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## Vitamin D in cutaneous carcinogenesis: Part I

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### Abstract

Skin cancer is the most common cancer in the United States. Exposure to ultraviolet radiation is a known risk factor for skin cancer but is also the principal means by which the body obtains vitamin D. Several studies have suggested that vitamin D plays a protective role in a variety of internal malignancies. With regard to skin cancer, epidemiologic and laboratory studies suggest that vitamin D and its metabolites may have a similar protective effect. These noncalcemic actions of vitamin D have called into question whether the current recommended intake of vitamin D is too low for optimal health and cancer prevention. Part I will review the role of vitamin D in the epidermis; part II will review the role of vitamin D in keratinocyte-derived tumors to help frame the discussion on the possible role of vitamin D in the prevention of skin cancer.

### Keywords

25(OH)D levels; cholecalciferol; supplements; vitamin D; ultraviolet radiation

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Vitamin D is a fat-soluble prohormone whose major biologic function is to maintain serum calcium and phosphorous homeostasis. It promotes calcium absorption in the gut and reabsorption from the kidneys and inhibits the secretion of parathyroid hormone. Vitamin D therefore enables the normal mineralization of bone by regulating bone growth and remodeling the activity of osteoblasts and osteoclasts.<sup>1</sup> Vitamin D deficiency has significant musculoskeletal consequences, causing rickets in children and osteomalacia and osteoporosis in adults<sup>2</sup>. In addition to its functions in the endocrine and skeletal systems, vitamin D has roles in modulating the immune, cardiovascular, and inflammatory systems; among other actions, it regulates macrophage phagocytosis<sup>3,4</sup> and inhibits macrophage activation.<sup>5,6</sup> Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated, in part, by vitamin D.<sup>7</sup>

Many (but not all) epidemiologic studies have found an association between low levels of vitamin D and all-cause mortality,<sup>8–11</sup> cancer mortality,<sup>12,13</sup> and cancer survival.<sup>14–18</sup> Others have linked lower rates of prostate and ovarian cancer<sup>19–25</sup> to residency at lower latitudes. Some studies have shown that cancer patients who undergo treatment in summer have better survival rates than those who undergo treatment in winter, suggesting that

variation in cancer survival may be associated with seasonal factors, including vitamin D levels.<sup>26–30</sup>

While the role of vitamin D in visceral cancers is under intensive research, the role of vitamin D in skin cancer is even more controversial. This is because the same spectrum of ultraviolet (UV) light necessary for vitamin D synthesis (290–320 nm) is also the most important environmental risk factor for the development of many skin cancer types. Nevertheless, laboratory studies suggest that vitamin D and its metabolites may reduce the risk of skin cancer by inhibiting the hedgehog signaling pathway,<sup>31,32</sup> the pathway underlying the development of basal cell carcinomas and upregulating DNA nucleotide excision repair enzymes.<sup>33–35</sup> Mice lacking the vitamin D receptor develop increased numbers of nonmelanoma skin cancers,<sup>36</sup> and the addition of vitamin D decreases the growth of nonmelanoma skin cancer and melanoma cells in vitro and in mouse models.<sup>31,37–39</sup> In humans, epidemiologic studies have reported mixed findings, with some reporting an association between higher vitamin D levels and increased skin cancer risk,<sup>40,41</sup> others showing a decreased skin cancer risk,<sup>42,43</sup> and still others showing no association.<sup>44–47</sup> Part II of this continuing medical education article will review the role of vitamin D in the skin and cutaneous tumors, review the existing literature, and frame the possible role of vitamin D in skin cancer prevention.

## BACKGROUND

### Key points

- Vitamin D<sub>3</sub> (cholecalciferol) is synthesized by keratinocytes in an ultraviolet light-dependent reaction occurring optimally at ultraviolet wavelengths of 290 to 320 nm
- Vitamin D<sub>2</sub> (ergocalciferol) is obtained only by diet
- Individuals with darker skin synthesize less vitamin D<sub>3</sub> from sunlight
- Vitamin D<sub>3</sub> precursors in the skin decrease with age; older individuals have a decreased ability to synthesize cutaneous vitamin D

### Vitamin D synthesis

Vitamin D comes in several forms (Table I); the 2 most important are D<sub>2</sub> (ergocalciferol, plant-derived) and D<sub>3</sub> (cholecalciferol), which is found in select animal products like oily fish (eg, salmon and cod). D<sub>3</sub> is also synthesized by keratinocytes, which convert 7-dehydrocholesterol to previtamin D<sub>3</sub> in a reaction catalyzed by UV radiation at wavelengths of 290 to 320 nm,<sup>48</sup> with peak synthesis occurring between 295 and 300 nm.<sup>49</sup> Whether obtained from sun exposure, food, or supplements, previtamins D<sub>2</sub> and D<sub>3</sub> are biologically inert and must undergo 2 hydroxylations in the body for activation (Fig 1). The first occurs in the liver and converts the previtamin to 25-hydroxyvitamin D (25[OH]D), or calcidiol. Because calcidiol has a half-life of several weeks<sup>50</sup> and reflects the body's circulating stores, it is the conventionally measured form of serum vitamin D, and levels typically range between 15 and 80 ng/mL (37.5–200 nmol/L). Most laboratories measure total 25(OH)D without differentiating between D<sub>2</sub> and D<sub>3</sub> forms. Levels of 25(OH)D are used to evaluate vitamin D status and screen for deficiency.

The second hydroxylation of vitamin D occurs in the kidney and results in the formation of the physiologically active 1,25-dihydroxyvitamin D<sub>3</sub> (1,25 [OH]<sub>2</sub>D), or calcitriol. Serum calcitriol has a half-life of 6 to 8 hours,<sup>50</sup> and its production by the kidney is tightly regulated by serum parathyroid, calcium, and phosphate levels. Normal serum levels of calcitriol range between 15 and 45 pg/mL—roughly 1000 times less than levels of 25(OH)D.<sup>51</sup> 1,25(OH)<sub>2</sub>D stimulates intestinal calcium and phosphorous absorption, and

only 10% of dietary calcium and 60% of phosphorous are absorbed in the absence of vitamin D. Serum 1,25(OH)<sub>2</sub>D does not reflect vitamin D reserves, and its measurement is not useful for monitoring the vitamin D status of patients. In fact, serum 1,25(OH)<sub>2</sub>D may be normal or even elevated in those with vitamin D deficiency because of secondary hyperparathyroidism. The measurement of serum 1,25(OH)<sub>2</sub>D is useful in chronic kidney disease, rickets, and chronic granulomatous diseases, such as sarcoidosis and some lymphomas.<sup>52</sup>

In addition to its production in the kidney, 1,25(OH)<sub>2</sub>D is produced within keratinocytes, which also have vitamin D receptors (VDRs).<sup>53</sup> The regulation of 1,25(OH)<sub>2</sub>D production by keratinocytes and other nonrenal cells differs from that of the kidney. However, the amount of keratinocyte-produced 1,25(OH)<sub>2</sub>D is small and does not contribute to circulating levels under normal circumstances, suggesting the existence of a local autocrine or paracrine regulatory pathway.<sup>53</sup> Recent studies show that keratinocyte-synthesized 1,25(OH)<sub>2</sub>D modulates epidermal cellular proliferation, differentiation, and apoptosis.<sup>35,54,55</sup>

### Vitamin D receptor

After synthesis in the kidney, 1,25(OH)<sub>2</sub>D is released into the circulatory system, where it binds to the carrier protein vitamin D binding protein (VDBP). Once it reaches its target cells, 1,25(OH)<sub>2</sub>D dissociates from the VDBP, presumably enters the cell by diffusion, and binds to the cell's intracellular nuclear VDR to regulate gene transcription. The VDR is present in most tissues and cells in the body, and has a wide range of biologic actions, including decreasing cellular proliferation, inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, and stimulating macrophage cathelicidin production.<sup>52</sup>

The VDR, a member of the steroid nuclear receptor superfamily, is expressed in a wide variety of cells and tumors.<sup>56-58</sup> Binding of 1,25(OH)<sub>2</sub>D to the VDR produces conformational changes, exposing surfaces for coactivating factor binding and dimerization. The VDR dimerizes with a retinoid receptor, generally the retinoid X receptor, a requisite step for full transactivation of the VDR. Dimerization enables interaction with the target gene promoter at the vitamin D response element (VDRE), where the coactivating proteins carried on the VDR initiate gene transcription of more than 200 genes.<sup>59-61</sup> These VDREs can be located throughout the gene, even at considerable distances from the transcription start site.

### Sources of vitamin D

**Diet**—A limited number of foods naturally contain vitamin D (Table II). Some mushrooms contain variable amounts of D<sub>2</sub>; other dietary sources contain the D<sub>3</sub> form, including fatty fish like herring, cod, salmon, and fish liver oil. Small amounts of D<sub>3</sub> are also found in beef liver and egg yolk. Given the paucity of natural dietary sources of vitamin D, select foods in the United States are fortified with vitamin D, usually in D<sub>3</sub> form, providing most of the vitamin D in the American diet.<sup>62</sup> Nearly all milk produced in the United States is fortified as a result of a program instituted in the 1930s to prevent rickets. Select other dairy products, breakfast cereals, some brands of orange juice, margarine, and infant formulas are also fortified (Table II).

**Supplements**—Intake reference values for nutrients are provided by the Food and Nutrition Board at the Institute of Medicine (IOM) of the National Academies.<sup>63,64</sup> The recommended dietary allowance (RDA) is the average daily level of intake sufficient to meet the nutrient requirements of nearly all (97.5%) healthy people. The RDA for vitamin D represents a daily intake sufficient to maintain bone health and normal calcium metabolism

in healthy people, assuming that little vitamin D is synthesized from sun exposure (Table III). In November 2010, the IOM reviewed nearly 1000 scientific studies of vitamin D in relation to not only bone health but also many other health outcomes. It concluded that there is clear evidence that vitamin D has bone benefits but that the current research is inconclusive as to whether higher vitamin D intake can reduce the risk for cancer, heart disease, stroke, or other chronic diseases. The IOM recommended 600 international units (IU) per day for people between 1 and 70 years of age and 800 IU per day for those 71 years of age (an increase from the 400–600 IU/day previously recommended for adults at midlife and older). This 600 IU recommendation is the same for women who are pregnant or lactating. The IOM RDA is based on the benefits of vitamin D to bone because the panel did not find conclusive evidence for nonskeletal actions; however, the report did not specifically exclude the possibility that vitamin D could have a role in cancer prevention.<sup>64</sup> This 600 IU RDA is controversial, because several vitamin D investigators have argued that these recommendations are only applicable to healthy individuals and may be too low for patients with disease or for physicians attempting to prevent disease in at-risk populations. The Vitamin D and Omega-3 Trial (VITAL; [clinicaltrials.gov](http://clinicaltrials.gov) identifier NCT01169259) is currently underway and will test in a randomized, controlled trial in 20,000 subjects to determine whether 2000 IU of vitamin D<sub>3</sub> will reduce the risk for developing cancer, heart disease, and stroke.

Controversy also exists over which form of vitamin D (D<sub>3</sub> or D<sub>2</sub>) is best for supplementation. Some studies suggest that D<sub>3</sub> is more potent than D<sub>2</sub>,<sup>65,66</sup> whereas others suggest that they are bioequivalent.<sup>67,68</sup> Trang et al<sup>66</sup> found that subjects who took approximately 4000 IU of D<sub>3</sub> daily for 14 days had a 1.7-fold increase in serum 25(OH)D levels compared to those who took D<sub>2</sub>.<sup>66</sup> Similarly, Armas et al<sup>65</sup> gave 20 healthy male volunteers one 50,000 IU dose of either D<sub>2</sub> or D<sub>3</sub> and followed serum 25(OH)D levels over 28 days. Although both D<sub>2</sub> and D<sub>3</sub> produced similar initial rises in serum 25(OH)D, levels fell rapidly in the D<sub>2</sub>-treated group and were not different from baseline at 14 days, while levels peaked at 14 days and remained high in the D<sub>3</sub> group. The authors speculate that D<sub>3</sub> has a greater affinity for serum VDBP and therefore greater bioavailability. These differences in binding to VDBP are well known in other animals. The VDBP in fish and fowl, for example, have very low affinity for D<sub>2</sub>.<sup>69</sup> In contrast, other studies suggest that D<sub>2</sub> is as effective as D<sub>3</sub> in maintaining circulating concentrations of 25(OH)D.<sup>67,68</sup> Holick et al<sup>67</sup> compared supplements containing 1000 IU of vitamin D<sub>3</sub>, 1000 IU of vitamin D<sub>2</sub>, or 500 IU vitamin D<sub>2</sub> and 500 IU vitamin D<sub>3</sub> given to healthy adults 18 to 84 years of age daily for 11 weeks in a randomized, placebo-controlled, double-blind study and found that circulating levels of 25(OH)D increased to the same extent in all supplement groups. The disparities in these study results may be attributed to differences in sun exposure or other dietary intake of vitamin D in participants, or differences in the supplement's stability, because D<sub>2</sub> and D<sub>3</sub> degrade differently with environmental exposures.<sup>70</sup> The Endocrine Society, along with the Canadian Society of Endocrinology and Metabolism and the National Osteoporosis Foundation, published a clinical practice guideline in 2011 titled "Evaluation, Treatment and Prevention of Vitamin D Deficiency." The Endocrine Society Clinical Guidelines suggests either vitamin D<sub>2</sub> or vitamin D<sub>3</sub> for the treatment and prevention of vitamin D deficiency.<sup>71</sup> The committee also recommended screening of only those individuals who are at high risk for vitamin D deficiency, including patients with osteoporosis, older patients with a history of falls, patients with malabsorption syndrome, chronic renal or hepatic disease, granulomatous diseases (sarcoid), and individuals with darker skin pigmentation (black and Hispanic individuals), obese persons (those with a body mass index [BMI] of >30 kg/m<sup>2</sup>), and those taking medications known to increase 25(OH)D metabolism, such as anticonvulsants, systemic glucocorticoids, ketoconazole, and HIV medications.

**Sun**—Ultraviolet B (UVB) light radiation is responsible for cutaneous vitamin D synthesis.<sup>52</sup> Interestingly, the portion of the UVB spectrum necessary for vitamin D synthesis coincides with wavelengths implicated in photocarcinogenesis.<sup>72</sup> The UVB radiation (290–320 nm) threshold dosage level of 18 to 20 mJ/cm<sup>2</sup> required for the conversion of 7-dehydrocholesterol to previtamin D<sub>3</sub> in vitro closely mirrors an 18 mJ/cm<sup>2</sup> in vivo threshold required for a significant increase in serum 25(OH)D levels in white males with Fitzpatrick type III.<sup>73</sup>

With full body exposure to sunlight enough to generate 1 minimal erythemal dose, the maximum production level is 10,000 to 25,000 IU per day.<sup>74</sup> Studies suggest that clinically significant increases in serum 25(OH)D levels can be seen with UVB doses small enough to produce tanning noticeable only to a colorimeter. Armas et al<sup>75</sup> found that subjects' serum levels of 25(OH)D increased an average of 12 ng/mL after 4 weeks of regular, measured exposure to UVB light. Another study<sup>76</sup> estimated that exposure of 25% of body surface to sunlight at noon for 3 to 8 minutes generates about 400 IU of vitamin D in the summer in Boston, Massachusetts and year-round in Miami, Florida. Holick's recent suggestions<sup>77</sup> of biweekly exposures lasting 5 to 30 minutes during midday hours have been the source of much discussion and additional study. Webb et al<sup>78</sup> and others examined several factors, including the effects of solar altitudes, air ozone composition, and time of day on cutaneous vitamin D synthesis and found that midday sun, accompanied by high solar altitude, offers the best ratio of vitamin D synthesis–erythema risk. Midday sun exposure corresponding with low solar zenith angles—observed during summer seasons and year-round at equatorial latitudes, and which results in solar rays traveling the shortest distance to the earth—results in optimal vitamin D synthesis.<sup>79,80</sup> Greater solar zenith angles occur during the winter season and at more northern latitudes. During these times, more exposure time is needed to achieve adequate vitamin D synthesis. However, one estimate found that very little vitamin D synthesis was possible in the winter in Boston.<sup>76</sup> Serum 25(OH)D can be tested in the summer or winter, but should only be done in individuals at risk for vitamin D deficiency as outlined by the Endocrine Society or in individuals who practice extreme photoprotection. There is no evidence showing benefits of screening for vitamin D deficiency in the general population.<sup>71</sup>

It is uncertain if a “safe” dose of UVB exists (ie, one that maximizes vitamin D synthesis while minimizing DNA damage and photocarcinogenesis). Cutaneous vitamin D<sub>3</sub> synthesis after UVB exposure follows an early exponential function.<sup>73</sup> With longer exposure to UVB rays, equilibrium is achieved in the skin, and the vitamin begins to degrade as fast as it is generated. Production appears to level off after approximately 10% to 20% of epithelial 7-dehydroxycholesterol stores are used. This maximum level of synthesis is reached after only a sub-minimal erythema dose amount of sunlight.<sup>49,81–83</sup> These data suggest that sunlight exposure follows an inverted J-curve in which an initial amount of beneficial sunlight gives way to harmful effects after a prolonged period. In its recent report, the IOM acknowledged the need for more research on whether the amount of sun exposure needed for cutaneous vitamin D synthesis is associated with an increased risk for skin cancer.

Aside from sunlight exposure timing and duration, other factors affect the amount of vitamin D that can be synthesized by exposure to sunlight alone.

**Skin pigmentation**—African Americans and those with darker skin types have greater difficulty synthesizing vitamin D from sunlight, because increased melanin in the epidermis absorbs much of the UVB radiation needed for vitamin D production.<sup>84,85</sup> In contrast, whites and those with lighter skin types can obtain substantial vitamin D synthesis in as little as 5 minutes of exposure to the hands.<sup>85</sup> Serum 25(OH)D levels can differ by skin pigmentation. Most<sup>84,86,87</sup> (but not all<sup>88</sup>) studies suggest that Fitzpatrick skin types I and II

have higher levels than darker skin types. Multiple observational studies have shown that African Americans and Hispanics in the United States are at higher risk for vitamin D deficiency than their white counterparts.<sup>86,89–92</sup> Research into additional potential genetic factors is ongoing.<sup>92</sup> Overall, data suggest that individuals with darker skin types are at increased risk of vitamin D deficiency.

**Latitude**—Both latitude and season affect the quantity and quality of UVB radiation reaching the earth's surface. UVB wavelengths of 295 to 300 nm are present in sunlight when the UV index is >3. At this solar intensity, which occurs daily within the tropics and during the spring and summer seasons in temperate regions, adequate amounts of D<sub>3</sub> can be made in the skin after only 10 to 15 minutes of twice-weekly sun exposure to the face, arms, hands, or back without sunscreen in most people.<sup>76,93,94</sup> At higher latitudes, greater solar zenith angles result in less UVB reaching the earth and lead to less favorable conditions for vitamin D synthesis.<sup>76</sup> During winter months, these conditions, coupled with cloud cover and seasonal weather changes, lead to decreased vitamin D synthesis—the so-called “vitamin D winter.”<sup>48,68,76</sup> For example, in one study, human skin exposed to sunlight on cloudless days in Boston, Massachusetts (42.2° N) from November through February and Edmonton, Alberta, Canada (52° N) from October through March produced no previtamin D<sub>3</sub>.<sup>48</sup> There is very little cutaneous vitamin D<sub>3</sub> synthesis above or below latitudes of approximately 33° N during the winter.

**Obesity**—Studies show that vitamin D levels and BMI are negatively correlated in both children and adults.<sup>86,95,96</sup> There is growing evidence that in obese individuals (BMI >30 kg/m<sup>2</sup>), vitamin D is efficiently stored in body fat reserves and consequently loses its bioavailability.<sup>97–99</sup> In addition, bariatric patients or patients with malabsorption syndromes are often unable to absorb vitamin D.<sup>52</sup>

**Age**—Average skin thickness (both dermal and epidermal) decreases with age.<sup>100,101</sup> As a result, cutaneous vitamin D synthesis decreases because of smaller stores of the precursor 7-dehydroxycholesterol.<sup>100</sup> The elderly may be at additional risk of deficiency because of decreased mobility and consequently decreased sun exposure.<sup>102</sup>

Because the cutaneous production of vitamin D is affected by age, skin pigmentation, and latitude of residence along with other factors, such as sunscreen use and sun-avoidant behavior, sunlight exposure may produce variable serum 25(OH)D results. Even living in sunny climates does not guarantee optimum levels of 25(OH)D; one study found that more than half of adults living in Hawaii with an average sun exposure of 30 hours per week still had insufficient serum 25(OH)D levels.<sup>103</sup> Other studies conducted in Arizona, Florida, and Chilean populations have all observed that vitamin D deficiency is still noticeable, with darker skinned individuals and those with lower amounts of sun exposure at particular risk.<sup>89,103–105</sup>

## PHOTOPROTECTION AND VITAMIN D LEVELS

### Key points

- Skin cancer patients and patients who practice extreme photoprotection (systemic lupus, xeroderma pigmentosum, and basal cell nevus syndrome) are at higher risk of vitamin D deficiency
- In controlled conditions, sunscreen with a sun protection factor of 15 to 30 can decrease vitamin D synthesis
- However, in typical use conditions, sunscreen use has not been shown to appreciably lower vitamin D levels

- Frequent shade use and long sleeve use is more likely to cause lower vitamin D levels than sunscreen use

Perhaps the most controversial topic in the debate on vitamin D centers on photoprotection and its effects on the cutaneous synthesis of vitamin D. Patients with systemic lupus erythematosus or individuals in nursing homes (who tend to have little sun exposure) have been shown to be at increased risk for vitamin D deficiency.<sup>106,107</sup> Several studies have shown that the regular use of sunscreen correlates with lower circulating levels of 25(OH)D. The use of sunscreens with a sun protection factor (SPF) of 8 inhibits >95% of vitamin D production in the skin.<sup>108</sup> After a successful sun safety health campaign encouraging Australians to avoid sun exposure to prevent skin cancer, an increased number of Australians became vitamin D-deficient.<sup>109</sup> Similarly, patients with basal cell nevus syndrome, who exhibit higher levels of sun-protective behavior, such as using sunscreen and avoiding the midday sun, have a higher prevalence of vitamin D deficiency than the general population.<sup>110</sup> One study even questions the notion that fair-skinned individuals are more likely to have adequate vitamin D levels because they can synthesize the molecule more efficiently than those with darker skin; in this study, fair-skinned subjects were more likely to be deficient, which was attributed to increased sunscreen use and sun-avoiding behavior.<sup>88,111</sup> Individuals who practice vigilant sun avoidance and sun protection may contribute to vitamin D deficiency.

In one of the earliest studies on the subject, Matsuoka et al<sup>108</sup> found that vitamin D levels are reduced by 95% with uniform, whole-body application of an SPF 30 sunscreen. Contrasting studies have observed a lack of differences in serum 25(OH)D levels between sunscreen and nonsunscreen users.<sup>93,112</sup> Other studies acknowledge a decrease of vitamin D levels yet argue that such decreases are not great enough to place sunscreen users at significant risk of vitamin D deficiency.<sup>113,114</sup> As discussed by Ness<sup>115</sup> and Marks et al,<sup>116</sup> these results show that sunscreen use does have appreciable effects on serum levels of vitamin D in either the 25(OH)D or 1,25(OH)<sub>2</sub>D<sub>3</sub> forms. Sunscreen is generally more effective at blocking the action spectrum of UVB radiation necessary for previtamin D synthesis than it is at blocking the action spectrum for erythema.<sup>79</sup>

Farrerons et al<sup>113</sup> suggests that typical sunscreen use is not nearly as efficient as in Matsuoka et al's laboratory controlled experiments, with proper application technique and whole-body application being unlikely. Such a lack of adherence to proper sunscreen application technique negatively affects the SPF<sup>117-119</sup> Finally, the use of inorganic ingredients (ie, zinc oxide and titanium oxide) in sunscreens that provide a broadband physical barrier to the action spectrum of UV light may mean these formulations reduce total transmitted UV radiation,<sup>120</sup> which in turn may affect cutaneous vitamin D synthesis.

In an attempt to determine the role of sun protection on vitamin D levels at the population level, one study used data from a cross sectional, nationally representative survey of 5920 adults to investigate the relationship between different types of sun protective behaviors and serum 25(OH)D levels in the general US population.<sup>121</sup> Overall sun protection was associated with lower 25(OH)D levels in whites, but not in Hispanics or blacks. Staying in the shade and wearing long sleeves were significantly associated with lower 25(OH)D levels and vitamin D deficiency, especially in whites, but wearing a hat and using sunscreen use were not (Fig 2). However, the use of a high SPF sunscreen was associated with a 2-fold increased risk of vitamin D deficiency, although this approached but did not reach statistical significance. The relationships between sun protective behaviors and lower 25(OH)D levels were much weaker among Hispanics and blacks, possibly because of the inherent natural sun protective effect of melanin in darkly pigmented skin. Because the natural pigment in darker skin is a potent UV blocker, any additional sun-protection above and beyond this may have a minimal relative impact. In conclusion, individuals who protect themselves from the

sun by seeking shade or wearing long sleeves may have lower 25(OH)D levels and be at risk for vitamin D deficiency.

Despite the fact that sunscreen use may block some cutaneous vitamin D synthesis, it is prudent to continue to recommend sun-cautious behavior given the known hazards of UV exposure. It is likely that in most healthy individuals, a diet that includes vitamin D-rich foods and moderate amounts of supplements combined with a modest amount of everyday sun exposure is enough to maintain adequate serum vitamin D levels, even if the individual photoprotects with sunscreen. What remains unclear is whether the vitamin D produced in the skin has a benefit to the skin that is greater than the equivalent amount of vitamin D ingested as a supplement. Sunlight exposure sufficient to burn the skin is clearly excessive and counterproductive to maintaining the proper balance between vitamin D production and skin health.

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## Abbreviations used

<b>1,25(OH)<sub>2</sub>D</b>	1,25-dihydroxyvitamin D <sub>3</sub> , the biologically active form of serum vitamin D
<b>25(OH)D</b>	25-hydroxyvitamin D
<b>BMI</b>	body mass index
<b>IOM</b>	Institute of Medicine
<b>IU</b>	International Unit
<b>NMSC</b>	nonmelanoma skin cancer
<b>RDA</b>	recommended dietary allowance
<b>SPF</b>	sun protection factor
<b>UV</b>	ultraviolet
<b>UVB</b>	ultraviolet B
<b>VDR</b>	vitamin D receptor
<b>VDBP</b>	vitamin D binding protein

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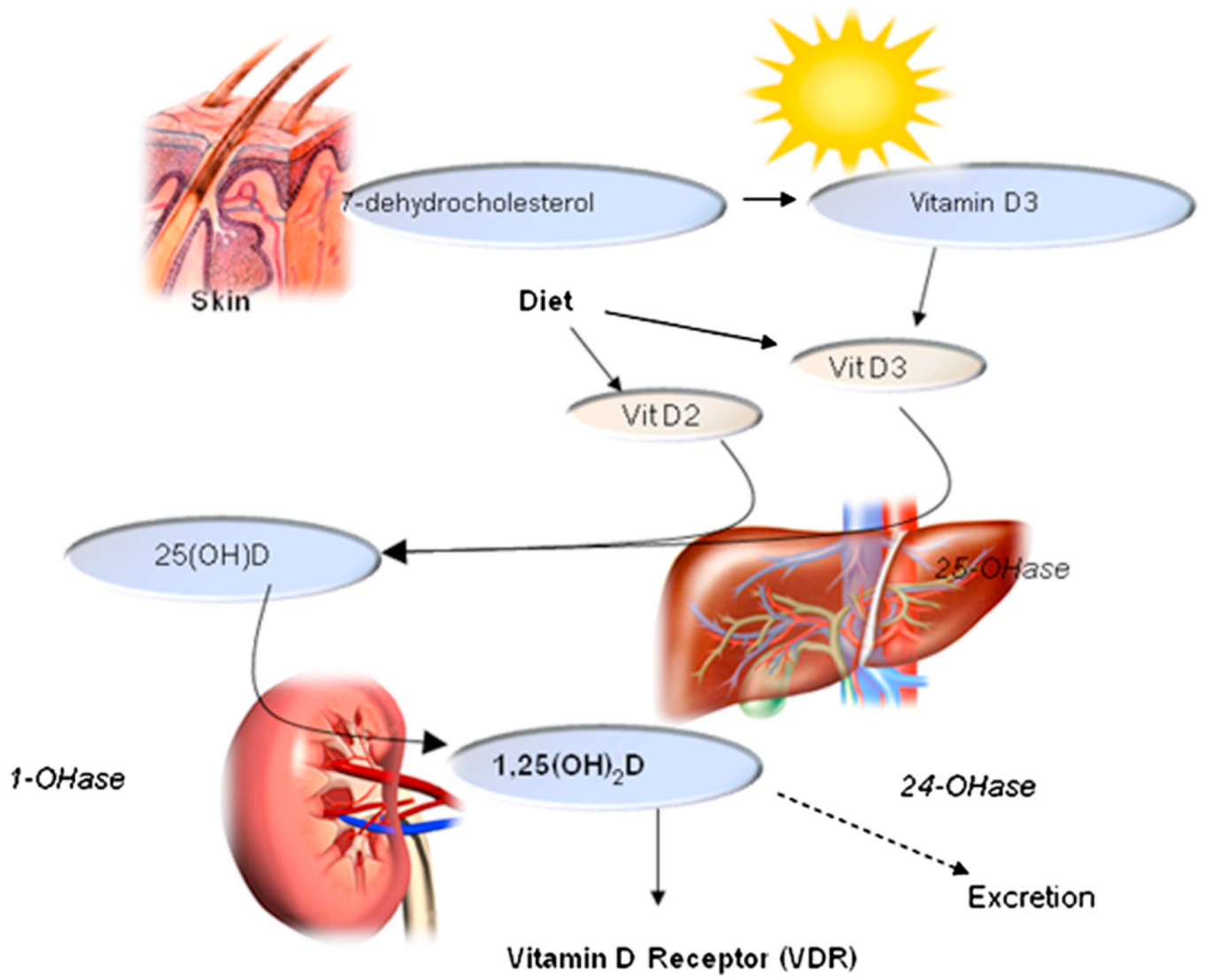
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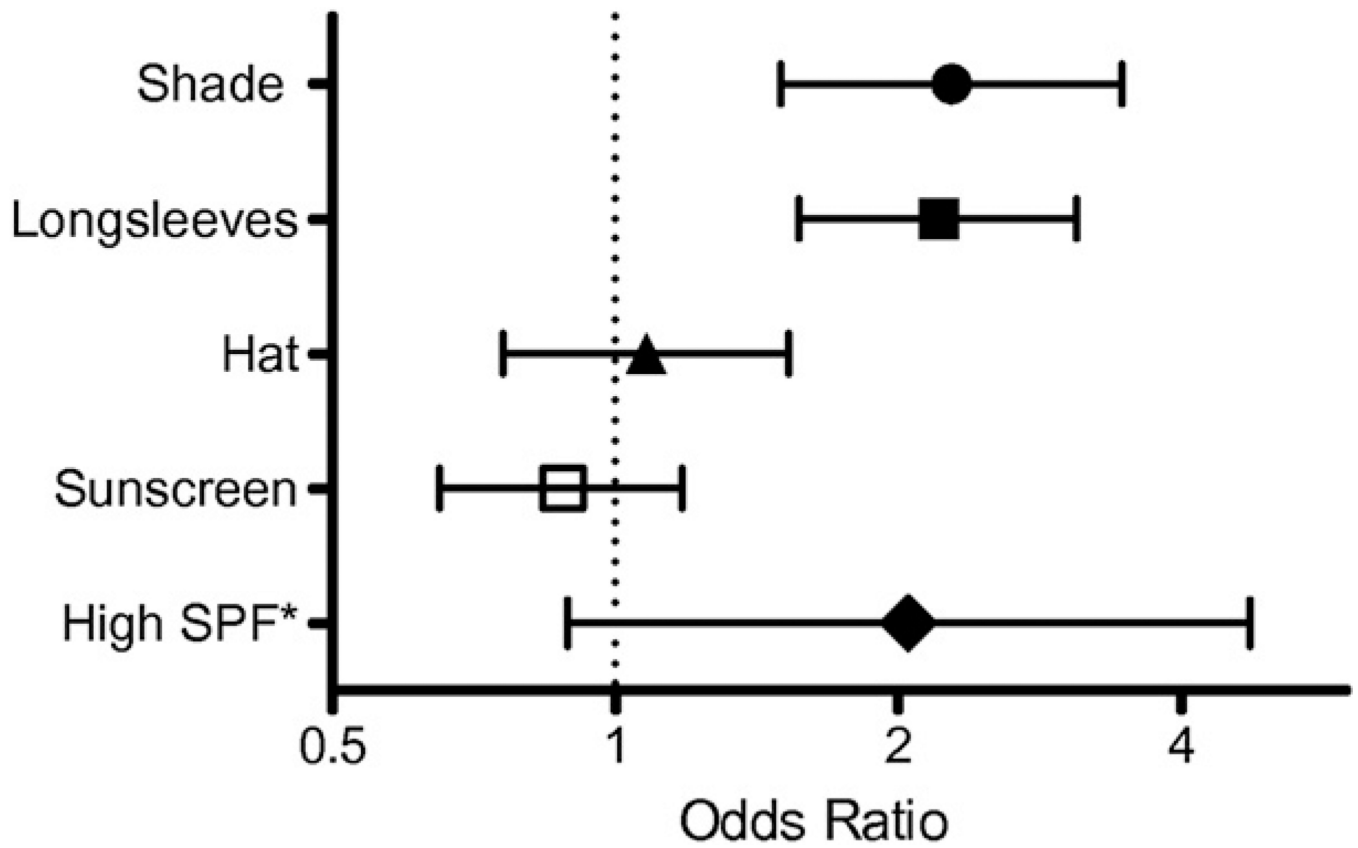
**CAPSULE SUMMARY**

- 25-hydroxyvitamin D, or 25(OH)D, is the circulating form of vitamin D used to determine vitamin D status and for screening for vitamin deficiency.
- The Institute of Medicine recommends 600 International Units of vitamin D daily for most children and adults.
- Both vitamin D<sub>2</sub> and vitamin D<sub>3</sub> are effective at correcting vitamin D deficiency.
- Cutaneous production of vitamin D<sub>3</sub> is affected by age, skin pigmentation, latitude, and sun avoidance behaviors



**Fig 1.**  
Vitamin D pathway.





**Fig 2.** Odds ratios of vitamin D deficiency comparing high frequency to low frequency users according to sun protective behaviors among whites in the United States. Data taken from National Health and Nutrition Examination Survey subjects who self-reported high versus low usage of shade, long sleeves, a hat, or sunscreen on a very sunny day (2003–2006). \*Multivariate adjusted odds ratio of vitamin D deficiency comparing high usage of sun protection factor >40 sunscreen to sun protection factor <20 sunscreen. The symbols indicate the odds ratios, and the whiskers indicate the 95% confidence intervals.

**Table I**

## Common forms of vitamin D

Name	Clinical name	Abbreviation	Source
Ergocalciferol	Vitamin D <sub>2</sub>	D <sub>2</sub>	Derived from irradiated ergosterol in fungal plants (mushrooms)
Cholecalciferol	Vitamin D <sub>3</sub>	D <sub>3</sub>	Select animal products, such as oil-rich fish (salmon, mackerel, and herring); derived from irradiated 7-dehydrocholesterol from lanolin
Calcidiol	25-hydroxyvitamin D	25(OH)D	Circulating form of vitamin D, used to evaluate vitamin D status
Calcitriol	1,25-hydroxyvitamin D	1,25(OH) <sub>2</sub> D	Hormonally active form of D, binds to the vitamin D receptor
Calcipotriene, topical	Calcipotriene	Dovonex	1,25(OH) <sub>2</sub> D derivative, topical treatment for psoriasis
Calcitriol, topical	Calcitriol	Vectical	Used as treatment for psoriasis

Table II

## Dietary sources of vitamin D\*

Source	Serving size	Vitamin D form	Amount (IU)
Natural			
Herring, cooked	3.0 OZ	D <sub>3</sub>	1,383
Cod liver oil	1 tbsp (15 mL)	D <sub>3</sub>	1,360
Salmon, wild	3.5 oz	D <sub>3</sub>	1,000
Salmon, farmed	3.5 oz	D <sub>3</sub>	300
Catfish, cooked	3.0 oz	D <sub>3</sub>	425
Sardines, canned	1.7 oz	D <sub>3</sub>	250
Mackerel, canned	3.5 oz	D <sub>3</sub>	345
Tuna, canned	3.0 oz	D <sub>3</sub>	200
Shiitake mushrooms			
Fresh	3.5 oz	D <sub>2</sub>	100
Sun-dried	3.5 oz	D <sub>2</sub>	1,600
Eel, cooked	3.5 oz	D <sub>3</sub>	200
Egg yolk	1.0 oz	D <sub>3</sub>	20
Liver (beef)	3.5 oz	D <sub>3</sub>	15
Supplemented			
Milk	8.0 oz	D <sub>3</sub>	100
Orange juice	8.0 oz	D <sub>3</sub>	100–150
Yogurt	8.0 oz	D <sub>3</sub>	100
Butter	3.5 oz	D <sub>3</sub>	50
Margarine	1 tbsp	D <sub>3</sub>	60
Cheese	3 oz	D <sub>3</sub>	100
Breakfast cereal	1 serving (0.75–1 cup)	D <sub>3</sub>	40

IU, International Unit.

\* Data taken from the National Institutes of Health web site ([http://www.grc.com/health/pdf/NIH\\_GOV\\_Dietary\\_Supplement\\_Fact\\_Sheet.pdf](http://www.grc.com/health/pdf/NIH_GOV_Dietary_Supplement_Fact_Sheet.pdf)) and the US Department of Agriculture's nutrient database web site (<http://www.nal.usda.gov/fnic/foodcomp/search>).

**Table III**

Current recommended daily intake of International Units of vitamin D that covers the needs of >97.5% of the US population \*

Age	Children	Adults
0–12 mo	400	—
1–13 yrs	600	—
14–50 yrs	—	600
51–70 yrs	—	600
71 yrs	—	800

\* Data taken from Ross et al.<sup>64</sup>