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Review

A critical review of *Vitamin D and Cancer*

A report of the IARC Working Group

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The International Agency for Research on Cancer (IARC) released a report, *Vitamin D and Cancer*, on November 25, 2008. The report focused on the current state of knowledge and level of evidence of a causal association between vitamin D status and cancer risk. Although presenting and evaluating evidence for the beneficial role of UVB and vitamin D in reducing the risk of cancer, it discounted or omitted important evidence in support of the efficacy of vitamin D. The report largely dismissed or ignored ecological studies on the grounds that confounding factors might have affected the findings. The report accepted a preventive role of vitamin D in colorectal cancer but not for breast cancer.

The only randomized controlled trial (RCT) on cancer incidence that used a sufficiently high dose of vitamin D (1,100 IU/day) and calcium (1,400–1,500 mg/day) found a 77% reduction in the risk of all-cancer incidence in postmenopausal women who received both, of which approximately 35% reduction in risk was attributed to vitamin D alone. Unfairly, the report dismissed these findings on the basis of a flawed critique.

The report called for RCTs of vitamin D supplementation to settle the issue. Although RCTs theoretically would be beneficial, development of sound and effective public health policies does not necessarily depend on them, and the field of vitamin D, calcium and chronic disease has reached the point where RCTs may not be ethical.

The IARC report should therefore not form the basis for public health policy decisions.

Introduction

The International Agency for Research on Cancer (IARC) recently released a report, *Vitamin D and Cancer*.[1] This report was ostensibly a comprehensive review of the evidence that vitamin D reduces the risk of cancer. The report lists 1,368 references, many of which supported a beneficial role of solar ultraviolet-B (UVB) and vitamin D in reducing the risk of many types of cancer. Despite listing these many studies with positive findings, the report's conclusions overemphasized the relatively few negative studies. Only the first and fifth conclusions are consistent with the data that were included in the studies that the report cited. Some of the conclusions seem to be incorrect or unfairly dismissive based on available evidence. The seven conclusions are as follows:

- The epidemiological observational evidence supports a role of vitamin D in reducing the risk of colorectal cancer; however, this evidence is not considered causal, and the randomized controlled trials (RCTs) to date have not supported the observational evidence.
- There is similar evidence for breast cancer, but that evidence is considered weaker.
- The observational evidence does not support a beneficial role of vitamin D in reducing the risk of prostate cancer.
- The evidence for other cancers was considered insufficient for evaluation.
- Results from observational studies and RCTs suggest that vitamin D supplements may lower all-cause mortality.
- There are no data available on the health hazards of long-term maintenance of high 25-hydroxyvitamin D [25(OH)D] serum levels over long periods. Also, past experiences with other compounds have shown adverse effects of chronic use of supplements or long-term maintenance of high serum levels.
- Hypotheses on vitamin D status and colorectal cancer, cardiovascular diseases and all-cause mortality should be tested in appropriately designed RCTs.

These conclusions are much weaker with regard to vitamin D and calcium for cancer prevention than a more comprehensive review of the scientific evidence warrants. Existing evidence from observational studies actually is consistent with a meaningful role of vitamin D in prevention of several types of cancer.[2] In the following, I comment on several flawed analyses in the IARC report.

Background

Several critical reviews have addressed the role of solar UVB and vitamin D in reducing the risk of cancer.[3-10] Although the IARC report's reference list (which should really be called a bibliography) includes several of these reviews, the text does not appear to discuss any of them. Any objective review of a field would acknowledge in more detail the contributions and conclusions of previous reviews, state whether the present report agrees or disagrees with the conclusions previous reviews, and describe possible reasons for discordant conclusions.

Detailed comments on the chapters follow.

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Chapter 3. Sunlight and Skin Cancer: Recall of Essential Issues

The IARC meta-analysis of the association of artificial UV sources with incidence of melanoma[11] did not attempt to adjust for skin type. Two early studies from the United Kingdom[12,13] included cases with Fitzpatrick skin type 1, who should never use sunbeds. Most of the other studies seemed to account for skin type. A reanalysis of the data was performed using RevMan.[14] When those two studies were omitted from the analysis, the relative risk of melanoma dropped by 0.07, putting the relative risk at 1.08 (95% confidence interval [CI], 0.93–1.24). When all five UK studies were omitted, the relative risk dropped by 0.11. This finding is also consistent with the large European multicenter study that found an odds ratio (OR) associated with ever sunbed use of 0.90 (95% CI, 0.71–1.14).[15]

The IARC report hypothesizes that use of artificial sources of UV, such as sunlamps, is implicated in the current epidemic of skin cancer and melanoma in The Netherlands and in Nordic countries. This attribution may be in error because increased solar exposure and sun burning during travel by individuals living in Northern Europe increases the incidence of melanoma.[16,17] Individuals living at the higher latitudes in Europe have the lightest skin, and darker skin pigmentation at lower latitudes may keep the risk of melanoma low even with increased solar exposure.[18] The authors considered excessive risk of melanoma an important reason to limit solar and artificial UV irradiance. Most artificial UV sources, such as ordinary fluorescent sunlamps, emit 2–4% of the UV as UVB; this level is about the same as for solar UV. Some fluorescent sunlamps emit a nonsolar spectrum (with higher ratio of UVA to UVB), which could be more problematic. Sunbeds with UVB are a good source of vitamin D.[19]

Chapter 5. Toxicity of Vitamin D and Long-Term Health Effects

Chapter 5 in the IARC report raised the issue of toxic effects from long-term high intake of vitamin D. A recent review of the literature found no reports of toxicity for less than 20,000 IU/day of vitamin D or a serum 25(OH)D level of less than 200 ng/mL over an extended period.[20]

The appendix to this chapter presented results of RCTs finding adverse effects with respect to cancer for supplements thought to reduce the risk of cancer. Although I agree that the results of RCTs for vitamin supplements such as beta-carotene and vitamins A, C and E did not meet expectations, I think that vitamin D should not be compared with them. The active metabolic form of vitamin D, $1,25(OH)_2D$, is a hormone and is naturally produced in the body, in contradistinction with the other vitamins.

Alternatively, I suggest that the history of disease eradication through identification of missing vitamins in the diet or from solar UVB provides a better guide to what could be accomplished with increased vitamin D from all sources. Table 1 summarizes the results for several nutrient deficiency diseases largely eradicated in the past three centuries.

Chapter 8. Biological Effects of Vitamin D Relevant to Cancer

Chapter 8 in the IARC report only superficially addressed what is known about the role of vitamin D in reducing the risk of cancer incidence and death. Certainly the anti-neoplastic properties of $1,25(OH)_2D$ at the cellular level are important in reducing the risk of cancer incidence. However, these properties do not explain why individuals diagnosed with cancer in summer or fall with breast, colon or prostate cancer and Hodgkin's lymphoma have a longer 3-year survival rate than those diagnosed in winter or spring.[27] Nor do they explain why postmenopausal women taking 1,100 IU/day of vitamin D had a 35% reduction in all-cancer risk between the ends of the first and fourth years of an RCT.[28] The reason seems to be vitamin D's role in reducing angiogenesis[29] or metastasis.[30] Vitamin D increases the absorption of calcium, which is an important risk reduction factor for many types of cancer[31] and all cancers combined.[28] Many research and review articles have isolated and described additional antineoplastic properties of vitamin D metabolites.[32-34]

Table 1 **Successful elimination of disease through dietary supplementation**

Disease	Nutrient deficiency	Year	Reference
Scurvy	Vitamin C	1753	21
Rickets	Vitamin D	Early 20th century	22
Pellagra	Niacin (vitamin B3)	1915	23
Beriberi	Thiamine (vitamin B1)	Early 20th century	24, 25
Spina bifida and anencephaly	Folate	Late 20th century	26

According to previous research, consumption of both vitamin D and calcium in combination micronutrients contributes to protection from incidence of colorectal cancer and probably to other cancers.[35] Micronutrients do not function in isolation, and joint roles of vitamin D and calcium in rickets and some types of cancer are reasonable. They are also consistent with a theory of carcinogenesis that explains the actions of vitamin D and calcium.[36] It is a fundamental principle of the theory that both vitamin D and calcium contribute to the integrity of intercellular junctions, more than either micronutrient in isolation, and both are desirable for preventing cancer. This critique is not relevant, because calcium and vitamin D operate cooperatively to prevent cancer.

Vitamin D, through production of human cathelicidin, LL-37, reduces the risk of viral infections.[37,38] The Epstein-Barr virus plays an important role in the risk of several types of cancer.[39] Later sections discuss the role of vitamin D in fighting viral infections such as the Epstein-Barr virus.

Chapter 9. Ecological Studies on Sun Exposure and Cancer

As pointed out recently,[4] the ecological approach often determines links between disease risk-modifying factors years to decades before confirmation by observational studies or RCTs. For example, Armstrong and Doll[41] reported that the most important risk factor for many cancers common in Western developed countries, such as breast, colon, ovarian and prostate cancer, was animal fat. For years, cohort studies, such as the Nurses' Health Study, could not confirm the link. It was only recently realized that diet early in life has the most important effect on cancer risk and that enrolling women after the age of 35 years in a cohort study was not the correct approach to study the link. When daughters of nurses were enrolled in a cohort study, eating large amounts of red meat doubled the risk of estrogen receptor-positive/progesterone receptor-positive breast cancer.[42] The

Table 2 **Observational studies finding strong correlations between dietary factors and risk of disease**

Cancer	Outcome	Risk factor	Finding	Reference
Bladder	Incidence	Salted meat	OR = 4.04 (95% CI, 2.24–7.27)	45
		Potatoes	OR = 0.38 (95% CI, 0.23–0.64)	45
Breast	Incidence	Alcohol	7%–15% increase for 10 g of ethanol per day	46
Colon	Incidence for men	Processed meat	RR = 1.98 (95% CI, 1.24–3.16), high vs. low	47
Lung	Incidence	Meat	OR = 1.6 (95% CI, 1.2–2.2) for total meat	48
Prostate	Death	Fish	RR = 0.53 (95% CI, 0.31–0.92) ≥5 vs. ≤1 time/wk	49

OR, odds ratio; RR, relative risk.

statement on p. 133 of the IARC report that "few strong dietary associations with risk of cancer have been observed"[43] overlooks many observational studies that found strong dietary associations. Table 2 summarizes the findings from several such studies. Stronger associations are found in countries where the traditional diet was not the Western diet; as Western foods are introduced, cancer rates increase.[44]

People have lived in harmony with the sun and solar UVB irradiance for most of human history, generally until the Industrial Revolution, when people spent less time outdoors and pollution reduced solar UVB reaching the earth's surface. Therefore, properly designed ecological and observational studies that account for the important risk-modifying factors should be able to reliably identify and quantify the health benefits and risks of solar UVB.[2]

Why the multifactorial ecological studies of cancer mortality rates in the United States[5,50] were not discussed in the IARC report is puzzling. Many types of cancer had the highest mortality rates in the Northeast and lowest rates in the Southwest,[51] just as Cedric and Frank Garland had noticed with earlier data for colon cancer.[52]

Data products from the NASA Total Ozone Mapping Spectrometer, including solar UVB doses at the surface of the United States for July 1992, became available in 1996.[53] UVB doses east of the Rocky Mountains are much lower than those at the same latitude to the west for two reasons: surface elevations are generally higher in the west, leading to reduced atmospheric attenuation, and the stratospheric ozone layer is thinner because of the westerly winds pushing the air masses over the Rocky Mountains. This east-west UVB asymmetry is key to understanding the geographical variation of cancer mortality rates in the United States.

Fourteen types of cancer had inverse correlations with solar UVB for July in multifactorial analyses including indices averaged at the state level for alcohol consumption, Hispanic heritage, poverty level, smoking and urban/rural residence. More recently, I added iron and zinc[54] and air pollution (acid rain for 1985).[55]

Ecological studies in the United States clearly identify a role of solar UVB in reducing cancer mortality rates for several reasons, including the following: solar UVB doses in summer are high enough in the Southwest to generate 1,000–2,000 IU/day of vitamin D from casual irradiance;[56] other risk-modifying factors are either similar throughout the country or can be well modeled at the state level through indices;[50,54,55] and 25- and 30-year datasets are available,[51] providing adequate statistical power for most cancers.

Whereas multicountry ecological studies of risk factors for cancer are complex owing to the important role of diet,[57-59] single-country studies are simpler as long as the country includes a significant portion of the population equatorward of about 40°, because at higher latitudes, solar UVB doses are often too low to produce much vitamin D. Single-country ecological studies overlooked in the IARC report include those in Australia[60] and Japan.[61] Although the Astbury[60] study sought to explain the observed latitudinal dependence of cancer mortality rates based on cosmic rays, it is really a UVB effect.

The discussion of ecological studies on pp. 133–135 of the IARC report, especially regarding confounding factors, should be dismissed because it overlooked Grant and Garland,[50] a study that was adjusted for multiple factors. The report does not suggest any other factor that could account for the robust correlation of solar UVB irradiance with so many cancers. According to U.S. Department of Agriculture surveys, most dietary factors do not vary much substantially across the United States because of fast food and supermarket chains.

Another index that can be used to investigate the role of solar UVB in the risk of internal cancers is incidence of or death from non-melanoma skin cancer (NMSC). The primary risk factor for squamous cell carcinoma (SCC) of the skin is integrated lifetime UVB irradiance.[62] UVB is also an important risk factor for basal cell carcinoma (BCC).[63] The relevant published reports were found through the National Library of Medicine's PubMed database. In the first application of this index in an ecological study,[64] it was found that four cancers had a significant or nearly significant risk reduction for males plus females: colon, gastric, rectal and renal. For females, cancers so identified were cervical, colon, esophageal, gallbladder and gastric. The IARC report criticized this article on pp. 126–127 on the basis that adjusting the data for lung cancer incidence rates was not a valid approach. While this approach will not be defended in detail here, it is noted that this study[64] also found that lung cancer incidence was inversely correlated with incidence of melanoma, first reported by Freedman et al.[65] Recently, it was shown that this is a robust finding, with elastosis from either UV irradiance or smoking reducing the risk of melanoma.[66] This finding provides further support for the use of lung cancer in the meta-analyses.

In a cancer registry study of second cancers after diagnosis of skin cancer, the standardised incidence ratio for all solid tumours except skin and lip after diagnosis of BCC in sunny countries was 0.86 (95% CI, 0.80–0.92), whereas that after diagnosis of SCC was 0.79 (95% CI, 0.68–0.91).[67] In the less sunny countries, the corresponding values were 1.36 (95% CI, 1.32–1.37) and 1.36 (95% CI, 1.33–1.38). The IARC report largely dismissed that study on pp. 123–124 on the basis that the authors had not explained

why different results were obtained in sunny and less-sunny countries. In a commentary on that study,[68] which the Working Group overlooked, it was pointed out that in the three sunny countries, Australia, Singapore and Spain, people would have more body area exposed when in the sun than in the less-sunny countries. The dividing line between sunny and less-sunny countries seems to be about 40°. Thus, the Chen et al.[69] study in Maryland, in which an increased risk of subsequent cancer after diagnosis of either BCC or SCC, discussed on p. 131, was on the border as pointed out in a letter to the editor.[70] Another recent study, in Switzerland, also found an increased risk of subsequent cancer.[71] Again, there is a letter to the editor in press pointing out that the high latitude of Switzerland (46.0°–47.5°) leads to a similar result.[72]

A study of cancer mortality rates in Spain using NMSC mortality rate as the index of UVB irradiance at the province level[73] was criticized by Philippe Autier at two conferences in 2007, one in Oslo, the other in Stockholm, on the basis of the fact that NMSC is rare in Spain and, therefore, was not a robust index for personal UVB irradiance. Upon further analysis, Grant realized that a multiple linear regression analysis using latitude, NMSC and lung cancer would have been more appropriate. A multiple linear regression analysis found that for 15 of the 17 cancers, either latitude or NMSC was significantly correlated with mortality rates, with only bladder cancer and leukemia failing to correlate with one of those indices for at least one sex when lung cancer was included in the analysis. The revised analysis is included in a book chapter.[74]

Chapter 11. Observational Studies on Dietary Intakes of Vitamin D and Cancer

Chapter 11 reviewed most of the studies in the literature. Surprisingly, the only study showing a strong inverse correlation with dietary vitamin D was for pancreatic cancer, a cohort study involving 112,000 participants.[75] There was a significantly reduced risk for three of the five quintiles of vitamin D from diet. The problem with most such observational studies is that diet provides too little vitamin D to have a significant effect on cancer risk. National diets including fish and fortified milk provide about 250–300 IU/day of vitamin D,[76] which is too little to have an effect.[77] Reducing the risk of cancer incidence by at least 30% takes at least 1,100 IU/day[28] to 1,500 IU/day.[36,78-80]

Chapter 12. Observational Studies on Serum 25-hydroxyvitqamin D, Cancer and All-Cause Mortality

Interestingly, the IARC report accepted the existence of a preventive role of vitamin D in colorectal cancer, yet it unfairly discounted similar evidence of approximately the same level of benefit in reducing the risk of breast cancer. This duality is inexplicable because the effect on breast cancer of being in the top half of the population distribution on 25(OH)D cancer mortality rates (0.28, $p < 0.0x$) was identical to that of being in the top tertile of the population distribution for colorectal cancer (0.28, $p < 0.02$).

Chapter 13. Meta-Analyses of Observational Studies on Vitamin D Levels on Colorectal, Breast and Prostate Cancer and Colorectal Adenoma

Although the Working Group's meta-analyses for colorectal and breast cancer in chapter 13 are good, their not discussing the similar meta-analyses by Gorham et al.[79] and Garland et al.[36] is puzzling. The data for incidence rate in these studies were plotted versus serum 25(OH)D, which gives a graphical representation of the relationships. In Gorham et al.[79] colorectal cancer incidence was reduced by 50% for a serum 25(OH)D level of 34 ng/mL. In Garland et al.[36] the 50% reduction point for breast cancer was 52 ng/mL.

For ovarian cancer, Garland,[81] using data from Tworoger et al.[82] calculated a 48% reduction in incidence for a serum 25(OH)D level of 30 ng/mL.

Chapter 14. Randomised Trials on Vitamin D, Cancer and Mortality

The analysis of the only vitamin D-cancer RCT that used more than 10 μg (400 IU)/day of vitamin D[28] is a further example of how the Working Group tried to discredit a strong finding regarding the role of vitamin D in reducing the risk of cancer.

The IARC report states that there was no significant difference between the calcium arm and the calcium plus vitamin D (Ca + D) arm. This conclusion is correct for the entire 4-year period. However, at the suggestion of a referee, the authors examined the data for years 2–4. In that period, the reduction in incidence for the Ca + D arm was 77%, and that for the Ca arm, 42%, with the difference being 35%, which the authors ascribed to vitamin D. That this is a reasonable value is supported by the meta-analyses of incidence of breast[36,80] and colorectal[79] cancer with respect to serum 25(OH)D levels with the conversion that 1,000 IU/day of vitamin D increases serum 25(OH)D levels by about 10 ng/mL.[28] They find that reducing the incidence of those cancers by 50% takes about 1,500 IU/day. Of course, not all cancers are vitamin D sensitive. Nonetheless, the value of 35% reduction in risk is consistent with the meta-analyses.

The IARC report's statement on p. 238 that the cancer incidence rate in the placebo group was unusually high is incorrect. Cancer incidence data available from the Surveillance, Epidemiology, and End Results (SEER) Program[83] can estimate the incidence rate for the approximately 340 women who completed the placebo arm. The age at time of enrollment was 66.7 ± 7.3 (mean ± SD) years. In the United States in 2000–2005, the all-cancer incidence rate for women around 69 years of age was about 1,600 cases/100,000/year. According to mortality rate data for 2004,[84] all-cancer mortality rates in Nebraska are about 92% of the U.S. average. The same ratio is assumed to hold for incidence rates. For the last three years of the study, those in the placebo arm, the expected number of cancer cases is 0.016 x 0.92 x 340 x 3 = 15. The actual number of cases was 18.

Another criticism of the study lodged elsewhere is that the 3- or 4-year period is too short to demonstrate a vitamin D effect. That criticism overlooks the beneficial role of vitamin D in reducing angiogenesis and metastasis that would also explain the findings regarding cancer survival with respect to season of diagnosis in Norway.[27]

Although it has some limitations, the Lappe et al.[28] study stands out as the only well-conducted vitamin D supplementation-cancer incidence RCT performed to date. That group is on the verge of receiving funding to extend their studies.

Historically, RCTs were not needed (or possible) to test the efficacy of intensive case finding in control of tuberculosis epidemics, the effect of contaminated water on risk of cholera or dysentery, the effect of air pollution on respiratory diseases, and many other

topics that are not well suited to clinical trials for practical or ethical reasons, or because the cost of the delay required to complete the RCT is high. With the current knowledge of the health benefits of vitamin D with regard to falls, low bone density, fractures, cancer and type 1 diabetes,[85,86] it would be unethical to carry out an RCT without reasonable intake, such as 1,000–2,000 IU of vitamin D3 or 1,000–1,500 mg/day of calcium from people enrolled in clinical RCTs.

Chapter 15. Vitamin D, Cancer Prognostic Factors and Cancer Survival

The IARC report's discussion of skin solar elastosis correctly concludes that solar elastosis is not a good marker of lifetime solar UVB irradiance and vitamin D production. However, one overlooked reason in this discussion is the role of smoking in elastosis. Smoking produces skin elastosis the same as does solar UV irradiance.[87] As recently found,[66] there is a strong inverse correlation between smoking and risk of melanoma. This effect, then, probably explains the finding of increased survival with melanoma for all measures of solar UV irradiance.[88] Other studies such as that by Tuohimaa et al.[67] and the study of cancer in Spain[73] did not find that incidence or death from melanoma was correlated with reduced risk of internal cancers.

A study of women diagnosed with breast cancer in Toronto found that during a 12-year follow-up period, those with serum 25(OH)D levels greater than 30 ng/mL at time of diagnosis had a 17% all-cause mortality rate, whereas those with a level less than 20 ng/mL had a 34% mortality rate.[89]

Chapter 17. Vitamin D in Specific Populations or Conditions

Chapter 17 of the IARC report discussed cancer rates for African Americans, Hispanic Americans and Native Americans. For African Americans, the IARC report discussed and largely dismissed the study by Giovannucci et al.[90] on the basis of the small number of cases (99) and lack of serum 25(OH)D measurements. For some reason, the report also did not discuss two ecological studies of cancer mortality rates for African Americans. Grant[91] reported that solar UVB doses for July 1992,[53] were inversely correlated with bladder, colon, lung and rectal cancer for males and breast, lung and pancreatic cancer for females. In a later study that also included indices for alcohol consumption, poverty, smoking and urban residence, UVB was inversely correlated with all less lung, colon, esophageal, gastric, lung and rectal cancer for males and all less lung, breast, gastric and rectal cancer for females with a p value of less than 0.05.[5] However, in a reanalysis that retained only the significant factors, and applied the Bernoulli criterion ($p < 0.05/n$, where n is the number of factors), beneficial effects were found only for all less lung, colon, lung and rectal cancer for males and all less lung and breast cancer for females. Although the results for lung cancer were not adjusted for smoking history, and so may be due to a geographical variation in smoking, there is evidence that vitamin D reduces the risk of lung cancer,[92] and the results for the other cancers seem to be linked to UVB.

Those with Hispanic heritage are included in the category "white males" and "white females" in the *Atlas of Cancer Mortality in the United States, 1950–94*.[51] Thus, Grant and Garland[50] used an index for Hispanic Americans in the analysis. Significantly increased mortality rates for Hispanic Americans in 1970–1994 were found for gallbladder, gastric and possibly rectal (males) cancer after considering the Bernoulli criterion. These associations are as expected for gastric and gallbladder cancer.[93] Thus, cancer rates among Hispanic Americans do not show evidence of much difference in cancer risk with respect to solar UVB than other white Americans.

Chapter 18. Vitamin D: Prediction or Cause of Cancer and other Chronic Health Conditions

Chapter 18 suggests that it is not known whether poor health leads to low serum 25(OH)D levels or, conversely, whether low serum 25(OH)D levels lead to increased risk of cancer and other chronic diseases. From our reading of the journal literature, the second statement is the more generally correct one. The chapter also indicates that an RCT is the only way to determine which statement is correct. The IARC report did not look far for evidence that low vitamin D levels increased the risk of disease.

Dental health is an example of how low solar UVB leads to chronic disease. An ecological study in the 1930s found that adolescent white males living in the southwestern United States, with more than 3,000 hours of sunlight/year, had half as many dental caries as those living in the Northeast, with fewer than 2,200 hours of sunlight/year, with those living between having a number of dental caries proportional to annual sunlight level.[94] The mechanism was unknown then but is now known to be the production of human cathelicidin (LL-37) by $1,25(OH)_2D$, which has strong antibacterial properties.[95,96] More recently, periodontal disease was linked to low serum 25(OH)D.[97,98] From these findings, as well as the series of studies this year reporting that low serum 25(OH)D is inversely correlated with vascular disease incidence and mortality rates,[99-102] and a recent analysis on the role of vitamin D in neuroprotection,[103] comes evidence that low serum 25(OH)D is an important risk factor for dementia (vascular dementia and Alzheimer's disease).[104]

The epidemiology of septicemia in the United States had all the hallmarks of variations in vitamin D production from solar UVB: age, geographical, racial and seasonal.[105,106] A report in the literature also pointed out that cathelicidins were antisepsis molecules.[107] A study outlining the evidence for solar UVB and vitamin D modulating the risk of septicemia was recently published.[108]

Because humanity has lived in harmony with and been dependent upon solar UVB since the beginning, and because vitamin D is the primary health benefit of solar UVB irradiance, a great deal of data can be harvested and used in ecological and observational studies.

Chapter 19. Should Recommendations for Sun Protection and Vitamin D Intakes be Changed?

There is a statement on p. 296 that is inconsistent with the results of the Lappe et al.[28] RCT: "Setting a lower limit of "adequate" serum 25-hydroxyvitamin D levels at 20 or 30 ng/mL is currently inappropriate since there are no results from randomised trials suggesting that maintenance of such "adequate" serum 25-hydroxyvitamin D level actually prevents any cancer and any other chronic condition."

In the Lappe et al.[28] study, the women taking 1,100 IU/day of vitamin D raised their serum 25(OH)D levels from 28 to 38 ng/mL and had a 35% reduction in all-cancer incidence between the ends of the first and fourth years of the study attributed to vitamin D supplementation.

Chapter 20. Further Research: A Plea for New Randomized Trials on Vitamin D

Vitamin D is not an artificial drug and has neither unknown benefits nor unknown adverse side effects. Although RCTs might be good to convince the skeptics, such trials are not required if the available evidence is carefully evaluated.

Ordinary doses of vitamin D have shown no influence in preventing any disease except rickets because 10 μg (400 IU) of vitamin D is sufficient only to reduce the risk of rickets. The first 400 IU of vitamin D is used for calcium absorption and metabolism.

Studies of populations with low vitamin D intake could not find a beneficial effect,[77] which was confirmed later by meta-analyses.[36,79] For breast cancer, it was recently reported that "The association was shown to be nonlinear ($p_{nonlinearity}$ = 0.06) in fractional polynomial analysis with a stronger effect in women at low plasma 25(OH) D levels, providing some evidence of a threshold effect (at circa 50 nmol/L)."[109]

As for contraindications of higher doses of vitamin D, there seem to be none for most people at levels less than 10,000 IU/day.[20] For those with granulomatous diseases such as sarcoidosis,[110] caution is advised for having increased serum $1,25(OH)_2D$ levels.

The recommendation for RCTs of vitamin D supplementation is a ploy to delay further, for 5–10 years, consideration of increasing the recommended oral intake or production of vitamin D. Sixteen vitamin D scientists have signed a Vitamin D Scientists' Call to Action Statement.[111] This statement was used to get the American Medical Association and the American Public Health Association to pass supporting resolutions at their annual meetings in July and October, respectively. Also, the National Academy of Science's Institute of Medicine is constituting an ad hoc committee to review vitamin D dietary guidelines.

In a paper published in December 2008, it was stated: "Perhaps clinical trials cannot be the only "gold standard" for cancer prevention research. Their size and duration, along with their inherent problems in long-term adherence, make them unfeasible for addressing many important questions, especially those related to behavior change."[111a]

Backgrounds of the Working Group Members

Constituting a working group to review a field involves maximizing expertise and minimizing bias. Strong proponents of the UVB—vitamin D—cancer theory would be expected to have a better understanding of the literature but might also be biased to more favorably accept evidence in favor of the theory. On the other hand, those who have spent much of their careers trying to reduce the risk of skin cancer would not know the UVB—vitamin D—cancer literature as well, and they might have a bias to look more critically at the evidence and, perhaps, reject evidence that did not conform to their expectations. Although constituting such a working group is a difficult task, one can get a reading on the panel from their publication records. To pursue this approach, I searched PubMed for publications associated with the names of the working group members and either "vitamin D" or "skin cancer." I assumed that "skin cancer" would also encompass any report that dealt with melanoma. For the 22 international scientists and Secretariat Working Group members, I found 116 entries associated with vitamin D and 267 with skin cancer, a ratio of 0.43 vitamin D entries to skin cancer entries. If the member with the most vitamin D studies is omitted, the number of articles in each category drops to 64 and 267, respectively, and the ratio drops to 0.24.

This group configuration represents a bias that appears to be reflected in the analysis and conclusions of the IARC report. In contrast, the National Institutes of Health conference "Vitamin D and Health in the 21st Century: an Update," held in September 2007, resulting in 20 reports published in the August 2008 issue of the *American Journal of Clinical Nutrition,* had 950 entries on vitamin D by the first authors and only seven on skin cancer.[112]

We compared the publication records for the two groups. In one case, those with expertise in vitamin D and health were tasked with telling what they knew. In the other case, those more concerned about protecting people against skin cancer seemed more intent on rejecting much of the scientific evidence of a beneficial role of vitamin D and modest UVB irradiance for cancer risk reduction in order to protect existing public messages about sun safety. It was unfortunate that the Working Group did not include more vitamin D-cancer experts.

The role of solar UVB and vitamin D in reducing the risk of cancer can be considered causal based on an evaluation of the evidence for the criteria for causality first developed by Robert Koch to show that tuberculosis was caused by a bacterium,[113] and codified in recent times by A. Bradford Hill.[2,114]

Many more lives are lost because of insufficient solar UVB and vitamin D than from skin cancer and melanoma.[51,115-117]

Scientific Method

Briefly reviewing the scientific method may be worthwhile. The acquisition and development of scientific knowledge proceed through observations, hypotheses, experiments and publications in various orders. Those representing the established paradigms often resist new paradigms as long as they can.

Decision Making

Many questions exist regarding adoption of new public health policies including the risk-benefit ratio, doses and restrictions on applicability. Even in some of the more successful public health policies, such as administration of the polio vaccine, there are risks and some people suffer some adverse effects. Even nonsteroidal anti-inflammatory drugs such as aspirin, often recommended as routine supplements for disease prevention, can cause serious gastrointestinal bleeding.[118] Colonoscopy, recommended to reduce the risk of colon cancer, causes intestinal perforation in about 0.1% of cases.[119] For vitamin D, the overwhelming evidence to date is that the health benefits are enormous and the adverse effects limited.

Summary and Conclusion

The health benefits of vitamin D extend beyond cancer to cardiovascular diseases,[78,120] bacterial[95,96] and viral infections,[37,38] autoimmune diseases,[34,121] dental caries[94] and periodontal disease[97,98] and dementia.[103,104]

While this paper includes reference to several papers published after the Working Group reviewed the literature and six papers by the author of this paper that are in press, most of these recent works are reviews based on published literature and, thus, could have been anticipated by members of the Working Group.

Increasing serum 25(OH)D levels at the population level will do much to reduce the economic burden of disease. Although people with a few types of granulomatous diseases such as sarcoidosis[110] should be careful about increasing serum 25(OH)D levels, and those with red hair and freckles should be careful in the sun, for nearly all people, the health benefits of careful solar UV irradiance and increased vitamin D supplementation greatly outweigh the adverse effects. Although I agree that positive results from well-designed RCTs will help convince the skeptics, the evidence to date is strong enough that vitamin D can be recommended to prevent and treat cancer. The sooner that health policies are changed based on present-day evidence, the better for disease prevention.

Quoting from A. Bradford Hill:[114] "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modifies by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge I already have, or to postpone the action that it appears to demand at a given time."

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