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Vitamin D Levels, Dietary Intake, and Photoprotective Behaviors Among Patients With Skin Cancer

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Photoprotection against ultraviolet light is an important part of our armamentarium against actinically derived skin cancers. However, there has been concern that adherence to photoprotection may lead to low vitamin D status, leading to negative effects on patients' health. In this work we discuss previous findings in this area, which do not give a clear picture as to the relationship between vitamin D levels and photoprotection measures, as well as research performed by the authors, who did not detect a relationship between serum 25(OH)D levels and adherence to photoprotection measures in subjects with skin cancer, as assessed by the use of sunscreen, clothing, hats, sunglasses, and umbrellas/shade through the Sun Protection Habits Index. Subjects who took vitamin D oral supplementation had greater serum 25(OH)D levels than those who did not, whereas dietary intake through foods did not predict 25(OH)D levels in the authors' study. However, there was a high prevalence of vitamin D insufficiency and deficiency in the authors' study population, highlighting the importance of assessing vitamin D status and recommending oral vitamin D supplementation when indicated.
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Ultraviolet radiation from the sun, in particular ultraviolet B (UVB), is the major environmental risk factor for skin cancers.[1,2] To protect from the photocarcinogenic nature of UVB, dermatologists recommend active prevention measures, including use of sunscreens, hats, clothing, sunglasses, and planning activities around times of low sun exposure. These recommendations have played a role in the evolving controversy surrounding vitamin D, a secosteroid hormone important in many health states, because the UVB spectrum that is at least partially responsible for photocarcinogenesis and photoaging is also the same wavelength that initiates the photosynthesis of vitamin D in the skin.[3,4] Physicians are increasingly trying to ensure that their patients' vitamin D status is sufficient, and with UVB as the main natural source of vitamin D, there is concern that photoprotective recommendations may put patients at risk for low vitamin D status. Alternate means of obtaining vitamin D include oral intake, both dietary and vitamin supplementation. However dietary intake is often poor, with few foods in the American diet containing sufficient amounts of vitamin D. Over-the-counter oral vitamin D supplements vary in vitamin D content and guidelines for appropriate dosing are changing, but oral supplementation may be an effective way to maintain a sufficient vitamin D status.[5]

There are comprehensive review articles dedicated to the synthesis of data that exist regarding the relationship between photoprotection and vitamin D status.[6,7] Other reviews have elucidated factors known to influence vitamin D production in the skin, which include environmental factors (latitude, season, time of day at UV exposure) and personal factors (skin pigmentation, body mass index, and age) among others.[8] In this work we will briefly review the issues raised by these previous papers but will focus on photoprotective behaviors, particularly in skin cancer populations, because

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these patients are likely the most motivated to comply with photoprotection after their diagnosis.

Photoprotection and Vitamin D Status

Primary research investigating the effect of photoprotection, mainly sunscreen use, and vitamin D status has been conducted in both controlled settings and in real world or population-based settings with conflicting results. In early studies on the use of a sunlamp to simulate UVB emitted from sunlight, Matsuoka et al[9] found that vitamin D levels were reduced in subjects who used sunscreen. In their subsequent study, in which they studied natural sunlight as the source, these authors found that mean 25(OH)D levels were also statistically significantly lower and deficient in 20 daily sunscreen users who also had a history of skin cancer compared with 20 matched controls (40.2 vs 91.3 nmol/L, respectively).[10] This group then investigated the impact of protective clothing in a controlled setting and also found this facet of photoprotection to prevent the production of previtamin D in the skin of study volunteers.[11] These studies, although provocative, must be taken in context. The last study was performed in a well-controlled setting, most likely with subject education on the proper manner to apply and reapply sunscreen. However, it is well known that sunscreen compliance in the real world in comprehensive application and reapplication is difficult.[12]

In contrast, in 2 other studies of populations exposed to natural sunlight, vitamin D status was not detected to be lower in subjects using sunscreen.[13,14] Specifically, in an Australian study of sun protection factor (SPF) 17 sunscreen use in subjects with solar keratoses, there was no statistically significant difference in 25(OH)D levels between 58 cases and 55 control patients; however, the mean 25(OH)D level was insufficient among both groups.[13] Similarly, in a subsequent study from Spain, Farreons et al[14] did not detect differences in mean 25(OH)D or parathyroid hormone levels, which may increase in a vitamin D-deficient state, in 24 SPF-15 sunscreen users and 19 control patients. Critics of these studies have hypothesized that the negative finding was likely attributable to improper use of this single component of photoprotection.[15] Other possibilities include the fact that there are other photoprotective behaviors, such as sun-protective clothing and sun avoidance behaviors, that were not taken into account in their analyses, nor were other factors that could influence 25(OH)D levels, such as personal factors (body mass index, gender, etc) and exogenous factors (dietary and supplements). Finally, these studies are relatively small and may not have had sufficient power to detect small differences of 25(OH)D.

In a recent analysis of the National Health and Nutrition Examination Survey (NHANES) 2003-2006 database, a much larger population-based study ($n = 5849$), Linos et al[16] investigated the relationship of each component of photoprotection with 25(OH)D status. They found that wearing long-sleeved clothing and staying in the shade were strong predictors of lower vitamin D status, whereas there was no association between wearing sunscreen or a hat and vitamin D status. This group also speculated that sunscreen use was not a predictor because of poor knowledge of and adherence to methods for proper application and reapplication, whereas clothing and shade-seeking behavior do not require much adjustment once implemented. In another analysis of the same database, Chen et al[17] incorporated multiple facets of photoprotection into one composite score, thus accounting for many forms of sun-protective behaviors in a given subject. They found that greater adherence of overall photoprotection was associated with vitamin D insufficiency (25(OH)D $<$ 32 ng/mL) but not deficiency (25(OH)D $<$ 10 ng/mL). One advantage to the NHANES studies is that they are population-based studies; thus they investigate what is occurring in real life. There are also sufficient numbers of subjects within NHANES. However, analysis of this preexisting dataset does not allow investigators to study specific populations who might be at particular risk for low vitamin D levels, such as patients with a history of nonmelanoma skin cancer (NMSC), which is a population who may have increased photoprotection adherence.

Vitamin D Status in Skin Cancer Patients

There are many populations that are at an increased risk for skin cancer development. One such group are the genodermatoses, in which photoprotection is paramount in the prevention of skin cancer, specifically xeroderma pigmentosum (XP) and basal cell nevus syndrome (BCNS).[18,19] In 1997, Sollitto et al[18] reported the mean 25(OH)D levels in 8 subjects with XP during a 6-year period to be 17.8 ng/mL with the interpretation of these levels to be normal, as the newer cutoff values for insufficiency/deficiency had yet to be determined at that time.[20] In response, there was a report of an additional 3 subjects with XP and 1 with BCNS who had mean 25(OH)D levels of 9.5 mg/mL, qualifying as deficient, along with a plea for vitamin D status for monitoring of 25(OH)D levels and oral supplementation in these patients.[19]

The solid-organ transplant population is another one that is at increased risk for aggressive skin cancers, given the level of immunosuppression necessary to prevent organ rejection. Vitamin D status in the solid-organ transplant population has been investigated.[21] In one study, all subjects reported using photoprotection, including sunscreens, sun avoidance, and protective clothing and had a mean 25(OH)D level of 10.9 ng/mL, which was statistically significantly lower that the control population. The authors note, however, that in addition to photoprotective adherence, this population is also at risk for low vitamin D status on the basis of increased glucocorticoid breakdown of 25(OH)D.

Melanoma patients also constitute a population that would be more likely to adhere to photoprotection, given the potential mortality of the disease. In a small study of vitamin D status in 14 melanoma patients in Germany, Reichrath and Querings[22] reported that the mean 25(OH)D level among these patients was 24 ng/mL and concluded that these melanoma patients had normal vitamin D status. Photoprotection was not addressed in this study, but now that the recommendations for insufficiency/deficiency cutoffs have been redefined over the past few years, these melanoma patients would be categorized as vitamin D insufficient similarly to the studies in patients with XP and BCNS.

The authors have also attempted to elucidate whether skin cancer patients with greater adherence to photoprotective behaviors have lower vitamin D status compared with subjects with less adherent photoprotective behaviors. We hypothesized that patients with melanoma may be more adherent to photoprotection than patients with NMSC given the increased morbidity and mortality of melanoma and might therefore be at greater risk for low vitamin D status. To investigate this question, from September to December of 2008 and 2009, adult patients with a skin cancer history were recruited from the Emory Dermatology Clinics. Patients excluded were those who were already actively undergoing vitamin D serum monitoring, oral vitamin D supplement deficiency or insufficiency repletion, and those with a systemic disease that might influence vitamin D status, including intestinal malabsorption syndromes, granulomatous conditions, liver, kidney, or parathyroid disease. Those patients casually taking daily supplements containing vitamin D, but had not had their levels monitored were eligible for the study.

Subjects completed paper surveys asking about skin cancer history, Fitzpatrick skin type,[23] oral vitamin D supplementation, dietary intake of vitamin D, and the Sun Protection Habits Instrument (SPH, range 0-4, a greater score implies greater adherence).[24] SPH scores reflect the use of sunscreen, clothing, hats, sunglasses, and umbrellas/shade. Subjects were dichotomized by use of the median of the population into nonadherent and adherent groups.

Oral vitamin D supplements were defined as at least one of the following: a multivitamin, a calcium supplement containing vitamin D, a fish oil supplement, or a vitamin D supplement. Dietary intake of vitamin D was measured by the use of a standardized food frequency questionnaire querying serving size and frequency of ingestion of foods containing vitamin D was and calculated using the National Institutes of Health dietary supplement fact sheet.[25]

Vitamin D insufficiency was defined as the range $>$ 20 and $\leq$32 ng/mL and deficiency as $\leq$20 ng/mL.[20] Univariate comparisons and multivariate linear regression were used to determine predictors of serum 25(OH)D levels.

The demographics and characteristics of subjects are displayed in Table 1. Types of skin cancers represented were melanoma (63%) and NMSC (55%). Of these subjects, 19% had both melanoma and NMSC and were placed in the "melanoma" category when analysis by skin cancer type was performed. A history of 1, 2, or $\geq$3 skin cancers was reported by 58%, 18%, and 24% of subjects, respectively. Mean $\pm$ SD time since first skin cancer diagnosis before enrollment was 11.5 $\pm$ 11.8 years. There was a trend, although not statistically significant, towards lower mean $\pm$ SD 25(OH)D levels in melanoma compared with NMSC subjects (melanoma: 27 $\pm$ 9 ng/mL vs NMSC: 30 $\pm$ 12 ng/mL, P = 0.1).

Table 1 Demographics/Characteristics of All Subjects (n = 144), Participation Rate 84% (144/172)

	Age, 55 ±16 Years	
	n	%
Male	76	53
Married	102	85
College education or beyond	135	94
White	142	99
Fitzpatrick skin type		
I	21	15
II	47	33
III	54	38
IV	18	13
Work outside	23	16
History of NMSC	91	63
History of MM	79	55
History of both MM and NMSC	27	19
Family history of MM	25	18

There was no statistically significant difference in the above variables between nonadherent and adherent groups.
MM, malignant melanoma; NMSC, nonmelanoma skin cancer.

The median SPH index was 2.7 and subjects were categorized into nonadherent ($<$2.7) or adherent ($\geq$2.7) photoprotection groups. There was no statistically significant difference in mean number of skin cancers, time since first skin cancer diagnosis, or hours outside per day between the nonadherent and adherent groups (data not shown). Subjects who worked outdoors spent on average more hours outside than those with indoor occupations (2.1 $\pm$ 1.6 vs 1.3 $\pm$ 0.8, P = 0.001). However, there was no difference in the percentage of subjects with outdoor occupations between the nonadherent and adherent groups (15% vs 18%, P = 0.6). Subjects with melanoma compared with NMSC subjects did not have a statistically significant difference in mean SPH index scores or the percentage taking oral vitamin D supplements (data not shown).

Mean $\pm$ SD 25(OH)D levels among total subjects and photoprotective adherence groups are displayed in Table 2. The prevalence of vitamin D insufficiency among total subjects was 51% and of deficiency was 17%. There was no detectable difference in 25(OH)D levels or the prevalence of insufficiency or deficiency between adherent and nonadherent groups. Even if the cut-off value for the adherent group was shifted to a lower SPH index score of $>$2, there was no detectable difference in mean $\pm$ SD 25(OH)D levels (data not shown). Similarly, if the cut-off value for the adherent group was shifted towards a more stringent level of adherence, a score $>$3, there was still no detectable difference in 25(OH)D between the adherence groups (data not shown).

Vitamin D levels were also analyzed among each of the 5 components of the SPH questionnaire: sunscreen, clothing, hats, sunglasses, and umbrellas/shade. The median score for each of these components was 3 and subjects were categorized into nonadherent ($<$3) and adherent groups ($\geq$3). Again, there was no statistically significant difference in 25(OH)D levels between adherence groups for each of the

Table 2 Serum 25-Hydroxyvitamin D Levels and the Prevalence of Vitamin D Insufficiency/Deficiency Among Groups Adherent Versus Nonadherent to Photoprotection and Groups Taking Oral Vitamin D Versus Not Taking Oral Vitamin D

	Adherent (n = 76)	Nonadherent (n = 68)	*P* Value*	Oral vitD (n = 86)	No Oral vitD (n = 58)	*P* Value*	Total (n = 144)
25(OH)D level, mean (±SD)†	28 (10)	29 (11)	NS	31 (11)	25 (8)	0.002	29 (10)
Prevalence of deficiency, % (n)‡	18 (14)	16 (11)	NS	10 (9)	26 (15)	NS	17 (24)
Prevalence of insufficiency	47 (36)	54 (37)	NS	51 (44)	50 (29)	0.013	51 (73)
Taking vitamin D supplements, % (n)‡	62 (47)	57 (39)	NS	—	—	—	60 (86)

NS, not significant; vitD, vitamin D.
*By *t* test for continuous variables and by χ^2 for categorical variables.
†Measured in ng/mL.
‡Insufficiency was defined as the range > 20 and ≤32 ng/mL and deficiency as ≤20 ng/mL.

photoprotective components of the questionnaire (data not shown).

Of subjects, 60% were taking at least 1 of 4 types of daily oral vitamin D supplementation of which 52% were taking multivitamins, 20% were taking calcium supplements containing vitamin D, 22% were taking a fish oil supplement, and 12% were taking a vitamin D supplement. Mean 25(OH) vitamin D levels and the prevalence of vitamin D insufficiency and deficiency by oral supplementation group are also displayed in Table 2. Those subjects taking a daily vitamin D containing supplement had higher (and almost sufficient) vitamin D levels compared with those who did not take a supplement (31 ± 11 vs 25 ± 8 ng/mL, $P = 0.002$). Similarly, the prevalence of vitamin D deficiency was statistically significantly higher in those subjects who were not taking an oral supplement. Mean ± SD daily dietary intake of vitamin D among subjects was 218 ± 187 IU, with a range of 0-1544 IU. Of subjects, 94% had average daily vitamin D dietary intakes of <400 IU.

The multivariable linear regression model of 25(OH)D levels is displayed in Table 3. Age and oral vitamin D supplementation were significant predictors of 25(OH)D levels while other covariates were controlled. Skin cancer type (melanoma vs NMSC) trended towards being a predictor of 25(OH)D levels. Serum 25(OH)D levels were not predicted by gender, education, skin type, SPH index, or dietary vitamin D intake, mean number of skin cancers, or time since first skin cancer diagnosis.

Table 3 Multivariate Linear Regression of Serum 25(OH)D Levels

Variable	Coefficient	*P* Value
Age	−0.15	0.02*
Gender	−0.7	0.72
Education ≥ college	−1.9	0.67
Skin type	1.02	0.29
Melanoma history	−3.76	0.06
Outdoor occupation	−0.98	0.68
SPH index	1.2	0.48
Taking a vitamin D supplement	6.57	0.001*
Dietary vitamin D > 400 IU/d	−0.59	0.88

SPH, sun protective habits.
*Statistically significant.

In our cross-sectional study of skin cancer patients, we found a high prevalence of vitamin D insufficiency and deficiency, around 50% and 20%, respectively. However, we did not detect a relationship between 25(OH)D levels and adherence to sun protection as measured by the SPH index. These results remained constant even when shifting the SPH index cutoff for group classification to a greater value corresponding to more adherent photoprotective behavior. Similarly, we were unable to detect a difference in 25(OH)D levels between adherent and nonadherent groups in an analysis of each of the 5 elements of photoprotection (sunscreen, clothing, sunglasses, hat, and shade/umbrella) that are averaged in the SPH index.

Our null finding is consistent with some earlier studies described previously[13,14] but differs from the recent NHANES study, which did detect an association between greater adherence to photoprotection and vitamin D insufficiency.[17] Also unlike our findings regarding the subcomponents of the SPH index, the authors of another analysis of the NHANES study found that use of protective clothing and staying in the shade were predictors of low vitamin D status.[16] Our findings most likely differ from these NHANES studies because of methodological differences. First, the NHANES study did not divide their population by adherence to examine mean vitamin D levels, but instead they examined level of adherence after dividing the population into deficiency and insufficiency. Second, in the regression models, the NHANES study used milk intake as a surrogate for oral vitamin D intake rather than explicitly taking into account supplementation and dietary intake, whereas our study took the latter approach. The NHANES study also did not take into account outdoor occupation and melanoma history. By contrast, our study did not take into account body mass index, which was found to be a strong predictor of vitamin D levels in the NHANES study. Furthermore, we may have been unable to detect these differences because our estimated effect size was too large as we had proposed a 50% difference in 25(OH)D levels between the adherent and nonadherent to photoprotection groups, (eg, 20.0 vs 30.0 ng/mL).

Serum 25(OH)D levels were greater and almost sufficient in patients who took oral vitamin D supplementation compared with those who did not. The use of oral supplementation still significantly influenced vitamin D status while photoprotective habits and other demographic factors were controlled. However, dietary intake was not a predictor of 25(OH)D levels, and this result is likely because diet was not a significant source of vitamin D intake. Dietary vitamin D was <400 IU in nearly 95% of subjects, further supporting that it is difficult to obtain a daily allowance of vitamin D from diet alone.[5]

Increased age was also a predictor of lower 25(OH)D levels. This finding supports the authors of previous studies that found elderly patients to be at risk for vitamin D deficiency because their skin contains less of the source compound for the synthesis of vitamin D, 7-hydrocholesterol.[26]

We were not able to detect a statistically significant difference in adherence to photoprotection or 25(OH)D levels between skin cancer types, although a history of melanoma compared with NMSC trended towards predicting lower vitamin D status. This finding may be because of our relatively small sample size or may be because NMSC patients are truly as adherent as melanoma patients regarding sun protective behaviors. Future studies should look into this issue.

Seasonal variation may have influenced vitamin D levels and our ability to detect a difference between photoprotective groups, although subjects were consistently recruited from September to December during 2 consecutive years in an attempt to minimize this effect.

Although we were unable to detect a difference in vitamin D levels between skin cancer subjects adherent to and non-adherent to photoprotection, most subjects had insufficient levels of vitamin D. A prospective study is needed to better relate the causal relationship between adherence to sun protection and vitamin D levels. In the meantime, our small study along with the results from published literature suggest that along with the message of photoprotection, physicians should be aware that, regardless of whether they are using sun protection measures, many patients will have serum vitamin D levels that are considered insufficient or deficient.

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