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Signature: _____

Christina Correnti

Date

APPROVAL SHEET

Sun Protection Adherence and Vitamin D Levels Among Dermatology Patients

By

Christina Correnti

Master of Science

Clinical Research

_____

Suephy Chen, MD MS

Advisor

_____

Amita Manatunga, PhD

Committee Member

_____

Igho Ofotokun, MD MS

Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

_____ Date

ABSTRACT COVER PAGE

Sun Protection Adherence and Vitamin D Levels Among Dermatology Patients

By

Christina Correnti

B.A., Boston College, 2008

Advisor: Suephy C. Chen, MD MS

An abstract of a thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

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Master of Science

in Clinical Research

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ABSTRACT

Sun Protection Adherence and Vitamin D Levels Among Dermatology Patients

By Christina Correnti

Background: Sun protection is a central dermatologic recommendation to decrease skin cancer risk, however an objective measure of sun protective adherence is lacking. Research relies upon self-reported measures such as the Sun Protection Habits Index (SPHI). Compliance with sun protection may place patients at risk for vitamin D deficiency and its associated adverse health outcomes. Due to lack of consensus among guidelines for adequate vitamin D levels and monitoring, serum testing and associated costs have increased exponentially across the past several decades.

Aims: Aim 1: To evaluate whether serum 25-hydroxyvitamin-D (25-OH-D) status (sufficient >32 ng/mL, versus deficient) acts as an objective measure of a SPHI <3.0 (sun protection non-adherence).

Aim 2: To evaluate whether the Health Professionals Follow-Up Study (HPFS) predictive 25-OH-D model can clinically categorize an individual's 25-OH-D level, obviating reliance on serum testing.

Methods: Survey information was collected from 214 English-speaking, adult, dermatology patients of the Emory Dermatology Clinics with known 25-OH-D levels from September 2008-November 2010. Exclusion criteria included medical conditions affecting 25-OH-D levels (e.g. intestinal malabsorption). Logistic regression evaluated whether sufficient 25-OH-D status predicted sun protection non-adherence (SPHI<3.0).

Published linear regression coefficients from the HPFS model were used to predict our sample's 25-OH-D levels. Cohen's kappa evaluated agreement between predicted and observed clinical categories of 25-OH-D level (sufficient, insufficient, deficient, severely deficient).

Results: In univariate logistic regression, the odds of non-adherence to sun protection among 25-OH-D sufficient (>32 ng/mL) patients were 0.53 times lower (95% CI: 0.29-0.99, p=0.049) than the odds among 25-OH-D deficient (≤ 32 ng/mL) patients. In multivariate logistic regression adjusting for skin cancer history, age, race and supplementation, the odds of non-adherence among sufficient patients were 0.64 times lower (95% CI: 0.33-1.25,p=0.26) than the odds among deficient patients.

Cohen's kappa for agreement between HPFS predicted and observed categories of 25-OH-D was 0.01 (95% confidence limits: -0.11-0.14).

Conclusions: Sufficient 25-OH-D levels were not associated sun protection non-adherence in multivariate logistic regression. Univariate logistic regression suggested that sufficient 25-OH-D status was associated with sun protection adherence.

There was no more than chance agreement between HPFS model predicted and observed clinical categories of 25-OH-D status.

COVER PAGE

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INTRODUCTION

Skin cancer, the most common cancer in the United States, is diagnosed in about 1 million Americans each year.(1, 2) Ultraviolet radiation from the sun is the major environmental risk factor for cancer. Sun protection habits such as applying sunscreen, shade seeking, and wearing hats, sunglasses, and long-sleeved clothing can be effective methods of preventing ultraviolet radiation exposure. (2-14) However an objective measure of sun protection adherence is lacking. Research has relied largely upon self-reported measures such as the Sun Protection Habits Index (SPHI), calculated based upon the average score of how often five sun protection habits are performed.(15) A measure of sun protection adherence might allow clinicians to identify non-compliant patients or those patients who are protecting ineffectively for additional sun safety intervention. An objective measure of sun protection adherence could also be a valuable adjunct or replacement for self-reported measures of adherence such as the SPHI in both clinical practice and in future research.

The same spectrum of light that causes skin cancer risk is also responsible for the photosynthesis of vitamin D in the skin.(2) The efficiency of vitamin D production in the skin is dependent on many factors.(2, 7-9, 16-23) Higher vitamin D levels are found in those with lower body mass index, younger age, higher dietary vitamin D intake, and those taking supplements. Those with lower melanin content of the skin, or lighter skin tones, produce vitamin D more quickly.(24) Higher vitamin D levels are achieved with increased length of ultraviolet radiation exposure and increased strength of exposure (such as in the Southern United States or during the summer). Thus, there is debate over whether compliance with sun protection may place patients at risk for vitamin D deficiency. (2-10)

Over the past several decades, there has been a surge in research exploring vitamin D, an important secosteroid discovered to have a myriad of noncalcemic effects via its many

receptors and gene targets throughout the entire body.(6) Vitamin D deficiency has been associated with a range of chronic diseases such as cardiovascular disease, diabetes, and multiple sclerosis, as well as solid cancer risk and even all-cause mortality.(7, 17, 18, 25-33) Other research suggests that vitamin D may even have protective effects against the development of skin cancer.(31, 34, 35) Given a lack of consensus among guidelines for adequate serum vitamin D levels and monitoring, (4, 36-40) over the past several decades the frequency of serum testing and associated costs have increased exponentially across healthcare disciplines.(36-38) In Australia, certain individuals underwent up to 79 tests between April 2006 and October 2010.(37) In Ontario Canada alone, vitamin D testing costs increased from $1.7 million in 2004 to over $21.0 million in 2008.(36) The ability to predict an individual's vitamin D status at the point-of-care would help decrease reliance on such repetitive serum testing, the associated costs to healthcare systems as a whole, and the minor patient burden associated with blood draws.

With this study we planned to address two aims. The first aim of this study was to evaluate whether serum 25-hydroxyvitamin-D (25-OH-D) status (sufficient >80 nmol/L or >32 ng/mL, versus deficient) can act as an objective measure of sun protection non-adherence, defined as an a SPHI score of <3.0. We hypothesized that sufficient vitamin D status would be associated with non-adherence to sun protection after controlling for vitamin D supplementation, race, skin cancer history, and age. The second aim of this study was to evaluate whether the Health Professionals Follow-Up Study (HPFS) predictive vitamin D model(18) could categorize an individual's clinical serum vitamin D status (normal >80 nmol/L, insufficient >50 to ≤80 nmol/L, deficient >25 to ≤50 nmol/L, severely deficient <25 nmol/L). We hypothesized that vitamin D level predictions generated using the HPFS model, which was developed and validated in a large national cohort, would correspond to clinical vitamin D status. We approached these aims via a cross-sectional

survey study of 214 dermatology patients who were free of disease affecting vitamin D production (e.g. intestinal malabsorption syndromes).

BACKGROUND

Skin cancer, the most common cancer in the United States, is diagnosed in about 1 million Americans each year.(1) Ultraviolet (UV) radiation from the sun is the major environmental risk factor for cancer, but the same spectrum of light is also responsible for the photosynthesis of vitamin D in the skin. Within the last 30 years, there has been controversy regarding the recommendation of sunscreen use, as it has been associated with vitamin D deficiency.(13, 41) Meanwhile the incidence of skin cancer has increased dramatically worldwide in the last decade becoming a major public health concern. Due to the morbidity and mortality associated with skin cancers, the American Academy of Dermatologists (AAD) recommends active UV prevention measures. Reduction of UV exposure and prevention of skin cancers can be achieved by using sunscreens, hats, clothing, sunglasses, and planning activities around times of low sun exposure. (2-14)

An objective measure of adherence with sun protection would help clinicians identify patients who might need additional sun safety intervention, due to non-compliance or ineffective methods. Since photoprotection has been associated with vitamin D deficiency,(13, 41) we hypothesized that vitamin D sufficiency might indicate that a patient was not adhering to sun protection, as defined by a low Sun Protection Habits Index. The Sun Protection Habits Index is a validated measure of sun protection, and consists of the average of self-reported scores for the performance of five habits: sunscreen use, shade seeking, and wearing hats, sunglasses, and long-sleeved clothing.(15) A higher score corresponds to performance of the sun protection habit more frequently. By addressing this research question, we will also gain further insight as to whether the most adherent patients are in fact at increased risk of vitamin D deficiency, since research has been conflicting as to whether sun protection contributes to deficiency outside of controlled circumstances.(41-43)

Patients with certain genodermatoses and transplant patients who are at increased risk of developing skin cancer have been found to have low vitamin D levels.(41) Research also suggests that skin cancer patients have low vitamin D levels in general, but it is still unclear whether this may related to increased adherence to photoprotection.(12, 41) In one study, adherence to photoprotection was not associated with vitamin D levels among skin cancer patients, however adherence was defined by the median photoprotection score in the study, and there was no available comparison to non-skin cancer patients.(41) Thus in the current study, we planned to include skin cancer history as a potentially important covariable.

The currently accepted low end of "normal" for serum 25-OH-D is 32 ng/mL.(23) Adequate vitamin D intake is difficult to achieve through diet alone, which may be why some studies have failed to find an association between dietary intake and serum vitamin D levels.(41) Diets based on oily fish may provide adequate levels of D3, however these diets are not typical. However, oral supplementation with enteral vitamins is an inexpensive, well tolerated, and safe over the counter remedy, and studies have found that supplementation is an important predictor of vitamin D levels.(41) Therefore in the current study we planned to collect information regarding the potentially important covariables of both dietary and supplemental vitamin D intake.

A surge of vitamin D research over the past several decades has highlighted its role in much more than bone health; its metabolic product is a potent secosteroid with multiple receptors and gene targets throughout the entire body.(6) Evidence suggests that vitamin D deficiency may be associated with a host of chronic diseases such as cardiovascular disease, diabetes, and multiple sclerosis, as well as solid cancer incidence and even all-cause mortality.(7, 17, 18, 25-33) Alarmingly, vitamin D deficiency (≤50 nmol/L) and insufficiency (≤80 nmol/L) are widespread, affecting people of all ages and geographic locations.(7-9, 19-

23) Growing concern over monitoring vitamin D status is evidenced by the explosion of testing for serum 25-OH-D worldwide and across medical specialties.(36-38) In Ontario Canada, the number of vitamin D tests more than doubled from 2007 to 2008.(36) From 2004 to 2008, the total annual cost of testing increased more than 12-fold, amounting to over $21.0 million in 2008.(36) In Australia, 42.9% of patients had more than one test between April 2006 and October 2010, with certain individuals undergoing up to 79 tests during that time period.(37) Over a single decade, 25-OH-D testing in Australia increased at a 94-fold rate, amounting to a cost increase from $0.7 to $40.5 million for 25-OH-D testing over the period from 2001-2011.(38)

Given the rise in serum 25-OH-D testing over the past several years,(36-38) the ability to predict vitamin D status could amount to a significant patient and healthcare systems cost savings. The use of electronic medical records enables clinicians to harness the power of information technology in the care of the individual patient. Soon it may be common for the medical record to consist not only of patient characteristics, but also of automatically embedded calculation and prediction algorithms drawn from evidence-based literature, allowing physicians to obtain and use personalized information without needing to invasively monitor patients. Some integrated healthcare delivery systems, such as the Kaiser Permanente Medical Care Program in Northern California, have already proven this concept. Using a comprehensive inpatient electronic medical record, investigators successfully developed an inpatient risk-adjustment model applicable to all hospitalized patients.(44) The electronic medical record was then used to develop a prediction model for unplanned transfer from the medical-surgical wards to intensive care.(45)

In the case of vitamin D levels, such an automatically populated prediction model could increase point of care counseling by removing the delays inherent in the process of sending patients for blood-work and waiting for blood-work results, which often occur

outside of a visit. Such predictions could also significantly decrease patient burden, however minor, in terms of the costs, time, and adverse events or stresses associated with blood draws by decreasing the number of tests needed over the course of a patient's lifetime. In our second aim, we sought to determine whether the predictive Vitamin D model developed and validated by Giovannucci *et al*. 2006 in large national U.S. cohorts,(18) could predict an individual's known clinical vitamin D status (normal, deficient, insufficient, severely deficient). Such a prediction model could help guide enteral supplementation efforts in a cost-effective and non-invasive manner.

METHODS

Research goals were as follows:

Aim 1: To evaluate whether serum 25-hydroxyvitamin D (25-OH-D) levels (sufficient >80 nmol/L or >32 ng/mL versus deficient) are associated with a SPHI <3.0, or sun protection non-adherence. We hypothesized that sufficient vitamin D status is associated with non-adherence to sun protection when controlling for vitamin D supplementation, age, skin cancer history, and race.

Aim 2: To evaluate whether the HPFS predictive vitamin D model(18) could categorize an individual's clinical vitamin D status, where clinical status was sufficient if serum 25-OH-D levels were >80 nmol/L, insufficient if >50 to ≤80 nmol/L, deficient if >25 to ≤50 nmol/L, and severely deficient if <25 nmol/L. We hypothesized that the HPFS predictions for serum 25-OH-D levels would correspond with individual clinical vitamin D status.

The study employed a cross-sectional survey design. After Institutional Review Board approval, dermatology patients were recruited from the Emory Dermatology Clinics from September 2008 to November 2010. Subjects completed surveys in person or by telephone. Missing information was supplemented with data abstraction from the medical record from January 2013 to July 2013. Serum 25-OH-vitamin D levels were drawn or known. Subjects included skin cancer patients who were part of the DeLong *et al.* 2010 study(41) as well an additional subset of general dermatology patients who completed extra surveys specific to the HPFS.

Subjects were eligible if Emory dermatology patients, subjects were English speaking, at least 18 years of age, not undergoing active vitamin D monitoring or oral repletion, and if they had no systemic disease affecting vitamin D status. Exclusion criteria included those subjects who were non-English speaking, under 18 years of age, undergoing

active vitamin D monitoring or repletion for insufficiency or deficiency, and/or those with systemic disease affect vitamin D status including: intestinal malabsorption syndromes, granulomatous conditions, liver, kidney or parathyroid disease.

Subjects provided information regarding skin cancer history (yes/no), type of skin cancer (melanoma, non-melanoma skin cancer, or other skin cancer), and Fitzpatrick skin type. Fitzpatrick Skin Types are defined as follows:

- Pale White (Does not tan, burns easily) =1
- White (Tans with difficulty, burns easily) =2
- White (Tans after initial sunburn) =3
- Light Brown (Tans easily) =4
- Brown (Tans easily) =5
- Black (Becomes Darker) =6.

Subjects provided data regarding race (White, Black, Hispanic, East Asian/Pacific Islander, South Asian/Indian, American Indian), oral vitamin D supplementation (IU/day), dietary intake of vitamin D (IU/day), and the Sun Protection Habits Instrument, with scores reflecting the use of sunscreen, clothing, hats, sunglasses, and umbrellas/shade. Each habit was scored 1-rarely/never performed, 2-sometimes performed, 3–often performed, 4–always performed. For the SPH Index, a cutoff of 3.0 was chosen to reflect adherence, representing an average of all five habits being performed often/always as opposed to sometimes/rarely/never. For certain subjects, medical records were abstracted for body mass index (kg/m2) data.

Oral vitamin D supplements were defined as any of the following: a multivitamin, a calcium and vitamin D supplement, 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 and daily vitamin D consumption was calculated using the National Institutes

of Health dietary supplement fact sheet and supplemented by the United States Department of Agriculture National Nutrient Database for Standard Reference, Release 24.(46, 47)

To address the question of whether the HPFS model's predictions would correspond to an individual's clinical vitamin D status, a subset of subjects completed additional questionnaires surveying physical activity as a proxy for outdoor ultraviolet radiation exposure, analogous to methods used in the HPFS.(18) The total leisure-time physical activity score was a sum of activity-specific metabolic-equivalents (MET)-hours/week, which was then divided into quintiles based on the cutoffs used by Giovannucci *et al*. 2006.(18) Medical records were abstracted for the season in which serum 25-OH-D was drawn.

Descriptive statistics were performed overall for each variable of interest. Since race need not correlate to skin tone, we also explored the distribution of races by Fitzpatrick Skin Type. Fisher's exact test evaluated associations between sun protection adherence and each categorical variable. Student's t-test was to compare the difference in the means of each continuous variable among adherent and non-adherent subjects. To address the question of whether sufficient vitamin D status was associated with a low (non-adherent) SPHI, univariate logistic regression was performed modeling each variable to determine any association to a SPHI <3.0 (non-adherence). The crude odds ratio for vitamin D status (sufficient versus deficient) was compared in multivariate models assessing for confounding and interaction by all other variables. The multivariate logistic regression model explored the log odds of the probability, p, of an SPHI <3.0 (or non-adherence to sun protection):

Log (p/1-p) = Intercept + B1* serum 25-OH-D status (sufficient=1) + B2* Skin Cancer History (yes=1) + B3*Age + B4-B7*Races 1-4 + B9*Supplementation (yes=1)

To address the question of whether the HPFS model predictions would categorize an individual's vitamin D status, descriptive statistics were performed to compare the demographic characteristics of our sample with the characteristics of the HPFS cohort. The published model intercept and parameter coefficients (for categories of race, BMI, physical activity quintile, dietary and supplementary vitamin D levels), were used to calculate each subject's predicted 25-OH-D level (nmol/L).(18) The model was developed and prospectively validated using multiple large U.S. cohorts such as in the Nurses' Health Study, the Nurses' Health Study II and the Health Professionals Follow-up Study.(17, 18) The model was developed for adequately predicting long-term vitamin D levels in order to rank individuals by vitamin D status for the purpose of large-scale epidemiologic studies.(18) Such predicted vitamin D rankings (e.g. predictions divided into deciles) have been incorporated into a variable that was then correlated with various cancer risks in epidemiologic studies.(17, 18)

Region of residence was significant predictor of 25-OH-D according to the published model, however for the current dermatology sample all subjects were assigned to the reference region of the South (the published model's parameter coefficient for the Southern region was zero), which dropped out of the predictive equation. While age was included in determining coefficients in the HPFS, a coefficient for age was not published. Thus the final linear regression model used to predict vitamin D levels in our sample became:

Estimated serum 25-OH-D (nmol/L) = Intercept + B1*Black + B2*Asian +

B3*Summer + B4*Winter + B5*Spring +

B6-B9 * Category of Dietary D (IU/day) +

B10-B12 * Category of Supplemental D (IU/day) +

B13-B16 * Category of BMI (kg/m2)+

B17-B20 * Quintile of physical activity (Met-hours/week) +

B21* Northeast/Midatlantic + B22*Midwest/West

A paired t-test was used to assess the difference between predicted and observed 25-OH-D levels. The predicted and observed 25-OH-D levels were then categorized into normal, insufficient, deficient, and severely deficient. The lower limit of normal for 25-OH-D was defined as >80 nmol/L, insufficiency was defined as >50 to ≤80 nmol/L, deficiency was defined as >25 to ≤50 nmol/L, and severe deficiency was defined as <25 nmol/L (multiple thresholds including these have been cited in the literature).(9, 23, 43) Inter-rater agreement between predicted and observed categories of vitamin D status was assessed using Cohen's kappa, where k=0 indicates no more than chance agreement and k=1 indicates perfect agreement. In post-hoc analyses we explored the value of Fitzpatrick Skin Type as a predictor of vitamin D in univariate and multivariate linear regression models.

RESULTS

A total of 445 dermatology patients were approached about participating in the study. A total of 214 eligible patients agreed to participate in the study. Of these, 144 were skin cancer subjects from the DeLong *et al.* 2006 study, and 70 were general dermatology patients who agreed to complete additional surveys related to the HPFS.

Demographic characteristics of the 214 dermatology patients are presented in Table 1. Overall 36.9% of subjects were adherent with sun protection as defined by a SPHI >3.0. Table 2 summarizes the difference in means comparing adherent and non-adherent groups by Student's t-test for each continuous variable (SPHI, vitamin D levels, dietary vitamin D intake, body mass index, and age). There were no significant differences ($p<0.05$) between means of the adherent and non-adherent groups for each continuous variable.

Table 3 summarizes the differences between adherent and non-adherent groups for categorical variables found with Chi-square or Fisher's exact test. There was a significantly higher percentage of adherent subjects among those with sufficient vitamin D levels compared to deficient vitamin D levels (48.1% versus 33.1%, $p=0.048$). There was no significant difference between the proportions of adherers and non-adherers among different races (blacks, whites, and other). There was a significantly higher percentage of adherent subjects among whites compared to blacks (39.9% versus 14.3%, $p=0.03$). There was no significant difference between the proportions of adherer and non-adherers among Fitzpatrick Skin Types, skin cancer patients compared to non-skin cancer patients, and those taking vitamin D supplements compared to those not taking supplements. Table 4 compares the distribution of race according to skin type. Whites ranged from Fitzpatrick Skin Types 1-4. Blacks ranged from Fitzpatrick Skin Types 4-6.

Tables 5-9 detail logistic regression results for modeling the probability of sun protection non-adherence. Table 5 summarizes univariate logistic regression results with

all variables of interest. Only vitamin D status (sufficient versus insufficient) had a significant estimated odds ratio of 0.53 (p=0.0495). Table 6 summarizes assessment for confounding of this crude vitamin D status odds ratio by each other variable of interest. The original crude odds ratio of 0.53 ranged up to 0.64 when the variable race was added to the model. None of the odds ratios were significant after adding each other variable of interest to the model. Table 7 summarizes investigation for interaction of vitamin D status with each variable of interest, where no variables were found to have interactions with a pre-defined significance level of $p < 0.10$. Interaction for race with vitamin D was not evaluated since no non-White subjects had a normal vitamin D level. Table 8 summarizes building of the final logistic regression model controlling for all *a priori* covariates of interest. The odds ratios for vitamin D status were non-significant and shifted towards the null in each of the multivariate logistic regression models. Table 9 summarizes a final model for the association between sun protection adherence and vitamin D status, including odds ratios and p-values for each *a priori* variable of interest. Model stratification was also attempted by race (White or Black), vitamin D supplementation (yes or no), and skin cancer history (yes or no), without yielding different (or significant, $p<0.05$) results for the odds ratio for vitamin D status.

To address the question of whether the HPFS model predictions would categorize an individual's vitamin D status, a total of 67 out of 70 subjects were included in the predictive model. One subject was excluded for missing body mass index information, one excluded for missing dietary questionnaire information, and one excluded for a missing physical activity questionnaire. Table 10 displays the demographic characteristics of the subset of our dermatology sample in the format used for reporting demographics in the HPFS study for ease of comparison.(18) In the current sample (n=67) 68% were female, (none were female in the HPFS), 57% were White (84-94% were White in the HPFS), and

100% were residents of the South (28-66% were from the South in the HPFS). As shown in Table 11, vitamin D levels were higher among skin cancer patients (70.92 nmol/L ± 33.92) compared to non-skin cancer patients (49.53 nmol/L ± 20.35). As shown in Table 12, vitamin D levels were higher among those supplementing with vitamin D (58.83±30.03) compared to those not supplementing (52.64±22.90). There were significant Pearson's correlations among vitamin D levels and age (r=0.33, p=0.01) and body mass index (r=-0.27, p=0.03) in our sample.

Figure 1 displays the HPFS model's predictions versus the current sample's observed 25-OH-D levels, with clinical categories of vitamin D status delineated and strata of race indicated. By Student's t-test, mean serum levels of 56±26 nmol/L were an average of 6.69 nmol/L less than predicted levels of 62±10 nmol/L (p=0.02). A pattern of mostly overestimation of vitamin D levels was observed in Figure 1 for the Black race, therefore Pearson's correlation was calculated among the Black subset (n=20), where r=0.05 (p=0.83). Among the White subset (n=38), Pearson's correlation was r=0.39 (p=0.01).

As shown in Table 13, HPFS model predictions encompassed three categories of vitamin D: deficient (n=6), insufficient (n=60), and sufficient (n=1). Cohen's kappa=0.01 (95% CI = -0.11-0.14), indicating no more than chance agreement between the three predicted and observed categories of vitamin D level. No subjects were predicted to have severe deficiency <25 nmol/L (seven observed).

Post-hoc analyses exploring Fitzpatrick Skin Type as a predictor of vitamin D levels are detailed in Tables 14-18. Table 14 displays the mean vitamin D level by Race. Table 15 displays the mean vitamin D levels by Fitzpatrick Skin Type. Table 16 displays univariate linear regression results modeling Fitzpatrick Skin Type and each of the HPFS variables as predictors of vitamin D levels in our sample. Fitzpatrick Skin Type (p=0.03), race(p=0.0067), age(p=0.0061) and body mass index(p=0.02) were significant predictors of

vitamin D by univariate linear regression in our sample. Table 17 details multivariate linear regression results exploring the predictors that were significant in univariate linear regression, and comparing Fitzpatrick Skin Type as a predictor to race as a predictor. Table 18 details the only multivariate model in which each parameter was a significant predictor of vitamin D level, including Fitzpatrick Skin Type (dichotomized into Types 1-4 versus Types 5-6).

DISCUSSION / CONCLUSIONS

Limitations and Strengths:

Limitations include our very small sample size and our very specific study sample consisting of dermatology patients from the Southeast region, with a large representation of patients with skin cancer. These issues limit the generalizability of our results, which need to be confirmed in larger and more diverse samples. In addressing the question of whether sufficient vitamin D status is associated with a low (non-adherent) SPHI, it is unknown whether subjects were performing sun protection habits correctly. Additionally since the SPH Instrument a self-report tool, the scores are subject to recall bias. In addressing the question of whether the HPFS model predictions could categorize an individual by their clinical vitamin D status, we were unable to account for age—a significant predictor of vitamin D levels in our sample—in generating predictions since its coefficient was not reported in the HPFS.

Strengths of the study include the detailed reporting of assessment of for confounding and search for interaction in exploring vitamin D status's association with the SPHI. Another strength includes the methodology used to determine whether existing models like the HPFS can be utilized at the point-of-care to predict vitamin D levels, as well as the exploration of Fitzpatrick Skin Type as a potential important new variable in vitamin D research.

Conclusions:

Vitamin D sufficiency was not associated with non-adherence to sun protection. Interestingly, our results seemed to indicate that vitamin D sufficiency was associated with roughly half the odds of non-adherence (alternatively, two times the odds of adherence) compared to those with deficiency. This association is the opposite of what we expected.

Our results may reflect the discrepancies between actual sun protective behavior and self-reported behavior as record in the SPHI. It may also reflect our inability to determine whether sun protection was performed correctly. This could be consistent with research showing that sunscreen is not always applied or reapplied sufficiently, and that those protecting are more likely to experience sunburns.(43, 48)

Our results may also reflect that those most likely to protect are those with the most vulnerable (lightest) skin types, the same types that also most efficiently produce vitamin D through the skin. Next steps might include exploring the relationship between vitamin D status and sun protection adherence using stricter cut-offs of the SPHI, or defining adherence by an overall score that is summed over each of the individual sun protection habits (rather than the index which was the average score across all five habits).

We also conclude that the HPFS model predictions for vitamin D levels did not clinically categorize individuals by their vitamin D status. Predictions were least accurate among the deficient, largely consisting of Blacks (all of whom had deficient vitamin D levels in our sample). This is consistent with findings of other authors(22) suggesting that future studies are needed to evaluate potential interaction or effect modification by race for predicting vitamin D. This is also consistent with recent findings which indicate that Blacks have lower circulating levels of vitamin D binding protein than Whites. Therefore, a lower serum vitamin D level compared to Whites does not necessarily correlate to a lower total body bioavailability of vitamin D in Blacks.(49)

This suggests that testing patients for levels of vitamin D binding protein needs to be explored since it better elucidates bioavailability of vitamin D in the body. Perhaps the development of different thresholds for normal serum vitamin D levels is also warranted for Blacks versus Whites. As next steps, we also encourage future studies in larger samples, broader demographic groups, including factors such as age, and evaluating models stratified

by race to determine the full potential of the HPFS or other validated models for predicting individual vitamin D status.

Finally, we conclude that Fitzpatrick Skin Type is an important determinant of vitamin D levels. Our results have highlighted the unpredictable relationship between race and Fitzpatrick Skin Type. Compared to race, Fitzpatrick Skin Type is a more accurate measure of skin tone and the reaction of the skin to ultraviolet radiation (and thus efficiency of vitamin D production in the skin). These results still need to be confirmed, however we encourage the exploration of substituting Fitzpatrick Skin Type for race in predictive vitamin D models as a direction in need of further research.

Of note, our results do not detract from the HPFS model's usefulness for ranking subjects by predicted vitamin D levels for the purposes of epidemiologic study (as it was initially developed for). However our results do shed light on how much remains unknown about predicting individual vitamin D status. Despite current insights into many significant determinants of vitamin D levels, our power to explain and predict vitamin D levels is at best modest.(5) Future research regarding vitamin D binding protein levels and Fitzpatrick Skin Type may aid in both our understanding of vitamin D and the development of more powerful predictive vitamin D models.

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TABLES / FIGURES

Table 1. Characteristics of Dermatology Sample, Categorical Variables, n=214

Characteristic	N	%
"Non-Adherent" Average Sun	135	63.1

Protective Habits Index: 0 – 2.9 "Adherent" Average Sun Protective Habits Index: 3.0 – 4.0	79	36.9
Male	98	45.8
Female	116	54.2
White	183	85.5
Black	21	9.8
East Asian/Pacific Islander	6	2.8
Hispanic	3	1.4
South Asian/Indian	1	0.5
Fitzpatrick Skin Type 1	25	11.9
Fitzpatrick Skin Type 2	62	29.4
Fitzpatrick Skin Type 3	70	33.2
Fitzpatrick Skin Type 4	41	19.4
Fitzpatrick Skin Type 5	8	3.8
Fitz Patrick Skin Type 6	5	2.4
Taking Vitamin D Supplement	122	57
Not Taking Vitamin D Supplement	92	43
Skin Cancer History	164	77
Melanoma	79	37
Non-Melanoma	110	51.4
Both	27	12.6
No Skin Cancer History	50	23
Deficient Vitamin D (≤ 32 ng/mL)	160	75
Sufficient Vitamin D (> 32 ng/mL)	54	25

Table 2. Characteristics of Dermatology Sample, Continuous Variables, n=214

			Student's t-test by Group		
Variable	Mean	Standard Deviation (SD)	Non-Adherent Index Mean (SD)	Adherent Index Mean (SD)	T-statistic P-value

Vitamin D Level (ng/mL)	26.9	11.8	26.3 (12.1)	27.8 (11.2)	0.40
Dietary Vitamin D (IU/day)	212.2	170	215.4 (195.3)	206.9 (116.4)	0.70
Body Mass Index (kg/m^2)	27.9	5.6	28.4 (6.2)	27.1 (4.5)	0.10
Age	56.0	15.3	55.3 (16.1)	57.2 (14.0)	0.37

Table 3. Frequency Of Characteristics By Adherence, n=214

Characteristic	Group		
	Non-Adherent Index 0-2.9	Adherent Index 3.0-4.0	Chi-Square P-value
Serum Vitamin D Status			**0.048***
Deficient (≤ 32 ng/mL)	107 (66.9)	53 (33.1)	
Sufficient (> 32 ng/mL)	28 (51.9)	26 (48.1)	
Race[¥]			0.054[‡]
White	110 (60.1)	73 (39.9)	
Black	18 (85.7)	3 (14.3)	
Other[§]	7 (70.0)	3 (30.0)	
Fitzpatrick Skin Type[†]			0.33[‡]
Type 1	15 (60)	10 (40)	
Type 2	34 (54.8)	28 (45.2)	
Type 3	45 (64.3)	25 (35.7)	
Type 4	27 (65.9)	14 (34.1)	
Types 5 and 6	11 (84.6)	2 (15.4)	
Supplementation			0.57
Taking Vitamin D	75 (61.5)	47 (38.5)	
Not Taking Vitamin D	60 (65.2)	32 (34.8)	
Skin Cancer History			0.068
No	37 (74)	13 (26)	
Yes	98 (59.8)	66 (40.2)	

*Significant p-values <0.05

[¥]Whites versus blacks, Fisher's exact test p=0.030

[§]East Asian/Pacific Islander (n=4), Hispanic (n=2), South Asian/Indian (n=1)

[‡]Fisher's Exact Test

[†]Skin types 1-4 versus types 5-6, Fisher's exact test p=0.090

Table 4. Distribution of Race versus Fitzpatrick Skin type, n=214

	Type 1	Type 2	Type 3	Type 4	Type 5	Type 6
White	25	62	69	24	0	0
Black	0	0	0	9	7	5
East Asian/Pacific Islander	0	0	1	4	1	0
Hispanic	0	0	0	3	0	0
South Asian/Indian	0	0	0	1	0	0

Table 5. Univariate Logistic Regression Results for Sun Protection Non-adherence, n=214

Modeling Non-adherence =	A1C	Overall Model Chi-Square P-value	C-Statistic
Vitamin D Status	282.00	**0.0495***	0.56
Race 1 – Race 4	284.84	0.32	0.56
Skin Cancer History	282.37	0.07	0.55
Supplementation	285.53	0.57	0.52
Age	285.04	0.37	0.54

*Significant p-values <0.05

Table 6. Assessment for Confounding in Logistic Regression Models of Sun Protection Non-adherence and Vitamin D Status, n=214

Modeling Non-adherence =	Odds Ratio (95% Confidence Limits) of Vitamin D Normal v. Deficient	P-value
Vitamin D Status	0.53 (0.29-0.99)	**0.049***
Vitamin D Status + Supplementation	0.56 (0.30-1.05)	0.07
Vitamin D Status + Race 1 – Race 4	0.64 (0.34-1.22)	0.16
Vitamin D Status + Skin Cancer History	0.63 (0.33-1.21)	0.16
Vitamin D Status + Age	0.53 (0.28-1.00)	0.05

*Significant p-values <0.05

Table 7. Assessment for Select Interactions in Logistic Regression Models of Sun Protection Non-adherence and Vitamin D Status, n=214

Modeling Non-adherence =	Overall Model Chi-Square P-value	P-value for interaction term
Vitamin D Status + Race + Vitamin D*Race	0.24	*
Vitamin D Status + Skin Cancer History + Vitamin D *Cancer History	0.13	0.65
Vitamin D Status + Supplementation + Vitamin D *Supplementation	0.30	0.75
Vitamin D Status + Age + Vitamin D *Age	0.59	0.16

*No interaction terms created, no non-White race with normal vitamin D levels

Table 8. Building Logistic Regression Models of Sun Protection Non-adherence and Vitamin D Status, n=214

Modeling Non-adherence =	Odds Ratio (95% Confidence Limits) of Vitamin D Status Normal v. Deficient	P-value
Vitamin D Status	0.53 (0.29-0.99)	**0.049***
Vitamin D Status + Skin Cancer Status	0.63 (0.33-1.21)	0.16
Vitamin D Status + Skin Cancer Status + Supplementation	0.64 (0.33-1.23)	0.18
Vitamin D Status + Skin Cancer Status + Supplementation + Race	0.67 (0.35-1.29)	0.23
Vitamin D Status + Skin Cancer Status + Supplementation + Race + Age	0.64 (0.33-1.25)	0.36

*Significant p-value <0.05

Table 9. Final Logistic Regression Results for Sun Protection Non-adherence and Vitamin D Status, n=214

Model:
Log (P/ 1-P) = Vitamin D Status + Skin Cancer Status + Supplementation + Race + Age, where p = probability of non-adherence to sun protection

Parameter	Odds Ratio (95% Confidence Limits) of Parameter	P-value
Vitamin D Normal versus Deficient	0.64 (0.33-1.25)	0.19
Skin Cancer History – Yes versus No	0.84 (0.34-2.08)	0.70
Age	1.03 (0.97-1.09)	0.41
Black	3.00 (0.68-12.10)	0.15
East Asian/ Pacific Islander	0.98 (0.15-6.22)	0.98
Hispanic	0.91 (0.07-12.05)	0.94
Supplementation—Yes versus No	0.95 (0.51-1.77)	0.88

Overall Model C-statistic = 0.63

Table 10. Demographic Characteristics by Quintile of Predicted Vitamin D levels of the Current Dermatology Sample for Comparison with the Health Professionals Follow-Up Study, n=67

Characteristic (Units)	**Predicted Serum 25-hydroxyvitamin D level**			
	Q1	Q3	Q5	Overall (SD)
Mean age (years)	53.2	56.0	63.0	57.7 (14)
Gender (%)				
Female	71.4	69.2	69.2	68.6
Male	28.6	30.8	30.8	31.3
Mean Physical Activity (MET-hours/week)	22.7	33.4	35.8	30.3(15.4)
Mean Body Mass Index (kg/m^2)	30.9	30.7	24.7	29.5 (6.9)
Race (%)				
White	21.4	61.5	92.3	56.7
Black/African American	78.6	15.4	7.7	29.9
Other	0	23.8	0	13.4
Asian		23.8		7.5
Hispanic		0		4.5
Indian				1.5
Multivitamin use (%)	21.4	0	15.4	47.8
Mean Total Vitamin D (IU/day)	542	431	535	5201 (632)
Diet	178	231	242	204 (133)
Supplement	364	200	292	316 (597)
Southern Region of Residence (%)	100	100	100	100

HPFS, Health Professionals Follow-up Study
MET, metabolic equivalent
SD, Standard Deviation
Q1, Q3, Q5 = 1st, 3rd, and 5th Quintiles of predicted vitamin D level, presented for direct comparison with the published HPFS where r^2=28%with parameters including age, race, region, season, leisure time physical activity, body mass index, dietary vitamin D, and supplementary vitamin

Table 11. Mean Serum Vitamin D Levels (nmol/L) by Skin Cancer History (n=67)

Variable	**Mean**	**Standard Deviation**	**95% Confidence limits of mean**
No Skin Cancer History (n= 48)	49.53	20.35	43.62 - 55.44
History of Skin Cancer (n=19)	70.92	33.92	54.57 - 87.27

Table 12. Mean Serum Vitamin D Levels (nmol/L) By Supplementation (n=67)

Variable	Mean	Standard Deviation	95% Confidence limits of mean
Not Taking Supplement (n=35)	52.64	22.90	44.78 - 60.51
Taking Supplement (n=32)	58.83	30.03	48.00 - 69.65

Table 13. Frequency of Predicted Versus Observed 25-hydroxyvitamin D Levels Using the Health Professionals Follow-Up Study Linear Regression Model (r^2=28%), n=67

Predicted	**Observed**			
	Severely Deficient <25 nmol/L	Deficient ≤50 nmol/L	Insufficient ≤80 nmol/L	Sufficient >80 nmol/L
Deficient	2	1	3	0
Insufficient	5	26	22	7
Sufficient	0	0	0	1

Cohen's kappa=0.01; 95% Confidence Interval = -0.11-0.14

Table 14. Mean Serum Vitamin D Levels (nmol/L) by Race (n=67)

Race	**N**	**Mean**	**Standard Deviation**	**Lower 95% CLM***	**Upper 95% CLM**
White	38	64.28	28.01	55.07	73.48
Black	20	39.00	18.13	30.52	47.48
Asian§	5	60.00	15.61	40.61	79.39
Hispanic	3	42.50	20.00	-7.18	92.18
Indian¥	1	75.00			

*Confidence limit of the mean
§ East Asian/Pacific Islander
¥ South Asian/Indian

Table 15. Mean Serum Vitamin D Levels (nmol/L) by Fitzpatrick Skin Type (n=67)

Skin Type	N	Mean	Standard Deviation	Lower 95% CLM*	Upper 95% CLM
1	4	80.00	28.72	34.30	125.70
2	13	64.23	32.79	44.41	84.05
3	15	61.33	27.38	46.17	76.50
4	23	52.17	18.31	44.25	60.09
5	8	35.63	20.34	18.62	52.63
6	4	41.25	26.65	-1.16	83.66

*Confidence limit of the mean

Table 16. Comparison of Bivariate Models Predicting Serum Vitamin D (nmol/L)

Predictor	**R^2**	**Overall Model P-value**
Fitzpatrick Skin Type	0.18	**0.03***
Season	0.09	0.10
Body Mass Index	0.07	**0.02***
Race	0.20	**0.0067***
Supplemental Vitamin D	0.0055	0.55
Dietary Vitamin D	0.0024	0.70
Physical Activity Level	0.00031	0.89
Age	0.11	**0.0061***

*Significant p-values <0.05

Table 17. Linear Regression Results Exploring Race and Fitzpatrick Skin Type as a Predictors of Vitamin D Levels, n=67

Model: Vitamin D Level (nmol/L) =	Model R-squared	Overall P-value
Age § + Race + Body Mass Index	0.27	**0.0039***
Age § + Skin Type + Body Mass Index §	0.28	**0.0059***
Age § + Skin Type (1 to 4 versus 5 to 6) §+ Body Mass Index §	0.23	**0.00090***

§ Parameters with significant Odds Ratios in the model, as defined by $p<0.05$
*Significant p-values <0.05

Table 18. Final Linear Regression Results for Fitzpatrick Skin Type as a Predictor of Vitamin D Levels, n=67

Model: Vitamin D Levels = Fitzpatrick Skin Type + Age + Body Mass Index (BMI), R-squared = 0.23, **p = 0.00090***			
Parameter	Estimate	Standard Error	P-value
Intercept	38.93	18.91	**0.044***
Age	0.50	0.21	**0.023***
Skin Type 1-4 versus 5-6	16.62	7.81	**0.037***
BMI	-0.88	0.43	**0.044***
*Significant p-values <0.05			

Figure 1. Predictions Versus Observed Vitamin D Levels (nmol/L) with Clinical Categories of Vitamin D Status Delineated and Race Indicated