Title
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Journal
Journal of the American Academy of Dermatology, 67(5)

ISSN
0190-9622

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Publication Date
2012-11-01

DOI
10.1016/j.jaad.2012.07.022

Peer reviewed

Published in final edited form as:
J Am Acad Dermatol. 2012 November ; 67(5): 817.e1–828. doi:10.1016/j.jaad.2012.07.022.

Vitamin D in cutaneous carcinogenesis Part II

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Abstract

The role of vitamin D in health maintenance and disease prevention in fields ranging from bone metabolism to cancer is currently under intensive investigation. A number of epidemiologic studies have suggested that vitamin D may have a protective effect on cancer risk and cancer-associated mortality. With regard to skin cancer, epidemiologic and laboratory studies suggest that vitamin D and its metabolites may have a similar risk reducing effect. Potential mechanisms of action include inhibition of the hedgehog signaling pathway and upregulation of nucleotide excision repair enzymes. The key factor complicating the association between vitamin D and skin cancer is ultraviolet B radiation. The same spectrum of ultraviolet B radiation that catalyzes the production of vitamin D in the skin also causes DNA damage that can lead to epidermal malignancies. Part II of this continuing medical education article will summarize the literature on vitamin D and skin cancer to identify evidence-based optimal serum levels of vitamin D and to recommend ways of achieving those levels while minimizing the risk of skin cancer.

Keywords

25(OH)D levels; basal cell carcinoma; melanoma; nonmelanoma skin cancer; vitamin D; vitamin D receptor; squamous cell carcinoma; sunlight

Overall, there is some evidence that vitamin D may play a role in nonmelanoma skin cancer (NMSC) and melanoma prevention, although as of yet there is no direct evidence to show a protective effect. The relative contributions of diet, supplementation, and cutaneous vitamin D synthesis to serum vitamin D levels need additional study. While some in vitro and animal data suggest that vitamin D may have protective effects against skin cancer, additional studies in humans are needed. Several laboratory studies suggest that vitamin D and its metabolites may reduce the risk of skin cancer by inhibiting the hedgehog signaling pathway, the pathway underlying development of basal cell carcinomas (BCCs), and upregulating DNA nucleotide excision repair enzymes. Mice lacking the vitamin D receptor (VDR) develop increased numbers of NMSCs, and the addition of vitamin D decreases the growth of NMSC and melanoma cells in vitro and in mouse models. In humans, epidemiologic studies have reported mixed findings, with some reporting an association

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between higher vitamin D levels and increased skin cancer risk, others showing a decreased skin cancer risk, and still others showing no association.

However, because ultraviolet (UV) rays are known to be carcinogenic, and because it is very difficult to discern when small amounts of sun exposure cross the line from potential benefit to harm, the American Academy of Dermatology recommends that an adequate amount of vitamin D should be obtained from a healthy diet that includes foods and beverages that are naturally rich in or fortified with vitamin D and/or vitamin D supplements; it should not be obtained from unprotected exposure to UV radiation. Therefore, given the current evidence, our recommendations are to follow the recent Institute of Medicine (IOM) guidelines: assuming minimal or no sun exposure, most healthy individuals will need 600 IU of vitamin D daily to maintain serum 25(OH)D levels above 20 ng/mL, and higher doses up to 4000 IU daily are safe but not necessarily beneficial.

For clinicians, it may be prudent to test serum 25(OH)D levels once in patients of clinical concern or in those at risk for vitamin D deficiency (ie, individuals with dark skin or who have little outdoor sun exposure, such as the elderly or those that practice rigorous sun protection); appropriate doses of vitamin D supplementation can then be calculated to achieve and maintain serum 25(OH)D levels above 20 ng/mL. According to the Endocrine Society Practice Guidelines, individuals without risk factors for vitamin D deficiency should not be screened. There is no evidence for the benefit of screening for vitamin D deficiency in the general population.

ROLE OF VITAMIN D IN KERATINOCYTES

Key points

- Laboratory and preclinical data suggest a role of vitamin D in the reduction and prevention of keratinocytic carcinomas
- Vitamin D receptor is present in basal cell and squamous cell carcinoma cells

In the skin, ultraviolet B (UVB) radiation catalyzes the conversion of 7-dehydroxycholesterol to previtamin D_3, thereby starting the synthesis of $1,25(OH)_2D$, the active compound that influences the growth and development of keratinocytes.[1] At high levels, $1,25(OH)_2D$ inhibits keratinocyte proliferation in vitro[2] and interacts with calcium to regulate keratinocyte differentiation.[3] Keratinocytes lacking VDR are hyperproliferative and exhibit decreased apoptosis.[4] Genetically engineered mice lacking the VDR (VDR knockout mice) have reduced alopecia, abnormal hair follicles, and dermal cysts, indicating a role of VDR in keratinocyte differentiation.[5] In humans, VDR polymorphisms are associated with increased development of solar keratoses[6] and differing melanoma risk.[7] Several cofactor proteins that modulate the interaction between VDR and the transcription machinery are differentially associated with the VDR in proliferating versus differentiating keratinocytes and also have a different profile in early and late cellular differentiation.[8] This allows keratinocytes to fine tune their response to $1,25(OH)_2D$.

UVB damages keratinocyte DNA through the formation of mutagenic cyclobutane dimers, and vitamin D may have a protective effect against UV radiation—induced dimer formation. Wong et al[9] and De Haes et al[10] showed exogenously applied $1,25(OH)_2D$ blocks the formation of cyclobutane dimers in vitro. Similarly, microarray studies of keratinocytes treated with $1,25(OH)_2D$ show the upregulated expression of 2 DNA repair genes, XPC and DDB2, suggesting that the protective effect of $1,25(OH)_2D$ is related to enhancement of the DNA repair process.[11] Similar results have been seen in mouse model studies.[12,13]

The photoprotective effect of $1,25(OH)_2D$ on keratinocytes may be dose-dependent.[14–16] In one study, pretreatment of keratinocytes with $1,25(OH)_2D$ before exposure to UVB radiation at 30 to 40 mJ/cm^2 decreased photodamage, but this effect was not seen at higher doses of UVB (50 mJ/ cm^2).[15] These findings suggest that $1,25(OH)_2D$ exerts its photoprotective effect against a moderate range of UVB irradiation, but that at higher doses, this effect is lost, possibly explaining why chronic, high-dose UVB exposure is associated with increased skin cancer risk.

Role of vitamin D in basal cell carcinoma

Vitamin D has been shown to inhibit the hedgehog signaling pathway, a key tumor pathway driving the development of BCCs.[17–19] This pathway is normally suppressed by the PATCHED1 (PTCH1) protein, and mutations in *PTCH1* gene lead the rare disease basal cell nevus syndrome.[20]

Like the keratinocytes from which they are derived, BCCs also express VDR.[21,22] In one study, peripheral cells in human BCC tumors had a greater expression of VDR than adjacent or unaffected epidermal cells. In an animal model, VDR knockout mice developed more skin tumors (primarily BCCs) when exposed to a carcinogen (oral 7,12-dimethylbenz[a] anthracene) than did their wildtype littermate.[23] The development of BCCs in these mice lacking functional VDR suggests the importance of the vitamin D pathway in regulating genes downstream of the hedgehog signaling pathway. In mice, topical application of vitamin D_3 reduces BCC cell proliferation and downregulates Gli1 mRNA both in vitro and in vivo.[24]

In humans, clinical studies of BCC patients also show a potential role for vitamin D. In a nested case control study of elderly men with NMSC (N = 178) or without skin cancer (N = 930) enrolled in the Osteoporotic Fractures in Men (MrOS) study, men with the highest baseline serum 25(OH)D levels (>30 ng/mL) had 47% lower odds of NMSC (95% confidence interval, 0.3–0.93; $P = .026$; P for trend, 0.04) compared to those with the lowest baseline 25(OH)D levels.[25] A diagnosis of NMSC is therefore not a surrogate for adequate 25(OH)D levels, and high 25(OH)D levels may be associated with a reduced risk of NMSC. In contrast, another case control study from the Kaiser population found that higher prediagnostic 25(OH)D levels were associated with a small increased risk of BCC.[26] However, an older prospective cohort study on vitamin D intake from dietary questionnaires found no association between vitamin D and BCC risk.[27] Eide et al[28] found that higher 25(OH)D levels were associated with an increased risk of NMSC in a prospective Health Maintenance Organization cohort of white patients who sought advice on the risk of osteoporosis.[28] The positive relationship of UVexposure with both vitaminDsynthesis and NMSC may explain their findings, and sunlight exposure is a highly likely confounder. These 3 observational epidemiologic studies are difficult to directly compare because study subjects differed in geographic location/latitudes, and study measurements varied between measuring $1,25(OH)_2D$ and 25(OH)D levels, accounting for total vitamin D versus using dietary intake journals, and including BCCs versus counting all NMSCs. Taken together, the current laboratory evidence suggests that vitamin D may prevent development of BCCs, but additional prospective studies in humans are needed to better define the true relationship between vitamin D levels and BCC risk.

Role of vitamin D in squamous cell carcinoma

Mice lacking VDR are predisposed to SCC formation when exposed to high and prolonged doses of UVB.[4] In addition, as in BCCs, $1,25(OH)_2D$ has been shown to inhibit the growth of SCCs both in vivo and in vitro. Vitamin D analogs inhibit cell growth by inducing cell cycle arrest, inhibiting DNA synthesis, and inducing apoptosis in SCC cell lines.[29] In mice,

topically applied $1,25(OH)_2D$ inhibits chemically induced tumor formation in a dose-dependent manner[30–32]; similar results have been shown with vitamin D analogs.[33] In addition, the topical application of $1,25(OH)_2D$ appears to accelerate the clearance of cyclobutane dimers that are characteristic of UV radiation—induced DNA damage.[9] The underlying molecular mechanism has not been fully elucidated, but molecular studies show that the VDR is induced by an isoform of the tumor suppressor gene p63, a gene that, along with p53, is critical for keratinocytes' ability to initiate the DNA repair process after UV exposure.[34] Therefore, vitamin D may interact with tumor suppressor genes (p53 or p63) to upregulate nucleotide excision repair genes or other DNA repair enzymes, such as XPC and DDB2.[11] This response may differ between normal keratinocytes and SCCs.[35]

To date, there are limited epidemiologic studies on the effect of vitamin D or its metabolites on SCC prevention or treatment in humans. Eide et al[28] showed a serum 25(OH)D level of 15 ng/mL or higher was associated, but not statistically significantly, with increased SCC risk. Despite a growing body of epidemiologic evidence to suggest an association between vitamin D and cancer risk in various visceral organs, data to assess this association in SCCs are lacking. Studies of the epidemiology of BCCs and SCCs are difficult in general to perform because most national registries, such as the Surveillance, Epidemiology, and End Results program, exclude them, leaving no easily accessible database with which to track the development of these cancers. Therefore, although the animal studies are suggestive, additional work is needed to assess the suitability of topical or oral vitamin D_3 for chemoprevention of both BCCs and SCCs in humans.

ROLE OF VITAMIN D IN MELANOCYTES

Key point

- Several studies have reported an association between serum vitamin D levels or intake and melanoma onset and progression

Like keratinocytes, melanocytes also have the capacity for autonomous local production of $1,25(OH)_2D$ and harbor VDR.[36] Such locally produced $1,25(OH)_2D$ may play a role in innate and acquired cutaneous immunity.[37] In vitro, $1,25(OH)_2D$ stimulates melanocyte maturation, possibly through the stimulation of tyrosinase activity.[38,39] It also protects cells from apoptosis[40] and upregulates VDR expression.[41] This has led some researchers to suggest treating vitiligo with vitamin D or a vitamin D analog.[42,43] However, a recent randomized, doubleblinded trial evaluating the efficacy of topical tacalcitol, a synthetic vitamin D_3 analogue, in adult nonsegmental vitiligo did not show any advantage as compared to sunlight exposure alone.[44] Nevertheless, there is at least experimental evidence to suggest that the vitamin D pathway plays an important role in melanocyte function and therefore may be involved in melanoma.

Role of vitamin D in melanoma

There is accumulating evidence that the vitamin D pathway may play a role in melanoma. VDR expression has been detected in cultured melanoma cells,[41,45] melanoma xenographs,[46] and in primary melanoma tissue.[47] As with BCCs, VDR expression is stronger in melanoma cell lines than in normal melanocytes.[41] A recent large, international, multicenter, population-based, case control study has identified polymorphisms in the promoter, coding, and 3′ gene region of VDR that are significantly associated with melanoma after adjusting for relevant covariates.[48]

The antiproliferative and prodifferentiative effects of vitamin D and its metabolites have been shown in some, but not all, melanoma cell lines.[36,46,49,50] $1,25(OH)_2D$ has been shown to inhibit tumor invasion and angiogenesis in melanoma cell lines[51] and to suppress the

growth of human-derived melanoma xenografts in immunosuppressed mice.[52] An inhibitory effect of vitamin D on melanoma migration, invasion, and metastasis has been shown in mice that have been inoculated with vitamin D—treated melanoma cells.[53] Finally, Albert et al[54] reported that vitamin D analogs inhibit the growth of pigmented ocular tumors in transgenic mice.

In humans, several studies have reported an association between serum vitamin D levels or intake and melanoma onset and progression, although others have failed to find any association. Studies on VDR polymorphisms and melanoma risk are also emerging. A summary of all published studies on the relationship between vitamin D serum levels or intake and melanoma risk is shown in Table I. In a prospective study by Newton-Bishop et al,[55] patients with high serum 25(OH)D levels at the time of melanoma diagnosis had thinner tumors, a lower risk of relapse, and a higher overall survival rate compared to those with low serum 25(OH)D levels. In this cohort, there was also evidence of interaction between the VDR BsmI genotype and serum 25(OH) D levels on relapse-free survival. In another case control study by Nurnberg et al,[56] 25(OH)D levels were significantly reduced in patients with stage IV melanoma patients compared to stage I patients, and patients with serum levels<10 ng/mL tended to have earlier distant metastases compared to patients with serum levels >20 ng/mL. Because serum 25(OH)D at presentation is likely to be a reflection of levels before and during early development of the melanoma, it would seem that vitamin D may inhibit local invasion and micrometastases during early tumor development. However, other studies have found no relationship between 25(OH)D levels and melanoma,[57] so the exact relationship between vitamin D and melanoma is yet to be elucidated.

Regarding the dietary intake of vitamin D, a large case control study of dietary and supplemental intake of vitamin D in melanoma found that high vitamin D intake from food was associated with a reduction in melanoma risk, although after accounting for vitamin D from supplements, the association between intake of vitamin D and risk for melanoma was no longer statistically significant.[58] Another dataset using a large prospective cohort found no association between dietary and supplemental vitamin D intake and melanoma risk among 68,611 men and women participating in the Vitamins and Lifestyle cohort study.[59] Interestingly, a large prospective study in Norway found an increased risk of melanoma in women who consumed significant amounts of cod liver oil, which contains about 400 to 1000 IU of vitamin D per teaspoon.[60] However, the cod liver oil effect may not be attributable to a vitamin D—specific effect, because it has other relatively unique nutritional characteristics, including a high concentration of vitamin A and n-3 fatty acids. Finally, a recent post hoc analysis of the Women's Health Initiative clinical trial (N = 36,282) found no effect of 1000 mg of calcium plus 400 IU of vitamin D supplementation on NMSC and melanoma risk. However, calcium plus vitamin D did reduce melanoma risk by 50% in a subgroup of women with a history of NMSC.[61]

At present, there is no current consensus on clinical recommendations for vitamin D intake and optimal serum levels in melanoma patients and those at risk for melanoma. However, laboratory evidence points to a role for vitamin D in melanoma development and tumor progression. A recent review by Field and Newton-Bishop[62] on melanoma and vitamin D suggests aiming for a target serum level of 70 to 100 nmol/L (28–40 ng/mL) for melanoma patients, because laboratory evidence has shown that maintaining higher serum vitamin D levels may influence tumor cell proliferation. There is currently insufficient evidence to recommend higher doses of vitamin D, and more work is needed to determine how vitamin D may play a protective role against melanoma in humans.

DEFINING OPTIMAL VITAMIN D LEVELS AND RECOMMENDATIONS FOR SUPPLEMENTATION

Key points

- The Institute of Medicine recommends that most healthy individuals will need 600 IU of vitamin D daily to maintain serum 25(OH)D levels above 20 ng/mL
- Higher doses up to 4000 IU daily are safe but not necessarily beneficial
- Symptoms of vitamin D toxicity are nonspecific and include nausea, vomiting, poor appetite, constipation, weakness, and weight loss

Serum concentration of 25(OH)D is the best indicator of vitamin D status given its long half-life of over 250 hours. It does not reflect total tissue stores, but shows the amount of available precursor to the active form, $1,25(OH)_2D$. Because of its short half-life and tight regulation, circulating levels of $1,25(OH)_2D$ are generally not a good indicator of vitamin D status; levels do not typically decrease until vitamin D deficiency is severe (with the exception of sarcoidosis).[63] The optimal serum vitamin D levels for health maintenance and disease prevention are still under debate, but the recent 2010 IOM recommendations state that vitamin D deficiency is defined as levels <20 ng/mL (<50 nmol/L); levels below this threshold are generally considered inadequate for maintaining bone health[64] (Table II). Some have argued that the role of vitamin D in other aspects of health necessitate higher 25(OH)D serum levels between 28 and 40 ng/mL,[65] but the IOM has concluded that compelling evidence for this recommendation does not yet exist.

Vitamin D toxicity

The IOM report addresses concerns that some people will oversupplement with vitamin D, leading to adverse side effects. Excessive sun exposure does not result in vitamin D toxicity, because with sustained exposure vitamin D_3 begins to degrade as it is formed.[66] Given that vitamin D is difficult to obtain from natural dietary sources, toxicity is unlikely to result from dietary intake unless large amounts of cod liver oil are consumed. It is more likely to occur from the excessive intake of supplements. Long-term intakes above the recommended maximum dose, or 4000 IU (Table III), can increase the risk of adverse health effects. However, short-term or periodic bursts with large doses (eg, 50,000 IU/week for 8 weeks) have been used clinically and do not appear to cause toxicity.[67] The excess supply is stored and used as needed to maintain normal serum 25(OH)D concentrations when vitamin D intake or sun exposure is limited. With regard to excessively high serum levels, although serum 25(OH)D concentrations ≤ 400 ng/ mL (≤ 1000 nmol/L) were not associated with harm in animal models,[68] in humans a serum 25(OH)D concentration that is consistently >200 ng/mL (>500 nmol/L) is considered to be potentially toxic.[69] Symptoms of vitamin D toxicity are nonspecific and include nausea, vomiting, poor appetite, constipation, weakness, and weight loss.[70,71] If the excess vitamin D leads to severe hypercalcemia, more serious side effects can arise, such as mental status changes, confusion, and cardiac arrhythmia. In fact, a study of 10 National Cancer Institute cohorts (with almost 2 million subjects), chronic 25(OH)D levels >40 ng/mL (100 nmol/L) were associated with an increased risk for pancreatic cancer.[72]

Although the effects of vitamin D supplements alone on kidney stone risk have not been evaluated, it is worth noting that in the Women's Health Initiative calcium and vitamin D trial, the use of supplements containing 1000 mg per day of calcium and 400 IU per day of vitamin D led to a 17% increase in the risk of kidney stones over 7 years[73] in postmenopausal women.

The current upper limits for vitamin D are listed in Table III and range from 1000 to 4000 IU daily, depending on age.[64] Some studies show that prolonged daily intake of 10,000 IU (250 μg) poses little risk.[74,75], However, given the small but real risks posed by even low doses, such as the 400 IU of vitamin D tested in the Women's Health Initiative trials, we recommend that most people should not exceed the 4000 IU daily limit set by the IOM.

Supplementation

The intake of 1 μg (40 IU) of vitamin D per day increases serum 25(OH)D by an average of 0.4 ng/ mL.[76,77] The recent IOM report on vitamin *D* states that 600 IU daily is enough to meet the needs of most North Americans.[64] For an individual with serum 25(OH)D levels <20 ng/mL, a daily dose of 600 IU would raise levels by about 6 ng/mL. Some organizations, including the Canadian Cancer Society, recommended that adults consider taking 1000 IU of vitamin D per day during the fall and winter[78] or if they are using photoprotection on a regular basis. The American Academy of Dermatology recently updated its recommendations on vitamin D to state that there is no known safe level of UVexposure, that regular photoprotection reduces risk for skin cancer, and to recommend that people follow the updated IOM recommendations for daily intake levels.[79]

For clinicians, it may be prudent to test serum 25(OH)D levels once in patients of clinical concern or in those at risk for vitamin D deficiency (ie, individuals with dark skin or individuals who have little outdoor sun exposure, such as the elderly or those that practice rigorous sun protection); appropriate doses of vitamin D supplementation can then be calculated to achieve and maintain serum 25(OH) D levels above 20 ng/mL. The Endocrine Society Practice Guidelines recommends that all adults who are vitamin D—deficient be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 weeks or its equivalent of 6000 IU per day of vitamin D_2 or vitamin D_3.[80] After 8 weeks, serum 25(OH)D levels should be rechecked and patients who do not have their vitamin D deficiency corrected should be referred to their primary care physician or endocrinologist for further management.

Overall, there is some evidence that vitamin D may play a role in NMSC and melanoma prevention, although as of yet there is no direct evidence to show a protective effect. The relative contributions of diet, supplementation, and cutaneous vitamin D synthesis to serum vitamin D levels require additional study. While some in vitro data suggest that vitamin D associated with low levels of UVexposure may have protective effects against skin cancer, additional studies in humans are needed. However, because UVrays are known to be carcinogenic, and because it is difficult to discern when small amounts of sun exposure cross the line from potential benefit to harm, one can argue that it is prudent to advise sun protection and to recommend obtaining vitamin D from supplemental sources that do not have a narrow therapeutic index.

The American Academy of Dermatology recommends that an adequate amount of vitamin D should be obtained from a healthy diet that includes foods and beverages that are naturally rich in or fortified with vitamin D and/or vitamin D supplements; it should not be obtained from unprotected exposure to UV radiation. Given the current evidence, our current recommendations are to follow the recent IOM guidelines: assuming minimal sun exposure, most healthy individuals will need 600 IU of vitamin D daily to maintain serum 25(OH)D levels above 20 ng/mL, and higher doses up to 4000 IU daily are safe but not necessarily beneficial. Those who regularly practice photoprotective behaviors may especially benefit from supplementation. Additional research is needed to better define the relationship between vitamin D intake, serum 25(OH)D levels, and the risk of NMSC and melanoma.

Acknowledgments

The authors thank Olena Mykhaylichenko for manuscript preparation.

Supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases grants K23 AR 051037-01 (Dr Asgari) and K23 AR 056736-01 (Dr Tang), the Damon Runyon Clinical Investigator Award (Dr Tang), and the VA Office of Research and Development Merit Award I01BX007080 (Dr Oh).

Abbreviations used

1,25(OH)$_2$D	1,25-dihydroxyvitamin D_3, the biologically active form of serum vitamin D
25(OH)D	25-hydroxyvitamin D
IOM	Institute of Medicine
IU	International Unit
NMSC	nonmelanoma skin cancer
UV	ultraviolet
UVB	ultraviolet B
VDR	vitamin D receptor

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CAPSULE SUMMARY

- Vitamin D deficiency is defined as serum 25(OH)D levels below 20 ng/mL.
- Vitamin D in vitro inhibits keratinocyte growth and promotes differentiation—factors that are important for skin cancer prevention.
- Mice lacking the vitamin D receptor have increased basal cell and squamous cell carcinoma tumors, suggesting a role of vitamin D in keratinocytic carcinoma.
- However, epidemiologic studies do not show a clear relationship between vitamin D levels and the risk of nonmelanoma skin cancer.
- Some, but not all, epidemiologic studies show that higher levels of vitamin D are correlated with reduced melanoma risk and improved survival.
- There is no current consensus on clinical recommendations for vitamin D intake and optimal vitamin D levels for skin cancer prevention.

Table I

Description of studies examining melanoma risk and Vitamin D status

Study design	Country	Risk measure	No. of cases	OR or RR (95% CI)	Protective effect	Covariates	Reference
Serum 25(OH)D levels							
Case control	USA	Melanoma risk	23	1.6 (0.5–6.1)	None	Age, sex, smoking, month of sampling, education, and supplement use	Cornwell et al,[81] 1992
Case control	England	Melanoma risk	941	0.94 (0.79–1.12)	None	Age, sex, month of sampling, and BMI	Randerson-Moor et al,[57] 2009
Prospective cohort	England	Melanoma relapse	872	0.79 (0.64–0.96)	Yes†	Age, sex, tumor site, BMI, Breslow thickness, and	Newton-Bishop et al,[55] 2010
		Overall survival	872	0.83 (0.68–1.02)	None	Townsend score	
Case control	Germany	Stage IV vs I patients	205	13.1 ng/mL vs 16.4 ng/mL (P = .006*)	Yes†	Age, gender, BMI, historical sun exposure, skin type, number of painful sunburns, and sunscreen use	Nurnberg et al,[56] 2009*
Vitamin D intake							
Case control	USA	Melanoma risk	165	1.80 (0.90–3.50)	None	Age, hair color, and family history	Weinstock et al,[82] 1992
Case control	USA	Melanoma risk	502	0.61 (0.40–0.95)	Yes†	Age, sex, dysplastic nevi, education, and skin type	Millen et al,[58] 2004
Case control	Italy	Melanoma risk	380	0.85 (0.74–0.97)	Yes	Age, gender, skin type, history of sun exposure, sunburns, use of sunscreen, and total energy intake	Vinceti et al[83]
Prospective cohort	USA	Melanoma risk	455	1.05 (0.79–1.40)	None	Age, gender, education, family history of melanoma, history of skin cancer, moles, freckles, sunburns, hair color, skin type, and total energy intake	Asgari et al,[59] 2009
Cod liver oil intake	Norway	Melanoma risk	108	Women, 2.9 (1.7–5.1); men, 1.1 (0.5–2.6)	None	Age, height, BMI, BSA, education, smoking, and physical activity	Veierød et al, 1997
Randomized controlled trial	USA	Melanoma risk	176/36, 282	Overall, 0.86 (0.64–1.16); previous NMSC, 0.43 (0.21–0.90)	Yes,† for women with previous NMSC	Placebo—18,106 women; calcium and Vitamin D (1000 mg, 400 IU)—18,176	Tang et al,[61] 2011

BMI, Body mass index; *BSA*, body surface area; *CI*, confidence interval; *IU*, International Unit; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *RR*, relative risk.

*Data from Nurnberg et al[56] do not allow for calculation of odds ratio.

† Study shows benefit of higher vitamin D serum levels or higher vitamin D intake.

Table II

Serum 25-hydroxyvitamin D (25[OH]D) concentrations and health*

ng/mL†	nmol/L	Health status
<12	<30	Associated with vitamin D deficiency and rickets in infants and young children
<12–20	<30–50	Generally considered inadequate for bone and overall health in healthy individuals
≥20	≥50	Generally considered adequate for bone and overall health in healthy individuals
≥30	≥75	Proposed by some as desirable for overall health and disease prevention, although a recent government-sponsored expert panel concluded that insufficient data are available to support these higher levels
>50	>125	Emerging evidence links potential adverse effects to high levels; can lead to hypercalcemia and hyperphosphatemia.

*Serum concentrations of 25(OH)D are reported in both nanograms per milliliter (ng/mL) and nanomoles per liter (nmol/L).

†1 ng/mL = 2.5 nmol/L.

Table III

Current recommended upper limit levels of International Units of vitamin D that covers the needs of >97.5% of the US population*

Age	Children	Adults
0–6 mo	1000	—
6–12 mo	1500	—
1–3 yrs	2500	—
4–8 yrs	3000	—
9–50 yrs	4000	4000
51–70 yrs	—	4000
≥71 yrs	—	4000

*Data taken from Ross et al.[64]