High Prevalence of Vitamin D Deficiency in Patients With Basal Cell Nevus Syndrome

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Objectives: To evaluate vitamin D status in patients with basal cell nevus syndrome (BCNS) who practice photoprotection because of their genetic predisposition to skin cancer and to determine risk factors for deficiency.

Design: Retrospective cohort study.

Setting: Academic medical centers.

Patients: Forty-one ambulatory patients with BCNS who participated in a 2-year chemoprevention clinical trial. Population-based controls (n=360) were selected and matched by age, sex, Fitzpatrick skin type, and season/geography.

Main Outcome Measures: Levels of 25-hydroxyvitamin D (25[OH]D) and vitamin D deficiency (defined as a 25[OH]D level of ≤20 ng/mL).

Results: Twenty-three patients with BCNS (56%) were vitamin D deficient. Patients with BCNS had mean 25(OH)D levels below those of the general population (−3 ng/mL; P=.02) and were 3 times more likely to be vitamin D deficient (56% vs 18%; P < .001). Levels of 25(OH)D were lower in patients who were overweight (−3.0 ng/mL; P=.04) and who had blood collected in the winter compared with the summer (−7.1 ng/mL; P<.001).

Conclusion: Patients with BCNS may be at increased risk for vitamin D deficiency, depending on their adherence to photoprotection practices.

Trial Registration: clinicaltrials.gov Identifier: NCT00023621

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Vitamin D deficiency has been associated with an increased risk of autoimmune disease, fractures, cancer, cardiovascular disease, and all-cause mortality. Results from the National Health and Nutrition Examination Survey (NHANES), which is representative of the US population, suggest that vitamin D deficiency is common, with approximately 20% of white participants considered deficient on the basis of serum levels of 25-hydroxyvitamin D (25[OH]D) 20 ng/mL or less (to convert to nanomoles per liter, multiply by 2.496). Vitamin D deficiency is more frequent in certain subgroups, including elderly, dark-skinned, or overweight individuals; nursing home residents; and people residing in areas of low UV exposure (≥35°N or [N]). There is increasing concern that sun protection, recommended by dermatologists to prevent further UV damage in populations susceptible to skin cancer, may result in abnormally low levels of 25(OH)D, which may have subsequent detrimental effects on health.

To address this issue, the American Academy of Dermatology recently issued a position statement on vitamin D deficiency and the potential need for dermatologists to recommend oral supplementation, especially for patients who adhere to strict photoprotection. Patients with a history of skin cancer are regularly advised to avoid sun exposure, but there are insufficient data on the prevalence and severity of vitamin D deficiency among patients with skin cancer and scarce information to identify those at highest risk for deficiency. Previous studies have reported increased vitamin D deficiency in patients with skin cancer, but these results have not been compared with those in individuals without skin cancer, and those studies did not adjust for known variables that affect 25(OH)D levels such as age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and Fitzpatrick skin types.
Our primary aims were to evaluate the vitamin D status of patients with basal cell nevus syndrome (BCNS) (Gorlin syndrome; Mendelian Inheritance in Man 109400) and to identify predictors of deficiency, which may be useful in clinical practice. We measured levels of 25(OH)D in patients with BCNS who are genetically predisposed to developing basal cell carcinomas (BCCs). In contrast to individuals with sporadic BCCs, which are few in number and generally acquired by patients in their sixth to seventh decades of life, patients with BCNS develop multiple BCCs in young adulthood.14,15 Individuals with BCNS inherit a mutated copy of the \textit{PITCH1} tumor suppressor gene (OMIM 601309)16 and display wide phenotypic variability. Some patients with BCNS develop a few BCCs in their lifetime, whereas others develop thousands.\textsuperscript{14,15} Similar to other UV-sensitive patients, such as those with xeroderma pigmentosum, patients with BCNS generally try self-photoprotection by using sunscreen and by avoiding the sun during peak hours in an attempt to prevent these skin cancers that can be locally destructive and can cause significant morbidity.\textsuperscript{12,15} Our goals were to identify predictors of low 25(OH)D levels and to assess the prevalence of vitamin D deficiency among patients with BCNS.

**METHODS**

**STUDY PARTICIPANTS**

We surveyed 41 ambulatory patients with BCNS undergoing a chemoprevention clinical trial with celecoxib, a type of oral non-steroidal anti-inflammatory drug.\textsuperscript{17} Sixty patients were initially enrolled in the clinical trial, 43 were enrolled for at least 1 year, and 41 had evaluable blood samples for 25(OH)D measurements. We obtained written consent for all subjects, and all aspects of the study were reviewed and approved by the institutional review board of the University of California, San Francisco, and Columbia University Medical Center. Patients who were at least 18 years of age were recruited from all parts of the United States. Enrollment began on May 11, 2001, and was completed on June 12, 2004. Study participants were seen at the following 4 study centers: Newport Beach, California; New York, New York; San Francisco, California; and South Euclid, Ohio. A diagnosis of BCNS was established if a subject had 2 of the following major criteria: multiple BCCs or a single BCC before age 20 years, jaw cysts, and palmar/plantar pits.14 Study dermatologists recorded subject age, BMI, geographic residence, and self-reported race/ethnicity. Race/ethnicity was assessed because BCCs are more likely to occur in white participants with lighter skin color (Fitzpatrick skin type <III). At the baseline visit, dermatologists classified subject Fitzpatrick skin type and assessed the number of BCC tumors by skin examination. A subset of 35 subjects completed a questionnaire that inquired about daily sunscreen use (never/rare/sometimes vs almost always/always), avoidance of peak hours of sunlight (yes or no), and use of any daily multivitamin supplement (yes or no). Most multivitamins have 200 to 400 IU of cholecalciferol (vitamin D),\textsuperscript{18} but in this retrospective study we did not record the name of the multivitamin or the actual cholecalciferol dosage.

For analysis of total 25(OH)D level, blood was drawn at the baseline visit and at 3- to 6-month intervals in the first 2 years of the study and stored at -80°C. The samples were centrifuged, and the plasma was isolated, put on dry ice, and shipped to ARUP Laboratories, Salt Lake City, Utah, for batch analysis. Total 25(OH)D levels were determined for the patients with BCNS using a 25(OH)D chemiluminescent immunoassay (Liaison; DiaSorin, Inc, Vercelli, Italy) with results given in units of nanograms per milliliter.\textsuperscript{19} Although there is no consensus on optimal levels of 25(OH)D, vitamin D deficiency is defined by most experts as a 25(OH)D level of 20 ng/mL or less.\textsuperscript{7,18,20} For this study, vitamin D insufficiency was defined as a 25(OH)D level of 30 ng/mL or less, deficiency as 20 ng/mL or less, and severe deficiency as 10 ng/mL or less.

The season of blood collection was assigned according to the following standard definitions: winter included January through March; spring, April through June; summer, July through September; and autumn, October through December. We used a latitude of 35°N as a cutoff for geographic areas of low vs high UV exposure\textsuperscript{1} and to compare 25(OH)D values with NHANES values because NHANES has an inherent season-latitude study design.21 Twenty-two of 41 patients had measurements in the summer and winter of the same year. Nineteen of 41 subjects had 25(OH)D levels measured in the summer or winter.

**DEMOGRAPHIC VARIABLES AND 25(OH)D LEVELS FROM NHANES**

Comparisons were made with 25(OH)D levels in the general population based on data collected for the 2003-2004 NHANES. The NHANES data included demographic characteristics (age, BMI, and self-reported race) for 10,122 participants in the household interviews, with a high response rate of 79%.\textsuperscript{22} Standardized digital photographs were taken of a random subset of these participants (n = 2996) during physical examination at nationally stationed mobile examination centers. Two independent dermatologists reviewed the photographs to assign a Fitzpatrick skin type\textsuperscript{23} on a scale of I to VI.\textsuperscript{24} We used univariate and multivariate (adjusting for BMI) regression techniques to determine the association between baseline characteristics and 25(OH)D levels in patients with BCNS.
Multivariate regression analysis using mixed-effects models with a random subject effect were used to account for the correlation of different 25(OH)D measurements from the same person. We checked for model fit by plotting residuals. Fisher exact test was used for comparisons of proportions. All P values were 2 sided. Statistical analyses were performed using commercially available software (SAS [SAS Institute Inc, Cary, North Carolina] and STATA [StataCorp, College Station, Texas]). Unless otherwise indicated, data are expressed as mean (SD).

### RESULTS

Forty-one patients with a diagnosis of BCNS were included in this study. Table 1 shows the baseline characteristics of our study population. The mean age of our cohort was 40.2 (11.0) years (range, 21–67 years) and 22 (54%) were men. All subjects were non-Hispanic white with Fitzpatrick skin types of I, II, or III as classified by a study dermatologist (MA, DRB, or EHE). Most subjects were overweight (BMI, >25.0) with a mean BMI of 30.1 (6.9), consistent with previous reports of the large body habitus in patients with BCNS. The average number of BCCs among our patients with BCNS was 22 at the start of the clinical trial. In our chemoprevention clinical trial, patients were stratified into a high (≥15 tumors at baseline) or low (<15 tumors) burden of disease. Patients in this study were balanced in terms of their burden of disease (20 of 41 patients with a high burden and 21 with a low burden), and there was no difference in 25(OH)D levels in patients with BCNS who had a low vs high burden of disease. In general, patients with BCNS practiced photoprotection by avoiding sunlight during peak hours (10 AM to 2 PM) and by using sunscreen daily. Twenty-eight of the 35 patients with BCNS surveyed (80%) reported almost always using sunscreen daily (sun protection factor of ≥15), and only 4 (11%) reported rarely or never using sunscreen daily. Subjects were equally distributed by geographic residence in the United States, with 22 (54%) of the participants living in low-UV-exposure areas (latitude, ≥35°N). On average, each subject had 3 plasma measurements (range, 1–6) throughout the 2-year study, and we calculated a mean 25(OH)D level per patient. The mean 25(OH)D level of all 41 subjects was 24.5 (12.4) ng/mL, which is in the insufficient range (≤30 ng/mL).

We sought to determine whether known risk factors for vitamin D deficiency such as age, BMI, sex, geographic residence, and season of blood collection could predict 25(OH)D levels in individuals with BCNS. Table 2 shows the results from multivariate regression analysis examining independent predictors of 25(OH)D levels. Season of blood collection and BMI were the only significant predictors. Comparing across subjects, every 5-U increase in BMI was associated with a −3-ng/mL decrease in 25(OH)D level (95% confidence interval [CI], −5.5 to −0.2; P = .001). After multivariate adjustment, subjects who reported using a daily vitamin supplement had 6.8-ng/mL-higher 25(OH)D levels (95% CI, −1.0 to 15.0; P = .09), which approached but did not reach statistical significance. Age, sex, and geographic residence were not associated with significant changes in 25(OH)D levels.

We compared 25(OH)D levels in 22 patients with BCNS who had serial blood collections in the summer and winter seasons of the same year (Figure 1). Patients with BCNS have significantly higher levels of 25(OH)D in the summer compared with the winter, in contrast to patients with xeroderma pigmentosum, who showed no seasonal variation. Levels of 25(OH)D were 7 ng/mL higher in the summer compared with winter (27.4 vs 20.3 ng/mL, P = .04) in patients with BCNS, simi-
Our key findings are that patients with BCNS have mean 25(OH)D levels below those of the general population and are 3 times more likely to be vitamin D deficient. Most of the patients with BCNS in this study (56%) were vitamin D deficient. Among the patients with BCNS, high BMI and blood collection during the winter were significant risk factors for lower 25(OH)D levels. Age, sex, and geographic residence were not associated with significant changes in 25(OH)D levels in this study, likely because of the limited sample size.

To our knowledge, this is the largest study of vitamin D status in patients with a genetic predisposition for skin cancer. Our findings are consistent with previous reports of vitamin D deficiency in patients with sporadic skin cancer and confirm the findings of Querings and Reichrath, who first showed low 25(OH)D levels in BCNS. In contrast to patients with xeroderma pigmentosum, who have no seasonal variation in their 25(OH)D levels presumably owing to extremely rigorous photoprotection, patients with BCNS in this study had higher levels of 25(OH)D in the summer compared with winter. It seems likely that patients with BCNS may be more similar to patients with sporadic skin cancers whose photoprotective practices do not completely block UV-induced cutaneous vitamin D synthesis, especially in the summer. One previous study of Australian patients with skin cancer showed a similar -5-ng/mL increase in summer 25(OH)D levels compared with winter levels. Among patients with BCNS, those with a high BMI had lower 25(OH)D levels, consistent with previous findings that obesity contributes to lower 25(OH)D levels owing to sequestration of vitamin D in body fat compartments. Our results support the hypothesis that obesity and increased photoprotection practices may contribute to the increasing trend of vitamin D deficiency in the United States.

Our study had several limitations. First, we had a relatively small number of patients because of the rarity of BCNS, which has a prevalence of 1 per 50 000 to 1 per 164 000. Second, controls were drawn from the population and were not individual subjects because this was a retrospective study of stored plasma samples from a completed multicenter clinical trial of celecoxib for BCC prevention. Celecoxib is not known to affect the synthesis of vitamin D.
Taking into account multiple health outcomes such as mortality and disease prevention is still being assessed. Abnormal findings in these measurements could have reflected more severe forms of vitamin D deficiency. Although patients with BCNS may be a fair proxy for photoprotecting patients with skin cancer, other factors may contribute to vitamin D deficiency in this disease; however, mice with mutations in Pch1 are not known to have any defects in the vitamin D synthesis pathway. We did not detect a difference in 25(OH)D levels in patients with BCNS who had a low vs high burden of disease, which could be because of the high phenotypic variability in patients with BCNS (range, 1-1000 BCCs per patient) or factors other than 25(OH)D levels that may influence the number of BCCs in these patients. Strengths of this study include the multiple measurements of 25(OH)D levels at different seasons and detailed information on covariates, such as Fitzpatrick skin type and BMI, that can affect cutaneous vitamin D synthesis or storage.

It may not be surprising that patients with a genetic predisposition to sun-induced cancers report a high frequency of photoprotection and may be vitamin D deficient. However, the magnitude of this deficiency and the possible additive effect of obesity, which is common in these patients, make individuals with BCNS optimal candidates for cholecalciferol supplementation. Furthermore, if the mechanism for the association between low 25(OH)D levels in patients with BCNS is indeed photoprotection, these results may be applicable to patients without BCNS who have sporadic BCCs and for whom photoprotection is currently recommended. Given that sporadic BCC is the most common cancer worldwide with more than 1 million cases reported annually in the United States and that most patients with BCC survive for many years after their diagnosis, screening for vitamin D deficiency may become an important part of the care of this population.

The optimal amount of serum vitamin D levels for health maintenance and disease prevention is still being defined. The intake level currently recommended to be adequate for adults younger than 70 years is 200 to 400 IU. Taking into account multiple health outcomes such as autoimmune disease, cancer prevention, and bone health, optimal concentrations of 25(OH)D of greater than 30 ng/mL have been suggested. A cholecalciferol supplement of 1000 IU increases 25(OH)D levels by an average of 10 ng/mL. Thus, patients with BCNS may require 1000 IU to increase their winter 25(OH)D level from 20.3 ng/mL to the sufficient range (≥30 ng/mL). Use of a daily multivitamin supplement led to a statistically non-significant increase in 25(OH)D levels in patients with BCNS; however, overall use was low. Our findings may be relevant for the Institute of Medicine review of vitamin D requirements to be conducted in November 2010. Further studies are needed to determine the optimal amount of cholecalciferol supplementation required for preventing deficiency in individuals using photoprotection at the population level.

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Author Contributions: Drs Tang and Epstein had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tang, Bickers, and Epstein. Acquisition of data: Tang, Wu, Lee, Aszterbaum, Bickers, and Epstein. Analysis and interpretation of data: Tang, Wu, Linos, Parimi, Asgari, and Epstein. Drafting of the manuscript: Tang, Wu, Linos, Lee, and Epstein. Critical revision of the manuscript for important intellectual content: Tang, Linos, Parimi, Aszterbaum, Asgari, and Epstein. Statistical analysis: Tang, Linos, and Parimi. Obtained funding: Tang, Bickers, and Epstein. Administrative, technical, and material support: Tang, Wu, Aszterbaum, Asgari, and Bickers. Study supervision: Tang and Epstein.

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