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## **Epidemiological evaluations of sun-induced vitamin D**

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### **Abstract**

The non-calcemic health benefits of solar ultraviolet-B (UVB) radiation and vitamin D are being recognized as very important for optimal health. The role of UVB in reducing the risk of cancer was suggested by the Garlands in 1980 based on inspection of the map of colon cancer mortality rates in the United States. Since then, numerous ecological, cohort, case-control, laboratory studies and one well-conducted prospective population-based, double-blind, randomized, placebo-controlled study have confirmed the beneficial role of both in reducing the risk of nearly 20 types of cancer, primarily those for the digestive tract, reproductive and urogenital organs, the female breast, and lymphomas. The evidence that vitamin D reduces the risk of many types of cancer is strong. More recently, several papers have provided evidence that vitamin D reduces the risk not only of diseases caused by bacterial infections but also those caused by viral infections. A corollary of this finding is that the beneficial role of UVB and vitamin D in reducing the risk of autoimmune diseases such as multiple sclerosis and cancers such as prostate cancer, both of which have incidence and mortality rates that increase rapidly with increasing latitude, a mark of wintertime UVB/vitamin D, especially in the United States, may be related to reducing the risk of viral infections. In addition, the role of vitamin D in reducing the risk of viral infections such as influenza helps explain the seasonal variation in birth rates for neurological diseases such as schizophrenia. There have also been a number of observational studies linking low serum 25-hydroxyvitamin D (calcidiol) levels to increased risk of metabolic diseases such as cardiovascular disease. It appears that serum 25-hydroxyvitamin D (calcidiol) levels should be above 40 ng/mL for significant health benefits.

## **Introduction**

Vitamin D is essential for optimal health, and solar ultraviolet-B (UVB) is the primary source of vitamin D for most people on Earth. Skin pigmentation adapted to local solar UV doses as humans migrated from Africa to less sunny locations (1). Pigmentation is dark enough to lessen the effects of free radical formation and folate destruction but light enough to permit enough UVB to penetrate the epidermis to produce vitamin D. However, in the past few centuries, the natural relation between humans and the sun changed in several profound ways: many people migrated to locations where their skin was either too pale or too dark for prevailing solar UVB doses and people began spending less time in the sun and more time indoors. Also, sunscreens were developed that enabled people to spend more time in the sun without burning but also reduced the production of vitamin D. These changes have led to reduced vitamin D production, which the health care system and the general public are slowly realizing (2). Vitamin D has now been recognized to be important not only for its role in calcium absorption and metabolism but also in reducing the risk of cancer (3), infectious diseases caused by bacteria (4) and viruses (5), autoimmune diseases (6), and circulatory diseases (7).

Ecological studies related to solar UVB and geographical location made many of these links. More studies on the health effects of solar UVB have been made using not only the ecological approach but also the case-control and cohort approaches, but few prospective studies have been conducted. Thus, reviewing and evaluating the ecological and observational studies, using the laboratory and prospective studies to help interpret the findings, is appropriate. All types of studies have strengths and weaknesses: ecological and observational studies may not have included some of the risk-modifying factors that are correlated with UVB and vitamin D; observational studies using serum 25-hydroxyvitamin D (calcidiol) several years prior to cancer discovery may not use a parameter appropriate for the entire period; and prospective studies may not be related to sufficient oral intake of vitamin D or may overlook photoproduction of vitamin D. Thus, the more studies of high scientific quality, with different design and approaches that support a beneficial role of UVB and vitamin D, the more likely the link can be considered causal.

### **Beneficial role of UVB in reducing the risk of disease**

#### **Cancer**

After seeing the atlas of colon cancer mortality rates in the United States, Garland and Garland (8) proposed the UVB/vitamin D/cancer theory. They realized that cancer rates were lowest in the sunniest parts of the country. They hypothesized that since vitamin D production is the most important

physiological effect of solar radiation, vitamin D must reduce the risk of cancer. This hypothesis was largely unacknowledged. In 1985, they showed that dietary vitamin D was inversely correlated with colorectal cancer incidence (9) and in 1989 that serum calcidiol was as well (10). In 1990, Schwartz hypothesized that solar UVB and vitamin D reduced the risk of prostate cancer (11). The Garlands added breast cancer (12) and ovarian cancer (13) to the list of vitamin D-sensitive cancers. About the same time that the Garland group reported their breast cancer findings, laboratory results on vitamin D and breast cancer were also reported (14).

When I entered the field around 2000, the updated *Atlas of Cancer Mortality in the United States, 1950-94* (15) had just been published. When I looked at the maps, I was struck by how many maps were similar to those for breast, colon, and ovarian cancer. Since I worked at NASA Langley Research Center in atmospheric sciences with an emphasis on ozone and aerosols, I was aware of the UVB dose map for July 1992 prepared by NASA Goddard Space Flight Center, using data from the Total Ozone Mapping Spectrometer (TOMS) (16). The asymmetry of the UVB doses was a good match to the cancer maps. UVB doses east of the Rocky Mountains are generally comparable to those to the west about 1000 to 1300 km to the north because of two important factors: surface elevation is generally higher in the west and the stratospheric ozone layer is lower in the west as the prevailing westerly winds push the tropopause higher as the air masses prepare to cross the Rocky Mountains. In winter, latitude is a better index of solar UVB dose. The half-life residence time of vitamin D in the body is 1–2 months, so that vitamin D produced in summer or fall will not last through winter. I digitized the UVB data to the approximately 500 state economic areas in the middle-resolution cancer maps and ran linear regression analyses for all of the cancers. I thus found 14 cancers that were UVB/vitamin D sensitive, nine more than had been determined up to that time (17). Although this finding got much attention, the study was criticized on two counts: (i) that the analysis did not include other cancer risk-modifying factors and (ii) that the analysis omitted several states (18). These states were primarily those along the U.S. border with Mexico, which had many residents of Hispanic heritage who were included in the category “white Americans.” In response, I redid the analysis, adding the following risk factors averaged at the state level: alcohol consumption, fraction of the population with Hispanic heritage, lung cancer as the index of the health effects of smoking, fraction of the population living below the poverty level, and fraction of the population living in urban centers. After I submitted the work to several journals, it was finally published in 2006 (19).

Other studies have provided more support for the UVB/vitamin D/cancer theory. A recent ecological study in the United States used recent incidence and mortality rate data and obtained results similar to those in Grant and Garland

(19), but adding some more cancers (20). One of the important findings in that study was that the correlations with solar UVB were stronger for cancer mortality rates than for cancer incidence rates. This finding suggests both that vitamin D is one of many risk modifying factors affecting cancer incidence and that vitamin D is more effective at fighting cancer in the later stages, perhaps through reducing angiogenesis and the risk of metastasis.

Giovannucci and coworkers at Harvard University applied the UVB/vitamin D/cancer theory to their Health Professionals Follow-up Study. They developed a vitamin D index based on oral vitamin D intake, skin pigmentation, and leisure time spent outdoors on the basis of information on serum calcidiol levels for about 1000 participants and then used this index to examine its relation to cancer incidence rates for the 50,000 members of the cohort. They found six cancers significantly inversely correlated with their vitamin D index and another six cancers insignificantly inversely correlated (21). They also found that their index was inversely correlated with total cancer incidence rates for the black participants (22), confirming my findings for black Americans for which I used data from the *Atlas of Cancer Mortality* in an ecological studies (19,23).

One of the criticisms of the ecological studies using solar UVB doses is that people living in sunnier locations may not receive higher UVB irradiances and produce higher levels of vitamin D. This criticism spurred me to find an index of UVB irradiance at the group level for further studies. The obvious index to use is incidence or mortality rate from nonmelanoma skin cancer (NMSC). The action spectrum for squamous cell carcinoma (SCC) is primarily the UVB region, based on studies of watermen in Maryland (38° N) (24) and use of sunscreen that blocks primarily erythemal UV (25). That of basal cell carcinoma (BCC) appears to be related to both UVA and UVB, based on latitudinal variations in incidence rates (26,27).

In the first of my studies on this topic, I found that diagnosis of NMSC was inversely correlated with development of several types of second primary cancers as long as the health effects of smoking, using lung cancer incidence rates in the study population as the index (28), were included. Smoking is also an important risk factor for SCC (29), so it must be taken into account. SCC accounts for about 80% of NMSC deaths in the United States (30) and other countries with pale-skinned inhabitants. In my other related study, I used NMSC mortality rates as the index of solar UVB irradiance for Spaniards living in 48 continental provinces to analyze the role of solar UVB on cancer mortality rates for 1978–93. I found 17 cancers inversely correlated with NMSC, including melanoma (31). However, it was pointed out that death rates from NMSC in Spain are low, so that the results of this study are not definitive. Thus, I redid the regression analysis as a multiple linear regression including NMSC, latitude, and lung cancer. Fifteen of the cancers retained a statistically significant

correlation with either NMSC or increasing latitude; bladder and endometrial cancer did not.

Several other recent studies have reported that diagnosis or death from NMSC is inversely correlated with internal cancer rates. A study in England found that risk of prostate cancer was reduced by the same sun exposure factors as increased the risk of BCC (32). A similar study in The Netherlands found that development of any type of skin cancer was also inversely correlated with prostate cancer (33). A larger-scale study found that BCC and SCC were inversely correlated with all solid tumors except skin and lip in sunny countries but were not in less sunny countries (34). I pointed out that the results in this study were consistent with UVB being a risk factor for SCC and BCC and UVA for melanoma, and that the results for less sunny countries were due to decoupling of high solar UV irradiance from vitamin D status, perhaps through travel to sunny locations on holiday (35).

Studies to date have found solar UVB and/or vitamin D most strongly protective against cancers of digestive and elimination tract organs, gynecological organs other than the cervix, female breast, urogenital organs, and lymphomas. There is limited evidence that vitamin D reduces the risk of respiratory tract organs (36); smoking is the most important risk factor, with air pollution also playing a role (37). While vitamin D can increase survival times for those diagnosed with lung cancer, it does not seem to prevent death eventually for those living in Norway (38).

The critics also raised another point, that the UVB/vitamin D/cancer theory had not been verified in a prospective population-based, double-blind, randomized, placebo-controlled study. Indeed, the Women's Health Initiative study found no protective effect of vitamin D and calcium for either hip fractures (39) or colon cancer (40). However, they used only 400 IU of vitamin D3 per day along with 1200 mg of calcium, which was insufficient (41); the present understanding is that takes 2800 IU per day to reduce the risk of colorectal cancer by 50% (42; E.D. Gorham, private communication). However, a more recent study in which the postmenopausal women with an average age of 67 years at enrollment were given 1500 mg of calcium and 1100 IU of vitamin D3 per day (which raised serum calcidiol from 29 ng/mL to 38 ng/mL) 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 than for those taking the placebo (43).

The World Cancer Research Fund and the American Institute for Cancer Research recently published a review of the risk of colorectal cancer with respect to oral intake of vitamin D and serum calcidiol (44). Based on a review of 11 cohort studies and 17 case-control studies on vitamin D-intake and four cohort studies of vitamin D status, they concluded "The evidence on vitamin D

was inconsistent. There is limited evidence suggesting that foods containing vitamin D or vitamin D status protect against colorectal cancer.” I reviewed many of the same papers in a paper in 2004 (41) and concluded that most of the studies on oral intake of vitamin D could not have found a significant risk reduction for colorectal cancer since the intake was generally too low. Unfortunately, the recent report did not consider ecological studies.

Thus, many studies nicely confirm the ecological studies based on solar UVB doses. More support for the UVB/vitamin D/cancer theory is found in studies that examine the mechanisms whereby vitamin D reduces the risk of cancer (45–49).

Several recent reviews of the UVB/vitamin D/cancer theory all conclude that the studies generally support the theory (4,50–53). The evidence has increased since these reviews, so the conclusion must be that the UVB/vitamin D/cancer theory should be considered scientifically accepted. This theory is also gaining more credibility in the policy arena. The Canadian Cancer Society recently adopted a policy of recommending 1000 IU of vitamin D<sub>3</sub> per day when adequate solar UVB is not available (54). The Cancer Council of Australia and allied organizations also recently released a position statement on the benefits of solar UVB but was cautious regarding the risk of skin cancer (55).

### **Infectious diseases**

Vitamin D also reduces the risk of bacterial and viral infectious diseases. The first indication was that solar UVB reduced the risk of *Mycobacterium tuberculosis* (TB). Oskar Bernhard used sunlight to treat those with TB starting in 1902, as did Auguste Rollier a bit later in an approach called heliotherapy (56). A discussion of this interesting history can be found in *The Healing Sun* (57). Vitamin D deficiency is still an important risk factor for TB (58). High doses of vitamin D<sub>2</sub> have been used to treat TB (59). 25-dihydroxyvitamin D (calcitriol) induces the production of human cathelicidin (LL-37) (60), which has powerful antimicrobial activity and potent antiendotoxin activity (61) and enhances the innate immune system to where it can combat bacterial (62,63) and viral (63) infections.

A recent study hypothesized that the annual solar UVB cycle explains the seasonal variation in influenza rates (64). Experimental support for this hypothesis was quickly supplied through an analysis of incidence rates of influenza and common colds in a prospective double-blind trial of supplemental vitamin D for prevention of bone disease in 208 African American postmenopausal women living in or near Mineola, New York. The women were enrolled in a 3-year randomized clinical trial. Half were given 800 IU per day of vitamin D<sub>3</sub> the first 2 years and 2000 IU the third year, and half were given a placebo. Every 3 months the women were interviewed and asked whether they

had experienced a cold or influenza in the previous 3 months. Twenty-six women taking the placebo reported having at least one of these illnesses, compared with seven taking 800 IU/day and only one taking 2000 IU/day (5).

More support came from a study of incidence of respiratory syncytial virus with respect to meteorological parameters in several cities (65). Solar UVB was found to explain 13% of the variance in Miami, Florida; 5% in Buffalo, New York; but only 0.6% in Winnipeg, Manitoba. The change with latitude is consistent with lower UVB at higher latitudes, especially since solar UVB doses are too low in winter to produce vitamin D above about 40° N (66). Low temperature and low relative humidity were also found to be important risk factors.

These findings very likely apply to other respiratory infections caused by viruses and bacteria, especially those that have higher incidence rates in winter. An extension of these findings is that low calcidiol levels probably increase the risk of severe sepsis (septicemia). Septicemia is generally caused by bacteria such as *Staphylococcus aureus* (67), sometimes after a respiratory disease caused by a viral infection (68). The epidemiology of septicemia in the United States (69,70) seems to be well explained by what is known about the epidemiology of solar UVB and calcidiol in the United States (Grant, *Alt Med Rev*, submitted). The seasonal variation of gastroenteritis caused by astrovirus, norovirus, and rotavirus in the United Kingdom is highly inversely correlated with serum calcidiol levels one month prior to the numbers of cases (71, Grant, submitted), and, thus, also likely related to calcidiol levels. However, it is also possible that solar UVB kills these viruses in the water as they flow from sewage treatment plants to the ocean where shellfish destined for human consumption live.

### **Multiple sclerosis**

Multiple sclerosis (MS) is a demyelinating disease marked by patches of hardened tissue in the brain on the spinal cord and associated with partial or complete paralysis and jerking tremor. It is an autoimmune disease, for which infectious mononucleosis, caused by the Epstein-Barr virus, is an important risk factor (72). The prevalence of MS has a pronounced increase with increasing latitude in Europe (73), the United States (74), and Australia (75). Vitamin D is a risk reduction factor for MS (6). I showed that the geographic variation of MS in the United States (74) can be fitted with a second-order function of latitude (76). This index is partly an index of wintertime solar UVB and vitamin D and partly an index of temperature and relative humidity. On the basis of the UVB doses for July from TOMS (16), it is definitely not an index of summertime UVB and vitamin D. Thus, it appears that the risk of MS is due largely to viral infections in winter (77). One role of vitamin D in reducing the risk of MS is then reducing the risk of viral infections. There are other mechanisms as well,

such as shifting the T-helper (Th) balance from Th-1 toward Th-2, thereby reducing the inflammatory response by cytokines (78,79).

### **Prostate cancer**

Prostate cancer has a geographical variation in mortality rate in the United States that is more closely linked to latitude than to summertime UVB (19). This variation is similar to that for MS (80). Given that MS is linked to viral infections, by analogy it appears that risk of prostate cancer might be, too. Indeed, there is evidence that viral infections increase the risk of prostate cancer (81–83) and that chronic inflammation, a hallmark of infection, is also an important risk factor for prostate cancer (84,85). Thus, I hypothesize that solar UVB, by reducing the risk of viral infections through vitamin D production, may explain why prostate cancer has a more symmetrical latitudinal variation in the United States than that of other cancers such as breast and colon cancer (77). Since viruses are also risk factors for other types of cancer, and since several other cancers also have a similar latitudinal component (bladder, gastric, testicular, thyroid cancer, Hodgkin's and non-Hodgkin's lymphoma) this hypothesis should apply to them as well (77).

### **Metabolic disease**

There is increasing observational evidence that vitamin D also reduces the risk of metabolic diseases. An ecological study (86) linked hypertension to low vitamin D levels. The results of a cohort study (87) and the analysis of data from the Third National Health and Nutrition Examination Survey (88) support this hypothesis. Several papers noted that serum calcidiol is inversely correlated with cardiovascular disease risk factors (89-91). Recently, it was reported from the Framingham Offspring Study that individuals with hypertension with 25-OH D < 15 ng/mL had a multivariable-adjusted hazard ratio of 2.13 (95% confidence interval 1.30 to 3.48) (7). While more work is required to evaluate this link, it seems reasonably likely.

### **Schizophrenia**

Schizophrenia is a disease for which there is a pronounced seasonality in birth rates, with higher rates in spring and lower rates in fall. McGrath has long suggested that low maternal serum calcidiol level during pregnancy was the primary cause of this phenomenon (92). He also showed that influenza epidemics are followed by an increased birth rate for schizophrenia 5 months later (93). Recent studies with rats support both the influenza (94) and the vitamin D (95) hypotheses. The mechanism involved appears to be hyperthermia, which is a well-known risk factor for birth defects (96).

There are several excellent reviews on the role of UVB and vitamin D in maintaining optimal health (3,41,76,97–103).

## Summary and conclusion

Solar UVB, through production of vitamin D, has been observed to be inversely correlated with a growing number of conditions and diseases. Prospective studies are finally being properly designed to test the UVB/vitamin D hypotheses. The adequate intake level of vitamin D<sub>3</sub> indicated by the emerging scientific studies is 1000–4000 IU/day (5,41-43,64,88,89) and that serum calcidiol should be above 40 ng/mL (43). Vitamin D<sub>2</sub> appears to be much less effective in reducing the risk of disease (104). Adequate vitamin D from all sources including oral intake and production from natural and artificial UVB is essential for optimal health. The health benefits of vitamin D appear to greatly outweigh the risks of UV irradiance (105).

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## References

1. Jablonski NG, Chaplin G. The evolution of human skin coloration. *J Hum Evol* 2000; **39** (1): 57-106.
2. van der Mei IA, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, Eyles DW, Blizzard L, Dwyer T, Lucas R, Jones G. The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. *Environ Health Perspect* 2007 Aug; **115**(8):1132-9.
3. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, Holick MF. The role of vitamin D in cancer prevention. *Am J Public Health* 2006; **96** (2): 252-261.
4. 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* 2007; **179** (4): 2060-2063.
5. Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. *Epidemiol Infect* 2007; **135** (7): 1095-1096; author reply 1097-1098.
6. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296** (23):2832-2838.
7. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; **117** (4): 503-511.

8. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* 1980; **9** (3): 227-231.
9. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Paul O. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* 1985; **1** (8424): 307-309.
10. Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet* 1989; **2** (8673): 1176-1178.
11. Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). *Anticancer Res* 1990; **10** (5A): 1307-1311.
12. 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* 1990; **19** (6): 614-622.
13. Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int J Epidemiol* 1994; **23** (6): 1133-1136.
14. Colston KW, Berger U, Coombes RC. Possible role for vitamin D in controlling breast cancer cell proliferation. *Lancet* 1989; **1** (8631): 188-191.
15. Devesa SS, Grauman DJ, Blot WJ, Pennello GA, Noover RN, Fraumeni JF, Jr. Atlas of Cancer Mortality in the United States, 1950-94. NIH Publication No. 99-4564, 1999. <http://cancer.gov/atlasplus/new.html> (accessed July 24, 2007).
16. Leffell DJ, Brash DE. Sunlight and skin cancer. *Sci Am* 1996; **275** (1): 52-53, 56-59. [http://toms.gsfc.nasa.gov/ery\\_uv/dna\\_exp.gif](http://toms.gsfc.nasa.gov/ery_uv/dna_exp.gif) (accessed July 31, 2007).
17. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 2002; **94** (6): 1867-1875.
18. Grant WB. Health benefits of solar UV-B radiation through the production of vitamin D. Comment and response. *Photochem Photobiol Sci* 2003; **2** (12): 1307-1308; discussion 1308-1310.
19. 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* 2006; **26** (4A): 2687-2699.
20. Boscoe FP, Schymura MJ. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993-2000. *BMC Cancer* 2006; **6**: 264
21. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WH. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *JNCI* 2006; **98**: 451-459.
22. Giovannucci E, Liu Y, Willett WC. Cancer incidence and mortality and vitamin D in black and white male health professionals. *Cancer Epidemiol Biomarkers Prev* 2006; **15** (12): 2467-2472.

23. Grant WB. Lower vitamin-D production from solar ultraviolet-B irradiance may explain some differences in cancer survival rates. *J Natl Med Assoc* 2006; **98** (3): 357-364.
24. Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, Ng SK, Munoz B, Emmett EA. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. *Cancer* 1990; **65**: 2811-2817.
25. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, Marks GC, Gaffney P, Battistutta D, Frost C, Lang C, Russell A. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999; **354**: 723-729.
26. Scotto J, Fears TR, Jraener KH, Fraumeni JF. Nonmelanoma skin cancer. In: Schottenfeld D, Fraumeni JF Jr., eds. *Cancer Epidemiology and Prevention*, 2nd edn. New York: Oxford University Press, 1996: 1313-1320.
27. Moan J, Dahlback A, Setlow RB. Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem Photobiol* 1999; **70**: 243-247.
28. 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* 2007; **103** (3-5): 668-674.
29. De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN; Leiden Skin Cancer Study. Relation between smoking and skin cancer. *J Clin Oncol* 2001; **19**: 231-238.
30. Weinstock MA, Bogaars HA, Ashley M, Litle V, Bilodeau E, Kimmell S. Nonmelanoma skin cancer mortality. A population-based study. *Arch Dermatol* 1991; **127** (8) :1194-1197.
31. Grant WB. An ecologic study of cancer mortality rates in Spain with respect to indices of solar UV irradiance and smoking. *Int J Cancer* 2007; **120**: 1123-1127.
32. Rukin NJ, Zeegers MP, Ramachandran S, Luscombe CJ, Liu S, Saxby M, Lear J, Strange RC. A comparison of sunlight exposure in men with prostate cancer and basal cell carcinoma. *Br J Cancer* 2007; **96** (3): 523-528.
33. 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* 2007; **165**: 966-972.

34. Tuohimaa P, Pukkala E, Scelo G, Olsen JH, Brewster DH, Hemminki K, Tracey E, Weiderpass E, Kliewer EV, Pompe-Kirn V, McBride ML, Martos C, Chia KS, Tonita JM, Jonasson JG, Boffetta P, Brennan P. Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: Vitamin D as a possible explanation. *Eur J Cancer* 2007; **43**: 1701-1712.
35. Grant WB. The effect of solar UVB doses and vitamin D production, skin cancer action spectra, and smoking in explaining links between skin cancers and solid tumours. *Eur J Cancer* 2008; **44** (1): 12-15.
36. Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC. Could ultraviolet B irradiance and vitamin D be associated with lower incidence rates of lung cancer? *J Epidemiol Community Health* 2008; **62** (1) :69-74.
37. Lewtas J. Air pollution combustion emissions: characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects. *Mutat Res* 2007; **636** (1-3): 95-133.
38. Porojnicu AC, Dahlback A, Moan J. Sun exposure and cancer survival in Norway: Changes in the risk of death with season of diagnosis and latitude. Ch. 4 in Reichrath J (ed), Sunlight, Vitamin D and Skin Cancer. Landes Bioscience/Springer Science+Business Media. New York. 2008; **4**: 43-54.
39. Jackson RD, LaCroix AZ, Gass M, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; **354** (7): 669-683.
40. Wactawski-Wende J, Kotchen JM, Anderson GL, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006; **354**: 684-696.
41. Grant WB, Garland CF. A critical review of studies on vitamin D in relation to colorectal cancer. *Nutr Cancer* 2004; **48** (2): 115-123.
42. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF. Optimal vitamin D status for colorectal cancer prevention a quantitative meta analysis. *Am J Prev Med* 2007; **32** (3): 210-216.
43. 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* 2007; **85** (6): 1586-1591.
44. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007.
45. van den Bemd GJ, Chang GT. Vitamin D and vitamin D analogs in cancer treatment. *Curr Drug Targets* 2002; **3** (1): 85-94.
46. Krishnan AV, Peehl DM, Feldman D. Inhibition of prostate cancer growth by vitamin D: Regulation of target gene expression. *J Cell Biochem* 2003; **88** (2): 363-371.

47. Lipkin M, Lamprecht SA. Mechanisms of action of vitamin D: recent findings and new questions. *J Med Food* 2006; **9** (2): 135-137.
48. Mullin GE, Dobs A. Vitamin D and its role in cancer and immunity: a prescription for sunlight. *Nutr Clin Pract* 2007; **22** (3): 305-322.
49. Ingraham BA, Bragdon B, Nohe A. Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin* 2008; **24**: 139-149.
50. Krause R, Matulla-Nolte B, Essers M, Brown A, Hopfenmuller W. UV radiation and cancer prevention: what is the evidence? *Anticancer Res* 2006; **26** (4A): 2723-2727.
51. Grant WB. Epidemiology of disease risks in relation to vitamin D insufficiency. *Prog Biophys Mol Biol* 2006; **92** (1): 65-79.
52. Krickler A, Armstrong B. Does sunlight have a beneficial influence on certain cancers? *Prog Biophys Mol Biol* 2006; **92** (1): 132-139.
53. Van der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. *Eur J Cancer* 2006; **42** (14): 2222-2232.
54. Canadian Cancer Society Announces Vitamin D Recommendation. June 8, 2007.  
[http://www.cancer.ca/ccs/internet/mediareleaselist/0,3208,3172\\_1613121606\\_1997621989\\_langId-en,00.html](http://www.cancer.ca/ccs/internet/mediareleaselist/0,3208,3172_1613121606_1997621989_langId-en,00.html) (accessed July 31, 2007).
55. Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, The Australasian College of Dermatologists, and the Cancer Council of Australia. Risks and Benefits of Sun Exposure; Position Statement. May 3, 2007.  
<http://www.cancer.org.au/documents/RisksBenefitsSunExposure03May07.pdf> (accessed July 31, 2007).
56. Rollier A. (The present status of heliotherapy in Leysin.) *Strahlentherapie*. 1952; **88** (3-4): 442-448.
57. Hobday R. *The Healing Sun*. Findhorn, Scotland: Findhorn Press, 1999: 99-106.
58. Ustianowski A, Shaffer R, Collin S, Wilkinson RJ, Davidson RN. Prevalence and associations of vitamin D deficiency in foreign-born persons with tuberculosis in London. *J Infect* 2005; **50** (5): 432-437.
59. Martineau AR, Wilkinson RJ, Wilkinson KA, Newton SM, Kampmann B, Hall BM, Packe GE, Davidson RN, Eldridge SM, Maunsell ZJ, Rainbow SJ, Berry JL, Griffiths CJ. A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 2007; **176** (2): 208-213.
60. Martineau AR, Wilkinson KA, Newton SM, Floto RA, Norman AW, Skolimowska K, Davidson RN, Sørensen OE, Kampmann B, Griffiths CJ, Wilkinson RJ. IFN-gamma- and TNF-independent vitamin D-inducible human suppression of mycobacteria: the role of cathelicidin LL-37. *J Immunol* 2007; **178** (11): 7190-7198.
61. Mookherjee N, Rehaume LM, Hancock RE. Cathelicidins and functional analogues as antiseptics molecules. *Expert Opin Ther Targets* 2007; **11**: 993-1004.

62. 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* 2007; **179** (4): 2060-2063.
63. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab* 2008; **4** (2):80-90.
64. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E. Epidemic influenza and vitamin D. *Epidemiol Infect* 2006; **134**: 1129-1140.
65. Yusuf S, Piedimonte G, Auais A, Demmler G, Krishnan S, VAN Caesele P, Singleton R, Broor S, Parveen S, Avendano L, Parra J, Chavez-Bueno S, Murguia DE Sierra T, Simoes EA, Shaha S, Welliver R.. The relationship of meteorological conditions to the epidemic activity of respiratory syncytial virus. *Epidemiol Infect* 2007; **135**: 1077-1090.
66. Webb AR, Engelsen O. Calculated ultraviolet exposure levels for a healthy vitamin D status. *Photochem Photobiol* 2006; **82**: 1697-1703.
67. van der Mee-Marquet N, Domelier AS, Girard N, Quentin R; Bloodstream Infection Study Group of the Relais d'Hygiene du Centre. Epidemiology and typing of *Staphylococcus aureus* strains isolated from bloodstream infections. *J Clin Microbiol* 2004; **42**: 5650-5657.
68. Beadling C, Slifka MK. How do viral infections predispose patients to bacterial infections? *Curr Opin Infect Dis* 2004; **17**: 185-191.
69. Danai PA, Moss M, Mannino DM, Martin GS. The epidemiology of sepsis in patients with malignancy. *Chest* 2006; **129**: 1432-1440.
70. Danai PA, Sinha S, Moss M, Haber MJ, Martin GS. Seasonal variation in the epidemiology of sepsis. *Crit Care Med* 2007; **35**: 410-415.
71. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr* 2007; **85** (3): 860-868.
72. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. *Ann Neurol* 2006; **59** (3): 499-503.
73. Kurtzke JF. Geographic distribution of multiple sclerosis: an update with special reference to Europe and the Mediterranean region. *Acta Neurol Scand* 1980; **62**: 65-80.
74. 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* 2004; **55**: 65-71.
75. 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* 2001; **20**: 168-174.
76. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. *Altern Med Rev* 2005; **10**: 94-111.

77. Grant WB. Hypothesis - ultraviolet-B irradiance and vitamin D reduce the risk of viral infections and thus their sequelae, including autoimmune diseases and some cancers. *Photochem Photobiol* 2008; **84**:356-365.
78. Embry AF. Vitamin D supplementation in the fight against multiple sclerosis. *J Orthomolec Med* 2004; **19**: 27-38.
79. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog Biophys Mol Biol* 2006; **92** (1): 60-64.
80. Schwartz GG. Multiple sclerosis and prostate cancer: what do their similar geographies suggest? *Neuroepidemiology* 1992; **11**: 244-254.
81. Zambrano A, Kalantari M, Simoneau A, Jensen JL and Villarreal LP: Detection of human polyomaviruses and papillomaviruses in prostatic tissue reveals the prostate as a habitat for multiple viral infections. *Prostate* 2002; **53**: 263-276.
82. Grinstein S, Preciado MV, Gattuso P, Chabay PA, Warren WH, De Matteo E, and Gould VE. Demonstration of Epstein-Barr virus in carcinomas of various sites. *Cancer Res* 2002; **62** (17): 4876-4878.
83. Samanta M, Harkins L, Klemm K, Britt WJ, and Cobbs CS. High prevalence of human cytomegalovirus in prostatic intraepithelial neoplasia and prostatic carcinoma. *J Urol* 2003; **170**: 998-1002.
84. Sugar LM: Inflammation and prostate cancer. *Can J Urol* 2006; **13** (Suppl 1): 46-47.
85. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG, Nakai Y, Isaacs WB, and Nelson WG. Inflammation in prostate carcinogenesis. *Nat Rev Cancer* 2007; **7**: 256-269.
86. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 1997; **30** (2 Pt 1): 150-156.
87. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007; **49** (5): 1063-1069.
88. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, Felsenfeld A, Levine B, Mehrotra R, Norris K. 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* 2007; **167** (11): 1159-1165.
89. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol*. 2006; **92** (1):39-48.
90. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, Felsenfeld A, Levine B, Mehrotra R, Norris K. 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* 2007; **167** (11):1159-1165.
91. Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. *Curr Opin Clin Nutr Metab Care* 2008; **11** (1):7-12.

92. McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophr Res* 1999; **40** (3):173-177.
93. McGrath JJ, Pemberton MR, Welham JL, Murray RM. Schizophrenia and the influenza epidemics of 1954, 1957 and 1959: a southern hemisphere study. *Schizophr Res* 1994; **14** (1): 1-8.
94. Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci* 2003; **23** (1): 297-302.
95. Almeras L, Eyles D, Benech P, Laffite D, Villard C, Patatian A, Boucraut J, Mackay-Sim A, McGrath J, Feron F. Developmental vitamin D deficiency alters brain protein expression in the adult rat: implications for neuropsychiatric disorders. *Proteomics* 2007; **7** (5): 769-780.
96. Edwards MJ. Hyperthermia in utero due to maternal influenza is an environmental risk factor for schizophrenia. *Congenit Anom (Kyoto)* 2007; **47** (3):84-89.
97. Peterlik M, Cross HS. Dysfunction of the vitamin D endocrine system as common cause for multiple malignant and other chronic diseases. *Anticancer Res* 2006; **26** (4A): 2581-2588.
98. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; **81** (3): 353-373.
99. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007; **357** (3): 266-281.
100. Mullin GE, Dobs A. Vitamin D and its role in cancer and immunity: a prescription for sunlight. *Nutr Clin Pract* 2007; **22** (3):305-322.
101. Cannell J, Hollis B, Zasloff M, Heaney R. Diagnosis and treatment of vitamin D deficiency. *Expert Opin Pharmacother* 2008; **9** (1):107-118.
102. 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* 2003; **77** (1): 204-210.
103. Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, Newmark H, Holick MF, Garland FC. Vitamin D and prevention of breast cancer: pooled analysis. *J Steroid Biochem Mol Biol* 2007; **103** (3-5): 708-711.
104. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D<sub>2</sub>) as a vitamin supplement. *Am J Clin Nutr* 2006; **84** (4): 694-697.
105. 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* 2005; **81** (6):1276-1286.