Vitamin D and Health: Implications for High-latitude Countries

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Introduction

There is increasing awareness that sufficient levels of vitamin D are required for optimal health. In addition to its role in calcium absorption and homeostasis and bone health, there is now strong evidence that vitamin D plays an important role in preventing cancer, multiple sclerosis, and type 1 diabetes mellitus (T1DM), and weaker evidence that it reduces the risk of osteo- and rheumatoid arthritis, hypertension, and T2DM.[1] There is also evidence that there is an epidemic of vitamin D insufficiency and deficiency in many countries including Australia,[2] Canada,[3,4] Northern Europe,[5] Southern Europe,[6] and the U.S.[4,7] Dark-skinned people living poleward of their ancestral homeland are always at risk of low serum 25-hydroxyvitamin D (25(OH)D).[8,9] Even childhood rickets is making a comeback.[10,11]

This paper will outline some of what is known about the beneficial roles of vitamin D in maintaining optimal health, emphasizing cancer, multiple sclerosis, and cardiovascular disease in the U.S. and Canada.

Background

Rickets is the first human disease associated with insufficient solar radiation. More than a century ago, people who developed rickets were likely to live in large cities such as London (52°N). It was eventually realized that lack of solar ultraviolet (UV) irradiance was the cause, and that rickets could be prevented through either solar UV irradiance or cod liver oil, a natural source of vitamin D.[12,13] In the 1960s, it was recognized that osteoporosis and related bone disorders were also linked to low levels of vitamin D.[12] Nonetheless, falls and hip fractures remain a significant problem in the U.S.[14] Eventually, the role of vitamin D in the absorption and homeostasis of calcium was worked out, and vitamin D recommendations were made based on this understanding.[15,16]

More recently, it was realized that there are a number of diseases that have large increases with indices for solar UVB irradiance such as cancer[17] and multiple sclerosis.[18,19] Further research has strengthened these links and identified other vitamin D-sensitive conditions and diseases as well.

This paper will briefly outline the evidence that vitamin D reduces the risk of cancer and multiple sclerosis and discuss the amount of vitamin D now considered required for optimal health and the various sources of vitamin D.

Solar UVB and vitamin D have been linked to reduction of cancer incidence and mortality rates and increases in survival in a number of observational studies. The first link was made in 1980 by Cedric and Frank Garland after they saw maps of cancer mortality rates in the U.S.[17] They noted that colon cancer rates were lowest in the southwest desert states and highest in the northeastern states. They used to hike in the desert states and knew that it was very sunny there. They also knew that the greatest physiological effect of solar radiation was production of vitamin D. In 1985, they were able to show that dietary vitamin D was inversely correlated with colon cancer risk.[20] A bit later, they were able to show that prediagnostic serum 25(OH)D was also inversely correlated with colon cancer risk.[21] Their group went on to do ecologic studies of

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breast and ovarian cancer, again showing that rates were inversely correlated with some measure of solar UVB radiation.[22,23] A personal review of the progress of this group is given in the recent commentary on the occasion of the reprinting of their seminal paper.[23] Gary Schwartz and colleagues added prostate cancer to the list about that time as well.[24]

These observational studies encouraged others to investigate the mechanisms whereby vitamin D might reduce the risk of cancer. One of the more puzzling aspects in the 1990s was that the active form of vitamin D in actually impacting cancer cells was 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), yet its concentration was tightly regulated in the serum. The mystery was solved when it was demonstrated that the cells and organs that required the active form could make it from 25(OH)D.[26,27] Others elucidated the mechanisms of 1,25$(OH)_2$D on cancer, which include increasing cell differentiation and apoptosis, attenuating growth signaling, reducing angiogenesis around tumors, and inhibiting metastasis,[28,29] and, in the case of colon cancer, increasing the absorption of calcium.[30]

When I entered the field in 2000 after seeing the *Atlas of Cancer Mortality Rate in the United States*,[31] I first attempted to develop a model to explain the geographic variation based on dietary factors since diet explains much of the difference in cancer rates for various countries.[32] However, I soon realized that it would take the northern European diet in the northeast and the Southeast Asian diet in the southwest to explain the factor-of-two variation in cancer mortality rates for many cancers, which, of course, was not the case. I then read the work by the Garlands and coworkers and decided that they had the correct interpretation. I then posed two questions: how many cancers are UVB/vitamin D-sensitive and how many people died prematurely from cancer each year due to insufficient UVB/vitamin D? I obtained a map of surface level solar UVB for July from the NASA Total Ozone Mapping Spectrometer[33] and proceeded to determine the correlations between UVB and cancer mortality rates. This analysis confirmed the original four and added eight cancers to the list of those thought to be vitamin D sensitive: bladder, esophageal, gastric, lung, rectal, renal, uterine corpus, and non-Hodgkin's lymphoma.[34] While the study was generally well received, it was pointed out that other cancer risk-modifying factors were not included in the model, so the findings could not be completely accepted.[35]

To remedy the situation, I added data for alcohol consumption, smoking, Hispanic heritage (they are included in the category white Americans), fraction of the population living below the poverty level, fraction of the population living in urban regions, all averaged at the state level. For smoking, I used lung cancer mortality rates since appropriate data for cigarette smoking were not available, and since it had been shown for black American males that non-lung cancer mortality rates closely followed lung cancer mortality rates.[36] While diet is an important risk-modifying factor, diet doesn't vary widely in the U.S. I also enlisted the aid of Cedric Garland and a statistician to the study. The finding of this analysis was that five more cancers could be considered UVB/vitamin D-sensitive: cervical, gallbladder, laryngeal, pancreatic cancer and Hodgkin's lymphoma. The analysis also found that 10 types of cancer were linked to smoking, nine to alcohol consumption, and four to Hispanic heritage, in excellent agreement with the literature.[37,38] This work is now in press.[39] Similar findings were made for black Americans and seem to explain much of the lower survival rates compared to white Americans for the same stage at discovery and same treatment.[9]

More recently, several studies have

found that cancer survival is associated with UVB and vitamin D. Studies in Norway found that 18-month survival rates for breast, colon, and prostate cancer and Hodgkin's lymphoma are about 30% higher for those whose cancer is discovered in fall compared to those whose cancer is discovered in winter or spring.[40-42] It is proposed that photoproduction of vitamin D in summer accounts for this finding. Also, an observational study in the Boston area found that for men diagnosed with non-small-cell lung cancer, the five year survival rate for those operated on in summer and having a high vitamin D index (oral intake plus leisure time outdoor activities) was 72% compared to 29% for those operated on in winter and having a low vitamin D index.[43]

The U.S. Surveillance, Epidemiology, and End Results (SEER) data[44] to show that those living in Hawaii in the period 1973-98 had a higher survival rate for a number of cancers compared to those living in most of the mainland U.S. registries.[45] We also observed that survival rates actually fell in Hawaii in the 1980s before heading back up in the 1990s, while survival rates in the contiguous states increased steadily from the 1970s on. The hypothesized reason for the fall in survival rates in Hawaii is that concern about the risk of skin cancer and melanoma from solar UV irradiance began to affect UVB irradiance in the 1980s. The hypothesized reason for the increases is improved detection and treatment of cancer. This work is being extended.

It is noted that many in the health community are asking for prospective vitamin D intervention trials before they will accept the hypothesis that vitamin D reduces the risk of cancer incidence and mortality. Such prospective intervention studies are, of course, required for pharmaceutical drugs, which do not occur in nature. However, mankind has been doing such experiments unwittingly ever since detailed records of cancer incidence and mortality rates have been collected, such as starting in at least 1950 in the U.S., so what appears to be required is additional analysis of existing cancer rate data that include a number of cancer risk-modifying factors in the analysis including an appropriate index for solar UVB production of vitamin D as well as oral intake.

Multiple Sclerosis

The increase of multiple sclerosis (MS) prevalence with increasing latitude has been known at least from the time of World War I from data for American servicemen at time of entry into the services.[46] The association was strengthened from additional studies of American servicemen at the time of enrolling in World War II and the Korean Conflict,[47] as well as in Europe.[48] In Europe, the prevalence increases up to about 57°N, then falls slightly with further increases in latitude. A strong latitudinal variation has also been found in Australia,[49] and that Australians who had higher wintertime solar UV irradiance had reduced risk of MS.[50] A recently paper examining MS in Newfoundland and Labrador found that the prevalence increased from about 80/100k at 47°N to 100/100k at 49.5°N.[51] This compares with the estimate of 85/100k in the U.S.[52]

While the variation in Europe probably has contributions from vitamin D and diet (high fat intake is also a risk for MS, while fish is likely associated with reduced risk[53,54] and fish oil generally has vitamin D), the variations in Australia and the U.S. probably don't. It has also been found that risk of MS is inversely associated with dietary vitamin D.[55] The number of MS lesions has been found to vary seasonally by a factor of two in Germany in association with solar UVB irradiance.[56]

The mechanisms appear to include that vitamin D increases the number of

T-helper 1 (Th1) cells while reducing the number of Th2 cells.[57,58] Th1 cells release interleukin-2 (IL2) and interferon (IFN) cytokines, which are pro-inflammatory and are associated with autoimmune response, while TH2 cells release IL4 cytokines, which are anti-inflammatory. The risk of MS is also linked to infectious diseases, especially in childhood or youth, and evidently vitamin D can reduce the risk of these infections leading to MS. The strong latitudinal dependence in the U.S. is indicative of wintertime serum 25(OH)D levels, since there is an asymmetrical UVB pattern in the summer.[33]

Additional evidence that vitamin D reduces the risk of MS is the finding from a study in New York that those with MS tend to have low serum 25(OH)D levels and reduced bone mass.[59] Thus, those with MS should be advised to make sure their vitamin D levels are sufficient.

Cardiovascular Diseases

There is observational evidence that low serum 25(OH)D levels are associated with increased blood pressure, hypertension, and risk of stroke.[60] An ecologic study found that blood pressure increased with distance from the equator.[61] However, it can't be excluded that dietary factors, smoking, or other factors explain this variation. On the other hand, laboratory studies have determined that 25(OH)D controls the renin-angiotensin system.[62] A recent paper from the UK reported that those diagnosed with acute stroke had very low serum 25(OH)D levels.[63] Further research is required to confirm that vitamin D reduces the risk of hypertension and stroke.

Other Diseases

A number of other conditions and diseases have been linked to low serum 25(OH)D levels. One that likely is important in Canada is non-specific muscle pain in winter.[64] Others include tuberculosis,[65] T1DM,[66] and insulin resistance.[67,68]

Implications for Canada

The situation in Canada regarding health status with respect to vitamin D is probably very similar to that of the U.S. states bordering Canada. In the periods 1950-69 and 1970-94, the highest mortality rates for many types of cancer were found in the northeastern states.[31] This is likely due primarily to lower solar UVB in the northeast.[17,34] It is noted that solar UVB irradiance is insufficient during the darkest 4-5 months of the year in Boston (42.4° N) to produce any vitamin D.[69] MS rates appear to be somewhat higher than the U.S. average. Hip fracture rates are decreasing in Ontario, from 410/100k/year for women over the age of 50 years from 1992-96 to an estimated 330/100k/year in 2005, possibly due to increased bone mass density testing.[70] The rate for hospitalization for hip fracture for women in New York for 1988-2000 was 459, 137, 143, and 174 per 100k.[71] The ethnic difference is quite striking, and is likely due to both dietary and genetic differences.

Vitamin D Requirements

The consensus of scientific understanding appears to be that vitamin D deficiency is reached for serum 25-hydroxyvitamin (25(OH)D) levels less than 20 ng/mL (50 nmol/L), insufficiency in the range from 20 to 32 ng/mL, and sufficiency in the range from 32 to 80 ng/mL, with normal in sunny countries (54–90 ng/mL), and excess greater than 100 ng/mL.[7]

Since vitamin D appears to be an important risk reduction factor for bone diseases, cancer, multiple sclerosis, and other diseases and conditions,[7] it is important that people try to maintain sufficient 25(OH)D levels throughout the year. As noted, it is impossible to produce vitamin D from solar UVB in Boston (42°N) for four to five of the darkest months of the year.[69] The residence time of serum 25(OH)D is approximately 1-2

months, so wintertime levels can become much lower than summertime levels if solar UVB irradiance is the sole source of vitamin D.

So, what is the body's requirement for vitamin D? A recent meta-analysis of colon cancer risk found that the equivalent of 1000 I.U. (25 μg) of vitamin D per day reduces the risk of colon cancer by 50%.[72] Other studies indicate that the body uses about 3000-5000 I.U. of vitamin D per day.[73] Doses of 4000 I.U./day were found to improve wellbeing scores much more than doses of 600 I.U./day.[74] Those who have more body fat need more vitamin D, since vitamin D is fat soluble.[75] It is also noted that the efficiency of vitamin D production from UVB decreases with age,[76] and that recommended vitamin D intake increases with age.[10] Vitamin D recommendations are in the process of being revised upward to take account of its role in non-calcemic diseases.[77-80]

What are the upper limits of safety? The U.S. National Academy of Sciences has concluded that 2000 I.U. per day is safe.[81] However, the scientific literature indicates that the toxic level is not reached until a daily intake of 40,000 I.U..[10,82]

Assuming that a daily intake or production of vitamin D from all sources should be at least 1000 I.U. and more likely 2000 I.U., what are the tradeoffs between the various sources? Solar UVB is the natural source, and skin pigmentation has adapted over the period of millennia to ambient solar UV levels in fall and normal outdoors activities.[83,84] However, solar UV irradiance entails the risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) and cutaneous malignant melanoma (CMM). SCC is linked to total lifetime UV irradiance[85] and UVB, which sunscreen blocks effectively,[86] while CMM is linked to intermittent UV exposure, UVA (320-400 nm) irradiance,[87] and skin that does not tan well, such as for people with freckles and red hair or a large number of moles (nevi).[88] It has been observed in Canada and elsewhere that chronic UV irradiance such as associated with occupation, is associated with reduced risk of CMM.[88,89] BCC, which is rarely fatal, is apparently primarily sensitive to UVA with some sensitivity to UVB.[85] It should also be noted that much of the concern about the risk of skin cancer and CMM is due to both pale-skinned people migrating to lower latitudes, as well as traveling to sunny vacation spots where sunburning, rather than tanning, is the likely outcome. Despite these concerns, it was recently estimated that the health risks from too little solar UVB irradiance and vitamin D outweigh the health risks from excess UV irradiance in the U.S. by a ratio of 5-10 to 1.[90]

If one prefers to obtain one's vitamin D orally, then dietary supplements are better than dietary sources. However, the amount of vitamin A with the vitamin D should be low or non-existent since it has been found that vitamin A increases the risk of hip fracture.[91] The problem with dietary sources is with the foods that are fortified: cow's milk, the primary dietary source of vitamin D for most Americans and Canadians, is associated with a variety of health risks including prostate cancer,[92,93] and other diseases, and has an inconsistent association with hip fracture rates.[94] In ecologic studies, breast, colon, and prostate cancer are associated with animal product consumption,[32,92] likely through increased production of insulin like growth factor I (IGF-I).[95] The lack of association with hip fracture may arise due to the high protein content of milk so that the calcium has to be involved in buffering the pH of the protein, or due to fortification with retinol (vitamin A). While orange juice can now be fortified with vitamin D and calcium in the U.S.,[96] it has too much simple sugar to be recommended as a regular source of vitamin D. On the other hand, whole-grain bread,

which is generally healthful, would be a good food to fortify with vitamin D[97] in addition to folate, which is already done successfully to reduce the risk of neural tube defect births[98] and likely has other health benefits as well such as lowering homocysteine levels and reducing the risk of coronary heart disease.[99]

Use of solaria is another way to obtain vitamin D. A recent study in Boston found that young men using solaria 2-3 times a week had higher serum 25(OH)D levels and higher bone mass density.[100] Most solaria in Canada and the U.S. have 3.5-5% of the UV in the UVB region, which is about the same as solar UV in midday in midlatitude in summer. However, those in Sweden and France are limited to 1.5%.[101] If using a solarium, ask what fraction of the UV is in the UVB region.

Sunscreen Use

Sunscreen is often recommended for those going into the sun, since it reduces the risk of erythema and sunburn. The spectral region for erythema extends from 290 to about 330 nm. However, those making such recommendations rarely mention that sunscreen very effectively blocks the solar UVB that produces vitamin D.[102,103] In addition, the sun protection factor (SPF) for sunscreen available in the U.S. has minimal SPF in the UVA spectral region. Since sunscreen with high SPF in the erythemal region greatly reduces the risk of erythema, use of sunscreen increases the time in the solar UV, which may increase the risk of melanoma.[104] While sunscreen available in Europe has much higher SPF in the UVA region, it still blocks UVB irradiation. It should be noted that tanning can result in an "induced protection factor" (IPF) of 2-4.[105,106]

Vitamin D Testing

For those concerned about their serum 25(OH)D levels and how much vitamin D they should be taking or producing from UVB irradiance, serum can be drawn for 25(OH)D measurements. There are some concerns about the accuracy of the measurements,[107] so some care should be exercised in choosing the proper test.

Conclusion

There is increasing evidence and awareness that sufficient vitamin D is required for optimal health. Research is still ongoing trying to determine the full range of benefits and amounts of vitamin D required for optimal health. In the meantime, people would do well to obtain adequate vitamin D by whatever means is most appropriate for their lifestyle. There are a number of additional papers on the health benefits of vitamin D, to which the reader is referred.[108-131] The reader should also find the information posted at www.sunarc.org to be of interest.

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