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“The role of the vitamin D in skin cancer  
patients”

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## Cancer Types, Epidemiology & Genetics – Acronyms and Abbreviations

Acronym / Term	Full Form / Meaning
BCC	Basal Cell Carcinoma
SCC	Squamous Cell Carcinoma
NMSC	Non-Melanoma Skin Cancer(s) (includes BCC + SCC)
CMM	Cutaneous Malignant Melanoma
RR	Relative Risk
OR	Odds Ratio
CI	Confidence Interval

## Genetics & Molecular Biology

Acronym / Term	Full Form / Meaning
p53 / p63	Tumor suppressor genes important in DNA repair
TGFBR1	Transforming Growth Factor Beta Receptor 1 gene (linked to MSSE)
MSSE	Multiple Self-Healing Squamous Epitheliomas

## Vitamin D & Biochemistry

Acronym / Term	Full Form / Meaning
UV-B / UVB	Ultraviolet B radiation (290–320 nm)
7-dehydrocholesterol	Precursor molecule in the skin for vitamin D synthesis
Pre-vitamin D <sub>3</sub>	Intermediate form before activation
1,25[OH] <sub>2</sub> D	1,25-dihydroxyvitamin D (active form, also called calcitriol)
25(OH)D / 25(OH)D <sub>3</sub>	25-hydroxyvitamin D (main circulating form, biomarker of vitamin D status)
VDR	Vitamin D Receptor
PPAR	Peroxisome Proliferator-Activated Receptor
D <sub>2</sub> (ergocalciferol) and D <sub>3</sub> (cholecalciferol)	Two major forms of vitamin D

I wish to begin by expressing my profound gratitude to Almighty God, whose guidance, blessings, and strength have sustained me throughout my academic journey and in the completion of this thesis. Without His presence, none of this would have been possible.

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I would also like to extend my sincere appreciation to the University of Padua, a beacon of academic excellence, for providing an environment of collaboration, inspiration, and intellectual rigor that has been essential to the realization of this work.

My deepest gratitude goes to my family, whose steadfast support, patience, and understanding have been the foundation upon which I could pursue and accomplish this milestone. Their belief in me has been a constant source of strength and motivation.

It is easy to feel proud and hopeful on a day like today, yet I am fully aware that there will be challenging days ahead, moments of uncertainty, and times when I may feel alone. It is precisely in those moments that perseverance matters most the commitment to keep moving forward, no matter what.

No matter how difficult the path may seem, I promise myself to hold on to hope, to continue striving, and to keep learning. We must rise above the obstacles we face. My wish for myself, and for all those who have supported me, is to transform that hope into action to make a meaningful difference in the world.

Time is a gift, fleeting and precious. I refuse to spend it living someone else's life. I will make mine count: to pursue knowledge, to fight for what truly matters, and to contribute positively to the world. Even if I fall short at times, there is no greater way to live than with purpose, determination, and passion.

As this chapter closes, the lessons learned, friendships forged, and experiences gained will remain with me, shaping the person I continue to become.

This journey has been extraordinary, and I am deeply grateful to everyone who has been part of it.

Thank you for helping me reach this milestone it is a memory I will cherish always.

## Abstract

Sunlight, especially its ultraviolet B (UV-B) rays, plays a complex role in human health. On one hand, it can be harmful UV-B exposure is known to damage DNA in skin cells, which can lead to mutations and, over time, increase the risk of skin cancer. This connection is supported by the high number of UV-related genetic mutations commonly found in different types of skin tumours.

On the other hand, UV-B is also essential for something our bodies can't do without: producing vitamin D. When our skin is exposed to sunlight, UV-B triggers a chemical reaction that starts with the conversion of 7-dehydrocholesterol into previtamin D<sub>3</sub>. Through a series of metabolic steps, this becomes active vitamin D a compound that has shown promising anti-cancer properties in lab studies. For example, vitamin D can help prompt cancer cells to self-destruct, slow down their uncontrolled growth, prevent the development of new blood vessels that feed tumors, and encourage normal skin cell development.

Interestingly, for people already diagnosed with skin cancer, having enough vitamin D might offer certain advantages. Some research suggests that maintaining adequate vitamin D levels could help slow the progression of the disease and potentially improve treatment outcomes. So while it's important to protect the skin from excessive sun exposure, it's equally important not to overlook the health benefits of moderate UV-B exposure and particularly its crucial role in vitamin D synthesis and its possible protective effects against cancer.

## Astratto

La luce solare, in particolare i raggi ultravioletti B (UV-B), svolge un ruolo complesso nella salute umana. Da un lato, può essere dannosa: l'esposizione agli UV-B è nota per danneggiare il DNA nelle cellule cutanee, causando mutazioni che, nel tempo, possono aumentare il rischio di sviluppare tumori della pelle. Questo legame è confermato dall'elevato numero di mutazioni genetiche correlate agli UV riscontrate comunemente in diversi tipi di tumori cutanei.

Dall'altro lato, gli UV-B sono essenziali per un processo che il nostro corpo non può svolgere da solo: la produzione di vitamina D. Quando la pelle è esposta alla luce solare, gli UV-B innescano una reazione chimica che inizia con la conversione del 7-deidrocolesterolo in previtamina D<sub>3</sub>. Attraverso una serie di passaggi metabolici, questa si trasforma nella vitamina D attiva, un composto che ha dimostrato promettenti proprietà anticancerogene in studi di laboratorio. Ad esempio, la vitamina D può indurre le cellule tumorali all'autodistruzione, rallentarne la crescita incontrollata, impedire lo sviluppo di nuovi vasi sanguigni che nutrono i tumori e favorire la normale differenziazione delle cellule cutanee.

In modo interessante, per le persone già diagnosticate con un tumore cutaneo, avere livelli adeguati di vitamina D potrebbe offrire alcuni vantaggi. Alcune ricerche suggeriscono che mantenere una quantità sufficiente di vitamina D potrebbe contribuire a rallentare la progressione della malattia e potenzialmente migliorare gli esiti dei trattamenti. Pertanto, sebbene sia importante proteggere la pelle da un'eccessiva esposizione al sole, è altrettanto fondamentale non trascurare i benefici per la salute di una moderata esposizione agli UV-B, in particolare il loro ruolo cruciale nella sintesi della vitamina D e i possibili effetti protettivi contro il cancro.

## 1. Introduction

Vitamin D, although commonly referred to as a vitamin, is a precursor to a hormone that plays a crucial role in our health, extending beyond its primary function of managing calcium and phosphorus levels. What makes vitamin D unique is that our skin can produce it when exposed to ultraviolet B (UV-B) rays, specifically within the 290–320 nm range. When UV-B hits the skin, it converts a substance called 7-dehydrocholesterol in skin cells into pre-vitamin D<sub>3</sub>. This molecule then travels to the liver and kidneys, where it undergoes two significant chemical changes to become the active hormone known as 1,25-dihydroxyvitamin D (1,25[OH]<sub>2</sub>D). Besides sunlight, we can also obtain vitamin D from foods such as oily fish, cod liver oil, fortified products, and supplements.

Vitamin D's role extends well beyond maintaining bone health. It has garnered significant attention for its impact on the immune system and its role in regulating the behaviour of various cells. Vitamin D receptors (VDRs) are found in many types of cells, including skin cells, which suggests vitamin D has both local and broader effects on tissue health. Laboratory studies have shown that the active form of vitamin D can slow down the growth of melanoma cells by encouraging them to mature properly, promoting their self-destruction, and reducing their multiplication. These effects are thought to work through specific signalling pathways involving the VDR and other molecules, such as PPAR.

Interestingly, skin cells called keratinocytes can produce the active form of vitamin D right where it's needed and have the receptors to respond to it themselves, which means vitamin D can act locally in the skin. While this local production doesn't change the overall vitamin D levels in the body significantly, it could have significant effects on skin health and how skin cancer develops at the cellular level.

However, understanding how vitamin D might protect against skin cancer isn't straightforward. The same UV rays that help our bodies produce vitamin D are also the leading cause of skin cancers, including melanoma and non-melanoma types. This creates a tricky balance when trying to figure out whether vitamin D helps prevent skin cancer or improves outcomes after diagnosis.

Some recent studies suggest that low blood levels of 25-hydroxyvitamin D (25[OH]D) may be linked to worse outcomes in several cancers, including skin cancer. While observational research and some meta-analyses point to a possible protective effect of higher vitamin D levels especially against cancers like colorectal cancer and clinical trials testing vitamin D supplements haven't yet provided clear evidence of a benefit, possibly because the doses used were too low.

This thesis aims to explore the complex and sometimes contradictory relationship between vitamin D and skin cancer. It examines both the benefits that vitamin D offers and the risks posed by UV exposure. Finding the right balance between these factors is crucial for guiding future prevention strategies, improving clinical care, and shaping public health advice.

## 1.1 Introduction

Over time, I've developed a genuine curiosity about vitamin D—not just because it's essential for bones, but because of how many different roles it might play in human health. What was once seen mainly as a nutrient that helps the body absorb calcium is now being studied for its possible role in protecting against various types of cancer. Interestingly, this idea isn't brand new. Decades ago, researchers in North America noticed something: cancer rates were generally lower in regions where people were exposed to more sunlight. That early observation sparked new questions and eventually led to a growing body of research into the connection between sun exposure, vitamin D, and cancer risk.

By the 1980s and 1990s, more focused studies began to suggest that lower levels of sunlight exposure has been suggested to contribute to a rise in colon and prostate cancers. This shifted the conversation vitamin D started to be seen not only as crucial for bone health, but as a possible protective factor in cancer development. Over time, this idea evolved into what many now call the UV vitamin D–cancer hypothesis. In simple terms, the hypothesis is based on the notion that UVB rays from sunlight help the skin produce vitamin D, and that this vitamin might help the body reduce the risk or slow down the progression of certain cancers.

A number of population studies have added weight to this idea. People with higher levels of 25-hydroxyvitamin D in their blood, the form used to measure vitamin D status—tend to show lower risks for cancers like colon, breast, prostate, and stomach. And in lab settings, vitamin D seems to affect cancer cells in powerful ways. It has been shown to stop them from growing too quickly or to trigger their death through natural processes like apoptosis. These results have encouraged scientists to explore vitamin D more seriously as a potential tool in both preventing and treating cancer.

However, things are rarely simple when it comes to clinical applications. High doses of vitamin D can create problems like hypercalcemia when there's too much calcium in the blood—which makes treatment tricky. On top of that, some types of cancer cells seem to find ways to avoid being affected by vitamin D. They can reduce how much of it is present in the cell or interfere with the receptors needed for it to work effectively.

Because of all these complexities, it's important to look more closely at how vitamin D works inside the body, especially in cancer cells. How do these cells bypass its protective effects? Can we find ways to overcome this resistance? These are the kinds of questions I'll explore in this part of my thesis, as I look at both the exciting potential and the current limitations of using vitamin D in the context of cancer.

## 2. Background

Basal cell carcinoma (BCC) and also squamous cell carcinoma (SCC) together referred to as non-melanoma skin cancers (NMSC) along with cutaneous malignant melanoma (CMM), are the three most common types of skin cancer. These cancers are strongly linked to ultraviolet (UV) radiation, whether they are from the sun or tanning beds, which can damage the DNA in skin cells and increase the likelihood of malignant transformation. However, the preventability of these cancers through sun protection measures empowers individuals to take control of their health. For this reason, they are often described as “sun-related” cancers.

Although NMSCs occur at very high rates, they are often not included in national cancer registries. This is partly because they are sometimes seen as having less clinical impact compared to other cancers, and also because many cases are treated without a tissue diagnosis, a process where a biopsy of the affected tissue is set to be performed to determine if cancer is present. Even so, NMSC is the single most frequently diagnosed cancer in places such as North America, Australia, and New Zealand, making it a public health concern that should not be underestimated.

Data from 2018 highlight the scale of the problem: around 1,042,056 new cases of NMSC were diagnosed worldwide, with 65,155 deaths recorded (about 6% of cases), most of them linked to SCC. While the number of SCC cases continues to climb, death rates have remained relatively stable over time.

Melanoma, on the other hand, is widely recognized as one of the most dangerous type of skin cancer. In many developed countries, the number of melanoma diagnoses has been rising, but much of this increase reflects earlier detection of thinner tumours, which generally carry a better prognosis. Mortality trends, however, show an interesting difference between men and women. In the United States, death rates in women have stayed steady at about 1.9 per 100,000, while in men, the rate has steadily gone up from 2.88 per 100,000 in 1975 to 4.44 per 100,000 during 2011–2015. Why men are more affected remains an open question, with possible explanations including lifestyle differences in sun protection, underlying genetic susceptibility, and the influence of hormones.

Vitamin D is a misnamed vitamin; biologically, it is a prohormone, yet it acts more like a hormone. It exists in two primary forms: D3 (cholecalciferol) and D2 (ergocalciferol). Both can be obtained from dietary sources, but the human body also has the unique ability to synthesize vitamin D3 in the skin when exposed to ultraviolet B (UVB) radiation. The efficiency of this cutaneous production which absolutely depends on numerous factors, that includes the intensity of UV radiation, the extent of skin exposed, the duration of exposure, age, body composition, and skin pigmentation.

Deficiency in vitamin D is now recognized as a significant global health issue. What makes the discussion more complex is that the “optimal” serum concentration of vitamin D particularly about bone health remains a matter of debate.

## 2.1 Background

Close to 90% of vitamin D is produced in the skin upon exposure to sunlight, primarily through the ultraviolet B (UVB) spectrum. A meta-analysis comprising 14 studies from northern Europe and one from New Zealand demonstrated that partial skin exposure (which is less than 10% of the skin surface) to comparing a single UVB doses from 0.75 to 3 standard erythemal doses (SED) is sufficient to maintain a healthy vitamin status. However, it's crucial to note that excessive solar exposure, especially to this part of the UV spectrum, can lead to serious health issues and should be avoided.

A study observed that most North American children do not receive enough UVB throughout the year to meet their minimal vitamin D requirements. In many populations, sun exposure is not a dependable source of vitamin D for children. An interesting Polish study involving 32 children at a summer camp on the Baltic Sea, where sun exposure was limited, revealed a modest improvement in serum vitamin D<sub>3</sub> levels of only 24%. This increase pales in comparison to the astonishing 1262% spike in urinary CPD levels linked to sun damage. The result why is it important to rethink underscore the urgent need to re-evaluate our reliance on sun exposure as a sufficient means of obtaining vitamin D, especially for vulnerable populations, such as children. This correspondent to the CPD levels observed in adults who were exposed to higher UV doses during a stay in Tenerife.

Dietary and supplemental vitamin D are functionally identical to the vitamin D produced through UV exposure, making them more reliable and quantifiable sources. However, the risks associated with maintaining high levels of vitamin D are not well-studied, which adds some uncertainty to the understanding.

For individuals who continue to seek sun exposure, it is almost essential to find balance sufficient Vitamin D levels t. There is a significant lack of consensus among specialists, dermatologists, endocrinologists, and family medicine doctors regarding the optimal amount of sun exposure required for adequate vitamin D synthesis. This highlights the importance of providing personalized advice on sun exposure, tailored to each patient's unique characteristics and circumstances.

Advice on sun exposure should be tailored to each individual's characteristics, as well as the specific geographic and climatic conditions they are in. When advising about sun safety, it's essential to look at both the UV index and how long someone spends outdoors. New tools, like computer-based decision aids and algorithms, can make this guidance more precise. At the same time, wearable devices have been successfully used to help people become more aware of their daily UV exposure.

### 3. Vitamin D and its Role in Cancer Development and Skin Malignancies

Cell culture and experimental studies demonstrated that vitamin D influences the differentiation, proliferation, and apoptosis of cancer cells, rendering it a promising candidate for cancer regulation. The role of the vitamin D in preventing cancer or slowing its progression in humans it is still unclear.

Vitamin D is likely to influence the development of carcinogenesis through its role in regulating processes such as cell growth, programmed cell death, angiogenesis, and cell differentiation. Its effects are mediated by vitamin D receptor (VDR), which is encoded by a gene on chromosome 12q13. Variants of this gene may alter receptor function, and emerging evidence suggests that VDR acts a tumour suppressor in the skin, which helps to protect against UV induced epidermal cancers.

It has often been proposed that sun exposure, through its role in stimulating vitamin D synthesis, may help protect against the development of several internal cancers. Yet, findings from a nested case–control study based on Swedish population registries challenge this assumption. The study compared over 100,000 individuals diagnosed with basal cell carcinoma (BCC) and it is used as a marker for higher sun exposure and greater endogenous vitamin D production and with approximately 1 million controls. The results showed that individuals with BCC had an increased likelihood of being diagnosed with other cancers prior to their BCC diagnosis.

Attempts have been made to determine the optimal daily intake of vitamin D for cancer protection.

In recent years, numerous studies have attempted to link blood levels of vitamin D3 (25-OH vitamin D) to the incidence of certain cancers. influence vitamin D levels, such as age or body mass index.

Adequate circulating concentrations of vitamin D have been shown to exert a protective effect against several forms of cancer. Evidence for this comes from clinical observations as well as experimental studies in animals and cell cultures. However, when it comes to skin cancer, the epidemiological data remain inconclusive. In fact, findings are inconsistent regarding whether vitamin D reduces risk. A meta-analysis that evaluated 13 prospective studies found that elevated vitamin D levels were linked with a higher occurrence of cutaneous malignant melanoma (CMM) as well as non-melanoma skin cancers (NMSC). The analysis indicated that for every 30 nmol/L that are a increase in serum 25(OH)D3, the risk rose by 42% for CMM, 30% for squamous cell carcinoma (SCC), and 41% for basal cell carcinoma (BCC). These associations are most likely confounded by factors such as sun exposure.

### 3.1. Vitamin D and Non - Melanoma skin cancer

Higher circulating levels of vitamin D3 are associated with a greater likelihood of developing non-melanoma skin cancer (NMSC) (OR: 2.07, CI: 1.52–2.80), with studies suggesting a linear dose-response relationship. This relationship likely reflects the dual action of ultraviolet B (UVB) radiation: it stimulates vitamin D production in the skin, but at the same time induces DNA damage that can trigger skin carcinogenesis. While UVB promotes vitamin D synthesis in the skin, it also causes DNA damage that can initiate skin carcinogenesis. Interestingly, patients with xeroderma pigmentosum who represent one of the groups at highest risk for NMSC are often vitamin D deficient.

Such findings emphasize the complexity of the link between serum vitamin D and susceptibility to skin cancer. Currently, the available evidence remains inconclusive, and it has not yet been determined whether vitamin D supplementation or sufficiency can reduce the incidence or severity of NMSC.

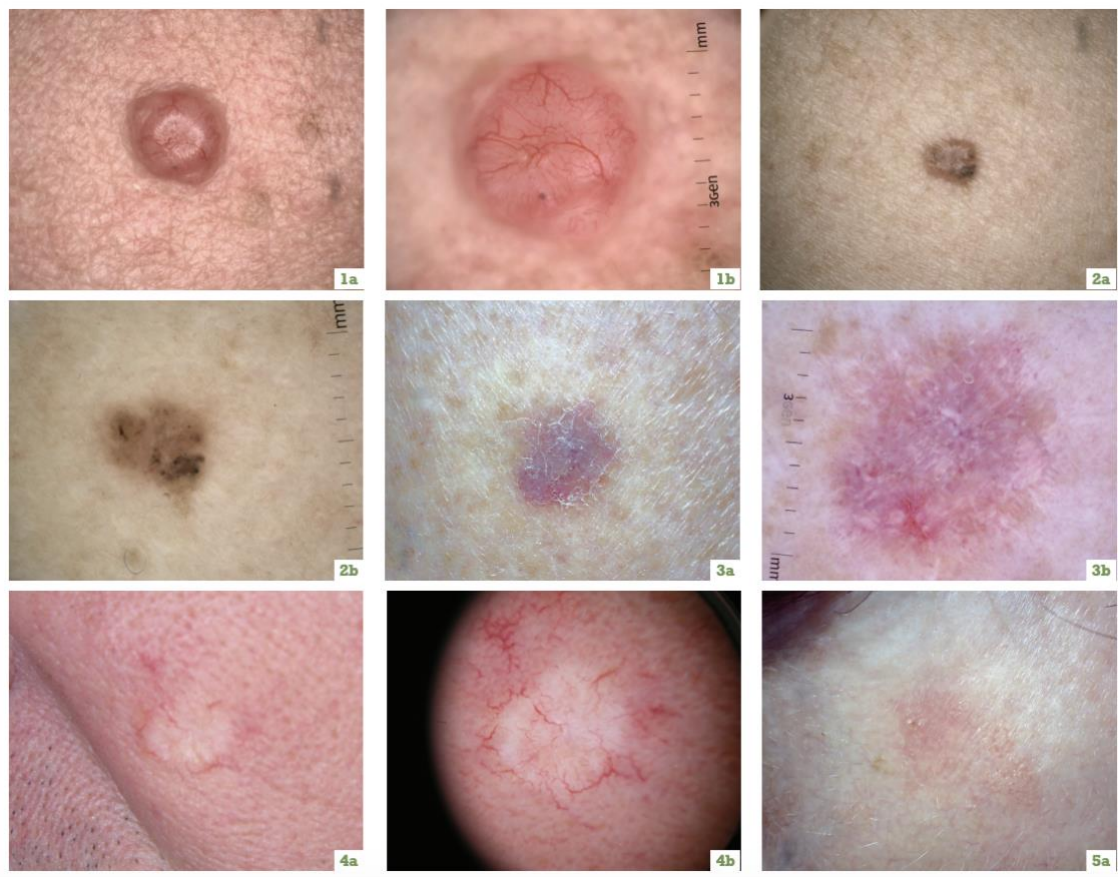


Fig 1. Non Melanoma

### 3.1.2 Basal cell carcinoma

Vitamin D, known for its involvement in the regulation of the hedgehog signaling pathway, remains an important subject for further investigation.

The conflicting findings show that the relationship between vitamin D status and skin carcinogenesis remains still unclear and may be affected by factors such as dosage, individual genetic makeup, and environmental influences. This inconsistency shows the importance of conducting more detailed investigations in human populations, where controlled studies may or could help establish clearer point of views or even casual links and determine whether vitamin D acts predominantly as a protective factor or, under certain conditions, as a potential risk enhancer.

The observed differences in findings highlight the importance of conducting more thorough research in humans to better understand the link between vitamin D levels and basal cell carcinoma (BCC). Although this topic has attracted increasing attention, the available evidence is still limited and often unclear, creating numerous uncertainties about how vitamin D may influence the development of BCC unanswered. This gap highlights the importance of conducting well-designed prospective studies in humans to establish a clearer understanding of whether circulating vitamin D levels contribute to the development of BCC, and to what extent they may serve as either a protective factor or a potential risk element

The slight increase in risk associated with elevated vitamin D levels suggests that even minor changes in circulating concentrations may influence the likelihood of developing basal cell carcinoma (BCC).

This observation highlights the complexity of the relationship between vitamin D status and skin cancer development. From a physiological perspective, vitamin D is vital for processes such as calcium homeostasis. On the other hand, the interplay that happens with molecular pathways in the skin may introduce mechanisms that contribute to carcinogenic processes.

Sustaining serum vitamin D3 levels above 25 ng/mL can be a valuable strategy in reducing the rates of basal cell carcinoma (BCC). Excitingly, vitamin D has been shown to positively influence the hedgehog signalling pathway, which plays a key role in BCC development. While current epidemiological studies exhibit some inconsistencies regarding vitamin D levels and BCC risk, this highlights an excellent opportunity for future prospective studies involving human subjects to deepen our understanding of the interaction between vitamin D levels and basal cell carcinoma. This potential protective mechanism highlights the importance of maintaining sufficient vitamin D status and opens new perspectives on its role in cancer prevention, particularly in relation to skin carcinogenesis. While current epidemiological studies exhibit some inconsistencies regarding vitamin D levels and BCC risk, this highlights an excellent opportunity for future prospective studies involving human subjects to deepen our understanding of the relationship.

It's worth mentioning that sustaining serum vitamin D3 levels above 25 ng/mL shows considerable potential in lowering the risk of basal cell carcinoma, and in this case offering a ray of hope in the fight against this form of skin cancer.

## 4. Squamous-Cell Carcinoma (SCC)

Exciting molecular research has revealed that the VDR is activated by the essential tumor suppressor gene p63, which, alongside p53, plays a vital role in helping keratinocytes kickstart the DNA repair process after UV exposure. While there has been an increase in SCC cases linked to higher vitamin D levels possibly influenced by excessive sun exposure—emerging studies are showing promise that vitamin D and calcium supplementation might have a positive outcome against SCC, boasting a noteworthy hazard ratio of 0.42 (95% CI: 0.19–0.91). Let us stay hopeful for brighter developments in skin health!

Skin squamous cell carcinoma (SCC) is one of the most common types of skin cancer, primarily occurring in immunocompromised patients and areas of the skin frequently exposed to sunlight (Lapouge et al., 2011; Thomson, 2018). It is also linked to several hereditary disorders, such as multiple self-healing squamous epitheliomas (MSSE), which affect individuals with mutations in the TGFBR1 gene (Goudie, 2020; Kang, Quigley, Kim, et al., 2013). In the United States, approximately 250,000 cases of skin SCC are diagnosed each year. While surgical excision can cure the majority of these cases, around 8% of patients experience a relapse, and 5% develop metastatic disease within five years (Durinck, Ho, Wang, et al., 2011). Metastatic SCC carries a poor prognosis, with only a 10–20% survival rate over a period of ten years. Environmental factors potentially contributing to SCC include UV radiation, arsenic exposure in drinking water, infections with human papillomavirus types 6 and 11, climate change, and lifestyle choices (Klein-Szanto, 1989; Waldman, 2019).



Fig 2. Squamous-Cell Carcinoma (SCC)

## 4.1 Vitamin D and Cutaneous Melanoma

The vitamin D pathway might influence the development or progression of melanoma, as VDR expression is detected in various melanoma samples and cells. Calcitriol has been shown to reduce tumor invasion and angiogenesis in melanoma cell lines and animal models.

Having sufficient vitamin D appears to be linked to a lower risk of melanoma occurrence (RR 0.62 [0.42–0.94]).

Lower serum vitamin D3 levels appear to be significantly connected with melanoma prognosis associated with worse prognostic traits, including Breslow thickness, as well as poorer melanoma survival, even after adjusting for inflammatory biomarkers. Several studies have reported similar findings; one investigated patients with variations in the gene encoding the vitamin D-binding protein, which led to lower serum vitamin D levels and was associated with worse melanoma-specific survival, further study found that vitamin D levels at the time of diagnosis were significantly linked to tumor location, mitotic activity, and the presence of ulceration.

A more recent study identified vitamin D levels below 9.25 ng/mL as an independent prognostic factor for overall survival in melanoma patients, also showing a connection with histologic ulceration. Similarly, reduced vitamin D levels have been linked to a higher risk of susceptibility to melanoma, as well as reduced melanoma survival. However, several large-scale studies have not been able to confirm these associations.

Further investigation is warranted to determine whether Vitamin D supplementation might offer benefits for patients with or at risk of melanoma. A recent study published in this journal confirmed that vitamin D3 supplementation (100,000 IU every 50 days) is safe in stage II melanoma patients. Vitamin D3 supplementation is considered safe in stage II melanoma patients. The study also indicated that Breslow thickness influences both disease-free survival and the change in serum vitamin D levels in response to supplementation.

A lower incidence of melanoma has been reported in patients who follow a diet rich in vitamin D; however, this has not been confirmed in case-control studies that include people consuming a vitamin D-rich diet, as well as patients taking supplements.

This may be related to variations in the VDR receptor gene that influence vitamin D's antitumor function. Conflicting evidence also exists: one study reported that high vitamin D intake was linked to a higher risk of melanoma in men, whereas it seemed to offer protection against invasive melanoma in women.

In any case, it seems reasonable to provide vitamin D supplementation to individuals with insufficient levels and to regularly monitor serum vitamin D in patients with, or at risk for, melanoma.

### 4.1.2 High-Dose Vitamin D Supplementation Fails to Enhance Outcomes in Patients with Cutaneous Melanoma

In a study that was performed (mean age 55 years, 54% female sex) vitamin D supplementation increased 25-hydroxyvitamin D serum levels after 6 months of supplementation in the treatment arm by a median 17 ng mL<sup>-1</sup> [95% confidence interval (CI) 9–26] compared with zero ng mL<sup>-1</sup> (95% CI 6–8) in the placebo arm (P < 0.001, Wilcoxon test). It remained at a steady state during the whole treatment period. The estimated event rate for relapse-free survival at 72 months after inclusion was 26.51% in the vitamin D-supplemented arm (95% CI 19.37–35.64) vs. 20.70% (95% CI 14.26–29.52) in the placebo arm (hazard ratio 1.27, 95% CI 0.79–2.03; P = 0.32). After checking for confounding factors (including baseline stage, body mass index, age, sex, and baseline season), the hazard ratio was 1.20 (95% CI 0.74–1.94, P = 0.46). The number of deaths from the progression of CM and non-melanoma-related deaths was similar in both the vitamin D-supplemented and placebo groups (deaths from progression of CM, n = 10 and n = 11, respectively; non-melanoma-related deaths, n = 3 and n = 2, respectively). No significant adverse events were observed during the study.

In patients with CM, monthly high-dose vitamin D supplementation was safe and resulted in a sustained increase in 25-hydroxyvitamin D levels during the treatment period; however, it did not improve relapse-free survival, melanoma-related death, or overall survival.

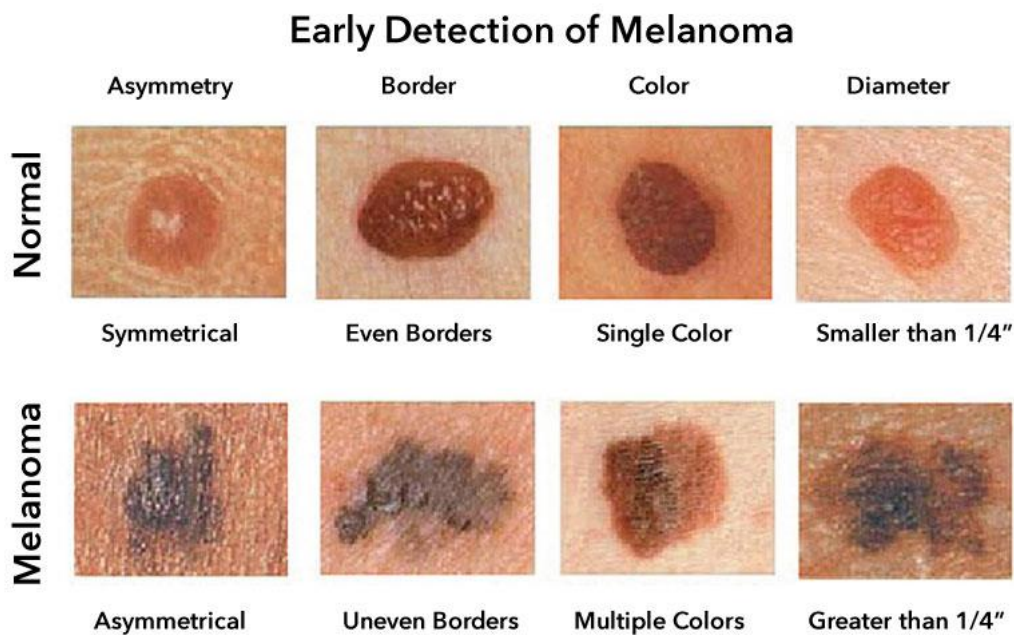


Fig 3. Cutaneous Melanoma

## 5. Impact of Vitamin D on Prognosis After Skin Cancer

Melanoma cells grown in culture express the 25-hydroxylase enzyme, which converts 25(OH)D into the active form 1,25(OH)<sub>2</sub>D. However, recent studies indicate that many melanoma cell lines exhibit resistance to the antiproliferative effects of 1,25(OH)<sub>2</sub>D. In one study using immunosuppressed mice with human solid xenograft melanoma lines, administration of pharmacological doses of 1,25(OH)<sub>2</sub>D suppressed the growth of the CMM and inhibited metastasis in one line but not another. A reduction in the expression of the VDR and CYP27B1 within CMM is correlated with more aggressive and advanced tumours, as well as lower survival rates, suggesting that 1,25(OH)<sub>2</sub>D may play a role in prognosis.

Results from human studies are consistent in showing us that low 25(OH)D levels are linked with thicker CMM, a later stage, or a worse prognosis (summarized in Table 1). However, in all the studies published to date, vitamin D status was measured several months after diagnosis, so reverse causality more aggressive CMM causing greater ill health and resulting in lower sun exposure and, therefore, lower vitamin D production cannot be ruled out (see Table 1).

Study (year)	Measure of prognosis	Sampling of 25(OH)D	Outcome	Ref.
Randerson-Moor <i>et al.</i> (2009)	Breslow thickness	At least 3–6 months after diagnosis	Inverse correlation between 25(OH)D level and Breslow thickness	[90]
Gambichler <i>et al.</i> (2013)	Breslow thickness	At baseline (up to 6 months after diagnosis) and 6 months later	Lower Breslow thickness was a predictor of high 25(OH)D concentration	[91]
Nurnberg <i>et al.</i> (2009)	CMM stage at diagnosis	Sampling between October and April (time between diagnosis and sampling highly variable)	Serum 25(OH)D levels significantly lower in stage IV vs stage 1 CMM	[92]
Newton-Bishop <i>et al.</i> 2009	Breslow thickness; relapse-free survival	Sampling 3–6 months after diagnosis	Significant trend toward lower 25(OH)D levels in association with higher Breslow thickness and lower relapse-free survival	[93]

Table 1.

## 6. VDR deficiency drives Hedgehog pathway activation, fostering epidermal tumorigenesis

Evidence from experimental models demonstrates that absence of the vitamin D receptor (VDR) results in pronounced hyperproliferation of both the hair follicle and epidermis, together with a significant reduction in epidermal differentiation. In contrast to their wild-type counterparts, these mice respond differently when exposed to carcinogenic stimulation, 7,12-dimethylbenzanthracene (DMBA) or UVB, they develop skin tumours, including some characteristic of overexpression of the hedgehog (Hh) pathway. Both the epidermis and utricles of the VDR null animals over-express elements of the Hh pathway [Sonic Hedgehog (Shh, 2.02 fold), Patched1 1.58 fold, Smoothed 3.54 fold, Gli1 1.17 fold, and Gli2 1.66 fold].

This overexpression occurs at an age (11 weeks) when epidermal hyperproliferation is most visible and is spatially controlled within the epidermis. DMBA- or UVB-induced tumours in VDR-null mice also overexpress elements of this pathway. Moreover, 1,25(OH)<sub>2</sub>D<sub>3</sub> down-regulates the expression of some members of the Hh pathway in an epidermal explant culture system, suggesting a direct regulation by 1,25(OH)<sub>2</sub>D<sub>3</sub>. Our results indicate in VDR-null keratinocytes, upregulated Shh expression drives Hedgehog pathway activation, increasing susceptibility to benign and malignant epidermal tumour formation.

Loss of VDR sensitized the epidermis to UVB, leading to marked thickening and heightened cellular proliferation

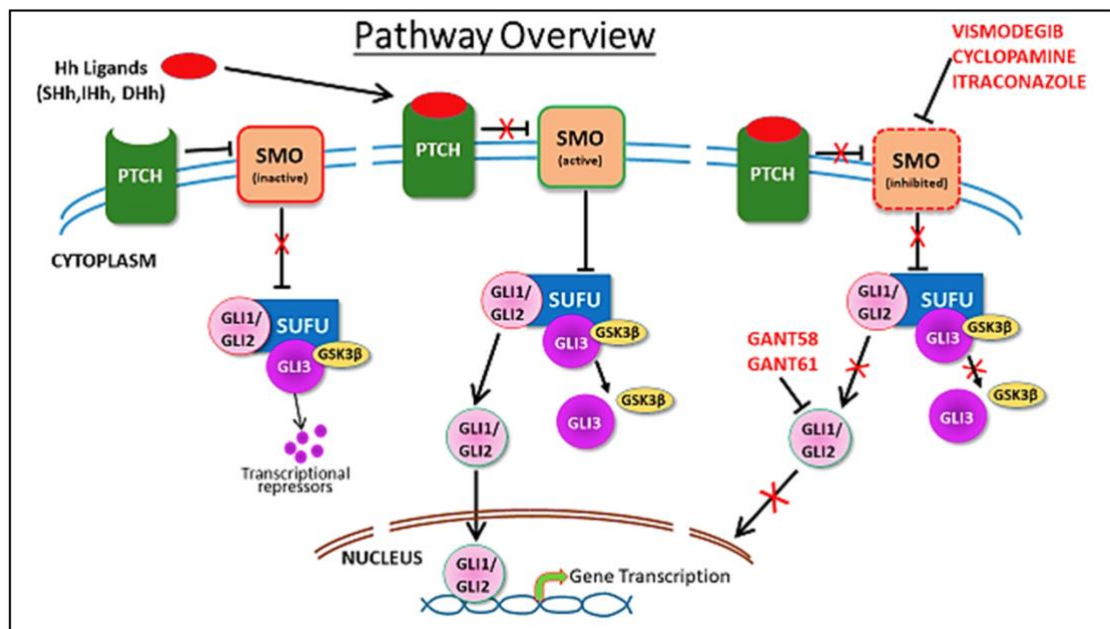


Fig 4. VDR Pathway

## 6.1 Loss of VDR sensitized the epidermis to UVB, leading to marked thickening and heightened cellular proliferation

To investigate the short-term response of the skin to UVB exposure, wild-type and VDR knockout (VDRKO) mice were subjected to a single UVB dose (400 mJ/cm<sup>2</sup>). In wild-type mice, UVB induced a noticeable increase in epidermal thickness at one h and 24 h post-exposure, with no further increase observed at 48 h (Fig. 1A). These morphological changes were accompanied by elevated PCNA staining, reflecting increased cellular proliferation at one h and 24 h, which stabilized by 48 h (Fig. 1B). By contrast, VDRKO mice displayed markedly greater epidermal hyperplasia at all time points relative to wild-type controls, indicating a more robust and persistent proliferative response (Fig. 1A). Correspondingly, the number of PCNA-positive cells in VDRKO epidermis was higher than in wild-type mice at one h and 24 h, and continued to rise through 48 h, consistent with the prolonged hyperplastic response (Fig. 1B).

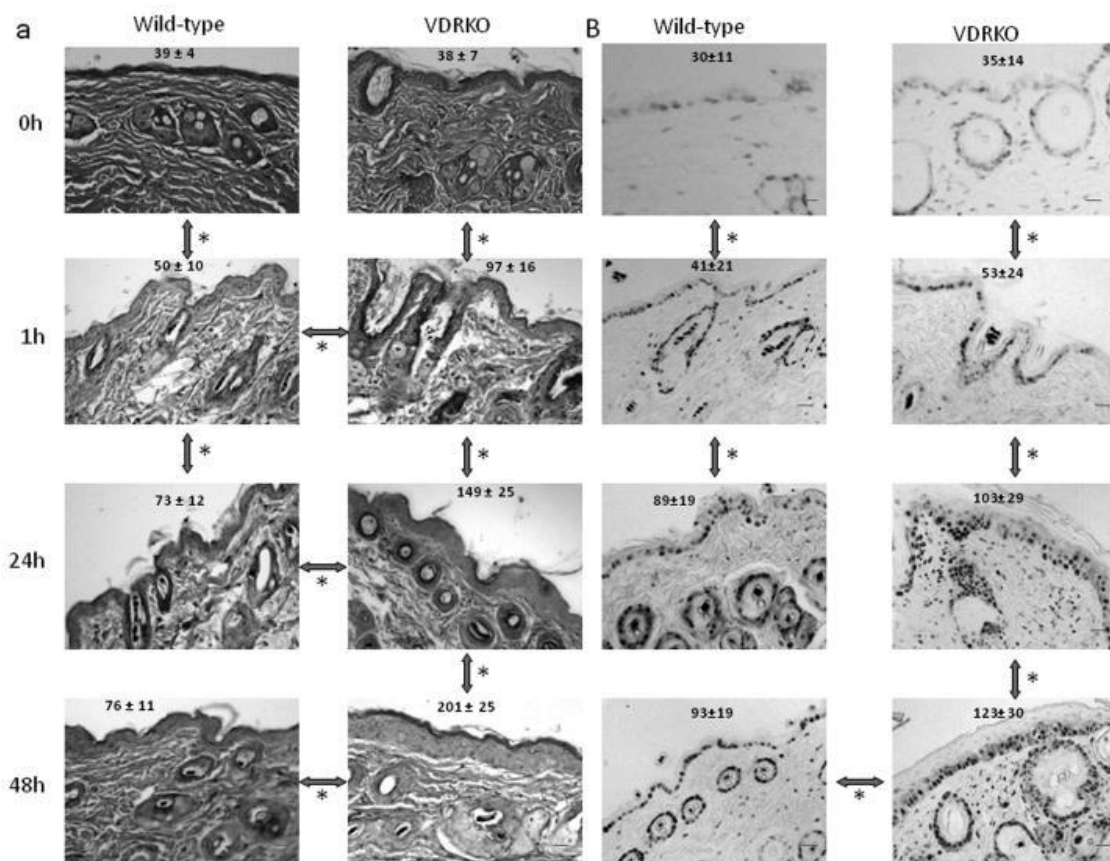


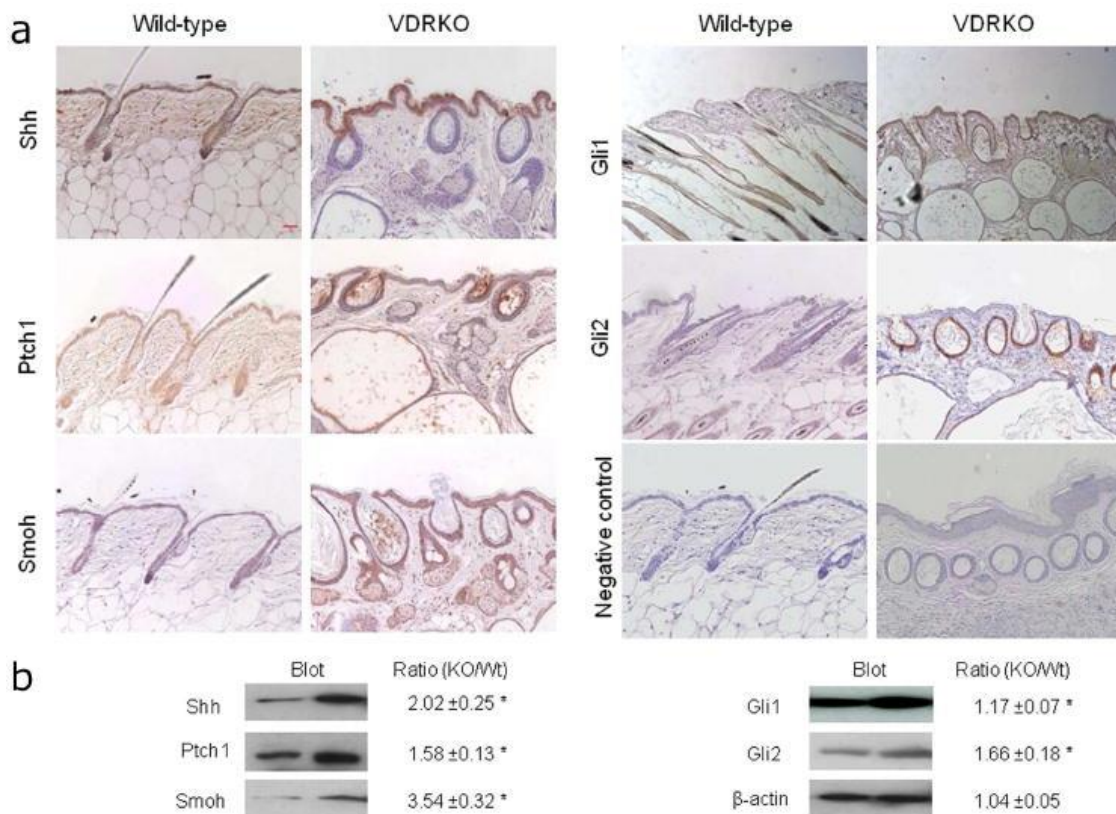
Figure 5. Increased hyperplasia and hyperproliferation in UVB exposed epidermis from VDRKO mice.

### 6.1.2 Overexpression of Hedgehog Pathway Components in VDRKO Mice

To examine the long-term susceptibility of the epidermis to tumour formation in vitamin D receptor knockout (VDRKO) mice, we assessed the expression of key components of the Hedgehog (Hh) signalling pathway in VDRKO mice and their wild-type littermates using immunohistochemistry and Western blot analysis. Eleven-week-old mice were selected for this study, corresponding to the age at which skin papilloma typically develop in VDRKO mice following DMBA treatment.

In wild-type mice, Shh, Ptch1, and Smoh were present in both hair follicles and interfollicular epidermis, whereas Gli1 expression was confined mainly to hair follicles, and Gli2 was not detectable. In contrast, VDRKO mice showed elevated expression of all these proteins, accompanied by changes in their spatial distribution within the epidermis and hair follicles. Specifically, Shh levels increased in the epidermis but were markedly reduced in the utricles, the residual structures of the hair follicles. Ptch1, which is usually expressed throughout the epidermis and hair follicles in wild-type mice, was mainly localized to utricles and dermal cysts in VDRKO mice. Smoh and Gli1, typically restricted to the outer root sheath of hair follicles in wild-type mice, exhibited increased expression in both hair follicles and interfollicular epidermis in VDRKO mice. Gli2, undetectable in wild-type mice, was strongly expressed in utricles and dermal cysts of VDRKO mice.

Figure 6. Increased protein levels of Hh signalling pathway members in VDRKO mice.



## 7. Review methodology

### 7.1 Data source and strategy

The research was conducted using findings from PubMed and Scopus, aiming to gather key data on the role of vitamin D in skin cancer patients and their underlying conditions. It explores the pathways involved and the impact of vitamin D through an analysis of individual patient cases.

The goal was to identify the correlation between vitamin D levels and the health status of skin cancer patients, particularly in relation to cancer progression. Furthermore, this research emphasizes human studies and the specific dosages of vitamin D administered, aiming to understand how supplementation or sufficient vitamin D levels could potentially improve patient health and prognosis.

The keywords that are used in the search included: "skin cancer" OR "melanoma" OR "non-melanoma skin cancer" and ("vitamin D" OR "cholecalciferol" OR "25-hydroxyvitamin D") and("serum levels" OR "deficiency" OR "supplementation" OR "dosage") AND (cohort OR prospective OR "case-control" OR trial OR "clinical study") AND (incidence OR progression OR prognosis OR outcome).

After identifying eligible articles and reviews, the reference lists were manually checked to locate additional relevant studies that searches were limited to studies involving humans, and in Scopus, the "medicine" subject area filter was applied.

After identifying eligible articles and reviews, we manually checked the reference lists to find additional relevant studies that may have been overlooked in the initial search.may have been missed in the initial search.

## 8. Limitations

This thesis is subject to several limitations that must be acknowledged when interpreting its findings. Most of the evidence concerning vitamin D and skin cancer comes from observational research, with considerable heterogeneity across study designs, patient populations, methods of vitamin D assessment, and clinical endpoints. Similarly, intervention studies differed substantially in supplementation protocols, including dosage, duration, and baseline patient status, which complicates comparisons across trials.

Although many studies employed multivariable adjustments, residual confounding remains a concern. Essential factors such as comorbidities, genetic background, phototype, lifestyle habits, or concurrent treatments may still influence both vitamin D levels and cancer outcomes. Furthermore, several studies suffered from methodological challenges, including small sample sizes, limited follow-up periods, or insufficient differentiation between melanoma and non-melanoma cancers, as well as between disease incidence and progression. The lack of standardized dosing guidelines and inconsistent endpoints further restricts the possibility of drawing firm conclusions regarding the therapeutic role of vitamin D in this patient population.

Overall, this review incorporates a body of evidence that sheds light on the potential role of vitamin D in skin cancer, but it does not provide a unified or definitive conclusion.

The results should therefore be preliminary, context-dependent, and open to further investigation. While the evidence suggests a possible protective and prognostic effect of adequate vitamin D levels, the quantitative estimates remain uncertain and should be interpreted with caution.

## 9. Conclusions

This evidence underscores the critical role of VDR-mediated signalling in maintaining epidermal homeostasis and counteracting tumour-promoting stimuli. For instance, while certain population-based studies suggest that sufficient circulating levels of 25-hydroxyvitamin D [25(OH)D] are associated with reduced risks of internal cancers, meta-analyses and prospective cohort studies have failed to establish a clear protective role in skin cancer. In fact, higher serum concentrations of 25(OH)D have been correlated with an increased incidence of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and cutaneous malignant melanoma (CMM). These associations, however, are strongly confounded by sun exposure, which simultaneously elevates vitamin D production and induces DNA damage that directly promotes carcinogenesis.

However, large-scale epidemiological studies have not uniformly confirmed these associations, raising questions about reverse causality—whether aggressive disease reduces sun exposure and vitamin D synthesis rather than vitamin D deficiency contributing to worse prognosis. Furthermore, evidence indicates that melanoma cell lines frequently exhibit resistance to the antiproliferative actions of calcitriol. This resistance has been linked to diminished levels of the vitamin D receptor (VDR) along with reduced activity of metabolic enzymes such as CYP27B1, both of which are critical for the local activation of vitamin D. These findings imply that although vitamin D signalling has the capacity to modulate tumour behaviour, certain melanoma subtypes may develop mechanisms that allow them to bypass or diminish its regulatory modulation.

Yet, observational studies remain inconclusive, with some suggesting a slight increase in risk at higher circulating levels, again likely reflecting UVB exposure as a confounding variable.

Taken together, the available evidence highlights a dualistic and context-dependent role for vitamin D in skin cancer biology. These discrepancies may be explained by confounding environmental exposures, genetic variability in VDR function, differential responsiveness of tumour subtypes, and methodological limitations in observational studies. From a clinical perspective, it remains premature to regard vitamin D supplementation as a definitive strategy for skin cancer prevention or treatment. Supplementation has been demonstrated as safe in stage II melanoma patients and may contribute to improved outcomes, though larger and more controlled trials are required to confirm these findings.

In conclusion, vitamin D emerges as a biologically plausible yet clinically uncertain factor in skin carcinogenesis. While it demonstrates protective mechanisms at the cellular level and appears linked with improved prognostic markers in melanoma, its role in preventing skin cancer incidence particularly BCC and SCC remains ambiguous due to confounding by UVB exposure. Future prospective research in human cohorts is necessary to determine causal associations and to refine the definition of optimal serum vitamin D levels. With this assessment, we can know whether targeted supplementation can meaningfully reduce the incidence and progression of skin cancer.

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