

## **Comparisons of Estimated Economic Burdens Due to Insufficient Solar Ultraviolet Irradiance and Vitamin D and Excess Solar UV Irradiance for the United States**

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William B. Grant, Ph.D.,  
Sunlight, Nutrition and Health Research Center (SUNARC)  
2107 Van Ness Avenue, Suite 403B  
San Francisco, CA 94109-2529, USA  
wgrant@sunarc.org  
www.sunarc.org

Cedric F. Garland, Dr.P.H.  
Professor  
Department of Family and Preventive Medicine  
University of California, San Diego  
9500 Gilman Drive, 0631C  
La Jolla CA 93093, USA  
cgarland@ucsd.edu

Michael F. Holick, Ph.D., M.D.  
Vitamin D, Skin and Bone Research Laboratory  
Professor  
Section of Endocrinology, Diabetes, and Nutrition  
Department of Medicine, Boston University Medical Center  
Boston University School of Medicine  
715 Albany Street, Boston, MA 02118  
mfholick@bu.edu

*Abbreviations:* B, billion ( $10^9$ ); CMM, cutaneous malignant melanoma; KC, Korean Conflict; M, million ( $10^6$ ); MR, mortality rates; MS, multiple sclerosis; NMSC, non-melanoma skin cancer; RR, risk reduction; SPF, sun protection factor; SUNARC, Sunlight, Nutrition and Health Research Center; Th1, T helper cells 1; U.K., United Kingdom; U.S., United States of America; UV, ultraviolet; UVA, ultraviolet A (315-400 nm); UVB, ultraviolet B (290-315 nm); UVR, ultraviolet radiation (290-400 nm); VDR, vitamin D receptors; WWII, World War II;  $1,25(\text{OH})_2\text{D}_3$ , 1,25-dihydroxy; vitamin  $\text{D}_3$ ,  $25(\text{OH})\text{D}$ ; 25-hydroxyvitamin D.

## **Abstract**

Vitamin D sufficiency is required for optimal health, and solar ultraviolet B (UVB) irradiance is an important source of vitamin D. UVB and/or vitamin D have been found in observational studies to be associated with reduced risk for over a dozen forms of cancer, multiple sclerosis, osteoporotic fractures, and several other diseases. On the other hand, excess UV irradiance is associated with adverse health outcomes such as cataracts, melanoma, and nonmelanoma skin cancer. Ecologic analyses are used to estimate the fraction of cancer mortality, multiple sclerosis prevalence, and cataract formation that can be prevented or delayed. Estimates from the literature are used for other diseases attributed to excess UV irradiation, additional cancer estimates, and osteoporotic fractures. These results are used to estimate the economic burdens of insufficient UVB irradiation and vitamin D insufficiency as well as excess UV irradiation in the United States for these diseases and conditions. We estimate that 50,000–63,000 Americans die prematurely from cancer annually due to insufficient vitamin D, and 19,000–25,000 in the United Kingdom. The U.S. economic burden due to vitamin D insufficiency from inadequate exposure to solar UVB irradiance, diet, and supplements is estimated at \$40–56 billion in 2004, whereas that for excess UV irradiance is estimated at \$6–7 billion. These results suggest that increased vitamin D through UVB irradiance, fortification of food and supplementation could reduce the health care burden in the U.S., U.K., and elsewhere. Further research is required to confirm these estimates.

## **Introduction**

There is rapidly mounting evidence that vitamin D has many important health benefits and that adequate serum levels of 25-hydroxyvitamin D (25(OH)D) are required for optimal health (1–12). There are also studies indicating that solar ultraviolet B (UVB) exposure is the primary source of vitamin D for most people outside the near-polar regions (13). However, despite this evidence, public health leaders have been slow to accept the role of solar UVB irradiance and vitamin D in maintaining optimal health, in part because of widespread concern regarding the risk of cutaneous malignant melanoma (CMM) and nonmelanoma skin cancer (NMSC) due to solar UV irradiance.

In this study, we estimate the economic burden of insufficient solar UVB irradiance and vitamin D in the United States and compare this estimate with the economic burden from excess UV irradiation over either short (sunburning) or long periods. The approach is to consider diseases for which a strong geographic variation in the United States can be identified for disease outcome and to then use these variations to estimate the fraction of the disease burden in the United States that can be attributed to insufficient UVB irradiance and/or vitamin D or to excess solar UV irradiance. For some diseases that are linked to vitamin D deficiency but for which geographical variations are not apparent within the United States, results in the literature are used. Following that, the results for the United States are extrapolated to the United Kingdom.

## **Materials and Methods**

The diseases for which economic burdens due to insufficient solar UVB irradiance and/or vitamin D are estimated are cancer, multiple sclerosis (MS), and osteoporotic bone fractures; those diseases related to excess UV irradiance are actinic keratosis, cataracts, CMM, and NMSC. For some diseases, the links between UVB and vitamin D are well known, but it is difficult to quantify either the economic burden of the disease in the United States or the dose–response relationship for vitamin D. Such diseases include rickets and tuberculosis and possibly MS; however, there is such a strong increase of MS prevalence with latitude that an estimate of the effect of vitamin D can be made. For several other diseases, the links are considered too preliminary. Such diseases include type 1 and 2 diabetes mellitus, as well as rheumatoid and osteoarthritis. Likewise, there are diseases for which UV irradiance has acute adverse health effects but that are, again, difficult to quantify. Such diseases include systemic lupus erythematosus (14) and systemic immunosuppression (15). It was assumed that omission of such diseases from the analysis would not substantially affect the evaluation of health benefits and risks of solar UVB irradiance in this work.

### Ecologic approach

The ecologic approach is used to estimate the quantitative link between solar UV irradiance and disease outcome for several diseases in this paper. In the ecologic approach, populations defined geographically by state are treated as entities, and average values for disease outcomes and potentially influencing factors for each population are used. The strengths and limitations of the ecologic approach have been reviewed (16-18). The primary strengths are that data for the analysis are generally available and that the analysis can be conducted rather quickly and inexpensively. The primary weaknesses are that the

associations found for the population as a whole may not apply to individuals, and that unmodeled factors may, in fact, drive the association. This effect is called the “ecologic fallacy.” The association between dietary fat and risk of breast cancer, identified in an ecologic study in 1975 (19) is often offered as an example of the ecologic fallacy since cohort studies generally fail to confirm the link. A more recent ecologic study found that the fraction of energy derived from animal products appears to be a better explanation of the diet-breast cancer link in multi-country ecologic studies (20), and suggests that insulin-like growth factor-I (IGF-I) is one of the likely mechanisms, although endogenous estrogen production probably contributes as well. Generally, associations are examined between suspected risk or protective factors and disease outcomes. Once associations are found, further analyses are conducted to determine whether the associations satisfy standard criteria for causality described by A. B. Hill in 1965 (21).

Although the ecologic approach is considered more useful in generating hypotheses than determining causality (22), it is noted that the approach has been used to make many of the first identifications of important dietary, environmental, and lifestyle links to chronic diseases that were confirmed years later using other epidemiologic approaches.

Successes of the ecologic approach for identifying and quantifying risk-modifying factors other than solar UV irradiance (discussed later) include identifying dietary factors affecting risk of Alzheimer’s disease (23), sweeteners (added sugars) as a risk factor for coronary heart disease for women but not men (24), and omega-3 fish oils as a risk reduction factor for bipolar disorder (25). Most of these findings have been well supported in subsequent independent studies. However, ecologic study findings regarding

diet are not always confirmed by other observational epidemiologic studies, which could be due, in part, to the design of the subsequent studies and limitations when trying to study one component of a complex system (26).

Thus, we are confident that the ecologic approach, when carefully applied, can be used to the quantification of risk or risk reduction for chronic disease through UV irradiance with a reasonable degree of accuracy. However, the results presented here should be considered preliminary pending the outcome of further research.

## Cancer

Cancer mortality rates in the United States have large geographic variations, with rates for some common cancers approximately twice as high in the Northeast than the Southwest (27). The Atlas of Cancer Mortality Rates (27) has data for two periods: 1950–69 and 1970–94. The reason for using the analysis for the period 1950–69 is that during that period the effect of solar UVB irradiance had a much larger effect on cancer mortality rates than during the period 1970–94. Fewer people lived in urban centers and, thus, spent more time out of doors. A recent paper highlighted this effect for breast cancer, showing that breast cancer mortality rates for women aged 65–79 years increased in the South and West by 5%–10% between the 1960s and 1970s and by 12%–15% between the 1970s and 1980s while increasing only 5%–6% per decade in the Northeast (28).

Solar UVB irradiance was used as the primary surrogate for vitamin D variation in the population since it appears to be the strongest determinant of geographical variation in serum 25(OH)D levels in the United States (29). Variations in serum 25(OH)D levels in the United States are related to solar UVB irradiance: for example, summertime values in Boston are up to 30% higher than wintertime values (30). Although dietary sources of vitamin D are important, there is no indication that dietary factors vary geographically throughout the United States in the amount required to explain the large regional variations in cancer mortality rates (31). Also, a review of vitamin D and risk of colorectal cancer found that dietary vitamin D was generally not associated with reduced risk of colorectal cancer, although higher values of total vitamin D intake and/or production of 25(OH)D were (32).

DNA-weighted UVB data for July 1992 derived from Total Ozone Mapping Spectrometer (TOMS) measurements (33) were averaged by state. DNA-weighted UVB is defined as that portion of the UV radiation reaching the earth's surface that directly alters DNA. This spectral region peaks near 300 nm, which is very similar to the spectral region important for vitamin D production. UVB radiation is absorbed by ozone, and column ozone is lower west of the Rocky Mountains (34) because the prevailing westerly winds push the lower stratosphere higher on that side. In addition, UVB is attenuated somewhat by molecular scattering, so the higher surface elevation west of the Rocky Mountains increases the amount of UVB reaching the surface. Thus, UVB has a skewed distribution, highest in the Southwest, lowest in the Northeast. Although UVB irradiance

throughout much of the year contributes to vitamin D production, the July DNA-weighted UVB data provide a convenient index.

A second index used for solar UVB-produced vitamin D is latitude. It is taken as an index of serum 25(OH)D levels in winter in response to late summer-to-autumn UVB irradiance since serum 25(OH)D has a residence half time of 2 weeks and solar UVB irradiance is the primary source of vitamin D for most Americans (10).

In addition, several other risk-modifying factors are also included: degree of urbanization, alcohol consumption, Hispanic heritage, lung cancer (a proxy for the health effects of smoking), and fraction of the population living below the poverty level (Grant and Garland, in preparation).

While the regression models are being developed for 18 types of cancer (Grant and Garland, in preparation), for the purposes of this analysis, a model is developed here for the “vitamin D-sensitive cancers.” Vitamin D cancers identified in these studies are bladder, breast, cervical, colon, esophageal, gallbladder, gastric, laryngeal, ovarian, pancreatic, prostate, rectal, renal, uterine corpus cancer and both Hodgkin’s and non-Hodgkin’s lymphoma. Once the model is developed, the method used to assign the fraction of mortality or prevalence rates to UVB production of vitamin D is as follows. The regression model is used to determine the lowest mortality rate as a function of UVB and degree of urbanization for the vitamin D-sensitive cancers. Assuming that the population is uniformly distributed along the regression model, the average difference

between the regression model and the minimum divided by the minimum regression value is taken as the maximum possible fraction of the mortality rate that can be considered premature. This fraction is multiplied by the adjusted  $R^2$  for the model to account for factors not included in the model.

We estimate the vitamin D consumption and requirements for cancer risk reduction as follows. The data on risk of colorectal cancer are the most robust (32). Three studies that reported odds ratios for oral intake of more than 600 IU/day (international units [ $5 \mu\text{g} = 40 \text{ IU}$ ]) (36–38) were used. From studies on vitamin D consumption among nurses and male health professionals in cohort studies (39), it is estimated that the mean intake of vitamin D at ages 50 years and older is approximately 320 IU/day in the United States, with about 200 IU/day coming from dietary sources (40).

#### Multiple sclerosis

For MS, the primary data used were for U.S. veterans at the time of enlistment for World War II (WWII) (1941–46) and the Korean Conflict (KC) (1950–55) (41,42). Case–control ratios were determined for each of the 48 contiguous states plus the District of Columbia. California was divided into northern and southern regions. Although veterans of several races and both sexes were included in these studies, only the data for white males were included in this analysis.

Since the U.S. data extend only to just below  $30^\circ$  from the equator, they may not adequately represent the effects of solar UVB in reducing the risk of MS. To address this

problem, we also considered data for Australia that extend to 19° from the equator (43). The prevalence data were obtained from surveys conducted in 1981 and based on populations as of June 30, 1981 (44). The crude observed prevalence varied from 11.1 per 100,000 in tropical Queensland (19° S) to 74.2 per 100,000 in Hobart (Tasmania) (43° S).

#### Osteoporotic fractures

Information on the effect of vitamin D in reducing the risk of osteoporotic fractures was obtained from several sources (39,45–49). Some of the studies are based on short-term supplementation studies. Such studies would indicate a lower bound for the benefits of vitamin D in reducing osteoporotic fractures.

#### Cataracts

Data on the latitudinal increase in risk of cataract formation were taken from Javitt and Taylor (50). The earlier results (50,51) have been supported in more recent studies (52,53). Cataract formation is increased by free radicals (54), and solar UV is an important source of free radicals in the eye.

#### Melanoma and NMSC

Solar UV irradiance is considered to be the most important cause of skin cancer, both CMM and NMSC (55,56). Data used to estimate the effect of solar UV irradiance on CMM and NMSC rates in the United States were obtained from the Atlas of Cancer Mortality Rates (27). Information on other factors affecting CMM was obtained from

Millen et al. (57). However, risk of CMM is a complex function of solar UV irradiance: painful sunburns before the age of 20 years are associated with an increased risk of CMM and the development of its precursors, melanocytic nevi and atypical nevi, but higher total lifetime irradiance to solar UV is associated with reduced risk of CMM in countries where people are living in their ancestral homelands (58,59) or at similar latitudes (60).

#### Economic burden

The total economic burdens for these diseases were obtained from the literature (61–69). Both direct and indirect costs are included. The direct costs are generally those of medical and surgical treatments. In some cases, the costs of prevention are also included. The indirect costs include, e.g., loss of ability to work, loss of life, and uncompensated caregiving by friends and relatives. Since a number of the estimates were made several years ago, the burdens were increased at a compound rate of 7% per year to obtain estimates for 2004 (70–72).

## **Results**

### Cancer

The multiple linear regression model result for cancer mortality rates (MR) was based on work that forms the basis of a manuscript in preparation. The factors used are UVB in the July 1992 DNA-weighted UVB (33), lung cancer mortality rate, LungC, for males or females for the period 1950–69 (27), the ethanol consumption rate for 1960–2, Alc60, (73), and the percent urbanization for 1960, Urb60 (74). All values are statewide averages. A recent paper reported that lung cancer was an excellent index of the risk of

smoking for cancers other than lung for black American males (75). Taking the square root (SR) reduces the influence of extreme values in a small data set. The results for white Americans for the period 1950–69 are:

$$\text{SR}(\text{MR}(\text{males})) = 10.3 - 0.28 \times \text{UVB} + 0.16 \times \text{Alc60} + 0.022 \times \text{LungC} + 1.65 \times \text{Urb60}$$

(adjusted  $R = 0.84$ ,  $p < 0.001$ )

$$\text{SR}(\text{MR}(\text{females})) = 10.5 - 0.29 \times \text{UVB} + 0.052 \times \text{Alc60} + 0.013 \times \text{LungC} + 1.17 \times \text{Urb60}$$

(adjusted  $R = 0.85$ ,  $p < 0.001$ )

Figures 1 and 2 show the results for white Americans. White Americans including those considered Hispanic of any race make up approximately 88% of all Americans (76). Black Americans represent about 12% of Americans and have a reduced ability to produce vitamin D from solar UVB irradiance because of the screening effect of skin melanin.

### Multiple sclerosis

A quadratic regression of MS with latitude was found to yield the best result. Latitude is assumed to be an index of wintertime vitamin D status as determined by serum 25(OH)D levels. As the solar zenith angle declines in the fall, the ability to produce vitamin D from solar UVB decreases, giving way to a vitamin D winter—i.e., a period when vitamin D

cannot be synthesized in the skin by exposure to solar UVB. The vitamin D winter is 4–5 months long in Boston (77). Serum 25(OH)D levels decline by 60% in 1–2 months.

The results are given in Figure 3. The prevalence of MS at time of entry by men into the armed forces during the period 1941–55 at high latitudes is four times that for low latitudes. A very similar result is given in Fig. 1 of van der Mei (43) for age-adjusted MS prevalence versus latitude in Australia for males and females combined. At 30° S, corresponding to Miami, FL, the prevalence is 22 cases/100k, whereas at 43° S, corresponding to Portland, ME, the prevalence is 75/100k. If it is assumed that all cases above the 30° S line could have been prevented in the United States from UVB alone, that is 55% of the cases. At 18° S, the prevalence is 13%. Assuming that this value represents the maximum effect of vitamin D, another 8% of the cases could have been prevented.

### CMM and NMSC

Although solar UV irradiance is a major contributing factor to CMM and NMSC, there are also other factors that play a role in the risk for death from CMM and NMSC, such as diet (57), skin type and sunburning (58), use of sunscreen (78), smoking (79), ionizing radiation therapy (80), and treatment (81). Improved screening for CMM and NMSC is estimated to have marginal utility in the United States (82). Thus, the fraction of risk for solar UV irradiance for CMM and NMSC is taken as 75%–95%.

### Cataracts

The prevalence of cataracts was reported to increase at a rate of 3% for each degree of latitude to the south (50). From this dependence, it can be calculated that 20% of cataracts in the United States can be attributed to UV doses. The estimate assumes that the population is fairly uniformly distributed with latitude from Miami (26° N) to Bangor, Maine (45° N) and that the fraction of cataract cases above the minimum at high latitudes is due to UVB irradiance. However, since the mean center of population is near 38° N, 20% is likely an underestimate. A value of 25% will be used for the economic burden estimate.

#### Risk reduction from vitamin D from diet and supplements

Many people in the United States do not get sufficient vitamin D from solar UVB irradiation. These groups include darker-skinned individuals, many urbanites, and those living primarily indoors, such as the institutionalized elderly. Therefore it is worthwhile to also consider the likely reduction in chronic disease possible by increasing the amount of vitamin D obtained orally.

For cancer, several cohort studies reviewed in Grant and Garland (32) can be used (36–38). The risk reductions (RRs) were about 0.5 for the highest quintile of intake (>600 IU of vitamin D/day) compared with the lowest intake (<150 IU/day). Estimates of colon cancer risk reduction based on stored serum 25(OH)D levels yielded similar results. Plotting 150 and 600 IU/day versus RRs of 1.0 and 0.54, respectively, gives an estimate of RR of 0.85 for 320 IU/day—assumed to be the average older American oral consumption value compared with 600 IU/day. Thus, those consuming more than 600 IU

of vitamin D per day should have a 0.3 reduction compared with the average. Assuming a linear range of vitamin D consumption versus fraction of the population, we estimate that there would be a 15% reduction in colon cancer mortality rates if the population average consumption were more than 600 IU of vitamin D/day. From regression models for colon cancer and vitamin D-sensitive cancers for the period 1950–69, it appears that the results for all vitamin D-sensitive cancers is about 60% of that for colorectal cancer. This factor would give a population average reduction of vitamin D-sensitive cancers from consumption of vitamin D of 10%. On the other hand, the cancer risk reduction for higher daily consumption of vitamin D likely increases at least to 1000 IU/day. Thus, we estimate that there would be a total of 30% reduction of the vitamin D-sensitive cancer mortality rates from a combination of UVB irradiance as experienced in the period 1950–69 plus vitamin D consumption in food and supplements. This is likely an underestimate, but until better data are available, we will use this estimate.

For osteoporotic hip fractures, one study reported a 37% lower risk for those consuming 500 IU vitamin D/day than for 140 IU/day (39). However, adequate calcium intake is also required for optimal bone health (83). Those who are homebound or live in nursing homes have very low serum 25(OH)D levels (46,47) and have very high osteoporotic hip fracture rates (48). Several studies have shown that vitamin D supplementation can reduce the risk of such fractures by up to 50% (47).

Based on the low serum 25(OH)D values generally found in the institutionalized elderly, who account for most osteoporotic fractures, it is estimated that adequate vitamin D and calcium intake would result in a 50%–70% reduction in osteoporotic fracture rates.

#### Economic burden data

The next step is to determine the total economic burdens in the United States of diseases related to suboptimal amounts of UVA, UVB, and vitamin D. The determinations are in terms of 2004 dollars. The total economic burden data are given in Tables 1 and 2.

#### Economic burden due to insufficient UVB in the United States

##### Cancer

For the vitamin D–sensitive cancers, premature cancer deaths due to insufficient UVB irradiance represented 13% of cancer mortality rates for the period 1950–69 for white Americans. The estimated economic burden is \$10–15 billion (Table 3).

##### Multiple sclerosis

For MS, the results from U.S. veterans enlisting in WWII and the Korean Conflict (41,42) indicate that approximately 50% can be attributed to living at a latitude higher than 30° N. However, the results from Australia indicate that MS rates continue to decline toward the equator (43). If people in the United States could achieve a serum 25(OH)D level in winter similar to that of people living at 18° S in Australia, 70% of MS might be prevented. This additional reduction will be attributed to vitamin D intake. It is also noted that the latitudinal dependence of MS prevalence is consistent with wintertime

values of serum 25(OH)D levels since in the United States there is a large difference between summertime UVB and latitude as shown by the TOMS data (33). In fact, for children living in Tasmania, Australia (41°–43° S), wintertime exposure to solar UVB radiation was a more important factor than summertime exposure for reducing the adult risk of MS (84).

#### Economic burden due to insufficient ingested vitamin D

Vitamin D from diet and supplements also plays an important role in reducing the risk of cancer, especially at the higher intake levels (32). It has been shown that intake of more than 600 IU/day of vitamin D is associated with a 46% risk reduction for colon cancer versus less than 150 IU/day (32). However, because these reductions were determined during the 1980s, when Americans were evidently not getting as much UVB irradiance as they had in the period 1950–69 (Grant and Garland, in preparation), they cannot be used independent of data for the effect of UVB irradiance for 1970–94 in reducing the risk of cancer.

Assuming that the average American ingests 320 IU of vitamin D/day, there would be about a 30% reduction in risk for non–lung cancer mortality rates if everyone not getting adequate solar UVB irradiance consumed more than 600 IU/day. However, we note that an optimal vitamin D intake is probably closer to 1000 IU/day (25µg) or more in the absence of UVB irradiance (85–90). This intake level of vitamin D would be most helpful in the times of the year when it is difficult to produce vitamin D from solar UVB radiation and for those who spend no time in the sun. This value would greatly increase

the protective effect of vitamin D; a linear extrapolation leads to an estimate of an RR of 0.2, or a reduction of the population-mean RR by 0.65. However, a linear extrapolation is likely an overestimate, and the differences in UVB irradiance for the two periods must also be considered. For a conservative estimate, we will assume that a national policy of more than 600 IU/day of vitamin D for those not getting vitamin D from solar UVB radiation, if put into practice, would decrease vitamin D-sensitive cancer rates by an additional 10%, with an estimated range of 5%–10%. This would result in a savings of \$5–9 billion/year. However, it cannot be ruled out that vitamin D consumption would not reduce the number of cancer deaths at all compared with the situation in the period 1950–69 when people routinely got much more UVB irradiance. Note that vitamin D may also reduce the risk of lung cancer (91,92). Given the \$60 billion economic burden for lung cancer, any benefit here would greatly increase the estimate.

#### Multiple sclerosis

For MS, a value of 10% reduction in risk is assumed in addition to that estimated if all people in the United States had the UVB doses corresponding to the lower latitudes in the United States or Australia, resulting in a savings of \$2 billion/year.

#### Osteoporotic fractures

Several studies indicate that vitamin D supplementation can reduce the risk of falls in nursing homes by up to 50% in short-term trials (47,93). Both bone health and neuromuscular function benefit from vitamin D (94–96). We assume that long-term adequate intake of vitamin D and calcium should be able to reduce the risk of

osteoporotic fractures by 50%–70% if not more, resulting in a savings of \$19–26 billion/year.

#### Economic burden summary

Economic burden summary results are summarized in Table 4. The additional reduction in economic burden of chronic disease due to inadequate vitamin D is estimated at \$25–36 billion. When combined with the estimate for UVB (\$15–20 billion), the total economic burden due to vitamin D insufficiency from UVB, diet, and supplements is estimated to be \$40–56 billion, even without including several additional diseases for which vitamin D intake is beneficial.

The economic burden due to excess UV irradiance can be estimated in a manner similar to that done for insufficient UVB and vitamin D (Table 5). The lower value for the skin diseases represents a value accounting for other factors that may influence the risk of disease, such as smoking in the case of NMSC (79), whereas the upper value is set arbitrarily at 1.0 for purposes of discussion.

Thus, the total economic burden of insufficient UVB exposure and vitamin D intake in the United States is approximately \$40–56 billion, not counting several diseases for which sufficient information is not available for quantitative estimates. This finding is contrasted with \$5–7 billion for excess UV irradiance in the United States, again not including diseases and conditions for which insufficient data exist for quantitative estimates, such as skin wrinkling and premature aging. The ratio of benefit to harm is

estimated to be between 6 and 11 to 1. These estimates are based on several assumptions that still must be confirmed, so they should be considered preliminary.

## United Kingdom

Having established an estimate for the United States, it is worthwhile to extrapolate these results to the United Kingdom. For this, we use the vitamin D-sensitive cancer mortality rates for 2002 (97). To estimate the effect of vitamin D insufficiency on cancer mortality rates in the United Kingdom, we assume that UVB irradiance has a quasi-linear reduction with latitude in the eastern United States and the United Kingdom of about 2% per degree of latitude. It is a bit difficult to use cancer mortality rate data to estimate the change with latitude due to the effect of degree of urbanization on the analysis. However, 2% per degree is a reasonable number. Thus, the reduction of vitamin D production from UVB irradiance in the United Kingdom is about 28%. Since milk or other foods are not routinely fortified with vitamin D in the United Kingdom and ocean fish consumption is not very high (98), the serum 25(OH)D levels of many people in the United Kingdom tend to be quite low. For example, 8% of elderly free-living inhabitants and 37% of institutionalized elderly inhabitants were found to be vitamin D deficient (99), and serum 25(OH)D levels in preschool children drop to 21 ng/ml in January-March, rising to 30 ng/ml in April-June (100). The rate of falls in the United Kingdom appears to be similar to that in the United States (101).

We will use a value of 30% reduction in population mean serum 25(OH)D level in the United Kingdom versus that in the United States, and we use the same factor for

increased risk of death from vitamin D-sensitive cancers. Note that the crude mortality rate for vitamin D-sensitive cancers is 43% higher in the United Kingdom than in the United States. To determine the reduction in cancer mortality rates possible in the United Kingdom, we multiply the fraction of vitamin D-sensitive cancer rates attributed to insufficient vitamin D for the United States by a factor of 1.3. The number of premature cancer deaths attributed to insufficient UVB and vitamin D in the United Kingdom and United States are given in Table 6. We note that lung cancer mortality rates are lower in the United Kingdom than in the United States (97), thus likely ruling out smoking as the cause.

It is also noted that MS rates in the United Kingdom are 40% higher than those in the United States (102,103), implying that almost all MS in the United Kingdom could be prevented with adequate vitamin D intake, especially in winter.

## **Discussion**

### Causality

The conclusion that irradiance with solar UVB and/or increasing vitamin D intake reduces the risk of the diseases discussed here should be subjected to the criteria for causality for a biological system (21,104,105). The most important criteria appear to be: 1) strength of association, 2) consistency in results for different populations, 3) generally linear dose-response gradients, 4) exclusion of possible confounding factors from explaining the observations, and 5) identification of mechanisms to explain the

observations. These criteria can be shown to be generally satisfied for several cancers in particular and many cancers in general as follows.

First, the strength of association is quite high for both solar UVB irradiance and vitamin D in several studies (106–114). Vitamin D was hypothesized as early as 1980 to explain the link between sunny regions and reduced cancer mortality rates (106). No other biochemical derived from solar radiation has been found that has such a profound impact on cancer cell growth, autoimmune diseases and cardiovascular heart disease among many other diseases (10). A concern in terms of strength of association is that some studies of dietary vitamin D failed to find a statistically significant inverse association. However, in a recent analysis, it was shown that the likely reason for failing to do so was that the dietary amounts were too low to have an effect. Studies in which total consumed vitamin D, total vitamin D from all sources, or serum 25(OH)D levels were considered, the results generally showed a statistically significant inverse correlation for the higher values. A diminished role of dietary vitamin D was also linked to the location of most of these studies in sunny areas, where most circulating vitamin D metabolites would have been from solar UVB but were not measured (32).

Second, there has been a consistency of association in different populations. For example, solar UVB irradiance has been shown to be inversely correlated with breast cancer in ecologic studies in Canada (106), the former Soviet Union (109), European countries (19), and the United States (110,112). Digestive tract cancers have been found to be

inversely correlated with annual solar radiation doses in the United States (35,106,112), Canada (108), and Japan (114).

Third, there is a distinct monotonic dose–response relationship between solar UVB irradiance and cancers of the colon (106) and breast (110). A similar monotonic dose–response relationship has been described for dietary vitamin D and colon cancer (37,38) and for serum 25(OH)D level and colon cancer (111,113).

Fourth, confounding factors can now generally be ruled out as explaining the geographic variation of cancer mortality rates in the United States. The extension of the ecologic study of solar UVB irradiance and cancer mortality rates in the United States (35,115; Grant and Garland, in preparation) demonstrates that several confounding factors can be ruled out. The primary factor not included in the analysis was diet. However, a study of micro- and macro-dietary factors for four regions of the United States in 1977-8 found that they did not vary by more than 10%-20% (116). Given the high correlation between the fraction of diet derived from animal products and cancers of the breast (19), colon (117), and prostate (118), it would take a diet similar to that of Northern Europe in the northeastern states and a diet similar to that of Southeast Asia in the southwestern states to generate the extremes of cancer mortality rates observed. That is simply not the case.

Fifth, the mechanisms whereby vitamin D reduces the risk of cancer are well known (10,119-121). In addition, most tissues have vitamin D receptors (VDRs) as well as the

ability to convert 25(OH)D to 1,25(OH)<sub>2</sub>D (122–124). Risk of cancer has been found to be associated with various VDR alleles (125,126).

For MS, similar latitudinal trends of prevalence in three different continents (127) along with proposed mechanisms whereby vitamin D reduces the risk and severity of disease help satisfy the causality criteria for this disease as well. Countries that have high ocean fish consumption, such as Japan and Scandinavian countries, have reduced MS rates compared with trends for the latitudes for those countries. Vitamin D modulates the immune system's ability to deal with infectious diseases. The vitamin D hormone, 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), is a potent immunomodulator and regulates the functions of T-helper cells (Th1) and dendritic cells and induces regulatory T-cell function (10,11,128–132).

Vitamin D has been shown in several studies to be essential to maximize bone health, improve neuromuscular function, and reduce the risk of falls (93–96).

The evidence is very strong that vitamin D, whether obtained by photoproduction from solar UVB irradiation, diet, or supplements, reduces the risk of many forms of cancer, MS, and osteoporotic fractures and provides a firm foundation on which to make a first-order estimate of the economic burden of insufficient solar UVB or vitamin D intake in the United States.

Thus, the criteria for causality seem to be satisfied for UVB and vitamin D for vitamin D-sensitive cancers, MS, and osteoporotic fractures.

#### Sunscreen use

Guidelines regarding sunscreen use might also be changed, since sunscreen preferentially absorbs UVB radiation and thus markedly impairs vitamin D production [SPF 8 can reduce vitamin D production by 95% (133)]. Sunscreen has been shown to be effective in reducing the risk of squamous cell carcinoma and actinic keratoses (134). Sunscreen use has been shown to not be effective in reducing the risk of either basal cell carcinoma (134) or CMM (135,136). The fact that CMM mortality rates nearly doubled from the 1950–69 period to the 1970–94 period, while those for NMSC fell approximately 50% (27), suggests that altered solar UV irradiance behavior and/or sunscreen use have likely played an important role (78). Note that tanning can generate increased “induced protection factor” (IPF) of about 3 (137).

#### Vitamin D recommendations

The consensus of scientific understanding defines vitamin D deficiency as serum 25(OH)D levels below 16 ng/ml (40 nmol/L), insufficiency in the range 20–32 ng/mL, and sufficiency in the range from 32–80 ng/mL, with normal in sunny countries (54–90 ng/mL), and excess greater than 100 ng/mL (85–90). To obtain high enough serum 25(OH)D levels now considered optimal, oral intakes of 1000 I.U. (25 µg) or more per day of vitamin D3 in the absence of UVB irradiance may be required.

It should be noted that vitamin D recommendations are in the process of being revised in the U.S. A National Institutes of Health conference addressed this issue in 2003, with many speakers reporting that current guidelines, which were based on bone health, are likely inadequate for optimal health when effects on soft tissues are included (138,139). An Experimental Biology symposium on vitamin D insufficiency was held in 2004 (88,140–142). We are pleased that four Australian organizations recently issued a recommendation that solar UVB be considered a useful source of vitamin D (143), also joining with similar organizations in New Zealand (144), and we hope that other organizations will follow suit (145).

### **Summary and conclusion**

The estimates of the economic burden and premature loss of life due to insufficient solar UVB irradiation and vitamin D in the United States are very high. These findings indicate that large savings to the health care system and improvement in quality of life might accrue if people made it a practice to obtain optimal amounts vitamin D through whichever combination of sources, UVB irradiance, natural or artificial (146), supplements, and/or fortified food, is most compatible with their lifestyle and concerns.

We note that while our estimates of economic burden due to insufficient UVB/vitamin D are based primarily on ecologic studies, these studies continue to find support in other epidemiologic studies, such as the recent reports that UVB exposure is associated with reduced risk of non-Hodgkin's lymphoma (147,148). While ecologic studies have both strengths and weaknesses, they have often identified and quantified important links

between diet, lifestyle, and environment years before case-control or cohort studies confirmed such links. Nonetheless, such confirmations are very important in gaining widespread acceptance of such findings and in making revisions to public health messages, and we encourage others to perform studies to check the links between UV irradiance and vitamin D contained in this study. A number of previous observational study results were not confirmed in intervention studies.

Public health advisories to minimize solar UVB irradiance, especially when given without any additional guidelines for the importance of vitamin D (149-151), could be more harmful than beneficial to public health (152-154), especially since the primary vitamin D source for many people is solar UVB irradiance (13). It is hoped that this work will lead to additional research to confirm the findings and to revised guidelines for vitamin D and UVB irradiance.

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**Figure Captions:**

Figure 1. The regression model (squared) for vitamin D-sensitive cancer mortality rate for males for the period 1950-69 (27).

Figure 2. The regression model (squared) for vitamin D-sensitive cancer mortality rate for females for the period 1950-69 (27).

Figure 3. Regression results for multiple sclerosis for veterans of WWII at the time of entry (41) vs. latitude.

Tables

Table 1. Economic burden of disease in 2004 for which vitamin D is a risk reduction factor in the United States or for which UV irradiance is a risk factor. All costs are in U.S.\$ billion.

Disease	Economic Burden, Direct Costs	Economic Burden, Indirect Costs, Morbidity	Economic Burden, Indirect Costs, Mortality	Total Economic Burden, (year)	Total Economic Burden, 2004	Reference
Cancer	\$74	\$17.5	\$118.4	\$209.9 (2005)	\$195	69
Lung Cancer					54	69
Multiple sclerosis				6.8 (1997)	11	61
Osteoporotic (Hip) fracture				23 (1998)	37	62
	17.5 (2002)					63
	15.4 (2000) \$14,300/ case					64

Table 2. U.S. costs for diseases for which UV irradiance is a risk factor.

Disease	Incidence or Prevalence	Annual mortality rate	Costs (direct, indirect, total)	Costs Adjusted for Inflation	Source or Reference
Actinic keratosis			\$202 M, Medicare	\$255 M	65
Cataracts	1.5 million operations/year		\$2500/eye	4.5 B	66
Melanoma	50,000	8000	567 M 1997 Incidence		67
				2.6 B	1.37% total cancer mortality
NMSC				630 M incidence	68
NMSC	1.2 m I	2000		640 M mortality	0.34% total cancer mortal. 68
NMSC			562 m, Medicare	711 M (treatment)	65

Table 3. Costs attributed to insufficient UVB doses in the United States, based on cancer data for 1950–69 and MS data for World War II and Korean Conflict veterans.

Disease	Total Economic Burden (\$billion)	Fraction Attributed to Insufficient UVB	Economic Burden Attributed to Insufficient UVB (\$billion)	References
Cancer, vitamin D-sensitive	97	0.10–0.15	10–15	27, 35, 115
Multiple Sclerosis	11	0.5	5	41-43
Total			15–20	

Table 4. Costs attributed to insufficient vitamin D in the United States separate from UVB doses.

Disease	Total Economic Burden (\$billion)	Fraction Preventable by Sufficient Vitamin D Consumption in Addition to Adequate Solar UVB	Economic Burden Attributed to Insufficient Vitamin D (\$billion)	Source or Reference
Cancer, vitamin D-sensitive	94	0.05–0.10	5–9	
Multiple Sclerosis	11	0.1	1	41-43
Osteoporotic Fractures	37	0.5–0.7	19–26	45-49
Total			25–36	

Table 5. U.S. economic burden attributed to excess UV doses in the United States

Disease	Total Economic Burden (\$billion)	Fraction Attributed to Excess UV	Cost due to UV (\$billion)	References
Actinic keratosis	<1	1.0	<1.0	65
Cataracts	4.5	0.25	1.1	50, 66
Melanoma	2.6	0.75–0.95	2.0–2.5	57, 67
NMSC	<2.0	0.75–0.95	<1.5–1.9	65, 68
Total			<5.6–6.5	

Table 6. A comparison of cancer mortality rates in the United Kingdom and United States due to insufficient UVB and vitamin D based on data for 2002 (97).

Country	Cancer Deaths— All	Cancer Deaths— Assumed Vitamin D— Sensitive	Fraction of Vitamin D— Sensitive Cancers Considered Premature	Premature Cancer Deaths Due to UVB/Vitamin D Insufficiency
UK 2002	156,488	82,758	0.23–0.30	19-25,000
US 2002	565,735	278,693	0.18–0.23	50-64,000

Figure 1.

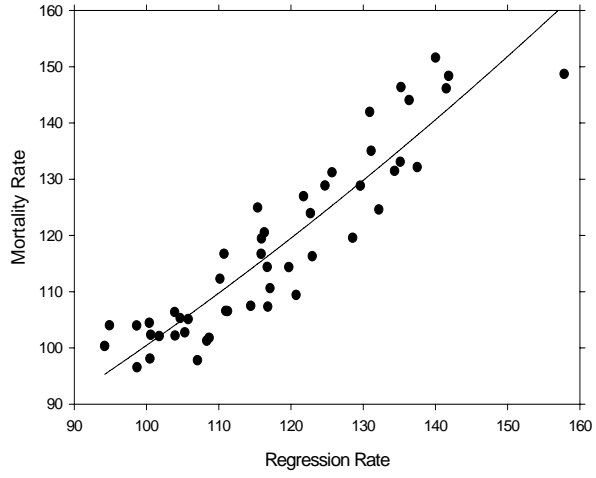


Figure 2.

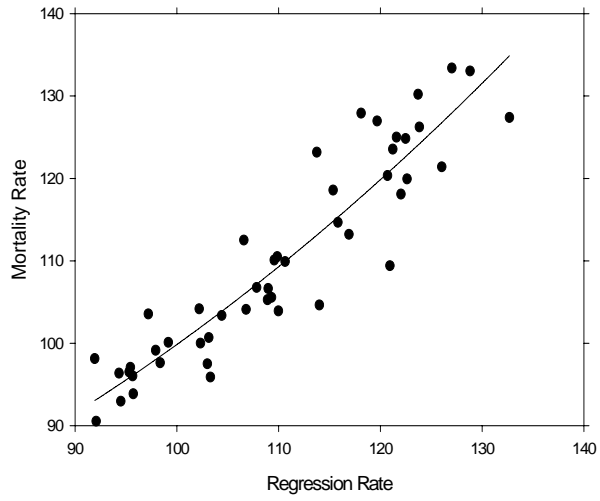


Figure 3.

