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Invited Review Vitamin D and skin cancer†

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Abstract

Vitamin D signaling plays a key role in various important processes, including cellular proliferation, differentiation, and apoptosis, immune regulation, hormone secretion, and skeletal health. Further, vitamin D production and supplementation have been shown to exert protective effects via an unknown signaling mechanism involving the vitamin D receptor (VDR) in several diseases and cancer types, including skin cancer. With over 3.5 million new diagnoses in 2 million patients annually, skin cancer is the most common cancer type in the United States. While ultraviolet B (UVB) radiation is the main etiologic factor for non-melanoma skin cancer (NMSC), UVB also induces cutaneous vitamin D production. This paradox has been the subject of contradictory findings in the literature in regards to amount of sun exposure necessary for appropriate vitamin D production, as well as any beneficial or detrimental effects of vitamin D supplementation for disease prevention. Further clinical and epidemiological studies are necessary to elucidate the role of vitamin D in skin carcinogenesis.

Introduction

Over the last century, great progress has been made in the understanding of the formation and activation of vitamin D. However, it was not until after the cloning of the vitamin D receptor in 1987 and the discovery of the presence of the VDR in nearly all cells that both basic and clinical studies examined the non-skeletal-related effects of vitamin D, especially in chronic disease models. Systemic effects of vitamin D are shown in Table 2. Though there are many studies examining the relationship of vitamin D and cancer, confounding variables and small sample sizes make it difficult to determine significant and valid results. We attempt herein to focus on the relationship between vitamin D and skin cancer in an effort to present the existing literature and suggest future studies to elucidate and verify the details of the complex relationship.

Vitamin D, a prohormone and secosteroid, is produced in the skin, which is the only known organ system able to produce each major component involved in the vitamin D signaling pathway, in response to ultraviolet light B (UVB; 290-320nm) exposure (1-4). There are two main forms of vitamin D, which include animal-derived (cholecalciferol D₃; from cholesterol) and plant-derived (ergocalciferol D₂; from ergosterol). A summary of the different forms can be found in Table 1. Briefly, UV irradiation of 7-dehydrocholesterol

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produces vitamin D₃, which is then metabolized through a hydroxylation process to 25-hydroxyvitamin D₃ in the liver, and eventually to 1- α ,25-dihydroxyvitamin D₃ in the kidney, which is the metabolically active form that is produced on a systemic level (reviewed in (5)). While this metabolic process is usually carried out in the liver and kidney, animal studies have revealed the presence of hydroxylases in the epidermis, which may indicate that active conversion occurs in the skin as well, without passage through the liver (6, 7). Interestingly, circulating 25-D₃ can be activated via 1- α hydroxylation in target tissues, which proceeds through the activity of CYP24, which is the classical pathway. Recently, an alternative *in vivo* pathway for activation of vitamin D₃ (8) and D₂ (9) was revealed, which begins with CYP11A1 activity and is further modified by CYP27B1 (10-12), and its activity in the skin is related to the expression of CYP11A1 in this organ (13, 14). Following activation, the metabolite, 1,25-D₃ acts as the ligand for the vitamin D receptor.

Vitamin D and the vitamin D receptor

The VDR, an intracellular receptor and transcription factor, belongs to a protein family that includes other receptors for steroid hormones, retinoids, isoprenoids, eicosanoids, and cholesterol metabolites (reviewed in (15)). The VDR is between 50-60kDa and contains a shorter N-terminal domain than many nuclear hormone receptors. The DNA-binding domain is the most conserved domain both among species and nuclear hormone receptors. The DNA-binding domain contains two zinc fingers, of which the N-terminal zinc finger is important for the specificity of DNA binding to the vitamin D response element (VDRE), and the other zinc finger is responsible for providing a heterodimerization site for the VDR and the retinoid X receptor (RXR). The ligand-binding domain is where 1,25-D₃ binds and this region also is important for RXR heterodimerization. AF-2, the major activation domain, is found at the C-terminal end of the VDR and is necessary for steroid receptor coactivator (SRC) and VDR-interacting protein (DRIP) binding (16), which can therefore regulate the VDR. A murine study demonstrated that the VDR plays a key role in the action of vitamin D as evidenced by a severe vitamin D deficiency in animals with the VDR deleted (17). In the human body, the VDR is found in over 60 cell types (18), leading to the breadth of processes and diseases affected by vitamin D (19).

Activated vitamin D can function through two major pathways, genomic and nongenomic. The genomic pathway results in the activation of VDRE which influences the expression of over 900 genes important for various physiological processes that may ultimately result in carcinogenesis (20). The VDRE is activated by the VDR/RXR heterodimer and the binding of 1,25-D₃ to the VDR. The non-genomic pathway consists of the intracrine actions of active vitamin D when it is synthesized from its precursor metabolite. Intracellular signaling cascades are stimulated when active vitamin D binds to the VDRs in the membrane, resulting in the regulation of chloride and calcium channel opening as well as further signaling molecule activation (21). This pathway may also be used for protection against DNA damage in addition to ionic homeostasis maintenance (22).

Other receptor targets for activated forms of vitamin D

Studies have revealed that other receptors besides the classical vitamin D receptor are targets for activated forms of vitamin D. Originally discovered as a cell surface receptor for 1,25D₃, the 1,25D₃ membrane-associated rapid response steroid-binding (MARRS) receptor preferentially binds analogs of 1,25D₃ that have a *cis* configuration, resembling hormones that have an intact B ring such as estradiol, rather than 1,25D₃ itself, which has a broken B ring (23). In this calcium-dependent membrane-mediated pathway (24-26), 1,25D₃ functions via a specific membrane-associated receptor protein disulfide isomerase family A, member 3 (Pdia3; also known as ERp57, ERp60, Grp58, and 1,25-MARRS) (27, 28) found in 50-100 nm lipid rafts enriched with both glycosphingolipids and cholesterol (29), which are called caveolae. The caveolae function as signaling platforms for several steroid hormones via their caveolin coat proteins.

Additionally, there are other nuclear receptors that are also targets for active forms of vitamin D, including the retinoic acid-related orphan receptors (ROR) alpha and gamma (30).

Vitamin D and skin

Regardless of ethnicity, circulating vitamin D levels are lower in non-Caucasians compared to Caucasians even though non-Caucasians exhibit increased bone mass (31). Interestingly, the lowest vitamin D levels in Caucasians are found in individuals with the fairest skin types, which may be due in part to lower amounts of UVB exposure in fair skinned individuals. Because decreased vitamin D levels have been linked with increased melanoma incidence as well as decreased survival (32), future studies are required to fully understand the implications of vitamin D supplementation and deficiency in terms of race and sun exposure requirements and recommendations (33).

In the United States and many countries in Europe, sufficient vitamin D levels are obtained via UVB-induced, cutaneous 7-dehydrocholesterol synthesis (90%) and nutrients found in the diet (10%) (34). There has been much discussion as to whether ingesting vitamin D from the diet or from a supplement is the same as producing vitamin D₃ in the skin. It has been observed that when produced in the skin, circulating vitamin D lasts 2-3 times longer than when it is ingested orally (35). In the skin, previtamin D takes nearly 8 hours to be fully converted into metabolically active vitamin D (36, 37) and then it takes more time to enter the dermal capillary bed. 100% of Vitamin D produced in the skin can be bound to the vitamin D binding protein. In contrast, vitamin D obtained through the diet is incorporated into chylomicrons and transported into the lymphatic and subsequently into the venous system where only around 60% of the vitamin D is bound to the vitamin D binding protein while the remainder is rapidly cleared.

While obtaining vitamin D through UVB exposure is cheaper than purchasing supplements or a constant supply of vitamin D-rich foods, it is not without detrimental effects. It is well documented that both brief periods of high-intensity UVB exposure and UVB exposure have been linked with cutaneous inflammation and DNA damage that can contribute to skin carcinogenesis (38-42). In the 1970s, sunscreens were designed with the purpose of

absorbing UVB radiation and therefore decreasing the harmful effects of the sun (43). Sunscreen that is labeled to have a sun protection factor (SPF) of 30 absorbs 95–98% of UVB radiation. The same sunscreen will also reduce the ability of the skin to synthesize metabolically active vitamin D by the same amount (18). One study demonstrated in a group of farmers with a NMSC history living in the Midwest that those who wore sunscreen exhibited significantly lower or deficient levels of vitamin D compared to the levels observed in the control group (44). In contrast, one study demonstrated that even with high levels of uv exposure, subjects were still vitamin D-deficient. Supplementing diet with vitamin D-rich foods is a better way to eliminate vitamin D deficiency, especially in darker skinned individuals, where cutaneous vitamin D production is not as effective with UVB exposure. There is a known and epidemiologically supported link between increased UVB exposure and NMSC development, so continuing safe sun practices will decrease NMSC risk and will not affect vitamin D status (45). It has been suggested that the effective slip, slap, slop educational campaign in Australia has resulted in vitamin D deficiency of over 40% of the population (46-49), and the subsequent recommendation of the Australian Dermatology Society for sensible sun exposure as a vitamin D source. A three-part strategy has been suggested for implementation to reduce vitamin D deficiency worldwide that consists of sensible sun exposure, the consumption of vitamin D-rich or fortified foods as well as a vitamin D supplement. Taken together, continuing safe sun practices along with the intake of vitamin D-rich foods and a vitamin D supplement, may help to decrease NMSC risk.

Vitamin D and immunomodulation

The effects of vitamin D on immune responses remain unclear. While some studies demonstrate that topical vitamin D can actually decrease against UV-induced responses such as DNA damage and immunosuppression, other studies have shown that vitamin D plays a key role in the development of T regulatory cells, which utilizes signaling through the vitamin D receptor (50), as well as other important immune cells (51). This mechanism is dependent on Langerhans cells (50), which ultimately results in the same outcome as UVB exposure used as treatment in psoriasis, which is an immunodermatological disease. It has been suggested that topical use of vitamin D may be a substitute for UVB treatment, which would eliminate DNA damage caused by UVB exposure, and in fact, vitamin D and its analogs may promote DNA damage repair responses (52). Additionally, signaling through the VDR, of which several polymorphisms have been reported and investigated, may provide a possible explanation for the genetic susceptibility to immunodermatological diseases such as non-melanoma and melanoma skin cancers in addition to psoriasis. Vitamin D deficiency may therefore decrease immune cell development and lead to immunosuppression, which has been shown to lead to increased NMSC development, especially in immunosuppressed patients such as solid organ transplant patients, who have 60-250-fold increased risk of developing skin cancer (53-58). Interestingly, regulatory T cells, the development of which is modulated in part by vitamin D signaling, are important mediators of UVB-induced immunosuppression (59-65), which can lead to skin cancer development.

Vitamin D and skin cancer

Vitamin D production and supplementation have been shown to exert protective effects via an unknown signaling mechanism involving the VDR in several diseases and cancer types, including skin cancer. With over 3.5 million new diagnoses in 2 million patients annually, skin cancer is the most common cancer type in the United States (66). While ultraviolet B (UVB) radiation is the main etiologic factor for non-melanoma skin cancer (NMSC), UVB also induces cutaneous vitamin D production. Epidemiological studies have reported a relationship between vitamin D synthesis and UV exposures (2, 4, 67). Breast cancer incidence has been reported to be 50% less in women with high levels of UVB exposure as compared to women with lower exposure (67). Likewise, men with high UVB exposure had a 50% lower incidence of fatal prostate cancer. Deficiency of vitamin D has been strongly associated with both the development and progression of several types of cancers (68-70). Interestingly, one study in postmenopausal women demonstrated that vitamin D₃ and calcium supplementation resulted in a substantial reduction of all cancer risks (71). While no studies have significantly linked vitamin D supplementation to NMSC prevention or treatment in large human populations, there is a link between vitamin D and several other cancer types (67, 72-74).

In a nested case-control study of elderly men, a lower occurrence of NMSC was found in subjects with the highest serum concentration of the previtamin D metabolite compared to subjects with the lowest concentrations (75). Further, increased previtamin D levels in plasma have been associated with better survival as well as decreased metastasis (22, 70, 76, 77). Additionally, vitamin D₃ and 1,25-D₃ levels have been shown to help determine survival and metastasis prognoses for skin cancer as well as cancers of the lung, breast, and prostate (74, 75, 77-83).

Vitamin D has also been shown to regulate the cell cycle by altering expression of cell cycle control genes (84, 85). Both human and animal studies have demonstrated a key role of the vitamin D pathway for skin homeostasis and keratinocyte growth and differentiation (86), as well as skin carcinogenesis (87-90).

In vitro studies have suggested that vitamin D supplementation is facilitated via the non-genomic pathway as illustrated by the use of analogs as agonists and antagonists for DNA damage prevention (91). Further studies in the hairless mouse model support these findings and suggest a mechanism for preventing UV-induced skin carcinogenesis with topical 1,25-D₃ treatment (90). It has also been suggested that vitamin D produced endogenously following exposure to UVB may result in a protective, photoadaptive effect against exposure to solar radiation following the initial exposure.

Vitamin D and melanoma

Several studies have implicated a role for the vitamin D₃/1,25-D₃/VDR axis in the determination of malignant melanoma as well as various other systemic cancers (summarized in (92)). VDR expression can be detected in melanoma cells and both the pro-differentiation and antiproliferative effects of 1,25-D₃ have been shown in human melanoma cells (93-95). In a xenograft mouse model, 1,25-D₃ has been shown to suppress

melanoma growth using VDR-positive human-derived malignant melanomas (96). In a human malignant melanoma cell line, 1,25-D₃ induced apoptosis; however, another cell line was unresponsive despite expressing the VDR (97). CYP24A1 mRNA has been shown to be upregulated with vitamin D supplementation in melanoma cells, which deactivates MAPK signaling and may partially control the anti-proliferative effects of vitamin D (98). Higher 25-D₃ levels were associated with thinner tumors (lower Breslow thickness) at diagnosis (32). Vitamin D levels were also independently protective of relapse and death. Low levels of circulating vitamin D in patients with stage IV melanoma compared to stage I also developed earlier distant metastatic disease (99). Further, decreased or lost expression of VDR or CYP27B1 has been shown to lead to the progression of melanocytic tumors (100) and melanoma (101), and to decrease overall and disease-free survival of melanoma patients (102).

In a randomized, placebo-controlled trial of postmenopausal women aged 50-79 enrolled in the Women's Health Initiative, the authors evaluated effects of vitamin D₃ combined with calcium supplementation on skin cancer for a mean follow-up of 7 years. Supplementation (1000mg Ca + 400 IU vit D₃ daily) did not reduce overall NMSC or melanoma incidence; however, in women with NMSC personal history, supplementation reduced melanoma risk (103). The amount of vitamin D₃ used in this study has been argued to be quite low, and therefore results may be seen with high supplementary levels.

VDR polymorphisms

An individual's susceptibility to skin cancer can be ascertained by the ability of vitamin D binding to their vitamin D receptor (VDR). Most of the studies have been conducted in European Caucasians, where small nucleotide polymorphisms (SNPs) were assessed for determining the risk of non-melanoma (SCCs and BCCs) and melanoma skin cancer in individuals. The SNPs in VDR have been associated with both the occurrence and outcome of skin cancer. More than sixty VDR polymorphisms have been discovered and are present in and around exons 2-9 and in the 3'UTR region of the promoter. Due to difficulty in analysis of these VDR SNPs, only few polymorphisms of this large gene have been studied extensively. Only few epidemiological studies have directly addressed the relationship between VDR SNPs and skin cancer. The most well studied VDR SNPs in skin cancers are Taq1, Bsm1, Apa1, and Fok1 (104).

Taq1 polymorphism

The TaqI polymorphism (rs731236) is a restriction fragment length polymorphism (RFLP), which occurs at codon 352 in exon 9 of the VDR gene. The products are digested into 2 fragments of 495 and 245 bp (T allele: absence of the restriction site) or 3 fragments of 290, 245 and 205 bp (t allele: presence of the restriction site) depending on the presence or absence of a TaqI restriction site in each allele. Individuals are usually classified as TT, Tt or tt. The TT allele has been shown to be associated with lower circulating levels of active vitamin D₃ (105-107). The TaqI polymorphism leads to a silent codon change (from ATT to ATC, which both result in an isoleucine at codon 352) (105).

Bsm1 polymorphism

The BsmI polymorphism (rs1544410) is an RFLP in intron 8 at the 3' end of the VDR gene. It is considered to be a silent SNP because it does not change the amino acid sequence of the encoded protein (108). However, it can affect mRNA stability and change the expression of gene (109).

Apa1 polymorphism

The ApaI polymorphism (rs7975232) is located in intron 8 at the 3' end of the VDR gene, like the BsmI polymorphism (110).

Fok1 polymorphism

The FokI polymorphism (rs2228570, formally known as rs10735810) is located at the first potential start site (111, 112), which can be detected using the FokI restriction enzyme by RFLP (113). It alters an ACG codon that is located ten base pairs upstream from the translation start codon, thus resulting in the generation of an additional start codon. If the translation is initiated from this alternative site (thymine variant), it results in the generation of a longer VDR protein. This polymorphism is referred to as the f allele (112). However, the f allele exerts less transcriptional activity (114), with the F variant being 1.7-fold more active (113, 115, 116). FokI polymorphism is the only known VDR gene polymorphism that actually results in the generation of an altered protein.

VDR SNPs in non-melanoma skin cancers

There has been a lot of variation in the studies linking VDR SNPs with SCCs and BCCs. When the association of VDR gene with solar keratosis (SK), a biomarker for skin cancer, was examined with skin phenotype, a significant difference in genotype frequencies of the TaqI polymorphism was found between affected and unaffected populations. The TT/tt genotype group was associated with a seven fold increase, whereas Tt group had a four fold increase in odds of being affected by SK. Fair-skinned people with VDR-Apa AA/aa genotypes had about an eightfold increase in odds of being affected by SK compared with a fivefold increase in individuals with the Aa genotype and fair skin. This study shows that the homozygote genotypes increase the odds of SK, thus suggesting that intermediate VDR activity is important in protection or that the heterodimer formed by a heterozygous genotype may have an altered binding potential (117). A meta-analysis of VDR SNPs showed that FokI, TaqI and ApaI may be the susceptibility biomarkers for skin cancer in Caucasians. No significant association was observed between the BsmI polymorphism and skin cancer risk (118). Another study evaluating the hedgehog pathway that drives most BCCs, and pathway-related gene variants contribute to the increased risk of subsequent cancers among those with a history of BCC. No significant associations were observed for any of the hedgehog pathway SNPs, or for the FAS SNPs. Thus, hedgehog pathway gene SNPs studied, along with the VDR and FAS SNPs studied, are not strongly associated with the BCC cancer-prone phenotype (119). In a German study, associations indicated that the ApaI and TaqI genotypes may be important for development of BCCs, but not for SCCs. Comparison of the VDR genotype frequencies by age (younger than 60 years vs. 60 years or older) revealed that it had no association with SNPs in patients with BCCs or SCCs (104).

UV radiation has a major influence on folate and vitamin D as UV radiation can break down plasma folate, and synthesize vitamin D in skin. Folate metabolism is involved in DNA synthesis and repair, whereas vitamin D can inhibit proliferation. Both these nutrients have important implications in skin carcinogenesis. In a study in Polish population, it was found that the presence of the TT genotype in the FokI VDR polymorphism resulted in a >10-fold higher risk of BCC development. The CT genotype in 677C/T MTHFR polymorphism and CC genotype in 1286A/C MTHFR (methylenetetrahydrofolate reductase) polymorphism also significantly increased the risk of BCC development. The expression of the VDR and MTHFR proteins was significantly higher in BCCs of the patients than in the healthy skin of the controls (120). In a nested case control Nurses' Health Study on melanoma and non-melanoma skin cancers, polymorphisms in MTHFR and VDR were associated with dietary intakes of folate and vitamin D in skin cancer development, especially for SCC (121).

VDR SNPs in malignant melanoma

Melanoma is one of the most aggressive human cancers. The vitamin D system contributes to the pathogenesis and prognosis of malignancies including cutaneous melanoma. An expression of the vitamin D receptor (VDR) and an anti-proliferative effect of vitamin D in melanocytes and melanoma cells have been shown in vitro. Studies examining associations of polymorphisms in genes coding for vitamin D metabolism-related proteins (1 α -hydroxylase [CYP27B1], 1,25(OH)(2)D-24hydroxylase [CYP24A1], vitamin D-binding protein [VDBP]) found no association of polymorphisms tested with melanoma risk as well as prognosis in logistic and linear regression models (122). In a large, international, multinational population-based case control study examining 38 VDR gene SNPs with known or suspected impact on VDR activity, haplotype tagging SNPs with 10% minor allele frequency in Caucasians, and SNPs reported as significant in other association studies were examined. Eight of 38 SNPs in the promoter, coding, and 3' gene regions were individually significantly associated with multiple primary melanoma after adjusting for covariates. The estimated increase in risk for individuals who were homozygous for the minor allele ranged from 25 to 33% for six polymorphisms: rs10875712, rs4760674, rs7139166, rs4516035, rs11168287 and rs1544410; for two polymorphisms, homozygous carriers had a decreased risk: rs7305032 and rs7965281. There were false positive findings because of multiple comparisons; however, the eight significant SNPs in this study outnumbered the two significant tests expected to occur by chance, thus indicating a possible role of VDR in melanomagenesis (123). In a study in Spanish population, an association was found between polymorphisms in GC and melanoma risk, thus confirming studies from different populations (106). Only the BsmI variant was found to be associated with multiple primary melanoma. Their results suggested that risk of multiple primary melanoma was increased in people who have the BsmI variant of VDR (124). The association between BsmI variant and melanoma led to the theory that sun exposure may have a protective effect against melanoma through activation of the vitamin D system (125). This study examined the association between BsmI polymorphism and prevalence of malignant melanoma together with Breslow thickness. In addition, they also determined FokI SNP in this population. All cases and controls were found to be in Hardy-Weinberg equilibrium for BsmI, FokI and A-1012G. Significant associations were found between the BsmI bb genotype frequency and malignant melanoma ($P = 0.02$) along with Breslow

thickness ($P = 0.001$). This same pattern was not observed for the FokI or A-1012G polymorphisms. Multivariate logistic regression analysis confirmed these significant results after they were corrected for age, gender, skin type and localization of malignant melanoma. Additional studies need to be done to verify this variant as a possible risk marker for malignant melanoma and its aggressiveness. However, it is possible that the real association may be due to other unknown genes linked to the BsmI b allele (126).

Future therapeutic interventions

Non-calcemic vitamin D analogs have been investigated and have been shown to have anti-proliferative, anti-inflammatory, and anti-fibrosing effects (127-129), resulting in a potential area for therapeutic interventions. Utilizing inhibitors of melanogenesis may be used in an attempt to improve the efficacy of various melanoma therapies (130). It has also been suggested that melatonin and vitamin D should be used as adjuvants due to their protective and anti-cancer properties as a therapy for advanced melanoma. This approach could take advantage of the easily monitored toxicity of vitamin D and the non-toxic melatonin, in attempt to prevent recurrent or progressing disease.

Conclusion

While vitamin D and the resultant signaling cascade play key roles in normal cellular processes and prevent against bone-related disorders, the topic of cutaneous health has remained controversial in terms of detrimental effects of the UVB exposure necessary for the production of metabolically active vitamin D in the skin. While several studies have demonstrated the benefits of adequate circulating vitamin D levels, there is a clear link between sun exposure and skin carcinogenesis. Vitamin D supplementation has also been linked to decreased cancer incidence as well as improved outcome and survival, including in skin cancer, however there are also studies that do not support this correlation. Difficulties in translating findings to large-scale, human studies include small study sizes, and the number of confounding factors present in each study. Future studies utilizing basic research, clinical interventions, and epidemiological studies are necessary to elucidate the intricacies of the relationship between vitamin D levels and skin cancer development in terms of sunscreen use, diet, and the use of vitamin D supplements.

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Biography

Nabiha Yusuf received her MS degree in Microbiology, and PhD degree in the area of Immunology from India. Dr. Yusuf joined the department of Dermatology at the University of Alabama at Birmingham in 2001 as a Postdoctoral Fellow.

After completing her postdoctoral training in the laboratory of Dr. Craig A. Elmetts, she became an Instructor in 2005. She received a Research Career Development Award from Dermatology Foundation, and became an Assistant Professor in 2009. Her major research interests focus on the role of innate immune system on the environmental influences such as chemical carcinogens and ultraviolet (UV) radiation on the development of skin cancer. Her other research interests include the modulation of non-melanoma skin cancer by dietary supplements, and the microbiome. She is currently collaborating with Dr. Elmetts to delineate the role of vitamin D receptor polymorphisms in nonmelanoma skin cancer.

Erin Burns received her PhD from The Ohio State University in 2013, where her dissertation research investigated sex differences in non-melanoma skin cancer, specifically focusing on anti-inflammatory and antioxidant compounds for UVB-induced squamous cell carcinoma prevention. She is currently a postdoctoral fellow in the Cancer Prevention and Control Training Program supported by NCI/NIH, under the mentorship of Dr. Nabih Yusuf and Dr. Craig Elmetts. Her current research is focused on non-melanoma skin cancer prevention and control, investigating the effects of dietary supplements, genetic markers, and the microbiome as new targets for risk assessment or therapeutic interventions.

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Table 1

Vitamin D forms and functions

Name	Other Names	Source	Function
7-dehydrocholesterol	Previtamin-D ₃	Cholesterol precursor	Biologically inactive
Vitamin D ₂	Ergocholecalciferol	Plants and fungi	Biologically inactive
Vitamin D ₃	Cholecalciferol; activated 7-dehydrocholesterol	Skin (following sun exposure); fish and meat	Biologically inactive
25-hydroxyvitamin D ₃	25-D3, calcidiol, calcifediol	Produced by hydroxylation of vitamin D ₃ in the liver	Inactivates vitamin D receptor; often mistakenly used as an indicator of vitamin D “deficiency”
1,25-dihydroxyvitamin D ₃	1,25-D3, 1,25-dihydroxycholecalciferol, calcitriol	25-hydroxyvitamin D is further hydroxylated in the kidneys by 1-alpha-hydroxylase	Primary biologically active form of vitamin D; activates the vitamin D receptor

Table 2

Systemic effects of vitamin D

Calcium and phosphorus homeostasis	Neuromuscular effects	Immunomodulatory effects	Cardiovascular effects	Cell growth and regulation
<ul style="list-style-type: none"> • Bone health 	<ul style="list-style-type: none"> • Muscle mass and strength • Better balance 	<ul style="list-style-type: none"> • Regulates immune system • Protects against MS, Type 1 diabetes, psoriasis, etc. 	<ul style="list-style-type: none"> • Renin-angiotensin regulation • Decreases risk for hypertension, Type 2 diabetes, heart failure 	<ul style="list-style-type: none"> • Antiproliferation • Prodifferentiation • Apoptotic • Antiangiogenic