortality rates in the United States for 1970–1994, and one for which the UVB index is latitude, found a significant inverse correlation with solar UVB for July.

Of the 16 types of cancer in Table 1, three have inconsistent results in ecological studies: bladder, lung and pancreatic cancer. Bladder cancer had a marginally insignificant inverse correlation with UVB in the air pollution study,[56] and smoking is an important risk factor for bladder cancer.[48] Lung cancer is strongly linked to smoking, but as discussed later some evidence indicates that vitamin D reduces this risk. Pancreatic cancer was directly correlated with latitude in Spain as well as in Japan.[27,34,35]

The cohort study by Giovannucci et al.,[60] also examined the correlation between a vitamin D index and cancer incidence in the Health Professionals Follow-Up Study of 50,000 male physicians. Those types with a significant inverse correlation were colorectal, esophageal, oral/pharyngeal and pancreatic cancer, as well as leukemia. Those with insignificant inverse correlation were gastric, lung, prostate (advanced) and renal cancer, as well as NHL.

Differences in cancer risk with respect to skin pigmentation can also support the UVB—vitamin D—cancer theory because black Americans produce vitamin D from UVB irradiance at about 20% of the efficiency of white Americans.[61] In the southeastern United States, hypovitaminosis D prevalence was 45% among blacks and 11% among whites.[62] In ecological studies of cancer mortality rates in the United States,[22,23] solar UVB was inversely correlated with several cancers for black Americans; however, the latitudes with similar mortality rates for cancers such as breast and colon were several degrees lower for black Americans than for white Americans.[7] In the Health Professionals Follow-Up Study, black American men with additional risk factors for poorer vitamin D status had a much higher cancer incidence (relative risk = 1.57; 95% CI, 1.16–2.11) and mortality risk (relative risk = 2.27; 95% CI, 1.57–3.28).[60]

For four types of cancer, UVB and/or vitamin D has directly correlated with incidence or mortality rates: esophageal, pancreatic and prostate cancer, as well as NHL. We now examine such studies to see whether they contradict the UVB—vitamin D—cancer theory.

Two studies reported that vitamin D was directly correlated with incidence of esophageal squamous dysplasia[63] and esophageal cancer[64] in Linxian, China, a population at high risk for developing esophageal squamous cell carcinoma. Human papillomavirus is an important risk factor in regions with high esophageal cancer rates in China.[65,66] Human papillomavirus is also linked to risk of NMSC and UVB irradiance.[67] The finding that higher vitamin D correlated with increased risk of esophageal cancer for men but not women in China[64] is consistent with men working out of doors more.

Several studies have found an inverse correlation between indices for solar UVB and/or vitamin D and pancreatic cancer.[10,26,27,34,35,68] However, a study of male Finnish smokers, aged 50–69 years at baseline, found that higher serum 25(OH)D at baseline was associated with a threefold increased risk of pancreatic cancer during an up to 16.7-year follow-up period (highest versus lowest quintile, >26.2 ng/mL versus <12.8 ng/mL; odds ratio, 2.92; 95% CI, 1.56–5.48; p_{trend} = 0.001).[69] With many articles reporting a beneficial role of UVB and vitamin D, perhaps some unusual factors in Finland affected the Finnish study.

Prostate cancer mortality rates have a different geographical variation in the United States from that of the preceding 12 types of cancer. It has high mortality rates across the entire northern United States

and low rates in all southern states. Prostate cancer is also unusual for vitamin D-sensitive cancers in that prediagnostic serum 25(OH)D has generally been found uncorrelated with incidence of prostate cancer;[70] however, it has also been found associated with increased risk[29,71] and decreased risk.[29,72] However, early life UVB is protective,[73] as is UVB around the time of cancer discovery,[74] suggesting that vitamin D may inhibit metastasis. Ecologic studies have consistently found an inverse correlation of prostate cancer with latitude.[75] Grant hypothesized that the geographic variation of prostate cancer mortality rates in the United States is related to a viral risk that is more common in winter and that higher serum 25(OH)D levels in winter reduce the risk of such infections.[76,77] An ecologic study determining that prostate cancer is diagnosed more often in winter supports this hypothesis.[78] Stat3 is involved in prostate cancer metastasis.[79] Grant showed that vitamin D can block Stat3, which might explain why vitamin D is beneficial once prostate cancer is discovered.[80]

Solar UV has been correlated with risk of NHL in the United Kingdom.[81] However, further study determined that other factors, such as economic status, were probably confounders.[82] The most recent analysis concludes that UVB irradiance reduces the risk of NHL.[58]

Evidence that vitamin D reduces the risk of lung cancer is limited. An observational study of early-stage non-small-cell lung cancer (NSCLC) associated higher serum 25(OH)D levels with increased survival.[83] However, in advanced NSCLC, survival depended on vitamin D receptor alleles rather than on circulating serum 25(OH)D levels.[84] In Norway, there is no survival advantage for discovery of NSCLC in summer or fall compared with winter or spring.[13] In an ecological study involving 111 countries, lung cancer was inversely correlated with indices of solar UVB.[39] However, this study did not consider dietary factors, which may have affected the finding because dietary fat seems to be a risk factor for lung cancer.[85] A recent cohort study in Finland found serum 25(OH)D level was inversely associated with lung cancer incidence for women (RR, 0.16; 95% CI, 0.04–0.59; P(trend) < 0.001) and younger participants (RR, 0.34; 95% CI, 0.13–0.90; P(trend) = 0.04) but not for men (RR, 1.05; 95% CI, 0.59–1.82; P(trend) = 0.81) or older individuals (RR, 0.92; 95% CI, 0.50–1.70; P(trend) = 0.79).[86] Thus, there is modest evidence that higher serum 25(OH)D levels confer protection against lung cancer.

Melanoma is an interesting cancer with respect to UV irradiance and vitamin D. Studies have found good evidence that UVA, not UVB, is the primary risk factor for melanoma.[87-92] Also, good evidence exists that vitamin D reduces the risk of melanoma,[93] including findings related to diet,[94] sunlight,[95] NMSC,[26] blocking solar UVB[92] and vitamin D receptor alleles.[96] Also, melanoma mortality rates increase with increasing latitude in Europe,[97] which reflects an effect of skin pigmentation, UVA and UVB.[87] UVA is also a double-edged sword in that it also produces elastosis, which reduces the risk of melanoma as evidenced by melanoma's developing later in life on the face and neck rather than on the trunk and legs.[98] Smoking also produces elastosis, which seems to explain why smokers have a reduced risk of developing melanoma.[56]

Specificity (one agent, one result). Specificity (one agent, one result) does not apply to vitamin D because it has benefits for many types of disease ranging from cardiovascular diseases to infectious diseases.[99,100]

Temporality (exposure precedes effect). Temporality (exposure precedes effect) is generally satisfied. However, a topic of ongoing research is the time lag between vitamin D increases and cancer risk reduction. Cancer can take anywhere from several years to several decades to progress from initiation to clinical detection or death. Vitamin D could play a role in reducing cancer initiation, such as for cancers linked to viruses (Epstein-Barr virus [EBV]) for Hodgkin's lymphoma, and probably for several others.[76] As mentioned, early life UVB irradiance was inversely correlated with prostate cancer risk.[73]

Vitamin D also seems to play an important role late in the development of cancer. The vitamin D and calcium randomized, controlled trial by Lappe et al.,[12] found a 77% reduction in all-cancer risk for postmenopausal women between the ends of the first and fourth years, of which 35% was attributed to vitamin D. Because most cancers take 15–20 years to proceed from initiation to clinical detection, this study is consistent with an important role in cancer prevention at the later stages of development, possibly through antiangiogenesis[101] and antimetastasis[102] mechanisms. The series of studies in Norway finding increased survival rates for those diagnosed with cancer in summer or fall compared with winter or spring for breast cancer, colorectal cancer, prostate cancer and Hodgkin's lymphoma[13] also support the role of vitamin D late in cancer. Some observational studies also reported increased survival rates associated with higher serum 25(OH)D levels, as for colorectal cancer[103] and breast cancer. In a study of postmenopausal Canadian women, distant disease-free survival during a period of up to 17 years was significantly worse in women with prediagnostic deficient (<20 ng/mL) versus adequate (>29 ng/mL) serum 25(OH)D levels (hazard ratio [HR] = 1.94, 95% CI, 1.16–3.24; p = 0.02], as was overall survival (HR = 1.73, 95% CI, 1.05–2.86; p = 0.02).[104]

Biological gradient (dose-response relation). Demonstrating a dose-response relation, preferably linear, between vitamin D and cancer risk is important for supporting vitamin D's beneficial role. Meta-analyses of case-control data have determined dose-response relations for serum calcidiol levels and incidence of breast and colon cancer. For colorectal cancer, a 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level of at least 33 ng/mL compared with 12 ng/mL or less.[55] For breast cancer, a meta-analysis found that serum 25(OH)D of approximately 52 ng/mL had 50% lower risk of breast cancer than those with a serum level less than 13 ng/mL.[54] However, the dose-response relation in Abbas et al.,[57] was similar to that for colorectal cancer.

Many vitamin D supplementation studies found no benefit in reducing the risk of cancer from using too little vitamin D, generally about 400 IU/day, as reviewed in Grant and Garland.[18] Even the Women's Health Initiative study, started in the mid-1990s, used too little vitamin D (400 IU/day) and generally found no benefit for colorectal cancer,[20] hip fractures[19] or diabetes.[21] However, there was a positive finding for colorectal cancer when estrogen therapy was also considered.[105]

Some evidence now exists that the vitamin D dose–cancer response relation for breast cancer is nonlinear, with a threshold effect at about 20 ng/mL.[57] This finding may help explain why 400 IU/day seemingly has no effect on cancer rates. Evidently serum vitamin D metabolites are used for an endocrine mechanism (regulation of calcium absorption) before they are used for autocrine mechanisms (facilitation of gene expression).[106]

Plausibility. The mechanisms whereby vitamin D reduces the risk of cancer are generally well known. These mechanisms include effects on cells such as improved differentiation and apoptosis, as well as effects at the tumor level such as antiangiogenesis[101] and antimetastasis.[102] One can find thorough reviews in several reports.[107-110]

Grant recently proposed that vitamin D, through strengthening the innate immune system, reduces the risk of viral infections that lead to cancer. The basis for this hypothesis was that the prostate cancer mortality rate distribution in the United States varies with latitude in a manner similar to that for multiple sclerosis. EBV is an important risk factor for multiple sclerosis.[111] EBV has also been associated with gastric, prostate and thyroid cancer, as well as Hodgkin's lymphoma and NHL, with references given in Grant.[76] These cancers, as well as testicular cancer and multiple myeloma, have the square of latitude correlated with mortality rate for 1950–1969, and some do for 1970–1994. Because latitude is an index of wintertime vitamin D production from solar UVB irradiance, and winter is the period of many viral infections such as EBV[112] and influenza,[113] this hypothesis is reasonable. Evaluating this hypothesis will, of course, require more work.

Coherency (no serious conflict with the generally known facts of the natural history and biology of the disease). Coherency is generally satisfied. However, it may not be useful because the Koch and Hill criteria may be more directly related to increased risk due to an agent rather than decreased risk due to a preventive agent.

Experiment. For the association between UVB and vitamin D, experimentation in general means a randomized, controlled trial. Two such trials were successful. In one, the primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence.[12] The subjects were 1179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged more than 55 years in a nine-county rural area of Nebraska centered at latitude 41.4° N. Subjects were randomly assigned to receive 1400–1500 mg of supplemental calcium/day alone (Ca only), supplemental calcium plus 1100 IU of vitamin D3/day (Ca + D), or placebo. Between the end of the first and fourth years, those taking both calcium and vitamin D had a 77% lower all-cancer incidence than those taking the placebo. Thirty-five percent of the cancer risk reduction was attributed to vitamin D, with the rest to calcium.

Because of the study's short duration, one might question the Lappe et al.,[12] study. However, a response might be that vitamin D is much more effective in reducing the risk of cancer in the later stages than in the earlier stages, unless through combating infections that could lead to cancer. Survival for breast, colorectal and prostate cancer and Hodgkin's lymphoma in Norway is better for those diagnosed in summer or fall rather than winter or spring,[13] thereby providing evidence for a greater benefit at the later stages of disease.

In a reanalysis of results of 400-IU/day vitamin D supplementation in the Women's Health Initiative Study, among women concurrently assigned to placebo arms of the estrogen trials, calcium plus vitamin D indicated suggestive benefits (HR = 0.71, 95% CI, 0.46–1.09; $p_{\text{estrogen interaction}} = 0.018$).[105]

Another line of experimental verification is to study the role of vitamin D on cancer by using animal models.[114-116] For example, in a colon cancer xenograft experiment, vitamin D metabolites slowed tumor growth.[117]

Analogy with other causal relationships. Analogy is a double-edged sword for vitamin D and risk of cancer incidence or mortality rate. On the positive side, I used the principle of analogy when I viewed the *Atlas of Cancer Mortality in the United States, 1950–94*.[7] Many cancers had geographical variations in mortality rate similar to those of cancers well known to be vitamin D sensitive, such as breast and colon cancer. I concluded that most of them were, therefore, also vitamin D sensitive.[22]

On the negative side, some studies have suggested that various vitamins reduce the risk of cancer only to learn after randomized, controlled trials that they did not. The best known case is that of beta carotene. Early studies of beta carotene found an inverse relation for lung cancer with respect to dietary intake for smokers[118] and nonsmokers.[119] However, when beta carotene supplements were taken, smokers had increased risk of lung cancer.[120] For beta carotene, it was one component of vegetables in the diet; as far as is known, vitamin D production is the only beneficial effect of solar UVB irradiance.

Response to Criticisms of the Ecological Approach

At a World Health Organization meeting in Munich in 2005, dermatologists expressed their opinion that ecological studies using solar UVB doses as the index of vitamin D were perhaps incorrect in that irradiance was not always correlated with dose. That statement spurred Grant to find a personal index of solar UVB irradiance. Because integrated lifetime UVB irradiance is the primary risk factor for squamous cell carcinoma (SCC), it seemed that incidence or death from SCC would be a suitable marker for long-term UVB irradiance. Basal cell carcinoma (BCC) is linked to both UVB and UVA irradiance, so it is also a useful index; however, melanoma is linked to UVA irradiance,[121] so it is not a useful indicator. The first report in this series was a meta-analysis of studies of second cancer after development of BCC, SCC or melanoma.[122] The studies had to be adjusted according to smoking among each population because smoking is a risk factor for both BCC and SCC but reduces the risk of melanoma.[123] Several cancers had incidence rates inversely correlated with BCC and/or SCC when adjusted for smoking. This study led to an ecologic study of cancer mortality rates in Spain that used NMSC as the index of solar UVB irradiance.[26] A total of 17 types of cancer were inversely correlated with NMSC in a linear regression analysis. However, when latitude and lung cancer mortality rate, the index used for smoking, were used with NMSC in a multiple linear regression analysis, bladder and renal cancer were no longer significantly correlated with NMSC.[59] Then a study of solid tumor development after diagnosis of BCC, SCC or melanoma for sunny and less sunny countries was reported.[29] For three countries equatorward of 40°, incidence of solid tumors is reduced after diagnosis of BCC or SCC, whereas for countries poleward of 40°, incidence is increased. The interpretation is that in the sunny countries, people can expose enough skin to produce sufficient vitamin D to reduce the risk of cancer, whereas in the less sunny countries, not enough skin is exposed.[124]

Summary and Conclusion

The solar UVB—vitamin D—cancer theory now satisfies most, if not all, of the criteria for causality in a biological system as initially postulated by Robert Koch and expanded by A. Bradford Hill. Thus, from a scientific point of view, vitamin D reduces the

risk of developing many types of cancer and increases survival once cancer reaches the detectable stage. Unfortunately, health policy often lags scientific discoveries by years to decades. An example from the mid-19th century was the discovery by Ignaz Semmelweis that doctors carried germs from autopsies to women giving birth and infected them, resulting in puerperal sepsis.[125] A more recent example is the announcement by Barry Marshall and Robin Warren that *Helicobacter pylori* caused stomach ulcers. Although Marshall infected himself with *H. pylori* in 1981 and developed an ulcer,[126] he concluded by 1995 that Koch's postulates were not well satisfied.[127] However, in 2005, Marshall and Warren were awarded the Nobel Prize in Medicine. It is hoped that the acceptance of the beneficial role of vitamin D in reducing the risk of cancer and many other diseases will not have to wait much longer. It is encouraging that the National Academy of Sciences' Institute of Medicine (http://www.iom.edu) is embarking on a 2-year study of vitamin D dietary requirements and is expected to issue a report in October 2010.

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