Roles of solar UV radiation and vitamin D in human health and how to obtain vitamin D

William B Grant

Exposure to solar UV radiation is a double-edged sword: the benefits include vitamin D3 production and tanning, while the risks include diseases linked to free-radical production and DNA damage. Research during the past few years has demonstrated that the health benefits of solar UVB (290–315 nm), the primary source of vitamin D3 for many people, now include reduced risk for bone diseases, many types of cancer and, to a lesser extent, autoimmune diseases such as multiple sclerosis and infectious diseases such as tuberculosis and influenza. Solar UVB may also play a beneficial role in other diseases and conditions. Recent studies indicate that the daily vitamin D3 requirement for optimal health is between 1000 and 4000 IU. The adverse health effects include skin cancer and melanoma, cataract development, premature skin aging and other lesser effects. However, the risk of melanoma seems to be due primarily to UVA (315–400 nm), and use of sunscreen that successfully blocks erythemal UV but does not provide good blockage of UVA seems to be associated with both reduced production of vitamin D and an increased risk of melanoma. In general, the health benefits of solar UVB irradiance greatly outweigh the risks of solar UV, taken in moderation. However, since solar UVB is not always an adequate or, for some, a safe source of vitamin D3, other sources of vitamin D3 should be considered as well, including supplements, dietary sources such as fish and fortified food, and supervised artificial UVB irradiance.

Expert Rev. Dermatol. 2(5), 563–577 (2007)

CONTENTS

Sunlight, Nutrition and Health Research Center, 2115 Van Ness Avenue, Suite 101, San Francisco, CA 94109, USA
Tel.: +1 415 409 1980
Fax: +1 415 931 6537
wbgrant@infionline.net
www.sunarc.org

KEYWORDS:
cancer, melanoma, multiple sclerosis, skin cancer, sunbeds, tanning, ultraviolet-A, ultraviolet-B, viral infections, vitamin D

Human skin pigmentation evolved to suit local solar UV doses as humans moved from the plains of Africa to the far corners of the earth. In the native African population, dark pigmentation protects against the effects of UV in generating free radicals and destroying folate, while permitting sufficient UVB (290–315 nm) to penetrate the epidermis to produce adequate amounts of vitamin D [1], with pigment levels adjusted to UVB doses in fall [2]. In the tropical forested regions, brown skin suffices [1]. However, as humans migrated farther to the north, skin pigmentation lightened to permit vitamin D production with much lower levels of solar UVB. At latitudes of greater than approximately 60°, there is too little UVB for more than 6 months of the year to produce vitamin D, so people living there had to rely on marine fish and mammals for their vitamin D requirements.

As people transitioned from being farmers to city dwellers, they received less solar UVB. An early manifestation of this change was the widespread development of rickets in England in the 18th Century [3]. A study of the causes of rickets eventually led to the use of cod liver oil with vitamin D to prevent rickets in the 20th Century. Another effect of increased urbanization was the association of fair complexion with aristocracy, since aristocrats did not have to work outdoors. In the 1920s and 1930s, sun exposure became more popular after it was realized that solar UVB produced vitamin D with its associated health benefits and Coco Chanel made the sun-tanned look fashionable [4]. However, by mid-century, it was realized that solar UV caused skin cancer, so the pendulum began to swing back toward reduced sun exposure [5].

10.1586/17469872.2.5.563

ISSN 1746-9872

To suggest a modern policy toward sun exposure, one must first review what is known regarding the beneficial and adverse health effects of solar UV irradiance and how they vary with geographic location, season and age. The next task is to evaluate how the health benefits of solar UVB irradiance can be achieved while minimizing the health risks.

Health benefits of UVB & vitamin D

Bone health

The original benefit of solar UVB and vitamin D was in the prevention of rickets [3]. Vitamin D plays an important role in the absorption and metabolism of calcium. Many studies have found the benefit of calcium and vitamin D in reducing the risk of osteoporosis and hip fractures [6]. The risk of hip fracture among the elderly is still high in many countries [7].

Cancer

Although the health benefit of vitamin D in regulating calcium absorption and metabolism was recognized early in the 20th Century, the other health benefits were not recognized until much later. Perhaps the most important noncalcemic benefit of vitamin D is the reduced risk of cancer. In 1980, Cedric and Frank Garland proposed the UVB-vitamin D-cancer theory, after observing from the map of US colon cancer mortality rates, that rates were much lower in the southwest than in the northeast [8]. They later added breast and ovarian cancer to the list of vitamin D-sensitive cancers [9,10]. Prostate cancer was added in 1990 [11] and non-Hodgkin's lymphoma (NHL) in 1997 [12]. After an updated cancer mortality rate atlas became available in the USA [13,201], nine more cancers were added by the author to the list of those where increased levels of UVB and vitamin D potentially reduce the risk [14]. Several other ecological and observational studies based on geographical location have strengthened the link between solar UVB and vitamin D and cancer risk reduction, bringing the list of cancers for which UVB and vitamin D are possibly beneficial to more than 20 [15–19]. It was estimated that 85,500 premature deaths from cancer for males in the USA (29% of all male cancer deaths) could be prevented if men increased their vitamin D3 from all sources by 1500 IU per day [16]. Several studies have also found that cancer survival depends on the season of discovery in Norway [20,21], the USA [22] and England [23]: being improved for discovery in summer or fall when serum 25-hydroxyvitamin D (calcidiol) levels are higher.

One of the criticisms of the ecological studies is that solar UVB irradiance at the population level may not be correlated with UVB doses on the basis of location of residence. One way to evaluate this criticism is to find and apply some index of solar UVB irradiance at the group or population level. An appropriate index is incidence or death from squamous cell carcinoma (SCC) and, to a lesser extent, basal cell carcinoma (BCC). SCC comprises approximately 80% of nonmelanoma skin cancer (NMSC) deaths in the USA [24], and is primarily due to lifetime solar UVB irradiance (as discussed later), so NMSC mortality rates can also be used as an index of solar UVB. A study from The Netherlands reported results of a study on men diagnosed with NMSC or melanoma in 1970 and monitored until 2005, regarding development of prostate cancer. Compared with the general population, skin cancer diagnosis was associated with a statistically significant risk reduction for prostate cancer, with a stronger effect found for advanced prostate cancer [25]. A study in England found that risk of prostate cancer was reduced by the same sun-exposure factors as increased the risk of BCC [26].

In my own meta-analysis study of second cancer diagnosis, following a diagnosis of NMSC in which I used lung cancer incidence rates in each population to account for the effects of smoking on both NMSC and other cancer risks, I found, for a diagnosis of SCC, relative risks (RRs) for subsequent colon, gastric and rectal cancers were significantly reduced, with that for renal cancer being marginally nonsignificant. For NMSC, RRs for cervical, esophageal, gastric and rectal cancer were significantly reduced; those for colon and gallbladder cancer were marginally nonsignificant, whereas those for female breast, laryngeal, ovarian, renal and uterine corpus cancers were nonsignificantly reduced [27]. This study paved the way for an ecological study of cancer mortality rates in Spain in which NMSC mortality rates were used as the index of solar UVB irradiance at the group level. The assumption was made that those living in Spain had skin well suited for the prevailing UV doses [1] and that increased risk of NMSC was generally associated with increased UV irradiance probably due to occupation. A total of 17 types of cancer were found to be inversely correlated with NMSC in this study [19]. FIGURE 1 shows the correlation between NMCS and breast cancer mortality rates for females using data employed in that study.

More recently, a linkage study was conducted using cancer registry data from three sunny countries (Australia, Singapore and Spain) and eight less-sunny countries [28].

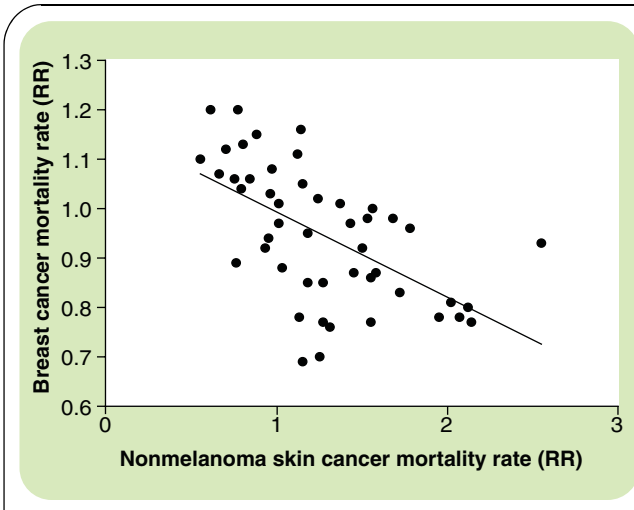

Figure 1. Relation between relative risk of breast cancer to that of nonmelanoma skin cancer for females in 48 continental provinces of Spain, 1978–92.
RR: Relative risk.
Created using data from [19].

Although there were too few cases of BCC and SCC in the sunny countries to find statistically significant correlations for second cancers, the standardized incidence ratios (SIRs) for all solid tumors except skin and lip were 0.79 (95% confidence interval [CI]: 0.68–0.19) for mostly SCC and 0.86 (95% CI: 0.80–0.92) for BCC. The SIR for melanoma was 1.03 (95% CI: 0.99–1.08). One of the tests of a hypothesis is whether predictions based on it are found to be correct. For the linkages to second cancers after diagnosis of skin cancer in sunny countries [28], the SIRs are as expected based on their relation to UVA and UVB, discussed later. There were no inverse relations between skin cancer and solid tumors for the less sunny countries, which is consistent with annual average vitamin D production from solar UVB being so low as to have little effect on cancer incidence rates in general.

The evidence for a beneficial role of solar UVB in reducing the risk of the various cancers ranges from very strong to preliminary. The higher the incidence or mortality rate, the easier it is to conduct epidemiological studies. One measure of the strength of the evidence is the number of studies that have reported a statistically significant inverse correlation between a measure of UVB and cancer incidence or mortality rate. My summary is given in TABLE 1. A total of 28 cancers are included. For the 15 cancers with five or more reports, the evidence is reasonably strong. Some of the other 12 are similar to other cancers so are also probably vitamin D sensitive. Other types of studies support a role of vitamin D for 17 of the 28 types of cancer, including melanoma [29].

The vitamin D–cancer dose–response relationships have been developed in three studies. A meta-analysis of five observational studies of serum calcidiol found that it takes approximately 1500 IU of vitamin D3 per day to reduce the risk by 50% for colorectal cancer, based on the assumption that calcidiol levels of the population are low [30]. In a cohort study of male health professionals, it was found that 1500 IU of vitamin D3 per day should reduce all-cancer mortality rates by 30% for males in the USA [16]. For breast cancer, based on two studies of calcidiol and breast cancer risk, it was determined that it takes approximately 4000 IU/day for a 50% reduction in risk for breast cancer [31].

Admittedly, the studies discussed so far are either ecological or observational. Although ecological studies have been criticized because of inconsistencies with observational intervention studies, they have an important advantage that is slowly being realized – they incorporate the effects of diet and lifestyle over a long period, perhaps starting *in utero*. Since cancer can take 15–40 years to progress from initiation to detection or death, this feature is an important advantage.

However, the criteria for causality in a biological system laid down by Hill [32] can be used to help evaluate vitamin D as a cancer risk-reduction factor. The primary criteria are strength of association, reproducibility in different populations, accounting for confounding factors, identification of the mechanisms and experimental confirmation. The strength of this association is strong in many studies and similar findings have been made in many populations. There are, however, some discrepancies for several types of cancer. Solar UV doses or irradiances are inversely correlated with risk of NHL at lower latitudes [12,33] but increased at higher latitudes [34]. A recent report indicated that vitamin D polymorphisms affect the risk of NHL in relation to solar UVB irradiance [35]. Although good observational data exist on the relation between serum calcidiol and risk of breast and colorectal cancer, the findings are mixed for pancreatic [36,37] and prostate [38] cancer. Some of the negative results are from Nordic countries, where solar UVB is not strong enough other than in summer to stimulate much vitamin D production. Perhaps the beneficial role of vitamin D occurs much earlier in life than within 20 years prior to cancer detection, and that recent serum calcidiol levels do not adequately reflect early calcidiol levels. Confounding factors have been included in at least one report on UVB doses and cancer mortality rates, with the finding that other cancer risk-modifying factors were correlated with cancer mortality rates, but did not detract from the correlation with solar UVB [17].

Table 1. Number of epidemiological studies that found various types of cancer inversely correlated with a measure of solar UVB

n	Cancer
>16	Breast, colon
10–15	Non-Hodgkin's lymphoma, ovarian, prostate, rectal
7–9	Gastric, lung, esophageal, pancreatic
5–6	Bladder, gallbladder, Hodgkin's lymphoma, renal, uterine corpus
3	Multiple myeloma
2	Cervical, leukemia, melanoma, oral, thyroid
1	Biliary, brain, pharyngeal, pleural, small intestine, soft tissue, vulvar

The mechanisms whereby vitamin D reduces the risk of cancer are generally well known from laboratory studies [39,40].

The most convincing evidence of a beneficial effect of vitamin D in reducing the risk of cancer would be a prospective, population-based, double-blind randomized placebo-controlled study. Unfortunately, the Women's Health Initiative study failed to find a protective effect of vitamin D and calcium for either hip fractures [41] or colon cancer [42]. However, they used only 400 IU of vitamin D3 per day along with 1200 mg of calcium, which was too little vitamin D [30,43]. However, a more recent study in which the postmenopausal women with an average age of 67 years at enrolment were given 1500 mg of calcium and 1100 IU of vitamin D3 per day found that from the end of the first year to the end of the fourth year, incidence of all cancers was 77% lower for those taking calcium plus vitamin D compared with those taking the placebo [44]. The cancer incidence rates for those taking

the placebo were similar to those for the general population in that age range. Thus, the main criteria for causality in a biological system [32] appear to be satisfied for solar UVB and vitamin D with respect to cancer-risk reduction.

This sentiment is echoed in several recent reviews that concluded that the evidence for protective roles of solar UVB and vitamin D against cancer was strong for at least some of the cancers [15,40,45–49]. Cancers for which the evidence is not as strong tend to be less frequent cancers, making studies more difficult. The Canadian Cancer Society recently reviewed the evidence and recommended that people should try to obtain 1000 IU of vitamin D3 when they cannot get a similar amount from solar UVB [202].

Infectious diseases

UVB and vitamin D are immunoprotective against *Mycobacterium tuberculosis* (TB) [50], and the mechanisms of action have recently been uncovered, including induction of human cathelicidin by calcitriol [51–54]. High doses of vitamin D2 have been used to treat TB [55]. A prospective, randomized, double-blind vitamin D supplement placebo-controlled study found that one dose of 2.5 mg (100,000 IU) of vitamin D enhanced immunity to TB [56]. While the role of vitamin D in reducing the risk of bacterial infections has been studied mostly for TB, the mechanisms seem to be applicable to a wide range of bacterial infections.

Chronic periodontitis is caused by enhanced resorption of the alveolar bone supporting the teeth and is associated with intraoral inflammation after infection with certain bacteria [57]. Vitamin D receptor gene polymorphism is associated with risk of periodontitis [57]. Calcidiol levels have been found inversely correlated with gingival inflammation [58].

Vitamin D has been hypothesized to reduce the risk of infectious diseases caused by viruses. A number of studies reported that hepatitis B infection was affected by polymorphism of vitamin D receptors [59]. More recently, Cannell and colleagues proposed that the annual solar UVB cycle explained much of the annual influenza cycle [60]. A study in support of this hypothesis was quickly published on results of a double-blind, placebo-controlled vitamin D study with 208 postmenopausal African–American women (mean age 60 ± 6 years) living in New York State (USA). During the 3-year period, 30 of the placebo group developed colds or influenza, compared with eight taking 800 IU/day and one taking 2000 IU/day of vitamin D3 [61]. However, another similar study in England and Scotland (UK) involving 3444 participants of mean age 77 ± 6 years in which 800 IU/day of vitamin D3 supplements were taken daily found only an insignificant reduction of risk for self-reported infections [62]. However, the participants were much older than those in the study in New York (NY, USA), and immune system response deteriorates with age due, in part, to reduced lymphocyte count and functionality. Another recent report investigated the relation between meteorological parameters and the incidence of respiratory syncytial virus during the year in nine cities, finding that solar UVB explained 13% of the variance in Miami (FL, USA), 5% in Buffalo (NY, USA) and 0.6% in Winnipeg (Manitoba, Canada) [63]. The mechanism may be through enhancement of the number and function of lymphocytes [64].

Although these findings on viral infections should be considered preliminary, if confirmed in larger studies they could have important implications for the control of viral diseases including, perhaps, pandemic influenza. In fact, during the 1951 influenza epidemic, mortality rates were higher in Canada and England than in the USA [65], which is consistent with there being higher calcidiol levels in the population in the USA than in the other two countries in winter.

One further extension of the increased understanding of the role of vitamin D in fighting infectious diseases is that it appears that low calcidiol level is a significant risk factor for sepsis or infections of the blood. Sepsis is due primarily to bacterial infections, but viral infections can pave the way for bacterial infections [66]. The primary epidemiological features of sepsis in the USA, such as seasonality, geographic variation, racial differences, age dependence and comorbidity with other diseases [67–69] are all highly correlated with the epidemiological features of solar UVB and vitamin D [GRANT WB; UNPUBLISHED DATA], thereby providing further support to the role of vitamin D in supporting the immune response.

Autoimmune diseases

There are several autoimmune diseases that appear to be affected by solar UVB and vitamin D, the most prominent of which is multiple sclerosis (MS). MS prevalence increases markedly with increasing latitude in Europe [70], the USA [71] and Australia [72]. Solar UVB irradiance has been found inversely correlated with prevalence of MS directly [72,73] or inferred from linkage to skin cancer in England [74]. Vitamin D has also been found inversely correlated with risk of MS in observational studies [75,76], and mechanisms to explain the link have been proposed [77]. There is emerging evidence that UVB and vitamin D also reduce the risk of Type I diabetes mellitus [78] and rheumatoid arthritis [79].

Other diseases

Several other diseases have also been reported to be reduced by solar UVB and vitamin D, including hypertension [80,81] and heart disease [82]. A recent study reported significantly poorer risk factors for cardiovascular disease for those with calcidiol levels less than 21 ng/ml versus those with levels greater than 37 ng/ml [83]. Although the study was cross-sectional, its findings suggest that vitamin D affects the risk of cardiovascular disease. A number of comprehensive reviews of the health benefits of solar UVB and vitamin D have been published recently [84–88].

Therefore, there are many health benefits from solar UVB and vitamin D. Although many of the studies that have identified these benefits are ecological or observational studies, the general consensus in the literature is that the beneficial

effects of vitamin D especially for bones, cancer, autoimmune diseases, and regulation of the immune system have been well substantiated, and that additional benefits are highly likely [40,88,89].

There are also some reviews that take a more skeptical viewpoint regarding the health benefits of solar UVB and vitamin D. A comprehensive review was commissioned by the WHO [90,203]. The review of the effects of UVB and vitamin D on cancer examined four cancers in detail – breast, colon, prostate and NHL – concluding that the evidence of a protective effect for each was weak or contradictory and that ecological studies could not be used to establish causality. Effects for other diseases such as cardiovascular effects and psychiatric disorders were also discussed briefly. Most of the report dealt with the adverse health effects of solar UV irradiance, which were deemed better substantiated. However, in the summary the authors stated that although globally excessive solar UV exposure contributed to 0.1% of the total global burden of disease and 60,000 premature deaths in 2000, a counterfactual of no UV exposure would not result in a minimum disease burden but rather a high disease burden owing to diseases of vitamin D deficiency. (This finding compares with 740,000 deaths estimated to be associated with hip fracture and 1.75 million disability adjusted life-years lost, representing 0.1% of the global burden of disease worldwide [91].) A related report was published in which the authors stated that gains were being made in reducing skin cancer and that it was time to also consider the health benefits of solar UVB [92]. I commented on this report, stating that the evidence of the beneficial effects of solar UVB were much stronger than in this report [93]. In response, the lead author of the report agreed that the economic and disease burden due to insufficient UVR exposure may be greater than that associated with excessive UVR exposure [93,204].

Another review from study groups more concerned with the adverse health effects of solar UV irradiance concluded; 'that there is accumulating evidence that UVR exposure, either directly or via stimulation of vitamin D production, has protective effects on the development of some autoimmune diseases, including multiple sclerosis and Type I diabetes mellitus. Adequate vitamin D may also be protective for the development of several internal cancers and infections' [94]. Although this report for the United Nations Environmental Program was a considerable advancement over the 2003 report [95], in that it demonstrated a much better recognition of the health benefits of solar UVB, it was felt that the report fell short on the benefits side, so a commentary was submitted pointing out evidence providing more support for the benefits of UVB and vitamin D, including some results not available when the report was written [96]. The authors' response was that 'while the adverse health effects of solar UVB exposure are well recognized, the evidence available currently to link solar UVB with protection against various diseases through the production of vitamin D is less certain' [97].

Health risks of UV

Melanoma & NMSC

The risk of both melanoma and NMSC is generally given as the reason people should limit their exposure to UV irradiance [98,99]. From my reading of the literature and analyzing various ecological datasets, I have formed an opinion regarding the wavelength regions and sun exposure practices associated with each of the three major forms of skin cancer that I present here:

- SCC appears to arise from integrated lifetime UVB irradiance [100];
- BCC appears to arise from both UVA and UVB irradiance [101], with sunburning also a risk factor;
- Melanoma, conversely, more probably arises from UVA irradiance [102].

Key support for these statements comes from a pair of ecological studies of the variation of BCC, SCC and melanoma for those of northern-European ancestry with respect to latitude. Solar UVB has a faster decline with increasing latitude than does UVA due to the absorption by ozone and scattering by the molecular atmosphere. Therefore, skin cancers linked to UVB will have a greater decrease with increasing latitude than those linked to UVA. In a study in the USA, SCC had a steep slope, BCC an intermediate one and melanoma a gradual one [103]. In a study of people of northern-European descent living in different countries a similar result was found [104]. Sunburning and excess UV irradiance is also an important risk factor, especially in childhood [105]. Total UV irradiance is also a risk factor for melanoma for those of European ancestry, with odds ratios between 1.4 and 2.1 for higher levels of UV irradiance as found in one study in Australia and the USA, although occupational sun exposure was not associated with increased risk [105]. Data from GLOBOCAN 2002 [106,205] show that melanoma rates increase with increasing latitude since darker pigment's provide protection against melanoma near the equator. Chronic UV irradiance for people living where their skin is suited for the usual ambient UV doses is generally associated with reduced risk for melanoma [19,107–109]. Both vitamin D production [29] and melanogenesis [110] appear to play roles in reducing risk from UVB irradiance and may help explain why occupational or chronic solar UV irradiance is often associated with reduced risk of melanoma [19,100–102]. Conversely, people of Scottish ancestry developed a gene for increased risk for melanoma approximately 1600 years ago [111], so those with red hair and freckles and who generally cannot tan are advised to limit their UV irradiance.

However, there is some literature supporting the role of UVB as the primary spectral region of risk for melanoma. The work on initiation of melanoma in neonatal mice supports the UVB hypothesis [112,113]. However, as pointed out in the literature, eumelanin predominates in the mouse melanoma cells and melanocytes; they are less likely than human cells to provide a satisfactory model for human solar melanomagenesis [114]. Those with more pheomelanin have an increased sensitivity to

UV [115] and a greater risk of melanoma [111]. In addition, use of animal models with darker pigmentation finds melanoma risk associated with UVA and not UVB [109]. UVA causes DNA damage via photosensitized reactions, which result in the production of oxygen-free radical species [116]. The finding that dietary factors that increase free radical production are associated with risk of melanoma, whereas dietary factors that provide antioxidants are associated with reduced risk [117], supports the role of free radicals in the etiology of melanoma.

Other work that supports the UVB hypothesis includes ecological studies. A study billed as showing a link to mid-range UV but implying that this was mainly UVB used data based on the Robertson–Berger meter that is sensitive from 290–330 nm and, therefore, contains a large contribution from the UVA spectral region [118]. Another study found strong correlations for melanoma with the National Oceanic and Atmospheric Administration/Environmental Protection Agency UV Index and with latitude [119]. This UV Index is an erythemal UV index [119] and again has a large contribution from the UVA spectral region.

The current epidemic of melanoma appears to be due to two primary factors: increased travel to sunny locations [120,121] and use of sunscreen that does not provide adequate protection against UVA [102]. Sunscreen that blocked the erythemal region well but not the UVA region came into widespread use after the development of sunscreens based on para-aminobenzoic acid in the 1960s [122]. That such sunscreen was an important factor in the divergent trends for melanoma and NMSC is corroborated by a recent study suggesting that with full-spectrum blocking, melanoma rates will be reduced [123]. An earlier review of case–control studies of sunscreen use and risk of melanoma concluded that sun sensitivity was a confounding factor that was not properly accounted for in such studies, limiting their usefulness [124]. Inspection of the studies included in the meta-analysis finds that two of the three with the largest reduction in odds ratio were from Spain [125,126]. According to a review [127], one Spanish study [116] did not provide an adequate description of sunscreen use. In addition, my study of cancer mortality rates in Spain found mortality rates for NMSC inversely correlated with those for melanoma in females [19]. However, a recent review stated that retrospective and prospective epidemiological studies have shown that sunscreen use is associated with a moderately increased risk for melanoma [128]. Use of sunscreen is also associated with increased duration in the sun for those in the sun intentionally, alongside higher sunburning rates [129]. This finding may support the role of UVA in the etiology of melanoma as most sunscreens block UVB better than UVA. Trends for melanoma and NMSC mortality rates in the USA also support a role of sunscreen use. As seen in TABLE 2, mortality rates for NMSC fell in 1970–1994 compared with 1950–1969, whereas mortality rates for melanoma rose. Since the guidelines for preventing melanoma and NMSC were the same, the divergent results would not be expected unless their etiologies are much different, which appears to be the case [130]. Whereas NMSC mortality rates in western-European countries decrease with latitude except for a high rate in Ireland, those for melanoma increase with latitude [131]. Both facultative skin pigmentation and vitamin D [29,117] probably play important roles. These results suggest that the results reported based on erythemal UV [118,119] may have missed the importance of longer-wavelength UVA in explaining their observations.

Other adverse health risks of UV irradiance

UV irradiance entails other risks as well, such as increased risk of cataracts from solar UVB irradiance [132], increased skin aging [133], flare-up of herpes simplex virus infections [134], and aggravation of systemic lupus vulgaris [135]. Various pharmaceutical drugs are photosensitive and produce free radicals under UV and visible irradiance, with adverse effects on the skin [136].

Vitamin D sources

The studies discussed previously indicate that vitamin D is essential for optimal health and that solar UVB is an important source. If diet provided enough vitamin D, it would not be so easy to do ecological studies with respect to vitamin D, unless some other factor was involved. Since there health risks are associated with UV irradiance and since UVB is not always available, the various sources of vitamin D should be considered and evaluated.

Photoproduction

Many people obtain most of their vitamin D from solar UVB irradiance [137]. UVB interacts with 7-dehydrocholesterol, producing pro-vitamin D3 [138]. The precursor converts into vitamin D3 through a thermal process in the epidermis. Since UV radiation up to approximately 330 nm also destroys vitamin D3 [139], the maximum production of vitamin D3 in a day is at least 10,000 IU [140]. Several reports have indicated the time required to produce given amounts of vitamin D on the basis of solar elevation angle expressed in season and time of day [141,142]. The Australian study based times on production of 200–600 IU for lightly pigmented young individuals with 15% of their body exposed, whereas the European study based times on production of 1000 IU for 25% of the body exposed. The use of 200–600 IU is unfortunate since the emerging scientific consensus is that at least 1500–4000 IU of vitamin D3 per day is required for optimal health [16,30,31,80,143]. Data from Webb and Engelsen suggest that, at latitudes grater than approximately 45° N, there are 6 months of the year when it would take more than 1 h to produce 1000 IU of vitamin D [142].

Vitamin D production rates depend strongly on skin pigmentation, with very dark-skinned people requiring approximately five times longer for the same amount of vitamin D as light-skinned individuals [144]. Vitamin D production rates also decline with age: those aged 20–30 years were found to produce vitamin D at four times the rate of those aged 62–80 years [145], and older people generally spend less time in the sun than younger people [146]. Since sunscreen blocks UVB radiation, using sunscreen reduces vitamin D production, especially during short UV exposures [147]. Although sunscreen use was not found to affect serum calcidiol levels in a placebo-controlled

Table 2. Mortality rates and their ratio for cutaneous malignant melanoma and nonmelanoma skin cancer for Caucasian–Americans for two periods of time.

Cancer	Sex	Mortality rate* (1950–1969)	Mortality rate* (1970-1994)	Ratio (1970–1994:1950–1969)
CMM	Male	1.57	2.96	1.89
	Female	1.13	1.61	1.42
NMSC	Male	1.70	1.17	0.69
	Female	0.81	0.43	0.53

*Deaths/100,000/year
CMM: Cutaneous malignant melanoma; NMSC: Nonmelanoma skin cancer.
Data from [13, 201].

study in Australia, 1,25-dihydroxyvitamin D3 (calcitriol) levels increased only 1.5%, compared with 13.3% for those not using sunscreen [148].

Solar UVB doses may be too low for sufficient vitamin D production for optimal health year round at higher latitudes, although patients diagnosed with cancer in England in summer and Norway in fall have better survival outcomes than those diagnosed with cancer in winter or spring [20,21]. In England, UVB irradiance was found to reduce cancer incidence rates for outdoor workers in a statistically significant manner for only three cancers: bladder, gallbladder and pharyngeal, and nonsignificantly for several more [149]. NMSC incidence rates were significantly increased for males. However, analysis of cancer incidence rates for England (50.5°–56°N) [150] with respect to an annual UV index [34] shows an inconsistent relationship between the rates of cancers found to be UVB sensitive in other studies [GRANT WB; UNPUBLISHED DATA].

The time of day for solar UV irradiance is important. The optimal time for vitamin D production is near solar noon, when time required for vitamin D production is minimal [138]. Thus, the shadow rule [151], (seek cover when the solar elevation angle is greater than 45°) is well intentioned and is useful for those spending prolonged times in the sun, but it presents a problem for those trying to obtain their vitamin D in a short time, since solar UVB intensities decrease with decreasing solar elevation angle: it takes approximately 50% longer to produce the same amount of vitamin D 2 h either side of solar noon in mid-latitude summer and twice as long at 3 h either side [141,142].

For people planning to get vitamin D from solar UVB, preparing the skin gradually for higher UV doses is important. Doing so could involve spending a few minutes a day in the sun in spring or early summer. The skin adapts to UV irradiance by increasing melanin production and thickening the stratum corneum. An induced tan provides an induced protection factor of 2–4 [103,152].

Sunbeds

Sunbeds are a possible source of vitamin D. One 5–10-min exposure can produce over 10,000 IU of vitamin D3 in young, lightly pigmented individuals [140]. In one study, a woman with Crohn's disease was then exposed to UVB radiation in a tanning bed wearing a one-piece bathing suit for 10 min, three times a week for 6 months. After 4 weeks, her serum calcidiol level increased from 7 to 32 ng/ml [153]. In a study of 43 women and 7 men with an average age of 34.2 ± 2.0 years who used tanning beds at least once a week were compared with 106 control subjects. Subjects who used a tanning bed had serum calcidiol concentrations 90% higher than those of control subjects (46.2 ± 3.2 and 24.1 ± 1.2 nmol/l, respectively; $p < 0.001$). Tanners had significantly higher bone mineral density and *z* scores at the total hip than did nontanners [154].

Supplements

The easiest way to obtain vitamin D without any of the risks associated with UV irradiance is from vitamin D3 (cholecalciferol) supplements. Although easy at the individual level, relying on this source may be more difficult to implement at the population level. First, vitamin D3 supplements must be made widely available. Vitamin D2 (ergocalciferol), made from vegetable sources, is considered much less effective than vitamin D3 [155]. Second, the amount of vitamin A taken with vitamin D3 should be no greater than 1500 IU per day [156]. Vitamin A (retinol), which competes with vitamin D [157], has been linked to increased risk of hip fracture [156]. My inspection of vitamin D supplements in vitamin and other stores in the USA indicates that there are few acceptable supplements for sale, either because they are ergocalciferol or contain too much vitamin A. Third, the health agencies and major disease organizations would have to promote the use of vitamin D supplements, as is now being done in Australia [206] and Canada [50]. The UK recently released a study on vitamin D that found benefits but did not go beyond the standard recommendation of 400 IU of vitamin D3 per day [158, 207].

Dietary sources

Another source of vitamin D3 is through dietary sources with either native vitamin D3, such as cold-water oily fish [159], or vitamin D3 fortification. Although diet can supply some of the daily vitamin D3 requirements, it does not in general provide enough for optimal health. First, most countries do not fortify food with vitamin D [160,161]. Even in the USA, where milk and

orange juice are fortified, the average person obtains approximately 200–300 IU of vitamin D3 per day [161]. Additional foods, such as bread, could be fortified with vitamin D3 [162]. However, not all food sources of vitamin D3 are healthy choices; fish can have mercury and other toxins [163]. There are many health problems associated with milk, such as increased risk of Type I diabetes mellitus in infancy [164], teenage acne [165], prostate cancer [166] and Parkinson's disease [167] and not everyone is lactose tolerant. Furthermore, ocean fish stocks are being rapidly depleted through over-fishing. In addition, milk consumption is not significantly associated with reduced hip fracture rate among postmenopausal women, although dietary vitamin D and dark fish are, based on an 18-year prospective analysis in 72,337 postmenopausal women [168]. Orange juice [169] has too much simple sugar to be consumed in large amounts. Thus, since eating too much of any type of food is not healthy, the more commonly consumed foods that are fortified with vitamin D3, the better.

Balancing benefits & risks

Public and individual guidelines should be based first on recognizing the profound health benefits of vitamin D3, and then on how to obtain vitamin D3 based on several factors related to obtaining vitamin D3 as well as balancing the health benefits against the health risks of UV irradiance [91,170,171]. A study was conducted regarding the economic burden of the health benefits and risks for the USA and the UK on the basis of the health benefits for cancer, hip fractures, and MS and the risks for actinic keratoses, cataracts, melanoma and NMSC. For the USA, the economic burden from insufficient UVB and vitamin D was estimated at US$40–56 billion in 2004, whereas the economic burden from excess UV irradiance was estimated at $6–7 billion [172]. Since more benefits of vitamin D3 are known now, the estimate of the benefits would be higher.

One action that all organizations recommending limited UV irradiance could take is discussing the health benefits of UVB and vitamin D and suggesting how individuals can obtain 1000–2000 IU of vitamin D3 per day [173]. Public-health agencies could also recommend an effective intake of vitamin D3 [89].

There is still uncertainty regarding the benefits of vitamin D and the risks associated with UVB irradiance and food sources of vitamin D. Nonetheless, the health benefits of vitamin D3 are great enough that individuals, organizations, and agencies should move forward with efforts to increase serum calcidiol levels in those they can influence.

A note on paradigm shifts

Paradigm shifts always take time and are met with considerable resistance by those who are aligned with the status quo. In my career as a scientist I watched at fairly close hand the development of the theory of ozone destruction by chlorofluorocarbons, saw the global warming/climate change controversy, and helped precipitate some myself with my pioneering study on dietary links to Alzheimer's disease [174,208] and my identification of an additional nine cancers that had mortality rates inversely correlated with solar UVB in the USA [14]. Revolutionary ideas are always greeted with resistance by those entrenched in positions of authority. One need only recall the trials of Galileo Galilei after he announced the heliocentric theory in 1610 to see how contentious revolutions can be. In modern times, corporate interests can thwart adoption of revolutionary ideas by challenging the scientific findings, often based on minor problems that are eventually resolved.

The medical and popular attitudes toward UV light exposure have gone through several phases during the past 100 years, fluctuating between welcoming and fearing the sun. During 1900–1920, vigilance against significant sun exposure, a relic of the 19th Century, was eroding and, medically, the view of sunlight as salutary was bolstered by the success of phototherapy, which was introduced in the 1890s [175]. In the 1920s and 1930s, the discovery that UV wavelengths played a role in vitamin D synthesis in the skin ushered in a period of enormous popularity for UV light exposure. It was also thought that UV had many health benefits, including increased resistance to disease [4]. In the 1940s and 1950s, the role of UV in the etiology of skin cancer was increasingly realized [5]. Starting in the 1960s and accelerating in the 1970s and 1980s, sunscreen use was advocated as a way to reduce the risk of skin cancer [115]. The Australians adopted the Slip! Slop! Slap! program in 1980 [176], and now it is recognized that serum calcidiol levels in Australia are low at the population level, with season and latitude explaining only a fifth of the variance [177]. It was suggested that guidelines for sun exposure practices be modified or other ways found to increase calcidiol levels. In addition, use of sunscreen that does not block UVA effectively can actually increase the risk of melanoma. The past decade has seen a large body of research documenting the noncalcemic health benefits of UVB and vitamin D, and the emerging scientific consensus is that the health benefits of UV irradiance greatly outweigh the harmful effects. However, nearly all stories in the popular press regarding UV irradiance emphasize the risks of skin cancer and melanoma. Admittedly, one can obtain vitamin D from supplements and dietary sources, but solar UVB is still the most important source for most people. Thus, in my opinion, the pendulums of public and medical opinion are again swinging toward acceptance of solar radiation as being generally beneficial. However, as for everything else, UV is best partaken in moderation and with care.

Expert commentary

For the past 20–30 years, public-health messages regarding solar UV irradiance have focused on the health risks while either ignoring or undervaluing the health benefits. Research findings during the past decade or more have documented the profound noncalcemic health benefits from solar UVB and vitamin D3. The health benefits greatly outweigh the health risks. As with any food, drink, or activity, people should avoid too much solar UV exposure. Without adequate solar UVB

irradiance, people should seek other sources of vitamin D3. Public-health policies should be revised in light of the emerging scientific findings, as is being done already in several countries.

Five-year view

The health benefits of solar UVB irradiance and vitamin D3 will be well understood for cancer, respiratory diseases arising from bacterial and viral infections, autoimmune diseases, heart diseases, periodontal disease and several other diseases. Recommendations for oral vitamin D3 intake and solar UVB irradiance will be revised upward to reflect the emerging scientific findings. Public announcements of the UV index will also include information on time required near solar noon to produce 1000 IU of vitamin D3. More countries will permit and encourage vitamin D3 fortification of commonly consumed foods, including bread and other grain products. All health practitioners, including dermatologists, will become well versed in the health benefits of vitamin D3 and will evaluate patients' health and treatment in terms of serum calcidiol levels and will recommend additional vitamin D3 as warranted for both disease prevention and treatment.

Financial & competing interests disclosure

WB Grant receives funding from the UV Foundation (McLean, VA, Australia) and the Vitamin D Society (Canada) and awaits funding from the European Sunlight Association. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Solar UVB irradiance is the major source of vitamin D3 for most people.
- Solar UVB and vitamin D3 have been reported to reduce the risk of over 16 types of cancer.
- The evidence for UVB and vitamin D3 reducing the risk of cancer generally satisfies the criteria for causality in biological systems for several cancers.
- Recent studies have provided evidence that solar UVB and vitamin D3 reduce the risk of respiratory diseases linked to infection, explaining in part why such diseases are more common in winter.
- Solar UVB and vitamin D3 reduce the risk of autoimmune diseases such as multiple sclerosis.
- Emerging scientific evidence suggests that humans require 1000–4000 IU of vitamin D3 per day for optimal health.
- Although nonmelanoma skin cancer is not desirable, it is generally not life threatening, and several recent studies found that development of nonmelanoma skin cancer is associated with reduced risk of numerous internal cancers, as long as the effects of smoking are considered, as well as multiple sclerosis.
- At latitudes greater than approximately 45°, it is difficult to obtain sufficient vitamin D3 year round from casual solar UVB irradiance to reduce the risk of cancer.
- Human epidemiological studies suggest that solar UVA is a more important risk factor for melanoma than UVB.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Jablonski NG, Chaplin G. The evolution of human skin coloration. *J. Hum. Evol.* 39, 57–106 (2000).
• Explains how skin coloration evolved in response to changing solar UV doses as humans migrated out of Africa.

2 Chaplin G. Geographic distribution of environmental factors influencing human skin coloration. *Am. J. Phys. Anthropol.* 125, 292–302 (2004).

3 Rajakumar K, Thomas SB. Reemerging nutritional rickets: a historical perspective. *Arch. Pediatr. Adolesc. Med.* 159, 335–341 (2005).

4 Albert MR, Ostheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 2. *J. Am. Acad. Dermatol.* 48, 909–918 (2003).

5 Albert MR, Ostheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 3. *J. Am. Acad. Dermatol.* 49, 1096–1106 (2003).

6 Bischoff-Ferrari HA, Willett WC, Wong JB *et al.* Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 293, 2257–2264 (2005).

7 Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos. Int.* 17, 1726–1733 (2006).

8 Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int. J. Epidemiol.* 9, 227–231 (1980).

9 Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev. Med.* 19, 614–622 (1990).

10 Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int. J. Epidemiol.* 23, 1133–1136 (1994).

11 Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). *Anticancer Res.* 10, 1307–1311 (1990).

12 Freedman DM, Zahm SH, Dosemeci M. Residential and occupational exposure to sunlight and mortality from non-Hodgkin's lymphoma: composite (threefold) case–control study. *Br. Med. J.* 314, 1451–1455 (1997).

13 Devesa SS, Grauman DJ, Blot WJ *et al. Atlas of Cancer Mortality in the United States, 1950–1994.* NIH Publication No. 99–4564, USA (1999).

14 Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 94, 1867–1875 (2002).

15 Garland CF, Garland FC, Gorham ED *et al.* The role of vitamin D in cancer prevention. *Am. J. Public Health.* 96, 252–261 (2006).

•• Excellent summary of 63 observational studies of vitamin D status in relation to cancer risk.

16 Giovannucci E, Liu Y, Rimm EB *et al.* Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J. Natl Cancer Inst.* 98, 451–459 (2006).

•• Reports inverse correlations with a vitamin D index for 11 types of cancer in a cohort study.

17 Grant WB, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. *Anticancer Res.* 26, 2687–2699 (2006).

•• Results of an ecological study of cancer mortality rates in the USA with respect to UVB and several other important cancer risk modifying factors.

18 Boscoe FP, Schymura MJ. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993–2000. *BMC Cancer* 6, 264 (2006).

•• Results of an ecological study of recent cancer incidence and mortality rates in the USA.

19 Grant WB. An ecologic study of cancer mortality rates in Spain with respect to indices of solar UV irradiance and smoking. *Int. J. Cancer* 120, 1123–1127 (2007).

•• Results of an ecologic study of cancer mortality rates in Spain using nonmelanoma skin cancer (NMSC) mortality rates as the index of UVB irradiance.

20 Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). *Cancer Causes Control.* 15, 149–158 (2004).

• First paper reporting that cancer survival rates were dependent on season of discovery.

21 Porojnicu A, Robsahm TE, Berg JP, Moan J. Season of diagnosis is a predictor of cancer survival. Sun-induced vitamin D may be involved: A possible role of sun-induced Vitamin D. *J. Steroid. Biochem. Mol.* 103, 675–678 (2007).

• Review of the extensive studies of cancer survival in Norway with respect to season of discovery.

22 Zhou W, Heist RS, Liu G *et al.* Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. *J. Clin. Oncol.* 25, 479–485 (2007).

• Reports a sizable increase in survival associated with a higher vitamin D index.

23 Lim HS, Roychoudhuri R, Peto J, Schwartz G, Baade P, Moller H. Cancer survival is dependent on season of diagnosis and sunlight exposure. *Int. J. Cancer* 119, 1530–1536 (2006).

24 Weinstock MA. Epidemiologic investigation of nonmelanoma skin cancer mortality: the Rhode Island Follow-Back Study. *J. Invest. Dermatol.* 102, S6–S9 (1994).

25 de Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: a protective role of ultraviolet radiation? *Am. J. Epidemiol.* 165, 966–972 (2007).

•• Skin cancer diagnosis is a good indication of solar UVB irradiance and reduced risk of prostate cancer.

26 Rukin NJ, Zeegers MP, Ramachandran S *et al.* A comparison of sunlight exposure in men with prostate cancer and basal cell carcinoma. *Br. J. Cancer* 96, 523–528 (2007).

27 Grant WB. A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: additional evidence that solar ultraviolet-B irradiance reduces the risk of internal cancers. *J. Steroid Biochem. Mol.* 103, 668–674 (2007).

•• Reports meta-analyses of incidence of second cancer after diagnosis where NMSC was inversely associated with several types of cancer as long as smoking by the population was accounted for.

28 Tuohimaa P, Pukkala E, Scelo G *et al.* Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: vitamin D as a possible explanation. *Eur. J. Cancer* 43, 1701–1712 (2007).

• Provides an extensive data set demonstrating the relation between UV irradiance measured by skin cancer incidence and incidence of other primary cancers.

29 Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: is this relevant to malignant melanoma? *Br. J. Dermatol.* 147, 197–213 (2002).

30 Gorham ED, Garland CF, Garland FC *et al.* Optimal vitamin D status for colorectal cancer prevention a quantitative meta analysis. *Am. J. Prev. Med.* 32, 210–216 (2007).

•• Provides the dose–response relation for vitamin D and colorectal cancer.

31 Garland CF, Gorham ED, Mohr SB *et al.* Vitamin D and prevention of breast cancer: Pooled analysis. *J. Steroid. Biochem. Mol. Biol.* 103, 708–711 (2007).

• Provides the dose–response relation for vitamin D and breast cancer.

32 Hill AB. The environment and disease: association or causation? *Proc. R. Soc. Med.* 58, 295–300 (1965).

33 Hughes AM, Armstrong BK, Vajdic CM *et al.* Sun exposure may protect against non-Hodgkin lymphoma: a case–control study. *Int. J. Cancer* 112, 865–871 (2004).

34 Bentham G. Association between incidence of non-Hodgkin's lymphoma and solar ultraviolet radiation in England and Wales. *Br. Med. J.* 312, 1128–1131 (1996).

35 Purdue MP, Hartge P, Davis S *et al.* Sun exposure, vitamin D receptor gene polymorphisms and risk of non-Hodgkin lymphoma. *Cancer Causes Control.* 18, 989–999 (2007).

36 Skinner HG, Michaud DS, Giovannucci E *et al.* Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epidemiol. Biomarkers Prev.* 15, 1688–1695 (2006).

• Reports strong evidence that vitamin D reduces the risk of pancreatic cancer.

37 Stolzenberg-Solomon RZ, Vieth R, Azad A *et al.* A prospective nested case-control study of vitamin D status and pancreatic cancer risk in male smokers. *Cancer Res.* 66, 10213–10219 (2006).

38 Tuohimaa P, Tenkanen L, Ahonen M *et al.* Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case–control study in the Nordic countries. *Int. J. Cancer* 108, 104–108 (2004).

39 Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat. Rev. Cancer* 3, 601–614 (2003).

40 Mullin GE, Dobs A. Vitamin D and its role in cancer and immunity: a prescription for sunlight. *Nutr. Clin. Pract.* 22, 305–322 (2007).

•• Good review of the role of UVB and vitamin D in health.

41 Jackson RD, LaCroix AZ, Gass M *et al.* Calcium plus vitamin D supplementation and the risk of fractures. *N. Engl. J. Med.* 354, 669–683 (2006).

42 Wactawski-Wende J, Kotchen JM, Anderson GL *et al.* Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N. Engl. J. Med.* 354, 684–696 (2006).

43 Grant WB, Garland CF. A critical review of studies on vitamin D in relation to colorectal cancer. *Nutr. Cancer* 48, 115–123 (2004).

44 Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am. J. Clin. Nutr.* 85, 1586–1591 (2007).

•• First prospective, double blind vitamin D supplementation study to show a large reduction in cancer incidence.

45 Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control.* 16, 83–95 (2005).

46 Grant WB. Epidemiology of disease risks in relation to vitamin D insufficiency. *Prog. Biophys. Mol. Biol.* 92, 65–79 (2006).

47 Krause R, Matulla-Nolte B, Essers M, Brown A, Hopfenmuller W. UV radiation and cancer prevention: what is the evidence? *Anticancer Res.* 26, 2723–2727 (2006).

48 Kricker A, Armstrong B. Does sunlight have a beneficial influence on certain cancers? *Prog. Biophys. Mol. Biol.* 92, 132–139 (2006).

49 Van der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. *Eur. J. Cancer* 42, 2222–2232 (2006).

50 Davies PD. A possible link between vitamin D deficiency and impaired host defence to *Mycobacterium tuberculosis*. *Tubercle* 66, 301–306 (1985).

51 Liu PT, Stenger S, Li H, Wenzel L *et al.* Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 311, 1770–1773 (2006).

•• Presents new data on how vitamin D helps the immune system fight bacterial infections.

52 Sadeghi K, Wessner B, Laggner U *et al.* Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur. J. Immunol.* 36, 361–370 (2006).

53 Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *J. Immunol.* 179(4), 2060–2063 (2007).

54 Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J. 2005;19:1067-77.

•• Paper further elucidates the mechanism on cathelicidin induction by calcitriol.

55 Martineau AR, Honecker FU, Wilkinson RJ, Griffiths CJ. Vitamin D in the treatment of pulmonary tuberculosis. *J. Steroid. Biochem. Mol. Biol.* 103, 793–798 (2007).

56 Martineau AR, Wilkinson RJ, Wilkinson KA *et al.* A single dose of vitamin D enhances immunity to mycobacteria. *Am. J. Respir. Crit. Care Med.* 176, 208–213 (2007).

57 Tachi Y, Shimpuku H, Nosaka Y *et al.* Vitamin D receptor gene polymorphism is associated with chronic periodontitis. *Life Sci.* 73, 3313–3321 (2003).

58 Dietrich T, Nunn M, Dawson-Hughes B, Bischoff-Ferrari HA. Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. *Am. J. Clin. Nutr.* 82, 575–580 (2005).

59 Mohammad Alizadeh AH, Ranjbar M *et al.* Association of promoter polymorphism of the CD14 C (-159) T endotoxin receptor gene with chronic hepatitis B. *World J. Gastroenterol.* 12, 5717–5720 (2006).

60 Cannell JJ, Vieth R, Umhau JC *et al.* Epidemic influenza and vitamin D. *Epidemiol. Infect.* 134, 1129–1140 (2006).

•• First paper to suggest that the seasonal variation in epidemic influenza was related to seasonal variations in solar UVB and vitamin D production.

61 Aloia JF, Li-Ng M. Correspondence. *Epidemiol. Infect.* (2007) (Epub ahead of print).

•• Provides experimental support to the hypothesis in [60].

62 Avenell A, Cook JA, Maclennan GS, Macpherson GC. Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing* (2007) (Epub ahead of print).

63 Yusuf S, Piedimonte G, Auais A *et al.* The relationship of meteorological conditions to the epidemic activity of respiratory syncytial virus. *Epidemiol. Infect.* 135(7), 1077–1090 (2007).

•• Reports that solar UVB explained some of the variance in annual variations in a viral infection.

64 van Etten E, Verlinden L, Giulietti A *et al.* The vitamin D receptor gene *FokI* polymorphism: functional impact on the immune system. *Eur. J. Immunol.* 37, 395–405 (2007).

65 Viboud C, Tam T, Fleming D, Miller MA, Simonsen L. 1951 influenza epidemic, England and Wales, Canada, and the United States. *Emerg. Infect. Dis.* 12, 661–668 (2006).

66 Beadling C, Slifka MK. How do viral infections predispose patients to bacterial infections? *Curr. Opin. Infect. Dis.* 17, 185–191 (2004).

67 Danai PA, Moss M, Mannino DM, Martin GS. The epidemiology of sepsis in patients with malignancy. *Chest.* 129, 1432–1440 (2006).

68 Esper AM, Moss M, Lewis CA, Nisbet R, Mannino DM, Martin GS. The role of infection and comorbidity: factors that influence disparities in sepsis. *Crit. Care. Med.* 34, 2576–2582 (2006).

69 Danai PA, Sinha S, Moss M, Haber MJ, Martin GS. Seasonal variation in the epidemiology of sepsis. *Crit. Care Med.* 35, 410–415 (2007).

70 Kurtzke JF. Geographic distribution of multiple sclerosis: an update with special reference to Europe and the Mediterranean region. *Acta Neurol. Scand.* 62, 65–80 (1980).

71 Wallin MT, Page WF, Kurtzke JF. Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. *Ann. Neurol.* 55, 65–71 (2004).

72 van der Mei IA, Ponsonby AL, Blizzard L, Dwyer T. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. *Neuroepidemiology* 20, 168–174 (2001).

• Links solar UVB irradiance in winter during childhood to reduced risk of multiple sclerosis (MS).

73 Islam T, Gauderman WJ, Cozen W, Mack TM. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. *Neurology* 69, 381–388 (2007).

- Provides additional evidence on the role of childhood UVB irradiance and risk of MS.

74 Goldacre MJ, Seagroatt V, Yeates D, Acheson ED. Skin cancer in people with multiple sclerosis: a record linkage study. *J. Epidemiol. Community Health.* 58, 142–144 (2004).

75 Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 296, 2832–2838 (2006).
- Reports that the risk of MS was inversely correlated with prediagnostic serum calcidiol level.

76 Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: noninfectious factors. *Ann. Neurol.* 61, 504–513 (2007).

77 Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog. Biophys. Mol. Biol.* 92, 60–64 (2006).

78 Hypponen E, Laara E, Reunanen A *et al.* Intake of vitamin D and risk of type I diabetes: a birth-cohort study. *Lancet.* 358, 1500–1503 (2001).

79 Merlino LA, Curtis J, Mikuls TR *et al.* Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis. Rheum.* 50, 72–77 (2004).

80 Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension.* 30, 150–156 (1997).

81 Forman JP, Giovannucci E, Holmes MD *et al.* Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension.* 49, 1063–1069 (2007).
- Good evidence that vitamin D reduces the risk of hypertension.

82 Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog. Biophys. Mol. Biol.* 92, 39–48 (2006).
- Reviews the evidence regarding the role of vitamin D in reducing the risk of cardiovascular disease.

83 Martins D, Wolf M, Pan D *et al.* Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the third national health and nutrition examination survey. *Arch. Intern. Med.* 167, 1159–1165 (2007).
•• Good evidence that calcidiol level is inversely correlated with many biological indicators of cardiovascular disease.

84 Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br. J. Nutr.* 89, 552–572 (2003).

85 Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am. J. Clin. Nutr.* 79, 362–371 (2004).
- Excellent review of the health benefits of vitamin D as known in 2004.

86 Peterlik M, Cross HS. Dysfunction of the vitamin D endocrine system as common cause for multiple malignant and other chronic diseases. *Anticancer Res.* 26, 2581–2588 (2006).

87 Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson–Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am. J. Clin. Nutr.* 84, 18–28 (2006).
- Estimate of vitamin D requirement for optimal health.

88 Holick MF. Vitamin D deficiency. *N. Engl. J. Med.* 357, 266–281 (2007).
•• Excellent review of the health benefits of vitamin D.

89 Vieth R, Bischoff-Ferrari H, Boucher BJ *et al.* The urgent need to recommend an intake of vitamin D that is effective. *Am. J. Clin. Nutr.* 85, 649–650 (2007).
- Impassioned plea to revise healthcare policies regarding vitamin D.

90 Lucas R, McMichael T, Smith W, Armstrong B. Solar ultraviolet radiation: global burden of disease from solar ultraviolet radiation. *Environmental Burden of Disease Series. No. 13.* World Health Organization (2006).
•• Tour de force review of the evidence regarding the role of solar UVB and vitamin D in many health outcomes.

91 Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int.* 15, 897–902 (2004).

92 Lucas RM, Repacholi MH, McMichael AJ. Is the current public health message on UV exposure correct? *Bull. World Health Organ.* 84, 485–491 (2006).

93 Grant WB. The current public health message on UV exposure overlooks many of the health benefits. *Bull. World Health Organ.* 85(5), A419 (2007).

94 Norval M, Cullen AP, de Gruijl FR *et al.* The effects on human health from stratospheric ozone depletion and its interactions with climate change. *Photochem. Photobiol. Sci.* 6, 232–251 (2007).

95 de Gruijl FR, Longstreth J, Norval M *et al.* Health effects from stratospheric ozone depletion and interactions with climate change. *Photochem. Photobiol. Sci.* 2, 16–28 (2003).

96 Grant WB, Moan J, Reichrath J. Comment on "The effects on human health from stratospheric ozone depletion and its interactions with climate change by M. Norval, A.P. Cullen, F.R. de Gruijl, J. Longstreth, Y. Takizawa, R.M. Lucas, F.P. Noonan and J.C. van der Leun, Photochem. Photobiol. Sci., 2007, 6, 232. *Photochem. Photobiol. Sci.* 6, 912–915 (2007).

97 Norval M, de Gruijl FR. Reply to the 'Comment on "The effects on human health from stratospheric ozone depletion and its interactions with climate change"' By WB Grant, J. Moan and J. Reichrath, Photochem. Photobiol. Sci., 2007, 6, DOI: 10.1039/b705482c. *Photochem. Photobiol. Sci.* 6, 916–918 (2007).

98 Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? *J. Am. Acad. Dermatol.* 54, 301–317 (2006).

99 Gilchrest BA. Sun protection and vitamin D: three dimensions of obfuscation. *J. Steroid. Biochem. Mol. Biol.* 103, 655–663 (2007).

100 English DR, Armstrong BK, Kricker A *et al.* Case–control study of sun exposure and squamous cell carcinoma of the skin. *Int. J. Cancer* 77, 347–353 (1998).

101 Agar NS, Halliday GM, Barnetson RS *et al.* The basal layer in human squamous tumors harbors more UVA than UVB fingerprint mutations: a role for UVA in human skin carcinogenesis. *Proc. Natl Acad. Sci. USA* 101, 4954–4959 (2004).

102 Garland CF, Garland FC, Gorham ED. Rising trends in melanoma. An hypothesis concerning sunscreen effectiveness. *Ann. Epidemiol.* 3, 103–110 (1993).
- Paper points out that UVA was an important risk factor for melanoma and that sunscreens not blocking UVA could increase the risk of melanoma.

103 Scotto J, Fears TR, Kraemer KH, Fraumeni JF Jr. Nonmelanoma skin cancer. In: *Cancer Epidemiology and Prevention (2nd Edition).* Schottenfeld D, Fraumeni JF Jr (Eds). Oxford University Press, NY, USA, 1313–1330 (1996).
- Data in this paper support the role of UVA in the etiology of melanoma.

104 Moan J, Dahlback A, Setlow RB. Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem. Photobiol.* 70, 243–247 (1999).

- Data in this paper support the role of UVA in the etiology of melanoma.

105 Kricker A, Armstrong BK, Goumas C *et al.* Ambient UV, personal sun exposure and risk of multiple primary melanomas. *Cancer Causes Control* 18, 295–304 (2007).

106 Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. Version 2.0.* IARC Press, Lyon, France (2004).

107 Kennedy C, Bajdik CD, Willemze R *et al.* 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 (2003).

108 Gandini S, Sera F, Cattaruzza MS *et al.* Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur. J. Cancer* 41, 45–60 (2005).
- Reports that, in many studies, chronic UV irradiance was correlated with reduced risk for melanoma.

109 Berwick M, Armstrong BK, Ben-Porat L *et al.* Sun exposure and mortality from melanoma. *J. Natl Cancer Inst.* 97, 195–199 (2005).
- Reports that all measures of long-term solar UV irradiance were associated with increased survival for melanoma.

110 Agar N, Young AR. Melanogenesis: a photoprotective response to DNA damage? *Mutat. Res.* 571, 121–132 (2005).

111 Lang J, Hayward N, Goldgar D *et al.* The *M53I* mutation in *CDKN2A* is a founder mutation that predominates in melanoma patients with Scottish ancestry. *Genes Chromosomes Cancer* 46, 277–287 (2007).

112 De Fabo EC, Noonan FP, Fears T, Merlino G. Ultraviolet B but not ultraviolet A radiation initiates melanoma. *Cancer Res.* 64, 6372–6376 (2004).

113 De Fabo EC. Initial studies on an *in vivo* action spectrum for melanoma induction. *Prog. Biophys. Mol. Biol.* 92, 97–104 (2006).

114 Hill HZ, Hill GJ. UVA, pheomelanin and the carcinogenesis of melanoma. *Pigment Cell Res.* 13(Suppl. 8), 140–144 (2000).

115 Azizi E, Lusky A, Kushelevsky AP, Schewach-Millet M. Skin type, hair color, and freckles are predictors of decreased minimal erythema ultraviolet radiation dose. *J. Am. Acad. Dermatol.* 19, 32–38 (1988).

116 Wang SQ, Setlow R, Berwick M, Polsky D, Marghoob AA, Kopf AW, Bart RS. Ultraviolet A and melanoma: a review. *J. Am. Acad. Dermatol.* 44, 837–846 (2001).

117 Millen AE, Tucker MA, Hartge P *et al.* Diet and melanoma in a case-control study. *Cancer Epidemiol. Biomarkers Prev.* 13, 1042–1051 (2004).
- Reports strong correlations for melanoma with dietary factors.

118 Fears TR, Bird CC, Guerry D 4th *et al.* Average midrange ultraviolet radiation flux and time outdoors predict melanoma risk. *Cancer Res.* 62, 3992–3996 (2002).

119 Eide MJ, Weinstock MA. Association of UV index, latitude, and melanoma incidence in nonwhite populations – US Surveillance, Epidemiology, and End Results (SEER) Program, 1992 to 2001. *Arch. Dermatol.* 141, 477–481 (2005).

120 Bentham G, Aase A. Incidence of malignant melanoma of the skin in Norway, 1955–1989: associations with solar ultraviolet radiation, income and holidays abroad. *Int. J. Epidemiol.* 25, 1132–1138 (1996).

121 Agredano YZ, Chan JL, Kimball RC, Kimball AB. Accessibility to air travel correlates strongly with increasing melanoma incidence. *Melanoma Res.* 16, 77–81 (2006).
- Provides strong evidence that air travel is linked to risk of melanoma.

122 Garcia RL, Davis CM. PABA. A more effective sunscreen. *Mil. Med.* 138, 331–333 (1973).

123 Diffey BL. Sunscreens and melanoma: the future looks bright. *Br. J. Dermatol.* 153, 378–381 (2005).

124 Dennis LK, Beane Freeman LE, VanBeek MJ. Sunscreen use and the risk for melanoma: a quantitative review. *Ann. Intern. Med.* 139, 966–978 (2003).

125 Rodenas JM, Delgado-Rodriguez M, Herranz MT, Tercedor J, Serrano S. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case–control study in a Mediterranean population. *Cancer Causes Control.* 7, 275–283 (1996).

126 Espinosa Arranz J, Sanchez Hernandez JJ, Bravo Fernandez P *et al.* Cutaneous malignant melanoma and sun exposure in Spain. *Melanoma Res.* 9, 199–205 (1999).

127 Gallagher RP, Lee TK, Bajdik CD. Sunscreens: can they prevent skin cancer? *Prevention of Skin Cancer.* Hill D, Elwood JM, English DR (Eds). Kluwer Academic Publishers, The Netherlands, 141–156 (2004).

128 Doré JF, Boniol M, Chignol MC, Autier P. The usefulness of sunscreens. In: *Skin Cancer Prevention.* Ringborg U, Brandberg Y, Breitbart EW, Greinert R (Eds). Informa Healthcare, NY, USA, 241–278 (2007).

129 Autier P, Boniol M, Dore JF. Sunscreen use and increased duration of intentional sun exposure: still a burning issue. *Int. J. Cancer* 121, 1–5 (2007).

130 Hussein MR. Ultraviolet radiation and skin cancer: molecular mechanisms. *J. Cutan. Pathol.* 32, 191–205 (2005).

131 Boniol M, Doré JF, Autier P, Smans M, Boyle P. Descriptive epidemiology of skin cancer incidence and mortality. In: *Skin Cancer Prevention.* Ringborg U, Brandberg Y, Breitbart EW, Greinert R (Eds). Informa Healthcare, NY, USA, 203–223 (2007).

132 Taylor HR. Ultraviolet radiation and the eye: an epidemiologic study. *Trans. Am. Ophthalmol. Soc.* 87, 802–853 (1989).

133 Fisher GJ, Kang S, Varani J *et al.* Mechanisms of photoaging and chronological skin aging. *Arch. Dermatol.* 138, 1462–1470 (2002).

134 Norval M. The effect of ultraviolet radiation on human viral infections. *Photochem. Photobiol.* 82, 1495–1504 (2006).

135 Sanders CJ, Van Weelden H, Kazzaz GA *et al.* Photosensitivity in patients with lupus erythematosus: a clinical and photobiological study of 100 patients using a prolonged phototest protocol. *Br. J. Dermatol.* 149, 131–137 (2003).

136 He YY, Ramirez DC, Detweiler CD, Mason RP, Chignell CF. UVA-ketoprofen-induced hemoglobin radicals detected by immuno-spin trapping. *Photochem. Photobiol.* 77, 585–591 (2003).

137 Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. *Altern. Med. Rev.* 10, 94–111 (2005).

138 Webb AR. Who, what, where and when – influences on cutaneous vitamin D synthesis. *Prog. Biophys. Mol. Biol.* 92, 17–25 (2006).
- Provides a good discussion of photoproduction of vitamin D.

139 Webb AR, DeCosta BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. *J. Clin. Endocrinol. Metab.* 68, 882–887 (1989).

140 Adams JS, Clemens TL, Parrish JA, Holick MF. Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects. *N. Engl. J. Med.* 306, 722–725 (1982).

141 Samanek AJ, Croager EJ, Gies P *et al.* Estimates of beneficial and harmful sun exposure times during the year for major Australian population centres. *Med. J. Aust.* 184, 338–341 (2006).

142 Webb AR, Engelsen O. Calculated ultraviolet exposure levels for a healthy vitamin D status. *Photochem. Photobiol.* 82, 1697–1703 (2006).

• Gives good estimates of time required for photoproduction of vitamin D from solar UVB.

143 Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am. J. Clin. Nutr.* 77, 204–210 (2003).

• This paper finds that the body can utilize about 3600 IU of vitamin D3 per day.

144 Harris SS. Vitamin D and African Americans. *J. Nutr.* 136, 1126–1129 (2006).

145 MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J. Clin. Invest.* 76, 1536–1538 (1985).

146 Looker AC, Dawson-Hughes B, Calvo MS *et al.* Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone* 30, 771–777 (2002).

147 Matsuoka LY, Wortsman J, Hanifan N, Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D. A preliminary study. *Arch. Dermatol.* 124, 1802–1804 (1988).

148 Marks R, Foley PA, Jolley D *et al.* The effect of regular sunscreen use on vitamin D levels in an Australian population. Results of a randomized controlled trial. *Arch. Dermatol.* 131, 415–421 (1995).

149 Newton R, Roman E, Fear N, Carpenter L. Non-Hodgkin's lymphoma and solar ultraviolet radiation. Data are inconsistent. *Br. Med. J.* 313, 298 (1996).

150 Gardner MJ, Winter PD, Taylor CP, Acheson ED. *Atlas of Cancer Mortality in England and Wales, 1968–1978.* John Wiley & Sons, NY, USA (1983).

151 Sliney DH, Wengraitis S. Is a differentiated advice by season and region necessary? *Prog. Biophys. Mol. Biol.* 92, 150–160 (2006).

152 Sheehan JM, Cragg N, Chadwick CA, Potten CS, Young AR. Repeated ultraviolet exposure affords the same protection against DNA photodamage and erythema in human skin types II and IV but is associated with faster DNA repair in skin type IV. *J. Invest. Dermatol.* 118, 825–829 (2002).

153 Koutkia P, Lu Z, Chen TC, Holick MF. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. *Gastroenterology.* 121, 1485–1488 (2001).

154 Tangpricha V, Turner A, Spina C *et al.* 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 (2004).

• Reports much higher calcidiol levels in young men who use sunbeds.

155 Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. *Am. J. Clin. Nutr.* 84, 694–697 (2006).

156 Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women. *JAMA* 287, 47–54 (2002).

157 Johansson S, Melhus H. Vitamin A antagonizes calcium response to vitamin D in man. *J. Bone Miner. Res.* 16, 1899–1905 (2001).

158 Scientific Advisory Committee on Nutrition. *Update on Vitamin D. Position Statement by the Scientific Advisory Committee on Nutrition.* Her Majesty's Stationary Office, Colegate, Norwich, UK, 68 (2007).

159 Lu Z, Chen TC, Zhang A *et al.* An evaluation of the vitamin D3 content in fish: is the vitamin D content adequate to satisfy the dietary requirement for vitamin D? *J. Steroid. Biochem. Mol. Biol.* 103, 642–644 (2007).

160 Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am. J. Clin. Nutr.* 80, S1710–S1716 (2004).

161 Whiting SJ, Calvo MS. Dietary recommendations to meet both endocrine and autocrine needs of Vitamin D. *J. Steroid. Biochem. Mol. Biol.* 97, 7–12 (2005).

162 Natri AM, Salo P, Vikstedt T *et al.* Bread fortified with cholecalciferol increases the serum 25-hydroxyvitamin D concentration in women as effectively as a cholecalciferol supplement. *J. Nutr.* 136, 123–127 (2006).

163 Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* 296, 1885–1899 (2006).

164 Dahl-Jorgensen K, Joner G, Hanssen KF. Relationship between cows' milk consumption and incidence of IDDM in childhood. *Diabetes Care.* 14, 1081–1083 (1991).

165 Adebamowo CA, Spiegelman D, Danby FW *et al.* High school dietary dairy intake and teenage acne. *J. Am. Acad. Dermatol.* 52, 207–214 (2005).

166 Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am. J. Clin. Nutr.* 81, 1147–1154 (2005).

167 Chen H, O'Reilly E, McCullough ML *et al.* Consumption of dairy products and risk of Parkinson's disease. *Am. J. Epidemiol.* 165, 998–1006 (2007).

168 Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am. J. Clin. Nutr.* 77, 504–511 (2003).

169 Tangpricha V, Koutkia P, Rieke SM *et al.* Fortification of orange juice with vitamin D: a novel approach for enhancing vitamin D nutritional health. *Am. J. Clin. Nutr.* 77, 1478–1483 (2003).

170 Reichrath J. The challenge resulting from positive and negative effects of sunlight: how much solar UV exposure is appropriate to balance between risks of vitamin D deficiency and skin cancer? *Prog. Biophys. Mol. Biol.* 92, 9–16 (2006).

171 Lucas RM, Ponsonby AL. Considering the potential benefits as well as adverse effects of sun exposure: can all the potential benefits be provided by oral vitamin D supplementation? *Prog. Biophys. Mol. Biol.* 92, 140–149 (2006).

172 Grant WB, Garland CF, Holick, MF. Comparisons of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar UV irradiance for the United States. *Photochem. Photobiol.* 81, 1276–1286 (2005).

• Demonstrates that the economic benefits of solar UVB and vitamin D greatly outweigh the adverse effects in the USA.

173 Grant WB. Insufficient sunlight may kill 45,000 Americans each year from internal cancer. *J. Cos. Dermatol.* 3, 176–178 (2004).

174 Grant WB. Dietary links to Alzheimer's disease. *Alz. Dis. Rev.* 2, 42–55 (1997).

175 Albert MR, Ostheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 1. *J. Am. Acad. Dermatol.* 47, 930–937 (2002).

176 Montague M, Borland R, Sinclair C. Slip! Slop! Slap! and SunSmart, 1980–2000: Skin cancer control and 20 years of population-based campaigning. *Health Educ. Behav.* 28, 290–305 (2001).

177 van der Mei IA, Ponsonby AL, Engelsen O *et al.* The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. *Environ. Health Perspect.* 115, 1132–1139 (2007).

• Results reported in this paper indicate the sun avoidance policy advocated in Australia may be reducing serum calcidiol levels.

Websites

201 Cancer Mortality Maps & Graphs http://cancer.gov/atlasplus/new.html

202 Canadian Cancer Society Announces Vitamin D Recommendation www.cancer.ca/ccs/internet/mediareleaselist/0,3208,3172_1613121606_1997621989_langId-en,00.html

•• This report shows that at least one major cancer organization accepts the role of vitamin D in reducing the risk of cancer.

203 Environmental Burden of Disease Series, No. 13 www.who.int/uv/health/solaruvradfull_180706.pdf

204 Current Public Health Message on UV Exposure Overlooks Many Health Benefits www.who.int/bulletin/volumes/85/5/06-035089.pdf

205 CANCERMondial Statistical Information System www-dep.iarc.fr

206 Risks and Benefits of Sun Exposure: Position Statement www.cancer.org.au/documents/RisksBenefitsSunExposure03May07.pdf

207 SACN: Scientific Advisory Committee on Nutrition Reports www.sacn.gov.uk/reports/#

208 Dietary Links to Alzheimer's Disease www.sunarc.org/JAD97.pdf

Affiliation

• *William B Grant, PhD*
Founding Director, Sunlight, Nutrition, and Health Research Center, 2115 Van Ness Avenue, Suite 101, San Francisco, CA 94109, USA
Tel.: +1 415 409 1980
Fax: +1 415 931 6537
wbgrant@infionline.net
www.sunarc.org