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UV Radiation, Vitamin D and Human Health: An Unfolding Controversy

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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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 individuals in the United States and 19 000–25 000 in the UK die prematurely from cancer annually due to insufficient vitamin D. The U.S. economic burden due to vitamin D insufficiency from inadequate exposure to solar UVB irradiance, diet, and supplements was estimated at $40–56 billion in 2004, whereas the economic burden for excess UV irradiance was 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 United States, UK, 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

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Abbreviations: B, billion (10^9); CMM, cutaneous malignant melanoma; KC, Korean Conflict; M, million (10^6); MR, mortality rates; MS, multiple sclerosis; NMSC, nonmelanoma skin cancer; RR, risk reduction; SPF, sun protection factor; SUNARC, Sunlight, Nutrition and Health Research Center; Th1, T helper cells 1; 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; $1,25(OH)_2D_3$, 1,25-dihydroxy vitamin D_3; 25(OH)D, 25-hydroxyvitamin D.

(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 because cohort studies, in general, 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 multicountry 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. In general, 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), 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 by 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 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 as in the Southwest (27). The Atlas of Cancer Mortality Rates (27) has data for two periods: 1950–1969 and 1970–1994. The analysis for the period 1950–1969 is used because, during that period, the effect of solar UVB irradiance had a much larger effect on cancer mortality rates than during the period 1970–1994. 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 because 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 because 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 μg = 40 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) (1941–1946) and the Korean Conflict (KC) (1950–1955) (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.

Because the U.S. data extend only to just below 30° 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 30 June 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.

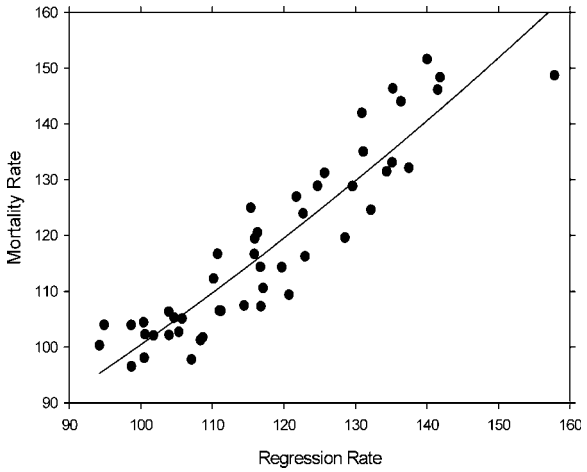

Figure 1. The regression model (squared) for vitamin D-sensitive cancer mortality rate for males for the period 1950–1969 (27).

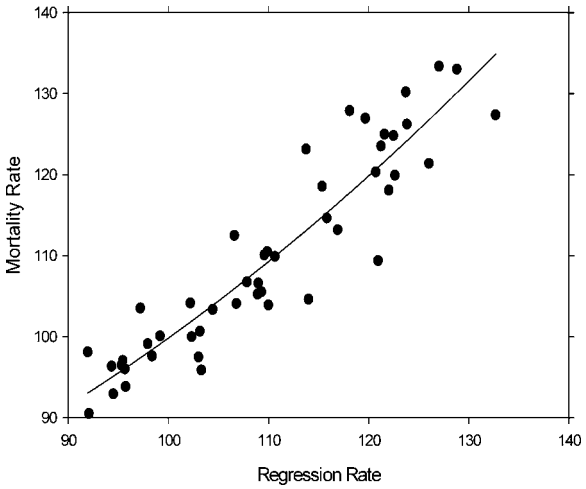

Figure 2. The regression model (squared) for vitamin D-sensitive cancer mortality rate for females for the period 1950–1969 (27).

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. In general, the direct costs are 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. Because 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 factors used are the July 1992 DNA-weighted UVB (33), lung cancer mortality rate, LungC, for males or females for the period 1950–1969 (27), the ethanol consumption rate for 1960–1962, Alc60 (73), and the percent urbanization for 1960, Urb60 (74). All values are statewide averages. A recent paper reported that lung cancer is a valid 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 1950–1969 are:

$$\begin{aligned}\mathrm{SR(MR(males))} &= 10.3 - 0.28 \times \mathrm{UVB} + 0.16 \times \mathrm{Alc60} \\ &\quad + 0.022 \times \mathrm{LungC} + 1.65 \times \mathrm{Urb60} \\ (\text{adjusted } R^2 &= 0.84,\ P < 0.001) \\ \mathrm{SR(MR(females))} &= 10.5 - 0.29 \times \mathrm{UVB} + 0.052 \times \mathrm{Alc60} \\ &\quad + 0.013 \times \mathrm{LungC} + 1.17 \times \mathrm{Urb60} \\ (\text{adjusted } R^2 &= 0.85,\ P < 0.001)\end{aligned}$$

Figures 1 and 2 show the results for white Americans. White Americans, including those considered Hispanic or 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 1941–1955 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

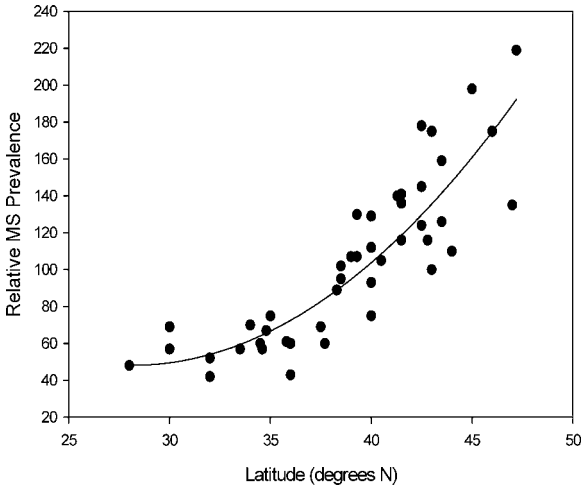

Figure 3. Regression results for multiple sclerosis for veterans of WWII at the time of entry (41) versus latitude.

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*

Disease	Economic burden, direct costs ($B)	Economic burden, indirect costs, morbidity ($B)	Economic burden, indirect costs, mortality ($B)	Total economic burden, $B (year)	Total economic burden, 2004 ($B)	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)	17.5 (2002)			23 (1998)	37	62
fracture	15.4 (2000)					63
	$14 300/ case					64

* All costs are in U.S.$ billion.

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, other factors also 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 (25.8° 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, because 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 1950–1969, 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 1950–1969 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 1950–1969 for white Americans. The estimated economic burden is $10–15 billion (Table 3).

Multiple sclerosis, or MS. 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

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 M operations/year		$2500/eye	4.5 B	66
Melanoma	50,000 Inc	8000	567 M 1997 incidence		67
				2.6 B	1.37% total cancer mortality
NMSC				630 M incidence	68
NMSC	1.2 M Inc	2000		640 M mortality	0.34% total cancer mortal (68)
NMSC			562 M, Medicare	711 M (treatment)	65

* M, million; B, billion; Inc, incidence.

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 would be attributed to vitamin D intake. Also, the latitudinal dependence of MS prevalence is consistent with wintertime values of serum 25(OH)D levels because 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 1950–1969 (Grant and Garland, in preparation), they cannot be used independent of data for the effect of UVB irradiance for 1970–1994 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 nonlung 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 (25 μg) 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 1950–1969 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 $1–26 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.

Table 3. Costs attributed to insufficient UVB doses in the United States, based on cancer data for 1950–1969 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	

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 difficult to use cancer mortality rate data to estimate the change with latitude because of 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%. Because 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 through March, rising to 30 ng/mL in April through June (100). The rate of falls in the United Kingdom appears to be similar to that in the United States (101).

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	19 000–25 000
US 2002	565 735	278 693	0.18–0.23	50 000–64 000

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.

Note also 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 macrodietary factors for four regions of the United States in 1977–1978 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 $1,25(OH)_2D$ (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_3 ($1,25(OH)_2D_3$), 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, because 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 1950–1969 period to the 1970–1994 period, whereas 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 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 D_3 in the absence of UVB irradiance may be required.

Note that vitamin D recommendations are in the process of being revised in the United States. 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 of 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, although 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). Although 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 because 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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REFERENCES

1. Holick, M. F. (2003) Vitamin D: A millenium perspective. *J. Cell Biochem.* **88**, 296–307.
2. Zittermann, A. (2003) Vitamin D in preventive medicine: are we ignoring the evidence? *Br. J. Nutr.* **89**, 552–572.
3. Heaney, R. P. (2003) Long-latency deficiency disease: insights from calcium and vitamin D. *Am. J. Clin. Nutr.* **78**, 912–919.
4. Hayes, C. E., F. E. Nashold, K. M. Spach and L. B. Pedersen (2003) The immunological functions of the vitamin D endocrine system. *Cell Mol. Biol. (Noisy-le-Grand).* **49**, 277–300.
5. Plotnikoff, G. A. and J. M. Quigley (2003) Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin. Proc.* **78**, 1463–1470.
6. Holick, M. F. (2004) Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am. J. Clin. Nutr.* **79**, 362–371. Erratum in: *Am. J. Clin. Nutr.* **79,** 890.
7. Hollis, B. W. and C. L. Wagner (2004) Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am. J. Clin. Nutr.* **79**, 717–726.
8. Grant, W. B., R. C. Strange and C. F. Garland (2003) Sunshine is good medicine: The health benefits of ultraviolet-B induced vitamin D production. *J. Cos. Dermatol.* **2**, 86–98.
9. Vasquez, A., G. Manso and J. Cannell (2004) The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern. Ther. Health Med.* **10**, 28–36; quiz 37, 94.
10. Holick, M. F. (2004) Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am. J. Clin. Nutr.* **80**, 1678S–1688S.
11. Cantorna, M. T. and B. D. Mahon (2004) Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp. Biol. Med. (Maywood).* **229**, 1136–1142.
12. Mosekilde, L. (2005) Vitamin D and the elderly. *Clin Endocrinol (Oxf).* **62**, 265–281.
13. Jablonski, N. G. and G. Chaplin (2000) The evolution of human skin coloration. *J. Hum. Evol.* **39**, 57–106.
14. Grant, W. B. (2004) Solar UV-B radiation is linked to the geographic variation of mortality from systemic lupus erythematosus in the United States. *Lupus* **13**, 281–282.
15. Sleijffers, A., J. Garssen and H. Van Loveren. (2002) Ultraviolet radiation, resistance to infectious diseases, and vaccination responses. *Methods* **28**, 111–121.
16. Morgenstern, H. (1998) Ecologic studies. In *Modern Epidemiology, 2nd ed.* (Edited by K. J. Rothman and S. Greenland), pp. 459–480. Lippincott, Philadelphia.
17. Greenland, S. (2001) Ecologic versus individual-level sources of confounding in ecologic estimates of contextual health effects. *Int. J. Epidemiol.* **30**, 1343–1350.
18. Greenland, S. (2002) A review of multilevel theory for ecologic analyses. *Stat. Med.* **21**, 389–395.
19. Armstrong, B. and R. Doll (1975) Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int. J. Cancer.* **15**, 617–631.
20. Grant, W. B. (2002) An ecologic study of dietary and solar UV-B links to breast carcinoma mortality rates. *Cancer* **94**, 272–281.
21. Hill, A. B. (1965) The environment and disease: Association or causation? *Proc. R. Soc. Med.* **58**, 295–300.
22. Doll, R. and R. Peto (1981) The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J. Natl. Cancer Inst.* **66**, 1191–1308.
23. Grant, W. B. (1997) Dietary links to Alzheimer's disease. *Alzheimer's Dis. Rev.* 2, 42–55. Available at: www.sunarc.org/JAD97.pdf. Accessed 26 March 2005.
24. Grant, W. B. (1998) Reassessing the role of sugar in the etiology of heart disease. *J. Orthomolec. Med.* **13**, 95–104.
25. Noaghiul, S. and J. R. Hibbeln (2003) Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am. J. Psychiatry* **160**, 2222–2227.
26. Meyskens, F. L. Jr and E. Szabo. (2005) Diet and cancer: the disconnect between epidemiology and randomized clinical trials. *Cancer Epidemiol. Biomarkers Prev.* **14**, 1366–1369.
27. Devesa, S. S., D. J. Grauman, W. J. Blot, G. A. Pennello, R. N. Hoover, and J. F. Fraumeni Jr. (1999) *Atlas of Cancer Mortality in the United States, 1950–94.* National Institutes of Health; National Cancer Institute. NIH Pub. No. 99-4564. Washington, DC. Available at: www3.cancer.gov/atlasplus/type.html. Accessed on 2 July 2005.
28. Sturgeon, S. R., C. Schairer, D. Grauman, L. El ghormli, and S. Devesa (2004) Trends in breast cancer mortality rates by region in the United States, 1950–1999. *Cancer Causes Control.* **15**, 987–999.
29. Holick, M. F. (1987) Photosynthesis of vitamin D in the skin: effect of environmental and life-style variables. *Fed. Proc.* **46**, 1876–1882.
30. Harris, S. S. and B. Dawson-Hughes (1998) Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am. J. Clin. Nutr.* **67**, 1232–1236.
31. Nutrition Monitoring Div., Human Nutrition Information Service, U.S. Dept. of Agriculture. (1985) Food and Nutrient Intakes: Individuals in Four Regions, Year 1977–78, Hyattsville, MD, Report No. I-3.
32. Grant, W. B. and C. F. Garland (2004) A critical review of studies on vitamin D in relation to colorectal cancer. *Nutr. Cancer.* **48**, 115–123.
33. Leffell, D. J. and D. E. Brash (1996) Sunlight and skin cancer. *Sci. Am.* **275**, 52–52, 56–59. Available at: http://toms.gsfc.nasa.gov/ery_uv/dna_exp.gif. Accessed 17 February 2005.
34. Lubin, D., E. H. Jensen and H. P. Gies (1998) Global surface ultraviolet radiation climatology from TOMS and ERBE data. *J. Geophys. Res.-Atmos.* **103**, 26 061–26 091.
35. Grant, W. B. (2002) An estimate of premature cancer mortality in the United States due to inadequate doses of solar ultraviolet-B radiation. *Cancer* **94**, 1867–1875.
36. Bostick, R. M., J. D. Potter, T. A. Sellers, D. R. McKenzie, L. H. Kushi and A. R. Folsom (1993) Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. *Am. J. Epidemiol.* **137**, 1302–1317.
37. Kearney, J., E. Giovannucci, E. B. Rimm, A. Ascherio, M. J. Stampfer, G. A. Colditz, A. Wing, E. Kampman and W. C. Willett (1996) Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am. J. Epidemiol.* **143**, 907–917.
38. Martinez, M. E., E. L. Giovannucci, G. A. Colditz, M. J. Stampfer, D. J. Hunter, F. E. Speizer, A. Wing and W. C. Willett (1996) Calcium, vitamin D, and the occurrence of colorectal cancer among women. *J. Natl. Cancer Inst.* **88**, 1375–1382.
39. Feskanich, D., W. C. Willett and G. A. Colditz (2003) Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am. J. Clin. Nutr.* **77**, 504–511.
40. Moore, C., M. M. Murphy, D. R. Keast and M. F. Holick (2004) Vitamin D intake in the United States. *J. Am. Diet Assoc.* **104**, 980–983.
41. Kurtzke, J. F. (1974) Data registries on selected segments of the population: Veterans. In *Neurological Epidemiology: Principies and Clinical Applications* (Edited by B. S. Schoenberg), pp. 55–67. Raven Press, New York.
42. Kurtzke, J. F., G. W. Beebe and J. E. Norman, Jr. (1979) Epidemiology of multiple sclerosis in U.S. veterans: 1. Race, sex, and geographic distribution. *Neurology* **29**, 1228–1235.
43. van der Mei, I. A., A. L. Ponsonby, L. Blizzard and T. Dwyer (2001) Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. *Neuroepidemiology* **20**, 168–174.
44. Hammond, S. R., J. G. McLeod, P. Macaskill and D. R. English (2000) Multiple sclerosis in Australia: prognostic factors. *J. Clin. Neurosci.* **7**, 16–19.
45. Chapuy, M. C., M. E. Arlot, F. Duboeuf, J. Brun, B. Crouzet, S. Arnaud, P. D. Delmas and P. J. Meunier (1992) Vitamin D_3 and

calcium to prevent hip fractures in the elderly women. *N. Engl. J. Med.* **327**, 1637–1642.
46. Gloth, F. M. 3rd, C. M. Gundberg, B. W. Hollis, J. G. Haddad Jr. and J. D. Tobin (1995) Vitamin D deficiency in homebound elderly persons. *JAMA* **274**, 1683–1686.
47. Bischoff, H. A., H. B. Stahelin, W. Dick, R. Akos, M. Knecht, C. Salis, M. Nebiker, R. Theiler, M. Pfeifer, B. Begerow, R. A. Lew and M. Conzelmann (2003) Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J. Bone Miner. Res.* **18**, 343–351.
48. Vu, M. Q., N. Weintraub and L. Z. Rubenstein (2004) Falls in the nursing home: are they preventable? *J. Am. Med. Dir. Assoc.* **5**, 401–406.
49. Bischoff-Ferrari, H. A., B. Dawson-Hughes, W. C. Willett, H. B. Staehelin, M. G. Bazemore, R. Y. Zee and J. B. Wong (2004) Effect of vitamin D on falls: a meta-analysis. *JAMA* **291**, 1999–2006.
50. Javitt, J. C. and H. R. Taylor (1994–95) Cataract and latitude. *Doc. Ophthalmol.* **88**, 307–325.
51. Taylor, H. R., S. K. West, F. S. Rosenthal, B. Munoz, H. S. Newland, H. Abbey and E. A. Emmett (1988) Effect of ultraviolet radiation on cataract formation. *N. Engl. J. Med.* **319**, 1429–1433.
52. McCarty, C. A. and H. R. Taylor (2002) A review of the epidemiologic evidence linking ultraviolet radiation and cataracts. *Dev. Ophthalmol.* **35**, 21–31.
53. Sasaki, H., Y. Kawakami, M. Ono, F. Jonasson, Y. B. Shui, H. M. Cheng, L. Robman, C. McCarty, S. J. Chew and K Sasaki (2003) Localization of cortical cataract in subjects of diverse races and latitude. *Invest. Ophthalmol. Vis. Sci.* **44**, 4210–4214.
54. Gale, C. R., N. F. Hall, D. I. Phillips and C. N. Martyn (2001) Plasma antioxidant vitamins and carotenoids and age-related cataract. *Ophthalmology* **108**, 1992–1998.
55. Armstrong, B. K., A. Kricker and D. R. English (1997) Sun exposure and skin cancer. *Australas. J. Dermatol.* **38**, S1–S6.
56. Green, A., D. Whiteman, C. Frost and D. Battistutta (1999) Sun exposure, skin cancers and related skin conditions. *J. Epidemiol.* **9**, S7–S13.
57. Millen, A. E., M. A. Tucker, P. Hartge, A. Halpern, D. E. Elder, D. Guerry 4th, E. A. Holly, R. W. Sagebiel and N. Potischman (2004) Diet and melanoma in a case-control study. *Cancer Epidemiol. Biomarkers Prev.* **13**, 1042–1051.
58. Kennedy, C., C. D. Bajdik, R. Willemze, F. R. De Gruijl, and J. N. Bouwes Bavinck Leiden Skin Cancer Study (2003) The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J. Invest. Dermatol.* **120**, 1087–1093.
59. Gandini, S., F. Serab, M. S. Cattaruzzac, P. Pasquinid, O. Picconid, P. Boylee and C. F. Melchif (2005) Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur. J. Cancer* **41**, 45–60.
60. Berwick, M., B. K. Armstrong, L. Ben-Porat, J. Fine, A. Kricker, C. Eberle and R. Barnhill (2005) Sun exposure and mortality from melanoma. *J. Natl. Cancer Inst.* **97**, 195–199.
61. Whetten-Goldstein, K., F. A. Sloan, L. B. Goldstein and E. D. Kulas (1998) A comprehensive assessment of the cost of multiple sclerosis in the United States. *Mult. Scler.* **4**, 419–425.
62. Max, W., P. Sinnot, C. Kao, H. Y. Sung and D. P. Rice (2002) The burden of osteoporosis in California, 1998. *Osteoporos. Int.* **13**, 493–500.
63. Melton, L. J. 3rd. (2003) Adverse outcomes of osteoporotic fractures in the general population. *J. Bone Miner. Res.* **18**, 1139–1141.
64. Burge, R. T., A. B. King, E. Balda and D. Worley (2003) Methodology for estimating current and future burden of osteoporosis in state populations: application to Florida in 2000 through 2025. *Value Health* **6**, 574–583.
65. Housman, T. S., S. R. Feldman, P. M. Williford, A. B. Fleischer Jr, N. D. Goldman, J. M. Acostamadiedo and G. J. Chen (2003) Skin cancer is among the most costly of all cancers to treat for the Medicare population. *J. Am. Acad. Dermatol.* **48**, 425–429.
66. Busbee, B. G., M. M. Brown, G. C. Brown and S. Sharma (2002) Incremental cost-effectiveness of initial cataract surgery. *Ophthalmology* **109**, 606–612; discussion 612–613.
67. Tsao, H., G. S. Rogers and A. J. Sober (1998) An estimate of the annual direct cost of treating cutaneous melanoma. *J. Am. Acad. Dermatol.* **38**, 669–680.
68. Chen, J. G., A. B. Fleischer Jr, E. D. Smith, C. Kancler, N. D. Goldman, P. M. Williford and S. R. Feldman (2001) Cost of nonmelanoma skin cancer treatment in the United States. *Dermatol. Surg.* **27**, 1035–1038.
69. National Institutes of Health, National Heart, Blood and Lung Institute (2005) *Fact Book, Fiscal Year 2004* Available at: www.nhlbi.nih.gov/about/04fackbk.pdf. Accessed on 25 March 2005.
70. Heffler, S., K. Levit, S. Smith, C. Smith, C. Cowan, H. Lazenby and M. Freeland (2001) Health spending growth up in 1999; faster growth expected in the future. *Health Aff. (Millwood)* **20**, 193–203. Erratum in: *Health Aff. (Millwood)* 20, 263.
71. Heffler, S., S. Smith, G. Won, M. K. Clemens, S. Keehan and M. Zezza (2002) Health spending projections for 2001–2011: the latest outlook. Faster health spending growth and a slowing economy drive the health spending projection for 2001 up sharply. *Health Aff. (Millwood)* **21**, 207–218.
72. Heffler, S., S. Smith, S. Keehan, M. K. Clemens, G. Won and M. Zezza (2003) Health spending projections for 2002–2012. *Health Aff. (Millwood)* Suppl Web Exclusives:W3-54-65.
73. Hyman, M. M., M. A. Zimmermann, C. Gurioli and A. Helrich (1980) *Drinkers, Drinking, and Alcohol-Related Mortality and Hospitalizations: A Statistical Compendium.* Center of Alcohol Studies, Rutgers University, New Brunswick, NJ.
74. Urban and Rural Populations: 1900 to 1990. Source: *1990 Census of Population and Housing*, ''1990 Population and Housing Unit Counts: United States,'' (CPH-2); and 1980 PC80-1-1. Available at: http://www.census.gov/population/censusdata/urpop0090.txt. Accessed on 26 March 2005.
75. Leistikow, B. (2004) Lung cancer rates as an index of tobacco smoke exposures: validation against black male approximate non-lung cancer death rates, 1969–2000. *Prev. Med.* **38**, 511–515.
76. U.S. Dept. of Commerce. (1994) *Statistical Abstract of the U.S.,* 114th edition.
77. Webb, A. R., L. Kline and M. F. Holick (1988) Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J. Clin. Endocrinol. Metab.* **67**, 373–378.
78. Garland, C. F., F. C. Garland and E. D. Gorham (1993) Rising trends in melanoma. An hypothesis concerning sunscreen effectiveness. *Ann. Epidemiol.* **3**, 103–110.
79. Grant, W. B. (2004) Smoking overlooked as an important risk factor for squamous cell carcinoma. *Arch. Dermatol.* **140**, 362–363.
80. Guerin, S., A. Dupuy, H. Anderson, A. Shamsaldin, G. Svahn-Tapper, T. Moller, E. Quiniou, S. Garwicz, M. Hawkins, M. F. Avril, O. Oberlin, J. Chavaudra and F. de Vathaire (2003) Radiation dose as a risk factor for malignant melanoma following childhood cancer. *Eur. J. Cancer* **39**, 2379–2386.
81. Chung, E. S., M. S. Sabel and V. K. Sondak (2004) Current state of treatment for primary cutaneous melanoma. *Clin. Exp. Med.* **4**, 65–77.
82. Helfand, M., S. M. Mahon, K. B. Eden, P. S. Frame and C. T. Orleans (2001) Screening for skin cancer. *Am. J. Prev. Med.* **20** (3 Suppl.), 47–58.
83. Malabanan, A. O. and M. F. Holick (2003) Vitamin D and bone health in postmenopausal women. *J. Womens Health (Larchmt)* **12**, 151–156.
84. van der Mei, I. A., A. L. Ponsonby, T. Dwyer, L. Blizzard, R. Simmons, B. V. Taylor, H. Butzkueven and T. Kilpatrick (2003) Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ.* **327**, 316.
85. Hollis, B. W. and C. L. Wagner (2004) Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am. J. Clin. Nutr.* **80**, 1752S–1758S.
86. Heaney, R. P. (2004) Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am. J. Clin. Nutr.* **80**, 1706S–1709S.
87. Vieth, R. (2004) Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. *J. Steroid Biochem. Mol. Biol.* **89–90**, 575–579.
88. Hollis, B. W. (2005) Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: Implications for establishing a new effective dietary intake recommendation for vitamin D. *J. Nutr.* **135**, 317–322.

89. Hanley, D. A, and K. S. Davison (2005) Disease-Specific Biomarkers of Vitamin D Sufficiency Vitamin D Insufficiency in North America. *J. Nutr.* **135**, 332–337.
90. Dawson-Hughes, B., R. P. Heaney, M. F. Holick, P. Lips, P. J. Meunier and R. Vieth (2005) Estimates of optimal vitamin D status. *Osteoporos. Int.* Mar 18 (Epub ahead of print).
91. Guzey, M., C. Sattler and H. F. DeLuca (1998) Combinational effects of vitamin D3 and retinoic acid (all trans and 9 cis) on proliferation, differentiation, and programmed cell death in two small cell lung carcinoma cell lines. *Biochem. Biophys. Res. Commun.* **249**, 735–744.
92. Nakagawa, K., A. Kawaura, S. Kato, E. Takeda and T. Okano (2005) 1 alpha,25-Dihydroxyvitamin D(3) is a preventive factor in the metastasis of lung cancer. *Carcinogenesis* **26**, 429–440.
93. Gallagher, J. C. (2004) The effects of calcitriol on falls and fractures and physical performance tests. *J. Steroid Biochem. Mol. Biol.* **89–90**, 497–501.
94. Pfeifer, M., B. Begerow and H. W. Minne (2002) Vitamin D and muscle function. *Osteoporos Int.* **13**, 187–194.
95. Dhesi, J. K., C. Moniz, J. C. Close, S. H. Jackson and T. J. Allain (2002) A rationale for vitamin D prescribing in a falls clinic population. *Age Ageing* **31**, 267–271.
96. Dhesi, J. K., S. H. Jackson, L. M. Bearne, C. Moniz, M. V. Hurley, C. G. Swift and T. J. Allain (2004) Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing* **33**, 589–595.
97. Ferlay, J., F. Bray, P. Pisani and D. M. Parkin (2004) *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide,* Version 2.0. IARC CancerBase No. 5. IARC Press, Lyon. Available at: www-depdb.iarc.fr/. Accessed on 1 October 2005.
98. FAOSTAT data (2004) Available at: faostat.fao.org/faostat/collections?subset=nutrition. Accessed on 26 March 2005.
99. Bates, C. J., A. Prentice, T. J. Cole, J. C. van der Pols, W. Doyle, S. Finch, G. Smithers and P. C. Clarke (1999) Micronutrients: highlights and research challenges from the 1994–5 National Diet and Nutrition Survey of people aged 65 years and over. *Br. J. Nutr.* **82**, 7–15.
100. Davies, P. S., C. J. Bates, T. J. Cole, A. Prentice and P. C. Clarke (1999) Vitamin D: seasonal and regional differences in preschool children in Great Britain. *Eur. J. Clin. Nutr.* **53**, 195–198. Erratum in: *Eur. J. Clin. Nutr.* **53,** 584.
101. Johansen, A., R. J. Evans, M. D. Stone, P. W. Richmond, S. V. Lo, and K. W. Woodhouse (1997) Fracture incidence in England and Wales: a study based on the population of Cardiff. *Injury* **28**, 655–660.
102. Noonan, C. W., S. J. Kathman and M. C. White (2002) Prevalence estimates for MS in the United States and evidence of an increasing trend for women. *Neurology* **58**, 136–138.
103. Fox, C. M., S. Bensa, I. Bray and J. P. Zajicek (2004) The epidemiology of multiple sclerosis in Devon: a comparison of the new and old classification criteria. *J. Neurol. Neurosurg. Psychiatry* **75**, 56–60.
104. Potischman, N. and D. L. Weed. (1999) Causal criteria in nutritional epidemiology. *Am J Clin Nutr.* **69**, 1309S–1314S.
105. Weed, D. L. (2002) Environmental epidemiology: basics and proof of cause-effect. *Toxicology* **181–182**, 399–403.
106. Garland, C. F. and F. C. Garland (1980) Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int. J. Epidemiol.* **9**, 227–231.
107. Garland, C., R. B. Shekelle, E. Barrett-Connor, M. H. Criqui, A. H. Rossof and O. Paul (1985) Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* **1**, 307–309.
108. Gorham, E. D., C. F. Garland and F. C. Garland (1989) Acid haze air pollution and breast and colon cancer mortality in 20 Canadian cities. *Can. J. Public Health* **80**, 96–100.
109. Gorham, E. D., F. C. Garland and C. F. Garland (1990) Sunlight and breast cancer incidence in the USSR. *Int. J. Epidemiol.* **19**, 820–824.
110. Garland, F. C., C. F. Garland, E. D. Gorham and J. F. Young (1990) Geographic varation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev. Med.* **19**, 614–622.
111. Tangrea, J., K. Helzlsouer, P. Pietinen, P. Taylor, B. Hollis, J. Virtamo and D. Albanes (1997) Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control* **8**, 615–625.
112. Freedman, D. M., M. Dosemeci and K. McGlynn (2002) Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. *Occup. Environ. Med.* **59**, 257–262.
113. Feskanich, D., J. Ma, C. S. Fuchs, G. J. Kirkner, S. E. Hankinson, B. W. Hollis and E. L. Giovannucci (2004) Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol. Biomarkers Prev.* **13**, 1502–1508.
114. Mizoue, T. (2004) Ecological study of solar radiation and cancer mortality in Japan. *Health Phys.* **87**, 532–538.
115. Grant, W. B. (2004) Benefits of UVB exposure to reduce the risk of cancer: ecologic studies of cancer mortality rates. In *Proceedings of the CIE Symposium '04; Light and Health: Non-visual effects,* 30 Sep.–2 Oct. 2004, Commission International de L'Eclairage, Vienna, Austria, 174–177.
116. Nutrition Monitoring Div., Human Nutrition Information Service, U.S. Dept. of Agriculture (1985) *Food and Nutrient Intakes: Individuals in Four Regions, Year 1977–78,* Hyattsville, MD, Report No. I-3.
117. Grant, W. B. (1999) Dietary fiber and colorectal cancer. *Townsend Lett.* **192**, 112–113.
118. Grant, W. B. (2004) A multicountry ecologic study of risk and risk reduction factors for prostate cancer mortality. *Eur. Urol.* **45**, 371–379.
119. van den Bemd, G. J. and G. T. Chang (2002) Vitamin D and vitamin D analogs in cancer treatment. *Curr. Drug Targets* **3**, 85–94.
120. Lamprecht, S. A. and M. Lipkin (2003) Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat. Rev. Cancer.* **3**, 601–614.
121. Garland, C. F., F. C. Garland and E. D. Gorham (1999) Epidemiology of cancer risk and vitamin D. In *Vitamin D: Molecular Biology, Physiology and Clinical Applications* (Edited by M. F. Holick), pp. 375–391. Humana, Totowa, NJ.
122. Cross, H. S., M. Peterlik, G. S. Reddy and I. Schuster (1997) Vitamin D metabolism in human colon adenocarcinoma-derived Caco-2 cells: expression of 25-hydroxyvitamin D3-1alpha-hydroxylase activity and regulation of side-chain metabolism. *J. Steroid Biochem. Mol. Biol.* **62**, 21–28.
123. Schwartz, G. G., L. W. Whitlatch, T. C. Chen, B. L. Lokeshwar and M. F. Holick (1998) Human prostate cells synthesize 1,25-dihydroxyvitamin D3 from 25-hydroxyvitamin D3. *Cancer Epidemiol. Biomarkers Prev.* **7**, 391–395.
124. Zehnder, D., R. Bland, M. C. Williams, R. W. McNinch, A. J. Howie, P. M. Stewart and M. Hewison (2001) Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J. Clin. Endocrinol. Metab.* **86**, 888–894.
125. Ingles, S. A., D. G. Garcia, W. Wang, A. Nieters, B. E. Henderson, L. N. Kolonel, R. W. Haile and G. A. Coetzee (2000) Vitamin D receptor genotype and breast cancer in Latinas (United States). *Cancer Causes Control.* **11**, 25–30.
126. Guy, M., L. C. Lowe, D. Bretherton-Watt, J. L. Mansi, C. Peckitt, J. Bliss, R. G. Wilson, V. Thomas and K. W. Colston (2004) Vitamin D receptor gene polymorphisms and breast cancer risk. *Clin. Cancer Res.* **10**, 5472–5481.
127. Kurtzke, J. F. (1975) A reassessment of the distribution of multiple sclerosis. Part one. *Acta Neurol. Scand.* **51**, 110–136.
128. Hayes, C. E., M. T. Cantorna and H. F. DeLuca (1997) Vitamin D and multiple sclerosis. *Proc. Soc. Exp. Biol. Med.* **216**, 21–27.
129. DeLuca, H. F. and M. T. Cantorna (2001) Vitamin D: its role and uses in immunology. *FASEB J.* **15**, 2579–2585.
130. Munger, K. L., S. M. Zhang, E. O'Reilly, M. A. Hernan, M. J. Olek, W. C. Willett and A. Ascherio (2004) Vitamin D intake and incidence of multiple sclerosis. *Neurology* **62**, 60–65.
131. Embry, A. (2004) Vitamin D supplementation in the fight against multiple sclerosis. *J. Orthomol. Med.* **19**, 27–38.
132. VanAmerongen, B. M., C. D. Dijkstra, P. Lips and C. H. Polman (2004) Multiple sclerosis and vitamin D: an update. *Eur. J. Clin. Nutr.* **58**, 1095–1109.
133. Matsuoka, L. Y., L. Ide, J. Wortsman, J. A. MacLaughlin and M. F. Holick (1987) Sunscreens suppress cutaneous vitamin D3 synthesis. *J. Clin. Endocrinol. Metab.* **64**, 1165–1168.
134. Green, A., D. Whiteman, C. Frost and D. Battistutta (1999) Sun exposure, skin cancers and related skin conditions. *J. Epidemiol.* **9**, S7–S13.

135. Bastuji-Garin, S. and T. J. Diepgen. (2002) Cutaneous malignant melanoma, sun exposure, and sunscreen use: epidemiological evidence. *Br. J. Dermatol.* **146** (Suppl 61), 24–30.
136. Dennis, L. K., L. E. Beane Freeman and M. J. VanBeek (2003) Sunscreen use and the risk for melanoma: a quantitative review. *Ann. Intern. Med.* **139**, 966–978.
137. Hoffmann, K., Kaspar, K., von Kobyletzki, G., Stucker, M. and P. Altmeyer (1999) UV transmission and UV protection factor (UPF) measured on split skin following exposure to UVB radiation–correlation with the minimal erythema dose (MED). *Photodermatol. Photoimmunol. Photomed.* **15**, 133–139.
138. Raiten, D. J. and M. F. Picciano (2004) Vitamin D and health in the 21st century: bone and beyond. Executive summary. *Am. J. Clin. Nutr.* **80**, 1673S–1677S.
139. Calvo, M. S., S. J. Whiting and C. N. Barton (2004) Vitamin D fortification in the United States and Canada: current status and data needs. *Am. J. Clin. Nutr.* **80**, 1710S–1716S.
140. Calvo, M. S. and S. J. Whiting (2005) Overview of the proceedings from Experimental Biology 2004 symposium: vitamin D insufficiency: a significant risk factor in chronic diseases and potential disease-specific biomarkers of vitamin D sufficiency. *J. Nutr.* **135**, 301–303.
141. Calvo, M. S., S. J. Whiting and C. N. Barton (2005) Vitamin D intake: a global perspective of current status. *J. Nutr.* **135**, 310–316.
142. Whiting, S. J. and M. S. Calvo (2005) Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J. Nutr.* **135**, 304–309.
143. Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, Australasian College of Dermatologists and the Cancer Council Australia. (2005) *Risks and Benefits of Sun Exposure*. Available at: www.cancer.org.au/documents/Risks_Benefits_Sun_Exposure_MAR05.pdf. Accessed 26 March 2005.
144. Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia (2005) Vitamin D and adult bone health in Australia and New Zealand: a position statement. *Med. J. Aust.* **182**, 281–285.
145. Grant, W. B. (2004) Insufficient sunlight may kill 45,000 Americans each year from internal cancer. *J. Cos. Dermatol.* **3**, 176–178.
146. Tangpricha, V., A. Turner, C. Spina, S. Decastro, T. C. Chen and M. F. Holick (2004) Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. *Am. J. Clin. Nutr.* **80**, 1645–1649.
147. Hughes, A. M., B. K. Armstrong, C. M. Vajdic, J. Turner, A. E. Grulich, L. Fritschi, S. Milliken, J. Kaldor, G. Benke and A. Kricker (2004) Sun exposure may protect against non-Hodgkin lymphoma: a case-control study. *Int J Cancer* **112**, 865–871.
148. Smedby, K. E., H. Hjalgrim, M. Melbye, A. Torrang, K. Rostgaard, L. Munksgaard, J. Adami, M. Hansen, A. Porwit-MacDonald, B. A. Jensen, G. Roos, B. B. Pedersen, C. Sundstrom, B. Glimelius and H. O. Adami (2005) Ultraviolet radiation exposure and risk of malignant lymphomas. *J. Natl. Cancer Inst.* **97**, 199–209.
149. Coogan, P. F., A. Geller, M. Adams, L. S. Benjes and H. K. Koh (2001) Sun protection practices in preadolescents and adolescents: a school-based survey of almost 25,000 Connecticut schoolchildren. *J. Am. Acad. Dermatol.* **44**, 512–519.
150. Benjes, L. S., D. R. Brooks, Z. Zhang, L. Livstone, L. Sayers, C. Powers, D. R. Miller, T. Heeren and A. C. Geller (2004) Changing patterns of sun protection between the first and second summers for very young children. *Arch. Dermatol.* **140**, 925–930.
151. Saraiya, M., K. Glanz, P. A. Briss, P. Nichols, C. White, D. Das, S. J. Smith, B. Tannor, A. B. Hutchinson, K. M. Wilson, N. Gandhi, N. C. Lee, B. Rimer, R. C. Coates, J. F. Kerner, R. A. Hiatt, P. Buffler and P. Rochester (2004) Interventions to prevent skin cancer by reducing exposure to ultraviolet radiation: a systematic review. *Am. J. Prev. Med.* **27**, 422–466.
152. Garland, C. F. (2003) More on preventing skin cancer: sun avoidance will increase incidence of cancers overall. *BMJ* **327**, 1228.
153. Reichrath, J. (2003) Protecting against adverse effects of sun protection. *J. Am. Acad. Dermatol.* **49**, 1204–1206.
154. Gillie, O. (2004) *Sunlight Robbery: Health Benefits of Sunlight Are Denied by Current Public Health Policy in the UK*. Available at: www.healthresearchforum.org.uk/reports/sunlightrobbery.pdf. Accessed on 26 March 2005.