

Symposium-in-Print UV Radiation, Vitamin D and Human Health: An Unfolding Controversy

Ultraviolet Radiation Exposure, Vitamin D, and Cancer

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ABSTRACT

This paper reviews briefly the evidence for an association between various measures of UV radiation (UVR) exposure and the development of cancer. Issues such as data quality, study design, measurement variation, comparability of studies, and quantification of UV exposure in relation to skin cancer are discussed. A range of exposure, based on skin type, might be appropriate: from 5 min a day three times a week for light-skinned individuals and 10 min a day three times a week for darker-skinned individuals. These exposures translate into 13 h per year, for a light-skinned individual, leading to 650 h of exposure from birth to age 50.

UV EXPOSURE AND CANCER

Many ecologic, cohort and case control studies have shown that as ground level UV radiation (UVR) increases, cancer mortality and in some cases cancer incidence decreases (1–4). Prostate, colorectal and breast are most studied, although new data have shown that non-Hodgkin lymphoma (5,6) is also inversely associated with sun exposure and that survival with melanoma (4) is inversely associated with sun exposure.

The major reason propounded for an association of sun exposure with a protective effect in the development of cancer and improved survival is that vitamin D synthesis is a critical component of cellular networks that inhibit cellular proliferation and encourage apoptosis (7). Therefore research has focused on measures of sun exposure, serum vitamin D levels (and associated metabolites), and genetic variants that may affect vitamin D synthesis. Few studies have combined all three measures, so that this review will not be able to provide integrated information that might be useful for validating the hypothesis. However, each component can be

assessed. The purpose of this review is to evaluate the quality of the evidence for health benefits of UVR-induced vitamin D in relationship to the risks of exposure to UVR-induced skin cancer.

VITAMIN D

Vitamin D is actually a term for two different molecules: cholecalciferol (vitamin D₃), formed in the skin by means of UV light on 7-dehydrocholesterol, and ergocalciferol (vitamin D₂), formed in the plant and fungal steroid ergosterol by UV light and a major form of supplemental vitamin D (8). Both molecules are metabolized in the liver to 25-hydroxyvitamin D (25-(OH)D). Hydroxylation occurs in the kidney and forms the very biologically active 1,25-dihydroxyvitamin D (1,25-(OH)₂D).

ISSUES OF STUDY DESIGN

Epidemiologic information about the role of sun exposure, vitamin D and cancer among humans is obtained through three major study designs with varying degrees of validity. Ecologic studies (*e.g.* 9,10) are subject to confounding by all the unmeasured variables that are likely to affect the results. For example, in Europe, cutaneous malignant melanoma rates are positively associated with latitude, whereas in Australia they are inversely associated with latitude. This is because, in Europe, darker-skinned people live nearer the equator, as in Italy and Portugal, and lighter-skinned people live further from the equator, as in Norway and Sweden. Skin pigmentation, then, is an important confounder for studies of skin cancer. Other confounders that might be associated with these ecologic associations might include socioeconomic status and activity patterns. In some of the case-control and cohort studies, however, these important variables have in fact been measured. The major problem for interpretation of these data is that few studies have measured all relevant confounders.

Case-control studies can provide good assessments of the association between an exposure and a disease, such as cancer. These studies are usually based on interview data and, more recently, have collected biological samples as well. The major drawback to case-control studies is that they are retrospective and so the fact that the case group has recently been diagnosed with cancer may affect the results, either through “biased” reporting or through the cancer itself affecting the biological sample. Genetic studies of germ line DNA variants overcome both these problems

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Abbreviations: BCC, basal cell carcinoma; CMM, cutaneous malignant melanoma; CPB, competitive protein binding; 1,25-(OH)₂ D, 1,25-dihydroxyvitamin D; HPLC, high-performance liquid chromatography; 25-(OH) D, 25-hydroxyvitamin D; RIA, radioimmunoassay; SNPs, single nucleotide polymorphisms; SCC, squamous cell carcinoma; UVR, UV radiation; VDR, vitamin D receptor.

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because studies of germ line mutations and cancer are not affected by reporting or experience.

Cohort studies have always been considered the gold standard for epidemiology. They have exposure measurement before disease onset, but often they do not have many intervening measures, so one must “impute” intervening exposure. In addition, cohort studies are vulnerable to selection bias as comparison groups are not randomly allocated and won't likely be similar in terms of measured and unmeasured baseline factors, *i.e.* factors that determine whether a person receives an intervention and thus could result in groups that differ in factors related to outcome due to individual choices. These differences could well bias the assessment of the outcome (11).

SOURCES OF VARIABILITY

In attempting to draw conclusions from many studies, one must consider the validity and reproducibility of the measures used. Sun exposure, serum vitamin D levels and genetic variants have been measured in epidemiologic studies to investigate the association of vitamin D and health. Each exposure measure has specific measurement issues that need to be addressed to evaluate the studies. Assessment of sun exposure history has no “gold standard.” In fact, ecologic studies are actually sometimes somewhat better than case-control or cohort studies because within the population evaluated there is usually ample variation to pick up differences between exposures and outcomes, if they exist. Case-control studies may use published measures of solar radiation, but often do not have enough variation in locations to draw conclusions about differences in exposure. Such study designs usually involve interview of subjects, with potential misclassification of exposure, through poor recall by subjects.

In sun exposure, subjects are asked about their lifetime recreational, occupational and other ultraviolet radiation exposures. There is inherent variability in the answers subjects give and their reliability (12–14), but this fact dictates a larger number of subjects to avoid incorrect inferences. Furthermore, all authors do not collect or report data in a similar and comparable manner. This is one reason that studies need large sample sizes to develop robust conclusions.

In serum measurements of vitamin D and its metabolites, one would think that these would provide definitive proof for the adequacy or inadequacy of exposure—either through UV exposure or dietary intake. Multiple issues are associated with serum measurements of vitamin D, however: treatment of sample during storage and method of analysis are the major ones. In a comparison of laboratory measurements of serum 25-hydroxyvitamin D concentration (25-(OH)D) (15) within one laboratory the mean serum 25-(OH)D level was 80% higher when measured by competitive protein binding (CPB) assay than by high-performance liquid chromatography (HPLC) with radioimmunoassay (RIA) intermediate. A full fifth to one quarter of serum 25-(OH)D values in the lowest quartile by HPLC were not recognized by CPB or RIA as being in that quartile. Although a comparison of eight serum samples by five laboratories in different countries ranked samples similarly, the differences between the mean values for the highest and lowest values was 38%. Because there is seldom cross-calibration, the definition of vitamin D deficiency by one laboratory may be misleading. Therefore, serum measures of 25-(OH)D in different populations or studies must be viewed with caution.

In addition, the optimal level of vitamin D is an important issue. The U.S. Food and Nutrition Board has recommended “adequate

intakes” for vitamin D. Adequate intake represents a recommended level of dietary intake when there are limited data on the relationship between intake and deficiency. These are intended to cover the needs of adults regardless of sunlight exposure. At ages up to 50 years, the daily intake is recommended as 200 IU (5 µg); between 51 and 70 years, the daily intake is recommended as 400 IU (10 µg); at ages 71 and older, the recommended daily intake is 600 IU (15 µg). Some investigators have suggested that the optimal requirement for vitamin D should be much higher than official recommendations (16,17) because a startling number of individuals seem to have low levels of vitamin D (18). Vitamin D deficiency has been variously defined as “mild” where 25-(OH)D levels in the range of 25–50 nmol/L (6.25–12.5 ng/mL) lead to high bone turnover (8); “moderate” in the 12.5–25 nmol/L (3.25–6.25 ng/mL) range, which is associated with reduced bone density (19); high bone turnover (20) and “severe” at levels less than 12.5 nmol/L (3.25 ng/mL), resulting in osteomalacia (8). If, in fact, the optimal level is higher than current standards, the conclusions of some important studies will change. For example, a small prospective study of Xeroderma pigmentosum patients found that although they were extremely well protected from sunlight, they still had levels of vitamin D within the optimal range (21). These levels, however, were at the very low end of the range, 17.8 ± 1.5 ng/mL (normal range specified as 10–55 ng/mL). Other recommendations suggest that 54–90 ng/mL should be considered normal (22).

In genetic variants, or single nucleotide polymorphisms (SNPs), in the vitamin D receptor (VDR) and the *AIB1* genes, there is likely to be less variability in measures and the measures are static, that is they do not change based on other exposures. Unfortunately, however, comparison of SNP measurement between laboratories has been rare.

COMPARABILITY OF STUDY RESULTS BASED ON MEASURES OF EXPOSURE

Measures of exposure differ widely among studies on melanoma, breast cancer, colorectal cancer and prostate cancer. The studies evaluating serum levels of vitamin D in highly sun protected individuals have found conflicting results. In one study, normal levels of serum vitamin D were found in Xeroderma pigmentosum (XP) patients who are highly sun protected (21). Another study, evaluating three XP patients at one point in time (23), reported very low levels of serum 25-(OH)D. One study evaluating melanoma patients found that their serum levels of vitamin D were no different from a control group (24). Another randomized study, in Australia, found that serum levels between sunscreen users and controls were not different (25). However, other studies have found that highly protected individuals—whether by sun exposure habits, clothing, or lack of outdoor exposure—have lower levels of vitamin D (10,17,18,40,42–45).

Studies evaluating diet as a risk factor for melanoma have in general found no effect. However, a very recent report (26) indicates that a diet high in vitamin D is very protective for the development of melanoma. This was a hospital-based study from Philadelphia and San Francisco. Several reports show an interaction of diet with genetic factors (27–30). As hinted at above, such studies are most likely preliminary only because of the small sample sizes that result from subgroup analyses.

The problem is even more severe in studies of genetic variants and their effect on vitamin D levels or risk of cancer. Observations of genetic variation are highly dependent on the underlying popu-

Table 1. Variation in frequency of *FokI* alleles in selected cancer studies

Cancer type	Controls			Cases		
	FF	Ff	ff	FF	Ff	ff
Melanoma (31)	0.48	0.41	0.11	0.36	0.48	0.16
Colorectal cancer (28)	0.27	0.51	0.22	0.19	0.53	0.27
Prostate, whites (33)	0.40	0.45	0.15	0.37	0.52	0.11
Prostate, blacks (33)	0.61	0.35	0.04	0.74	0.22	0.04
Prostate, Asians (38)	0.23	0.51	0.21	0.27	0.51	0.22

lation structure, that is, the racial/ethnic composition, as well as the sample size, and the Japanese population appears to have different associations than other Caucasian populations, for example, in ecologic studies of skin cancer (3). One can obtain opposite results with the same genetic variant in the same population, simply by adding more subjects to the control group or the case group. The fact that this problem is an important one is illustrated by the different results obtained by association studies of *FokI*, a SNP in the VDR. In a relatively small hospital-based study of melanoma cases and controls from a dermatology clinic (31), the FF, homozygous wild-type alleles of *FokI* were associated with decreased risk of approximately 24% for melanoma. In colorectal cancer this genotype was also associated with increased risk (28), whereas in several studies of prostate cancer this genotype was associated with a decreased proportion of subjects with a high Gleason grade (32) and several studies in prostate cancer have shown no effect of this genotype on risk (33–38) (Table 1). Most of

these discrepancies can be explained by sample selection and sample size. That is, the inconsistency of effect is undoubtedly random, and these studies cannot provide evidence of an effect. On the other hand, there is also stratification by racial ethnic group, as seen clearly in the different genotype frequencies among controls in Table 2. However, it is also possible that VDR polymorphisms would affect different tissues in different ways; that is, the effect of individual SNPs may vary by tissue site.

Where does this leave us? Perhaps the “Precautionary Principle” can be invoked, that is, “one should take reasonable measures to avoid threats that are serious and plausible” (39). On balance is the issue of solar exposure that is the principle source of vitamin D (40) versus the harm that can be caused by excessive solar exposure in the form of skin cancer. Inadequate evidence exists to suggest that current vitamin D standards are too low, but it seems likely that they could be (17,33). Conflicting evidence suggests that current management strategies to avoid excessive solar exposure, such as sunscreen application, allow adequate vitamin D metabolism (21,25,41,42). If the current standards for healthy vitamin D levels and their range are too low, then the sparse data supporting the extreme position that total coverup under the sun at all times may be incorrect. Older individuals in nursing homes without sun exposure are at risk for inadequate circulating levels of vitamin D (43). Furthermore, darker-skinned individuals who have moved to more northern latitudes and who cover themselves with clothing for traditional reasons, such as Pakistani women and children in the UK or Norway, may have serious vitamin D deficiencies (44,45).

Multiple questions urgently require answers. What is the healthy range of vitamin D for individuals at different ages? What is the

Table 2. Quantitative measures of exposure to solar radiation and the development of skin cancer*

Author, year	Subjects	Study design	Results	Covariates
Fears, 2002 (46) USA (San Francisco and Philadelphia)	718 CMM, 945 controls	Hospital-based case-control study	Cumulative daily UV exposure by the age of 20 is about 27 000 h and not different between cases and controls	Not included in these analyses
Rosso, 1999 (47) Switzerland	25 SCC, 120 BCC, 144 controls	Population-based case-control study	<5000 h is baseline for overall sun exposure. No real increase for BCC, but at 64 200 h SCC risk almost doubles	Not included in the analyses for hours of sun exposure
Rosso, 1996 (48) eight centers in Europe	1549 BCC, 228 SCC, 1795 controls	Population- and hospital-based case-control study	After 70 000 cumulative hours in a lifetime, SCC and BCC increased 2-fold	Differed by tanning ability
Rosso, 1998 (49) Italy	260 CMM, 425 BCC, two sets controls	Population-based case-control study	More than 22 000 h in a lifetime increases risk	Adjusted for skin phenotype and intermittent sun exposure
Kricker, 1995 (50) Australia	175 BCC, 700 controls	Population-based case-control study	After 35 000 h risk decreased	In those who tan well, risk increases with increasing exposure
Espinosa Arranz, 1999 (51) Spain	116 CMM, 235 controls	Hospital-based case-control study	More than 120 h sunbathing within the previous two years leads to a two-fold increased risk of CMM	Adjusted for age, skin type and the number of nevi
Green, 1985 (52) Australia	232 CMM, 232 controls	Population-based case-control study	More than 2000 h of cumulative sun exposure increased risk 80%	
Holman, 1984 (53)	511 CMM, 511 controls	Population-based case-control study	After 2600 h of cumulative exposure risk increased to 1.3 (95% CI 0.9–1.9)	Not used in analysis of sun exposure. Nodular melanoma has a reduced odds ratio with additional sun exposure.

* BCC = basal cell carcinoma; CMM = cutaneous malignant melanoma; SCC = squamous cell carcinoma.

appropriate means of covering up to avoid excessive solar exposure? Is dietary intake of vitamin D an adequate way to meet the healthy range during all seasons and at all latitudes and in all cultures?

We can turn to quantitative data on UV exposure and its relationship to the development of skin cancer to find some insight into the optimal UV exposure.

QUANTITATIVE STUDIES OF UVR AND SKIN CANCER

A number of studies of the development of skin cancer have quantified UV exposure and estimated the exposures that lead to skin cancer (46–53). These studies will be used to set a benchmark to assess unprotected sun exposure to maintain optimal vitamin D status (Table 2). Studies that have used cumulative lifetime hours of exposure are reported below because that measure is more relevant to the consideration of the risk of interest in this paper, regular short-term exposure to UV. Many papers report such factors as number of and age of sunburns, annual weeks of sunbathing at the beach (54), or similar measures. It is difficult to translate weeks of sunbathing at the beach to risk for melanoma or other skin cancers to 5–10 min per day of unprotected sun exposure and, therefore, these measures are not referenced. There is a difference in terms of the types of exposures that likely lead to cutaneous malignant melanoma (CMM), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) (55,56). Intermittent, intense UV is associated with CMM; regular, chronic, high levels of UV are associated with SCC; exposures associated with BCC are somewhat in between.

THE BALANCE FOR UV EXPOSURE FOR VITAMIN D SYNTHESIS AND THE DEVELOPMENT OF SKIN CANCER

As discussed, a multitude of data supports the need for vitamin D supplementation (8) for medical conditions that arise secondary to a deficiency in vitamin D. Rickets seen in populations has been of concern for generations and continues to be seen today. In addition, the links to cancer of the colon and osteoporosis in the presence of a vitamin D deficiency have been shown (8,57–60). The recommendation for increased intake of vitamin D is validated by the increased bone mass (19) seen with vitamin D supplementation. This is well recognized as is demonstrated by the widespread fortification of foods with vitamin D.

How to best supplement must be considered. Diet alone does not provide a sufficient amount of vitamin D (8). Fortification and supplementation certainly increase the amount available. Recommended supplementation by daily vitamin pill intake can bring vitamin D levels to sufficient levels; however care must be taken. Excessive supplementation (*i.e.* >0.05 µg or 2000 IU) can have adverse effects as toxicity in the form of soft tissue calcification and hypercalcemia can then result (61).

In addition to supplementation, limited sunlight exposure could be an appropriate means of getting sufficient vitamin D (8,16). The support for such guidelines is based on two assumptions: (1) that sun exposure is the most effective method for obtaining vitamin D₃, and (2) that a large proportion of the world's populations receives inadequate vitamin D. The position statement of the

Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia supports both assumptions. They do suggest that for individuals for whom sun exposure is not possible, a vitamin D supplement of at least 400 IU per day should be taken. In fact, they suggest daily exposure of the hands, face and arms, outside the hours of 10 A.M. and 3 P.M., if possible.

Holick suggests (62) that exposure of the hands, arms and face for 5–10 min 2–3 days per week in Boston at noon would give a person with skin type 2 “more than adequate” vitamin D. Another remedy he suggests is 50 000 IU of vitamin D once a month. Based on the information gleaned from epidemiology (Table 2), it is obvious that 5 min of unprotected sun exposure in a latitude similar to Boston's at noon, is unlikely to add substantially to one's risk for skin cancer, and, although the evidence is far from persuasive, might actually reduce risk of other cancers and diseases. A range based on skin type might be indicated: from 5 min a day three times a week for light-skinned individuals and 10 min a day three times a week for darker-skinned individuals. These exposures translate into 13 h per year, for a light-skinned individual, leading to 650–1300 h of exposure over from birth to age 50, or near the mean age for developing melanoma. When considering the amount of sun exposure that might be useful for the synthesis of vitamin D, other factors, such as melanin and skin type are important.

Sunlight would be an appropriate source for several reasons. It is inexpensive and easily available to the vast majority of individuals. It would be advantageous in that exposure in the sunny season could produce stores allowing for sufficient vitamin D levels in the winter seasons. A small amount of sunlight would suffice, even for those with more inefficient vitamin D processes such as the elderly. However, there are practical issues of concern such as relying on individuals to keep track of the amount of exposure required before applying sunscreen. Actually limiting oneself to 5 min per day may be difficult and keeping recommendations consistent with the season, latitude, time of day while also addressing skin pigmentation and age variation also call into question how practical it would be to make consistent guidelines that are easily followed by the general population. In addition, Holick's recommendations call for exposure of the face and arms.

It is important to consider whether there are special populations that may benefit more from such recommendations than the general population. Although vitamin D insufficiency is found in much of the population including young healthy adults (10), those with a higher risk of deficiency or with a higher need for vitamin D would especially benefit. These populations include the elderly, those with existing deficiency, breastfed infants, and those with osteoporosis or other medical conditions related to vitamin D levels. Teen and young adult women appear to have the highest level of vitamin D deficiency in general (64), so this population could also be targeted for supplementation recommendations, which are critical as this population develops osteoporosis later in life, with the possibility of hip fractures from falling. The frequency of falling has been seen to occur less often in the elderly (65) who have sufficient vitamin D levels. Addressing the importance of vitamin D in this population before the development of deficiencies would result in improved health and decreased health care costs for the individual as well as society.

Vitamin D insufficiency is a substantial problem worldwide, resulting in widespread illness. In addition protective health effects have been seen in those with sufficient vitamin D levels. Recommendations for enhancing population vitamin D levels

should be vigorously pursued. Given that sunlight, artificial sunlight, and oral supplementation have all been seen to improve the vitamin D status of individuals, it may be best to have multiple recommendations for methods of increasing Vitamin D.

In the face of uncertain scientific understanding of the role of vitamin D synthesis in cancer protection, it seems prudent to urge caution in solar exposure and to be very clear that 5–10 min three times a week is not a license to get sunburned or to disregard sun protection.

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