Vitamin D and Nonmelanoma Skin Cancer in a Health Maintenance Organization Cohort

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Objective: To examine the association of serum 25-hydroxyvitamin D (25-OHD) with the risk of nonmelanoma skin cancer (NMSC), defined as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).

Design: Cohort study.

Setting: Health maintenance organization.

Patients: The study included 3223 white health maintenance organization patients who sought osteoporosis- or low-bone-density–related advice from 1997 to 2001.

Interventions: Vitamin D levels were ascertained at the time of the initial appointment, and a sufficient vitamin D level was defined as a baseline serum 25-OHD level greater than or equal to 30 ng/mL (to convert to nanomoles per liter, multiply by 2.496) and as a deficient vitamin D level less than 15 ng/mL.

Main Outcome Measures: The NMSC cases diagnosed between 1997 and 2009 were ascertained using claims data, considering first occurrence of specified disease outcome and complete person-years of follow-up since baseline. Charts were abstracted for histologic subtype and anatomical location.

Results: More patients were vitamin D insufficient (n=2257) than sufficient (n=966). There were 240 patients with NMSC: 49 had an SCC, 163 had a BCC, and 28 had both. Vitamin D levels greater than 15 ng/mL (“not deficient level”) were positively associated with NMSC (unadjusted odds ratio [OR], 1.7; 95% confidence interval [CI], 1.04-2.7), and this association was sustained after additional risk factors were adjusted for (adjusted OR, 1.8; 95% CI, 1.1-2.9). The 25-OHD levels were similarly positively associated, though statistically insignificant, with NMSC occurring on less UV-exposed anatomical locations (adjusted OR, 2.2; 95% CI, 0.7-7.0), whether for SCC (adjusted OR, 3.2; 95% CI, 0.4-24.0) or for BCC, although the risk estimate for BCC was lower (adjusted OR, 1.7; 95% CI, 0.5-5.8).

Conclusions: An increased baseline serum 25-OHD level was significantly associated with an increased NMSC risk. This association was positive, though nonsignificant on less UV-exposed body sites, and UV exposure remains a likely confounder. The complex and confounded relationship of vitamin D, UV, and NMSC makes classic epidemiological investigation difficult in the absence of carefully measured history of cumulative UV exposure.


ONLINE FIRST

ONMELANOMA SKIN CANCER (NMSC) is the most common malignant neoplasm in the United States, with more cases diagnosed annually than prostate, lung, colorectal, ovarian, and breast cancer combined. 1 The incidence of NMSC, which includes both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), has been rising over the past decades, especially in young women. 1-4 Epidemiological evidence has established a clear association between exposure to solar radiation and skin cancer, and UV exposure is recognized as an important risk factor for NMSC, especially SCC. 5-6 Exposure to UV-B radiation results in cutaneous vitamin D synthesis. Both vitamin D insufficiency and deficiency have been shown to be associated with an increased incidence of some diseases, including some cancers, although, to our knowledge, no causal relationship has been established. 7 Studies have assessed the association of serum vitamin D and vitamin D consumption with a wide range of cancers, including non–small cell lung, breast, prostate, ovarian, and colorectal

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cancers, and of these, the evidence is most supportive for colorectal cancer. Evidence of the association of vitamin D levels with skin cancer has been inconsistent. However, the relationship between serum vitamin D levels and NMSC is particularly complex. Because of the relationship of higher UV exposure with NMSC risk as well as vitamin D production, NMSC has even been used as a proxy for higher UV exposure in epidemiological investigations. However, the development of BCC, the most common subtype of NMSC, is associated with abnormalities in the activation of the sonic hedgehog signaling pathway, a pathway that may be inhibited by vitamin D, suggesting that vitamin D would decrease the risk for BCC. Two case-control studies, one of US men with osteoporosis and a second epidemiological investigation in a general health maintenance organization (HMO) population, have suggested opposite associations of NMSC with serum vitamin D levels.

The purpose of this study was to further evaluate the relationship of NMSC occurrence, as well as NMSC histologic subtypes (BCC and SCC), with baseline serum 25-hydroxyvitamin D (25-OHD) levels in a cohort of white HMO patients who sought advice about the risk of osteoporosis or low bone density from the Henry Ford Hospital Bone and Mineral Disorders Clinic, Detroit, Michigan. Serum levels of 25-OHD, the best available index of vitamin D nutrition and its storage form of vitamin D, were used to estimate an individual’s vitamin D status.

**METHODS**

The study population was derived from the Henry Ford Health System (HFHS), which includes a large multispecialty group practice and an HMO. The HMO population served by the health system and its medical group reflects the diverse sociodemographic background of the Detroit metropolitan area, with 10 hospitals and 70 clinics dispersed throughout the tricounty metropolitan area. As of 2006, the staff model health plan used for this study had an enrollment of 295,000, with a 1-year retention rate of 84% and a 5-year retention rate of 56%, and provided health information on more than 450,000 members during the period of interest.

This study was approved by the HFHS institutional review board. A prospective cohort was identified, which had originally been constructed for the purposes of describing vitamin D levels from all patients seeking advice for osteoporosis or osteoporosis prevention in the outpatients HFHS Bone and Mineral Disorders Clinic over a 3-year period (January 1, 1997, through December 31, 2001). Criteria for clinic referral included either low bone density with a dual-energy x-ray absorptiometry T score of less than −1 SD or osteoporosis (T score, <-2.5 SD). At the time of the initial evaluation, which occurred throughout the year, these patients underwent assessment of serum 25-OHD levels as well as parathyroid hormone, creatinine, and calcium levels. A description of the cohort and serum assays has previously been published.

The original cohort, which consisted of 4205 patients, was assembled to determine vitamin D level clinical cut points. For the purposes of this investigation, we limited our population to white patients who were known to have a high probability of developing NMSC (N=3333). Also, because of important risk factors for skin and other cancers, cases involving comorbid conditions of human immunodeficiency virus (n=5), solid organ transplantation (n=102), or both (n=3) were ascertained using *International Classification of Diseases, Ninth Revision, Clinical Modification* (human immunodeficiency virus, 042 or V08), and/or diagnosis-related group codes for transplantation (heart, 103, V42.1, and 996.83; liver, 480, V42.7, and 996.82; lung: 495, V42.6, and 996.84; and kidney, 302, V42.0, and 996.81) and subsequently excluded, leaving 3223 patients in the cohort.

A computerized HMO claims database was used to ascertain NMSC cases diagnosed after cohort enrollment. An algorithm that included both the *International Classification of Diseases, Ninth Revision, Clinical Modification*, and *Current Procedural Terminology* codes was used to ascertain the incident cases of NMSC. This NMSC claims-based ascertainment algorithm has been previously validated and described. The NMSC incident cases were further validated. A trained abstractor reviewed the electronic pathology records to determine histologic subtype, which included BCC, SCC, and SCC in situ (Bowen disease), and anatomical location.

Michigan is located in the north-central region of the United States, and in a May 2010 survey, the US National Oceanic and Atmospheric Administration found that Michigan was in the highest quartile of estimated heating degree days and heating fuel demand. As an example, Michigan in 2008-2009 (7179 accumulated heating degree days [weighted by the 2009 US population]) had nearly a 10-fold higher number of estimated heating degree days and heating fuel demand than Florida (734 accumulated weighted heating degree days). With consideration of this northern climate, NMSC anatomical locations were classified a priori as occurring on chronically UV-exposed sites (face, scalp, neck, and hands) and lesser-exposed sites (trunk, arms, and legs) to allow subsequent analyses that attempted to take UV exposure into consideration as a confounder.

Demographic information, including patient sex and date of birth, was obtained at the time of enrollment. Using the date of birth, patient age was calculated at the time of osteoporosis advice visit (entry into cohort). Data on smoking status estimates (ever/never) and height and weight for body mass index (BMI) calculation were limited, and because of the large numbers of missing values, smoking status and BMI had to be excluded from analyses. Season of serum laboratory analysis was defined as spring (March 1–May 31), summer (June 1–August 31), fall (September 1–November 30), and winter (December 1–February 28). Vitamin D levels were examined both by quartiles and using the clinically relevant cut points of less than 19, 19 through 30, and greater than 30 ng/mL (to convert to nanomoles per liter, multiply by 2.496). The serum level of 25-OHD was used as a reflection of the status of vitamin D. Serum 25-OHD is the most widely used, most clinically meaningful indicator of vitamin D levels and has been used historically to define vitamin D deficiency and insufficiency, allowing comparison to other research studies. Vitamin D insufficiency was defined as a serum 25-OHD level greater than or equal to 30 ng/mL. Vitamin D deficiency was defined as a serum 25-OHD level less than 15 ng/mL. A comparison of demographic and other characteristics by vitamin D sufficient status was performed using χ², Fisher exact, t test, or Wilcoxon rank sum test, as appropriate, to assess for differences.

The total persons-years of observation was calculated for each participant. To determine the end of follow-up or censorship, the study end date (January 30, 2009), the date of the last office visit to the HFHS (if the patient left the health system during the study period), or the date of the first histopathologic diagnosis of skin cancer was used. Logistic regression analyses, with adjustment for age and sex, were performed and reported as odds ratios (ORs) with 95% confidence intervals (CIs).

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Analyses were repeated for the outcome of NMSC on less UV-exposed body sites and by histologic subtype. Statistical significance was determined a priori as $P / H_{1021} < 0.05$.

## RESULTS

The cohort consisted of 3223 white patients, of whom 2878 (89.3%) were female and 345 (10.7%) were male. The mean (SD) age of the overall cohort at baseline was 65.9 (12.8) years, and the mean (SD) duration of follow-up was 9.8 (1.5) years. A comparison of the patients stratified by vitamin D status is presented in Table 1. Because samples were collected at the time of the initial visit, which occurred throughout the year, serum 25-OHD levels were analyzed for different seasons. The mean (SD) serum 25-OHD level was 25.2 (11.9) ng/mL for spring, 27.6 (10.5) ng/mL for summer, 26.3 (11.8) ng/mL for fall, and 24.0 (10.7) ng/mL for winter ($P < 0.001$).

During the study period, 240 patients with NMSC were identified, a number that included incident cases of SCC ($n=49$), incident cases of BCC ($n=163$), and 28 patients with both diseases. More of these NMSC cases occurred on frequently sun-exposed sites ($n=193$ [80%]) than on less-exposed body sites ($n=47$ [20%]). There was a significant trend between serum 25-OHD level quartile cut points and risk for NMSC ($P < 0.02$), with the highest odds (OR, 1.6; 95% CI, 1.1-2.3) associated with the highest quartile of baseline vitamin D level.

A serum 25-OHD level of 15 ng/mL or higher was significantly related to NMSC (unadjusted OR [unadjOR], 1.7; 95% CI, 1.04-2.7), and this remained after adjustment for demographics (adjusted OR [adjOR], 1.8; 95% CI, 1.1-2.9).

### Table 1. Characteristics of 3223 Patients by Serum 25-Hydroxyvitamin D (25-OHD) Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>25-OHD &lt; 30 ng/mL (n=2257)</th>
<th>25-OHD ≥ 30 ng/mL (n=966)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, No. (%)</td>
<td>1990 (88.2)</td>
<td>888 (91.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age on entering cohort, mean (SD), y</td>
<td>66.1 (12.9)</td>
<td>65.4 (12.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.7 (5.4)</td>
<td>25.4 (4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up time, mean (SD), y</td>
<td>9.8 (1.4)</td>
<td>10.0 (1.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factor: To convert 25-OHD to nanomoles per liter, multiply by 2.496.

### Table 2. Relationship of Serum 25-Hydroxyvitamin D (25-OHD) Levels With Odds of Nonmelanoma Skin Cancer (NMSC) in 3064 Patients

<table>
<thead>
<tr>
<th>Quartile, 25-OHD Level</th>
<th>No. (%) of Cases of NMSC</th>
<th>OR (95% CI) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>First, &lt;19 ng/mL</td>
<td>46 (6.1)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Second, 19-24 ng/mL</td>
<td>56 (7.6)</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>Third, 25-30 ng/mL</td>
<td>62 (8.4)</td>
<td>1.4 (0.96-2.1)</td>
</tr>
<tr>
<td>Fourth, ≥31 ng/mL</td>
<td>76 (9.2)</td>
<td>1.6 (1.1-2.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

SI conversion factor: To convert 25-OHD to nanomoles per liter, multiply by 2.496.

a $P$ for trend, .02.

### Table 3. Predictors of Nonmelanoma Skin Cancer (NMSC) in 3064 Patients

<table>
<thead>
<tr>
<th>Outcome a</th>
<th>Covariate</th>
<th>Univariable OR (95% CI)</th>
<th>Multivariable OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMSC (n=240)</td>
<td>25-OHD ≥15 ng/mL</td>
<td>1.7 b (1.04-2.7)</td>
<td>1.8 b (1.1-2.9)</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>1.03 b (1.02-1.04)</td>
<td>1.03 b (1.02-1.04)</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>0.6 b (0.4-0.9)</td>
<td>0.6 b (0.4-0.9)</td>
</tr>
<tr>
<td></td>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spring vs winter</td>
<td>0.8 (0.6-1.1)</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td></td>
<td>Summer vs winter</td>
<td>0.7 b (0.4-0.98)</td>
<td>0.6 b (0.4-0.9)</td>
</tr>
<tr>
<td></td>
<td>Fall vs winter</td>
<td>0.7 (0.5-1.1)</td>
<td>0.7 (0.5-1.04)</td>
</tr>
<tr>
<td>SCC (n=77)</td>
<td>25-OHD ≥15 ng/mL</td>
<td>1.7 (0.7-3.9)</td>
<td>1.7 (0.7-4.0)</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>1.04 b (1.02-10.6)</td>
<td>1.04 b (1.02-10.6)</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>0.4 b (0.2-0.7)</td>
<td>0.4 b (0.2-0.7)</td>
</tr>
<tr>
<td></td>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spring vs winter</td>
<td>0.9 (0.5-1.6)</td>
<td>0.9 (0.5-1.6)</td>
</tr>
<tr>
<td></td>
<td>Summer vs winter</td>
<td>0.8 (0.4-1.6)</td>
<td>0.8 (0.4-1.6)</td>
</tr>
<tr>
<td></td>
<td>Fall vs winter</td>
<td>0.9 (0.5-1.7)</td>
<td>0.9 (0.5-1.7)</td>
</tr>
<tr>
<td>BCC (n=191)</td>
<td>25-OHD ≥15 ng/mL</td>
<td>1.7 b (1.02-2.6)</td>
<td>1.7 b (1.05-2.9)</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>1.03 b (1.01-1.04)</td>
<td>1.03 b (1.01-1.04)</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>0.7 (0.4-1.03)</td>
<td>0.6 b (0.4-0.99)</td>
</tr>
<tr>
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<td>0.6 b (0.4-0.9)</td>
<td>0.6 b (0.4-0.9)</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio; SCC, squamous cell carcinoma; 25-OHD, 25-hydroxyvitamin D (to convert values to nanomoles per liter, multiply by 2.496).

a Twenty-eight patients had both an SCC and a BCC.

b Logistic regression $P$ value $<.05$. 

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We report an association of serum 25-OHD levels with NMSC in a prospective HMO cohort of white patients who sought advice on the risk of osteoporosis. A higher level of 25-OHD was associated with an increased risk of NMSC, even after demographic and other risk factors were controlled for. The positive relationship of UV exposure with both vitamin D synthesis and NMSC may explain these findings, and sunlight exposure is a highly likely confounder.

Our study contributes important additional information on this highly clinically relevant topic. With a prospective cohort of more than 3000 HMO patients, our study is one of the largest to date to analyze the relationship of serum 25-OHD level with incident NMSC by histologic subtype.

The first study to suggest the confounded nature of sun exposure, NMSC, and vitamin D did not actually have vitamin D estimates. In 2007, Srikanth et al published their investigation of the incidence of NMSC, including both BCC and SCC, in a retrospective cohort of 2283 patients older than 50 years with osteoporotic fractures in the Australian state of Tasmania. They found a statistically significant lower incidence (standardized incidence ratio, 0.69; 95% CI, 0.61-0.78) of NMSC in the fracture cohort than in the general Tasmanian population, regardless of NMSC subtype. They concluded that NMSC can be used as a marker for higher cumulative sun exposure (a surrogate for higher serum vitamin D levels) and that older persons with fractures may therefore have lower sun exposure (associated with lower serum vitamin D levels). However, Srikanth and colleagues did not have direct serum vitamin D measurements for their cohort. Our study confirmed their findings by demonstrating that both types of NMSC (especially SCC) were associated with higher serum 25-OHD levels.

Two recently published case-control studies examining the association between serum vitamin D levels and NMSC demonstrated conflicting conclusions. In 2009, Tang et al published their examination of the association of NMSC prevalence with serum 25-OHD using a nested case-control design with data from the Osteoporotic Fractures in Men Study. The Osteoporotic Fractures in Men Study assembled a prospective cohort of men older than 65 years who were recruited to assess risk factors for osteoporotic fracture; a subset of the men were randomly chosen for serum measurement of 25-OHD levels. Prevalent NMSC status was obtained from a self
reported questionnaire administered at baseline and at a 5-year follow-up visit. In their cohort of 930 white men, Tang and colleagues found a decreased odds of self-reported prevalent NMSC with serum 25-OHD levels greater than 30 ng/mL (OR, 0.6; 95% CI, 0.37-0.98), with a trend noted by 25-OHD levels (ie, higher 25-OHD levels were associated with a lower risk of NMSC). It should be noted that Tang and coauthors relied on self-reporting at both the study onset and at the 5-year follow-up visit to define their cases; there was no review of pathology reports or medical records. Self-reported skin cancer has been found to have both a low sensitivity and a positive predictive value. In contrast, our study using the electronic medical record and claims data of a prospective HMO cohort was more than 3 times larger than that of Tang and colleagues (3223 cases vs 930 cases), and most of the patients were women. All the patients in our study had documented, histologically confirmed incident cases of NMSC (including anatomical location and histologic subtype). These reasons may explain the differences in association noted between our findings and those of Tang and coauthors.

In 2010, Asgari et al reported findings from a nested case-control study of 220 patients with BCC and 220 matched controls who were members of Kaiser Permanente Northern California HMO and who had completed a multiphasic health checkup between 1968 and 1970. They found an increased risk of BCC with higher vitamin D levels, and the increased risk persisted even after adjustment for BMI, smoking, personal history of cancer, hours of exercise, occupational sun exposure level, exposure to x-rays, and education (first vs fifth quintile: unadjOR, 2.32; 95% CI, 1.20-4.50; adjOR, 2.09; 95% CI, 0.95, 4.58). Our findings confirm those of Asgari and colleagues, and similarly demonstrate moderate, though nonsignificant, risk estimates for BCC. Asgari and coauthors’ study was also able to adjust only for past sun exposure in a crude fashion (occupation).

Our study, one of the largest prospective cohort reported to date, makes a notable contribution to the limited and conflicting epidemiological investigation regarding the relationship between vitamin D and NMSC. A validated claims-based NMSC ascertainment algorithm and HMO electronic medical records permitted identification of incident skin cancer by histologic subtype and allowed us to ascertain chronically UV-exposed and lesser-exposed anatomical tumor locations. Use of electronic medical records also eliminated recall bias, which may have been present in a prior investigation in which NMSC was self-reported. Furthermore, our cohort was followed up for almost 10 years and excluded those with human immunodeficiency virus or solid organ transplant recipients. There are limitations, however, to our analysis. Our study was limited to a single institution. Furthermore, HMO patients who seek osteoporosis risk advice from endocrinologists represent a select population. Our sample was predominately female, which may also have biased results, although our findings are consistent with those of Asgari et al, whose HMO enrollee study consisted of approximately equal portions of men and women. Similar to other previous studies, we did not have the ability to consider important NMSC risk factors, such as individual sun exposure history, family history, and skin type of white patients. Because of the limited study size and missing information, we were unable to explore the relationship of factors such as exercise/activity level, bone density, menopausal status/estrogen levels, smoking, or BMI, which may possibly confound the relationship of vitamin D and NMSC.

Our data were limited to an initial single serum 25-OHD measurement obtained at the time of study enrollment, and we recognize that this 1 measurement does not reflect lifetime or likely critical period vitamin D levels, such as childhood or young adult exposure. Furthermore, we were unable to consider the intervening exposure of vitamin D supplementation, either before or after presentation, as this information was unavailable. However, because the serum 25-OHD level measurements were gathered from an initial intake examination for osteoporosis advice (and hence presumably before treatment if so advised), supplemental use was likely low, as noted by Srikanth et al. Furthermore, 2 earlier cohort studies investigating the association of dietary intake of vitamin D and skin cancer failed to show a significant association between diets rich in vitamin D and BCC.

In conclusion, our findings in a prospective study of an HMO cohort of 2332 white patients who sought advice on osteoporosis suggest that there is a direct association of high serum 25-OHD levels with NMSC. Serum 25-OHD levels of 15 ng/mL or higher were significantly associated with a higher risk of NMSC, both when examined alone or after adjustment for other risk factors. The direct relationship of UV exposure with both vitamin D and NMSC makes it a likely profound confounder in this, and other, studies. In the future, analysis of a prospective cohort that is representative of the general population, ideally with available UV-exposure estimates, risk factor, and dietary and supplemental vitamin D information, is essential to further elucidate the highly complex relationship between vitamin D and NMSC.

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REFERENCES