

Deciphering the role of vitamin D on skin cancers and tumour microenvironment

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Abstract

Skin cancer is a significant health burden being the fourth most common cancer globally and accounts for 6.2% of the total combined cancer cases. However, mortality rates due to skin cancer are less when compared with other cancers, but it is significantly high in the Asian population (43%). DNA mutations and environmental and genetic factors are linked with skin cancer prognosis; however, long-term exposure to ultraviolet (UV) radiation remains one of the leading factors worldwide. Sun exposure is a major environmental risk factor for skin cancers but is also an essential source of vitamin D. On the other hand, studies exploring the relationship between skin cancer risk and vitamin D show mixed, somewhat conflicting results. This study investigates the role of vitamin D and skin carcinogenesis to clarify the associations. Moreover, in addition to suppressing cancer stem cells, it has been observed that vitamin D also regulates tumour initiation and metastasis. In conclusion, the incorporation of well-designed studies on the metabolism of vitamin D from a genotypic and phenotypic perspective is required to understand the intricate mechanisms linking the role of vitamin D in skin carcinogenesis. These new findings will open up new pathways in targeting the disease and lead to novel opportunities for its treatment and cure.

Key words: DNA damage, skin cancer, tumour microenvironment, ultraviolet radiation, vitamin D

Skin Cancer

Introduction

Cancer, the emperor of all maladies, has coexisted with humankind since 1600 BC, when the first documented case of breast cancer was found in Edwin Smith Papyrus.¹ Since then, the disease has co-evolved with us and has caused a significant burden across the globe. Cancer affects almost every part of the body, including the lungs, breasts, skin, liver, colon and rectum. According to the global cancer statistics in 2020, skin cancer accounts for 6.2% of all new cancer cases.² The abnormal growth of cells in the epidermis due to mutations, which arise from unrepaired DNA damage, causes skin cancer. Generally, the head and neck are the sites where most cases of skin cancers occur. Skin cancer can be broadly classified into non-melanoma

and melanoma as represented in Figure 1. Non-melanoma skin cancers (NMSC) comprise basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Basal cell carcinoma is generally found in the basal cells of the lower epidermis. Though it grows slowly and rarely spreads to other parts of the body, if left undiagnosed and untreated, it may spread to the surrounding tissues.³

On the other hand, squamous cell carcinoma is a type of cancer that develops in the squamous cells. Figure 2 shows the classification of skin cancers and the outermost cell layer of the epidermis.⁴ Melanomas are cancers that arise in the melanocytes, pigment-producing cells (melanin), present throughout the skin cells.⁵ Ultraviolet radiations is one of the primary causes of this type of cancer.

How to cite this article: Nautiyal R, Bhatnagar P. Deciphering the role of vitamin D on skin cancers and tumour microenvironment. Indian J Dermatol Venereol Leprol. 2024;90:192–201. doi: 10.25259/IJDVL_1236_2021

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Received: December, 2021 **Accepted:** May, 2023 **Epub Ahead of Print:** July, 2023 **Published:** February, 2024

DOI: 10.25259/IJDVL_1236_2021 **PMID:** 37609744

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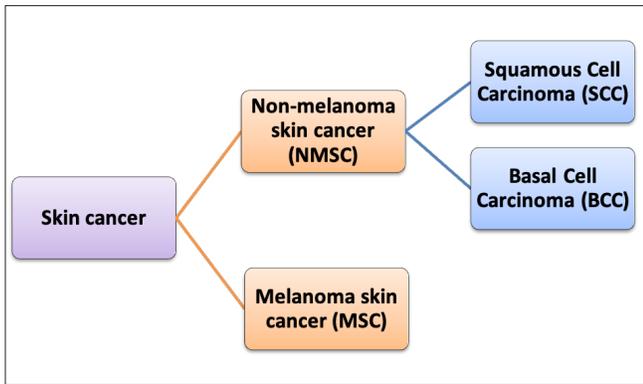


Figure 1: Classification of skin cancers

Incidence, burden and mortality

According to the global cancer statistics (GLOBOCAN) 2020, the estimates of worldwide incidence and mortality of 36 cancer types in 185 countries were analysed, and it was observed that skin cancer accounted for 1,198,073 new cases every year, which represents 6.2% of the total combined cancer cases in 2020 (Figure 3a).² The number of deaths due to skin cancer globally was estimated to be 63,731, accounting for 0.6% of total deaths reported in the year 2020.² It was also observed that melanoma of the skin was the fifteenth most common cause of cancer in males, with an incidence rate of 5.2 per 100,000 males and 0.4 per 100,000 males in countries with higher and lower human development index (HDI), respectively. Figure 3d represents the percentage incidences

of melanoma and non-melanoma skin cancers with respect to other cancers in India. However, the mortality rates were least when compared with other cancers, that is, 0.9 per 100,000 males and 0.2 per 100,000 males in higher and lower human development index countries, respectively.² In the case of females, the incidence rates were approximately two folds lower than the males (i.e. 7.9% in females and 15.1% in males respectively).²

The National Cancer Registry Program and GLOBOCAN 2018 reports were collected and analysed to understand the incidence of skin cancer in India. It is believed that, in the Indian population, the incidence rate of different skin cancers is lower, which is attributed to the protective effects of melanin.⁶ However, the unavailability of reports from national surveys and cross-country data and indirect indications from several small reports indicate an increase in the incidences of skin cancer in the country. The incidence of non-melanoma skin cancers and melanomas in India, specifically among the male population, was observed to be the highest in the north-eastern region. Additionally, among males, the incidence of non-melanoma skin cancers and melanoma was observed highest in Pasighat and Nagaland, respectively. However, melanomas and non-melanoma skin cancers were highest among females in the Northern (Delhi) and north-eastern regions (Pasighat). Amongst melanoma and non-melanoma skin cancers, the latter was found to be more common among the Asian population.⁷ Figure 3b represents the incidence of non-melanoma skin cancers worldwide in both sexes. It can be

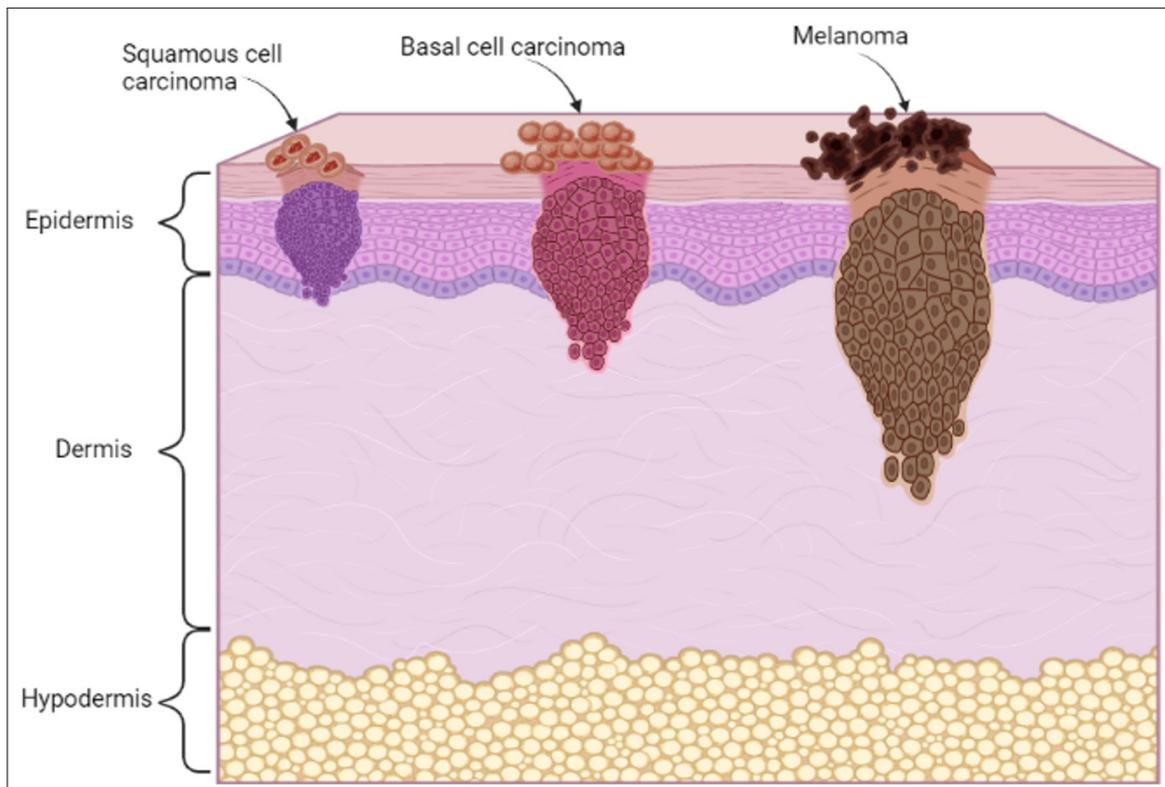


Figure 2: Types of skin cancer

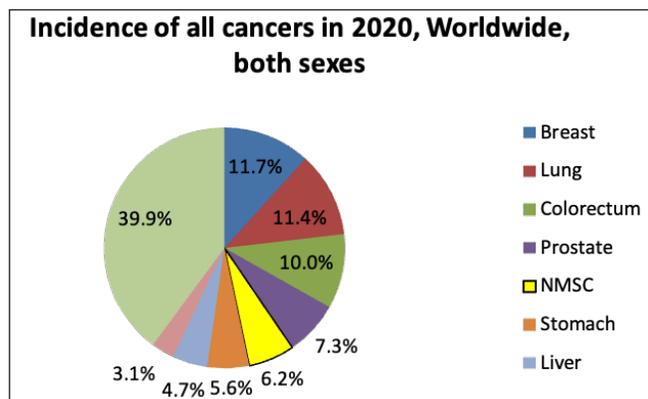


Figure 3a: Pie charts representing status of skin cancers in India and worldwide

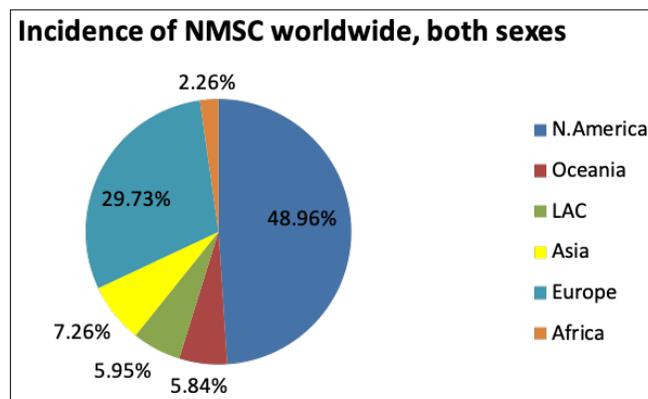


Figure 3b: Pie charts representing status of skin cancers in India and worldwide

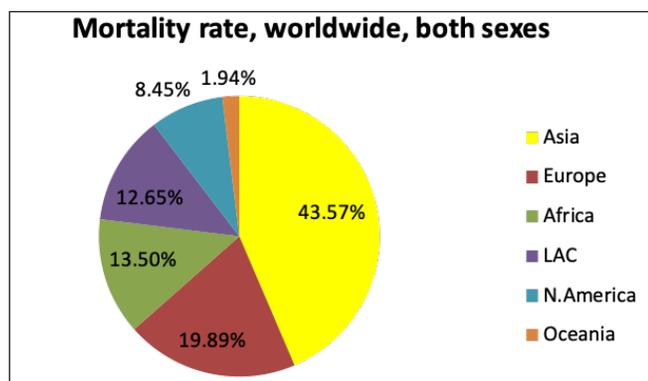


Figure 3c: Pie charts representing status of skin cancers in India and worldwide

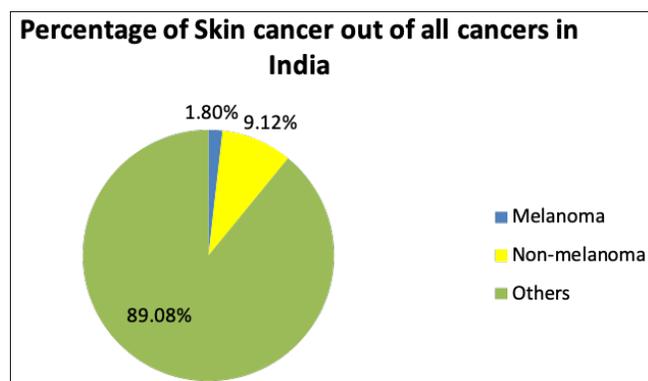


Figure 3d: Pie charts representing status of skin cancers in India and worldwide

seen that the incidence in Asian countries is 7.26%. However, the mortality rate due to all cancers is relatively high in Asian countries, that is, 43.5%, as shown in Figure 3c.⁸

Causes and risk factors

Skin cancer is caused due to mutations in the DNA of the skin cells, which leads to uncontrolled growth and formation of tumours. However, the combination of environmental and genetic factors is responsible for the risk of developing skin cancer. Long-term exposure to ultraviolet rays remains one of the most common causes. This chronic ultraviolet exposure has been associated with 90% of cutaneous squamous cell carcinoma and basal cell carcinoma cases and 65% of cutaneous melanomas.⁹

Current treatment strategies

The gold standard strategy for diagnosing non-melanoma skin cancers is primary physical examination, followed by biopsy and histopathologic examination.¹⁰ However, squamous cell carcinoma is susceptible to metastasize to adjacent tissues and therefore a thorough lymph node examination is also required for a complete diagnosis. To avoid invasive procedures for diagnostic purposes, several non-invasive tools have been developed, including dermoscopy, multiphoton microscopy, confocal microscopy, Raman spectroscopy, cross-polarized light and fluorescence

photography and coherence tomography with high-frequency ultrasound.¹⁰ These technologies help in characterising the features of non-melanoma skin cancers before going with the biopsy method. Dermoscopy, which is mainly used to identify melanocytic lesions, also screens squamous cell carcinoma and basal cell carcinomas.^{11,12} The most commonly used technique for treating non-melanoma skin cancers is the surgical removal of the lesion, which has the highest curing rate among other existing methods.^{13,14} Other methods which are employed to treat cases of non-melanoma skin cancers include cryotherapy, laser therapy, pharmacotherapy, radiation therapy and photodynamic therapy (PDT).^{15,16} However, a detailed discussion about the current treatment or management strategies is out of scope of this review.

Vitamin D

Introduction

Vitamin D, also known as calciferol, belongs to the family of fat-soluble vitamins that promote calcium absorption, regulate bone mineral metabolism and maintain muscle function.¹⁷ In nature, vitamin D exists in two primary forms, that is, vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol) derived from animal or plant sources. Because the human body is not able to synthesise vitamin D₂, it is generally added to foods. In contrast, vitamin D₃ is synthesised in the skin of the

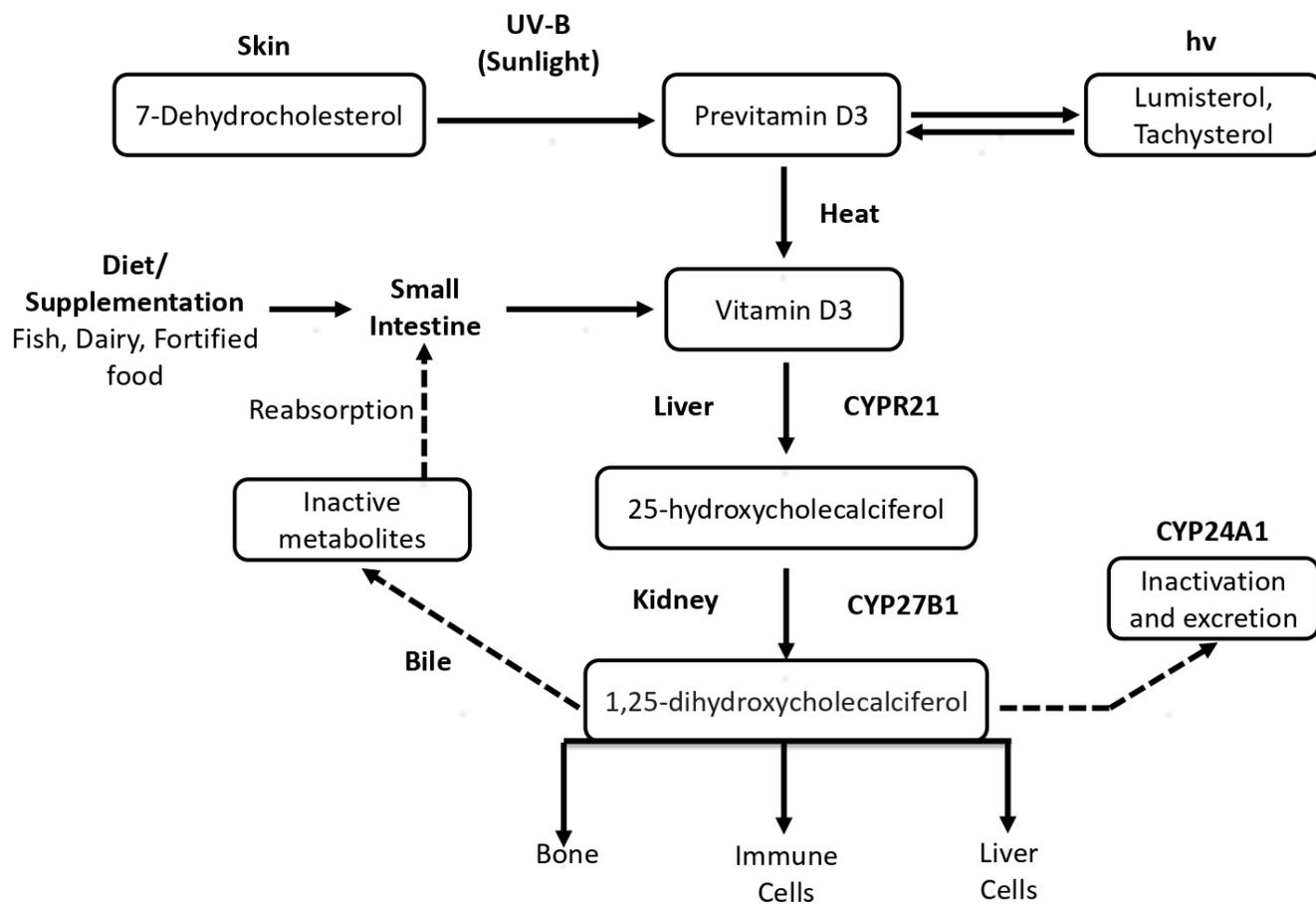


Figure 4: Endogenous synthesis of vitamin D and its metabolism

human body from endogenous 7-dehydrocholesterol through photochemical reaction by ultraviolet radiation. However, it can also be taken via the consumption of specific foods.¹⁸ Moreover, because vitamin D₃ is pharmacologically more potent than the D₂ form, it is generally preferred as a treatment option for vitamin D deficiency.¹⁹ However, vitamin D₃ is frequently used for the treatment of medical conditions such as refractory rickets and hypothyroidism. Apart from medical uses, it is also commonly used to supplement individuals suffering from low vitamin D levels in their bodies.

Synthesis and metabolism in the human body

The endogenous synthesis of vitamin D₃ begins with the skin exposure to ultraviolet-B radiation of wavelength between 295 nm and 315 nm.²⁰ Upon exposure to ultraviolet-B, the provitamin D₃ (7-dehydrocholesterol), a compound present in skin, is photo-isomerised into previtamin D₃ (precholecalciferol), which is converted into vitamin D₃ via a heat-dependent reaction.^{21,22} Later, the hydroxylation of vitamin D₃ occurs in the liver, which uses 25-hydroxylase to convert vitamin D₃ to 25-hydroxy-vitamin D₃ (25(OH)D), also known as calcidiol. The calcidiol is further hydroxylated in the kidneys to form calcitriol, an active metabolite in the hormonal form, with the help of the 1- α -hydroxylase enzyme. The flow chart of vitamin D synthesis and its metabolism

is shown in Figure 4.²³ The figure depicts the endogenous synthesis and metabolism pathway in the human body. To quantify vitamin D levels in the body, serum-free calcidiol is the best candidate because it has a half-life of 2–3 weeks, and it can be easily measured as well.^{24,25}

Source

Vitamin D can be obtained via three resources, namely, via conversion of 7-dehydrocholesterol into vitamin D₃ (cholecalciferol) upon sun exposure, from food and supplements. Dietary sources include natural food such as fish, beef liver, egg yolk, cheese and mushrooms. The Food and Drug Administration (FDA) has also approved ultraviolet-treated mushroom powders as a source of vitamin D₂ and as a food additive.²⁶ Table 1 shows the different food sources of vitamin D.²⁷ Sun exposure is one of the prominent sources of vitamin D, which fulfills its daily requirement. Specifically, ultraviolet-B, which falls in the wavelength range of 290–320 nm, is required to synthesise vitamin D₃. This radiation has poor penetration through glass, and therefore, the sun’s exposure indoors through a window does not help in vitamin D synthesis.²⁸ According to the literature, approximately 5–30 mins of sun exposure, twice a week or daily without sunscreen, is crucial for the synthesis of vitamin D that is adequate for the body.^{28,29} Various other factors such

Table 1: Food sources rich in vitamin D

Food source	UI per serving
Cod liver oil (1 tablespoon/5 mL)	1360
Swordfish (3 ounces)	566
Sardines in oil (3 ounces)	450
Salmon (3 ounces)	447
Mackerel (3 ounces)	30
Tuna in oil (3 ounces)	200
Tuna fish 3 ounces	154
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137
Milk, non-fat, reduced fat, and whole, vitamin D-fortified, 1 cup	115–124
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80
Liver, beef, cooked, 3 ounces	42
Egg, 1 large (vitamin D is found in yolk)	41
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75–1 cup (more heavily fortified cereals might provide more of the DV)	40
Cheese, Swiss, 1 ounce	6
Mushrooms, morel, raw (½ cup)	40

DV: Daily value

as latitude, colour and season also affect vitamin D synthesis in the body.²⁹ However, it is important to note that its overall synthesis can occur within the epidermis in order to associate this potentially with skin cancer.³⁰ Induction of 25-hydroxylase mRNA release by vitamin D₃ and ultraviolet-B radiation leads to the activation of 1,25(OH)₂D that causes local effects within the cell.³¹ Within the epidermis, the 2D action takes place via vitamin D receptor (VDR), which helps in the regulation of proliferation in the basal cells and also promotes the differentiation of keratinocytes as they start to form the upper layer of the epidermis.^{30,32}

Vitamin D and Skin Carcinogenesis

It is crucial and challenging to identify the role of vitamin D in the etiology of skin cancer in humans as exposure to sun is required for vitamin D production which may also, in some instance, is responsible for skin cancer. Various studies have been generated from *in vitro* and *in vivo* trials along with epidemiological and genetic studies in humans for deciphering the relationship between sun exposure, vitamin D and skin cancer.³³ Some include genetic studies on normal and cancerous skin cells, suggesting the role of vitamin D in specific vitamin D pathway gene abnormalities. Though some clinical data provide information linking the incidence or progression of skin cancer with vitamin D levels, it becomes complicated to differentiate the effects of vitamin D versus the effects of sun exposure as the latter is a principal determinant of vitamin D levels.³³

Shreds of evidence suggest that endogenous synthesis of vitamin D, metabolism and vitamin D receptor-regulated transcripts can control the growth and behaviour of cancer

cells.³⁴ Several clinical trials and *in vitro* studies have demonstrated the inhibitory effects of vitamin D in non-melanoma skin cancer, and their positive effects in the prevention of skin cancer. However, the exact relationship between these metabolic enzymes (CYP27A1, CYP27B1 and CYP24A1) and vitamin D receptor in the genesis and progression of non-melanoma skin cancer is not fully understood.³⁵

The enzyme CYP27A1 is a mitochondrial protein which plays an important role in the overall cholesterol homeostasis. The enzyme CYP27B1 is located in inner mitochondrial membrane and is involved in hydroxylation of 25(OH)D at the 1-alpha position. The enzyme CYP24A1 regulates the levels of vitamin D₃ by initiating the degradation of 1,25(OH)₂D₃. In a study of aggressive type melanomas by Brożyna *et al.*,³⁶ a decrease in the enzymatic activity of one of the above enzymes, CYP27B1, during melanoma progression was also reported.³⁶

Nemazannikova *et al.*³⁵ studied the intra tumoral expression of mitochondrial vitamin D metabolic enzymes and vitamin D receptors in non-melanoma skin cancer using standard immunohistochemistry. In the case of basal and squamous cell carcinomas, there was a strong expression of CYP27A1 that was associated with the CYP24A1 expression. Moreover, the above association was observed more significantly in case of squamous cell carcinoma. However, in the case of association between CYP27B1 and CYP24A1 expression levels, an inverse significant association is observed in all non-melanoma skin cancer cases.³⁵ Ellison *et al.*³⁷ observed an enhanced susceptibility to ultraviolet-induced tumorigenesis in murine skin after the inactivation of vitamin D receptors. They studied the role of vitamin D receptors in skin cancer. They observed a rapid development of chemically induced skin tumours in vitamin D receptor (–/–) mice; however, there was no such observation in the case of CYP27B1 (–/–) and wild-type mice [vitamin D receptor (+/+)]. This indicated that it is a vitamin D receptor and not a vitamin D₃ ligand, which is crucial for the protective effects against skin tumorigenesis. Moreover, there was a rapid development of ultraviolet-induced tumours in the case of vitamin D receptors (–/–) mice with greater penetrance than in wild-type mice. Also, the levels of p53 proteins were observed to be upregulated at similar rates in ultraviolet-treated keratinocytes of vitamin D receptor (–/–) than wild-type mice. Additionally, the results from *in-vivo* experiments reported an increased development of ultraviolet-induced tumours with higher penetrance when compared with wild-type mice, suggesting a critical role of vitamin D receptor in the repair and removal of severely damaged keratinocytes and adaptation of the skin to chronic ultraviolet exposure.³⁷

Muralidhar *et al.*³⁸ demonstrated the relationship between vitamin D and vitamin D receptor signaling using 703 primary melanoma transcriptomes.³⁸ Additionally, they tried

to replicate these findings in The Cancer Genome Atlas metastases. This study demonstrated the protective effects of vitamin D–vitamin D receptor signaling for melanoma-related deaths via inhibiting the Wnt/ β -Catenin pathway, impacting melanoma progression and antitumour immune response. Moreover, the overexpression of vitamin D receptor in murine melanoma cells resulted in fewer pulmonary metastases than the controls in tail vein metastasis assays. Therefore, the expression profile of vitamin D receptor could be used as a potential biomarker to differentiate melanoma patients that might respond better to immunotherapy.³⁷

On the other hand, Burns *et al.*³⁹ studied the association of vitamin D receptor polymorphisms with the risk of non-melanoma skin cancer in adults. The importance of vitamin D signaling confers protective effects against non-melanoma skin cancer upon ultraviolet-B exposure, which is mediated via vitamin D receptor.³⁹ However, recent examination of single nucleotide polymorphisms (SNPs) in the vitamin D receptor has resulted in contradictory results, which causes ambiguity, whether these polymorphisms increase an individual's risk of developing non-melanoma skin cancer. Hence, they examined the association of vitamin D receptor polymorphisms with non-melanoma skin cancer development and participants' demographic characteristics.

Basal cell carcinomas also arise due to defects in another major signaling pathway known as the Hedgehog pathway.⁴⁰ Sonic hedgehog (Shh) instigates the nuclear activation transcription factor Gli, which increases the anti-apoptotic and cyclin factors expressions with simultaneous suppression in keratinocyte differentiation genes.⁴¹ The components of the sonic hedgehog pathway get upregulated upon chemical carcinogenesis and ultraviolet-B exposure to the epidermal cells.⁴² According to a study, in vitamin D receptor-null mice, sonic hedgehog is elevated in the epidermis, utricles of dysplastic hair follicles and the outer rim of cells that make up the lipid-laden cells in dermal cysts.³⁹ These findings propose significant antagonistic functions of vitamin D receptor towards the sonic hedgehog signaling pathway and play a protective role during basal cell carcinoma formation.

Moreover, it is also suggested that vitamin D plays a significant regulatory role in the formation and prognosis of cutaneous malignant melanoma. Recently reported genetic variations in the vitamin D receptor gene are potent risk factors for the development and pathogenesis of melanoma, studied via single nucleotide polymorphism.⁴³ However, the causal effect relationship is unknown; it was observed that the individuals with low levels of 25(OH)D showed increase in cutaneous malignant melanoma.⁴⁴ *In vitro* studies also suggested the anti-proliferative effects of vitamin D on cultured melanoma cells as vitamin D blocks the proliferation of melanoma cells.⁴⁵ Some recent studies also demonstrated that responsive (MeWo), and resistant (SK-Mel-5) melanoma cell lines are implicated in the anti-proliferative effects of vitamin D governed by the degree by which vitamin D receptor and

Cyp24a1 is induced.⁴⁶ However, it was concluded that most melanoma cell lines were resistant to the anti-proliferative effects of vitamin D₃ and that vitamin D would positively affect a minority of melanoma cases in patients. On the other hand, co-treatment of melanoma cell lines with drugs that modulate epigenetics increased the responsiveness to vitamin D₃, suggesting possible combined therapy in some instances.⁴⁷

Protective effects of vitamin D from ultraviolet rays

The long wave ultraviolet-A and short wave ultraviolet-B are the types of ultraviolet rays in sunlight that damage DNA. In the case of ultraviolet-A, it penetrates into the deeper layers of skin and leads to production of free radicals, which then cause oxidative and DNA damage. Whereas ultraviolet-B usually affects the superficial layers of the skin, causing DNA damage leading to driver and bystander mutations followed by cellular transformations and malignancies.⁴⁸ Despite the photocarcinogenic⁴⁹ and immunosuppressive effects⁵⁰ of ultraviolet-B components, it is also crucial for the synthesis of vitamin D for its various functions in the body. In order to repair DNA damage post-ultraviolet exposure, the growth of the cell is arrested, wherein faulty repair or improper removal of damaged cells results in clonally expanded cells that constitute tumours.^{37,51–54} *In vivo* studies, trying to understand the role of vitamin D receptors upon short-term ultraviolet exposure, observed a decrease in the proliferation of normal mouse keratinocytes, however, the vitamin D receptor–ablated cells showed more proliferation. These results suggest the role of vitamin D receptor in promoting growth arrest upon short ultraviolet treatment.³⁷ Additionally, fewer apoptotic cells were observed in vitamin D receptor–null skin than in normal skin post-ultraviolet exposure, demonstrating the critical role of vitamin D receptor in eliminating severely damaged cells. Apart from ultraviolet exposure, the application of either oral or topical agents containing carcinogens also increases skin tumours in vitamin D receptor–null mice.⁵⁴

Dixon *et al.*⁵⁵ studied the inhibitory effects of 1 α ,25(OH)-vitamin D, and non-genomic vitamin D analogue against ultraviolet-induced skin carcinogenesis.⁵⁵ They demonstrated that both vitamin D₃ and 1 α ,25(OH)₂-lumisterol, a conformational analogue, were effective inhibitors of ultraviolet damage in an immunocompetent mouse (Skh:hr1) model susceptible to ultraviolet-induced tumours. Additionally, in mice, they observed inhibition of the development of skin cancer in the case of squamous cell carcinoma. These observations suggest the protective role of these compounds in the prevention of skin carcinogenesis.

In another study by Zhang *et al.*,⁵³ they investigated the role of DNA damage-inducible transcript 4 (DDIT4) in human squamous cell carcinoma.⁵² They observed a significant suppression of DDIT4 in the case of squamous cell carcinoma and A431 cell lines. Moreover, the reduction of DDIT4 accelerated the proliferation of keratinocytes but obstructed the autophagy flux through the mTORC1 pathway by affecting the downstream S6 kinase1, 4E-BP1, beclin1 and LC3 II/I.

The *in vivo* studies revealed the anti-carcinogenic effect of vitamin D in case of xenograft tumour-bearing mice treated with different concentrations of 1,25(OH)₂D₃ and DDIT4.

Apart from environmental factors, genetic factors also play a role in the development of skin cancer. For example, people with fairer skin are at an increased risk of developing skin cancer. Moreover, individuals with freckling and red hair carry two copies of the R allele variant of the *MC1R* gene and are also at increased risk of developing skin cancer. Xeroderma pigmentosum, a rare autosomal recessive disease, is a condition where the individuals suffering from this disease cannot repair the ultraviolet-induced damage leading to mutations in the genes that form an integral part of the nucleotide excision repair pathway. This pathway plays a vital role in repairing the damage caused due to ultraviolet rays.¹⁸ This abnormal condition predisposes an individual to an increased risk of developing freckling, sunburn and early childhood malignancies.

Daily requirement of vitamin D and preventive strategies

The daily requirement of vitamin D is dependent on an individual's age, but the standard concentration required for daily intake has been a topic of discussion. The Institute of Medicine, an independent, non-profit organisation, has provided data on daily vitamin D intake for individuals of different age groups, as shown in Table 2.¹⁸ The daily intake of vitamin D varies with age of an individual. For example, infants require a daily intake of 400 IU vitamin D₃, whereas individuals in the age group 1–70 years require 600 IU and for individuals above 70 years of age, the recommended intake is 800 IU/day.

Seamans et al.⁵⁶ validated the reliability and robustness of circulating levels of vitamin D as a marker of vitamin D status in the human body.⁵⁶ According to the American Endocrine Society, serum levels of vitamin D under 20 ng/mL are considered deficient. In contrast, serum levels in the range of 20–30 ng/mL are considered insufficient and levels above 30 ng/mL are considered essential for maintaining good health.⁵⁷

The Institute of Medicine has specified 20 ng/mL as the lower limit indicating healthy and sufficient vitamin D levels [Table 3].¹⁸ A higher level of vitamin D in serum, particularly above 200 ng/mL, is considered toxic, and the associated symptoms include weight loss, polyuria, anorexia and cardiac arrhythmia. Moreover, vitamin D toxicity also increases the risks of calcification of tissues and blood vessels and formation of kidney stones.²⁷

Table 2: Daily intake of vitamin D on the basis of age groups

Age group (years)	Daily intake (IU/d)
<1	400
1–70	600
>70	800

IU: International unit; d: Day

Table 3: Circulating levels of 25(OH) D₃ in human body

nmol/L	ng/mL	Health status
<30	<12	Linked with deficiency of vitamin D, which can cause rickets and osteomalacia in infants and adults, respectively
30–50	12–20	Considered as inadequate for bone health
≥50	≥20	Considered as adequate for bone and general health
>125	>50	High levels can be linked to potential adverse effects (>60 ng/mL)

A few lifestyle changes in daily life could help maintain healthy levels of vitamin D in the body and prevent its deficiency. This includes getting enough sun exposure as it is the primary source for vitamin D synthesis, daily intake of foods rich in vitamin D and being proactive to maintain overall health. However, for patients who have skin cancer and cannot get sensible sun exposure, the administration of vitamin D as a supplement could be employed as an alternative way to meet the daily requirements.

Effects of vitamin D on tumour microenvironment

Studies also demonstrated that vitamin D inhibits the growth of cancer cells and cancer stem cells⁵⁸ and plays an essential role in regulating the tumour microenvironment. Various studies suggest regulating tumour initiation and metastasis by influencing cell-microenvironment interactions by vitamin D.⁵⁹ A large number of tumour cells and a small portion of cancer stem cells exist in the stromal microenvironment, along with vasculature for nourishment, cancer-associated fibroblasts, immune cells and extracellular components. It is well demonstrated that chronic inflammation is the main contributor to the initiation of tumours.⁶⁰ In this regard, vitamin D is known to exert its anti-inflammatory effects with tumour-specific outcomes. For example, vitamin D₃ is responsible for the inhibition of the prostaglandin pathway that is involved in pro-inflammatory responses via inhibition of cyclooxygenase-2, prostaglandin receptors and degradation of prostaglandin in prostate^{61,62} and breast⁶³ tumour cells.

Vitamin D₃ is also known to suppress the p38 MAPK-regulated pro-inflammatory pathway in prostate cancer cells.⁶⁴ Blocking of pro-inflammatory nuclear factor kappa B (NFκB) pathway was also reported via vitamin D₃, and also the inhibition of Akt within macrophages.⁶⁵ Modulation of cancer and immune cell phenotypes by suppressing pro-inflammatory cytokines such as TNF-α and IL-6 by vitamin D₃ was also demonstrated.⁶⁶ Vitamin D receptor-null mice developed impaired cutaneous wound healing at the expense of F4/80+ macrophages recruited to the wound site.⁶⁷ Whether this impaired innate immune response observed in the skin can also contribute to the tumour microenvironment remains unexplored.

Most important question

Vitamin D: How much is enough?

Various studies cited above correlated elevated serum levels of vitamin D with higher exposure to the sun. A study by

Hart *et al.*⁶⁸ demonstrated possible independent effects of sun exposure on health, particularly immune-mediated effects not occurring through a vitamin D pathway.⁶⁸ This can be related to an issue linked to skin cancer development and its prognosis. Berwick *et al.*⁶⁹ were the first to validate the advantageous effect of the sun's ultraviolet rays on melanoma prognosis. The study reported that high intermittent exposure to the sun is associated with low death risk in patients with melanoma within 5 years of diagnosis.⁶⁹

Arguments have always been there regarding the optimal levels of vitamin D required for good health conditions. Various observational studies associate low levels of vitamin D with an increased risk of internal cancers. However, considering the various reviews of associations with a wide range of disease outcomes, the United States Institute of Medicine suggested a significant causal association of vitamin D levels with good bone health, and recommended serum levels of 50 nmol/L should be considered sufficient.¹⁸

The ultraviolet index, or UVI, is an international standard measurement of the strength of sunburn-producing ultraviolet radiation at a particular place and time. There was a consensus that vitamin D levels less than 25 nmol/L are considered deficient.⁷⁰ The Institute of Medicine concluded that vitamin D levels less than 30 nmol/L should be considered a deficiency risk.¹⁸ Upon diagnosis of skin cancer or in persons with increased risk of skin cancer, it may be appropriate to avoid sun exposure as much as possible and ensure adequate vitamin D status. There is considerable evidence that suggests a fall in vitamin D status following a diagnosis of skin cancer, for example the study by Idorn *et al.*⁷¹ The findings from this study suggested that patients with cutaneous malignant melanoma had a higher ultraviolet exposure in the summer before the diagnosis than did controls.

The production of vitamin D is primarily induced only by ultraviolet-B radiation. It is thus most effective when the intensity of ultraviolet-B is the highest throughout the day, that is, at noon, with simultaneous minimization of the risk of erythema.⁷² A general notion that directly correlates the production of vitamin D₃ with the surface area of the skin is that the more the skin area, the more will be the production of vitamin D₃.

On the other hand, erythema of skin or epidermal cells induces DNA damage and increases the risk of skin cancer. As a result, there should be maximum exposure to the skin when ultraviolet index is highest but for a short period for adequate vitamin D production.

Although, the absolute difference in time required to achieve the above condition when vitamin D₃ production and erythema being optimal at high ultraviolet index is narrow. For example, based on current dose-response models and International Commission on Illumination (CIE) action spectra, when the ultraviolet index is 12, it takes less than 5 min to produce an acceptable daily dose of vitamin D with only face and

arms exposed. On the other hand, it takes about 15 min for somebody to experience erythema.⁷³ While extreme caution would be required to avoid harmful levels of sun exposure, the appropriate strategy for people at high risk of skin cancer may be to apply sunscreen to the hands, face and arms routinely but to deliberately expose less frequently exposed areas of skin for a short time at a high ultraviolet index.

Future Perspective

The pleiotropic activities of vitamin D, in addition to the regulation of body calcium homeostasis, and anti-carcinogenic activities are consistent with the actions of multiple vitamin D derivatives produced in the human body. *In vivo* and *in vitro* studies were reviewed to document the role of vitamin D in photoprotection and the prevention or attenuation of non-melanoma skin cancers. Although the role of vitamin D in reducing the risk of skin cancer has been well established, its mechanism of action is not well understood. More experimental data on the mechanism of vitamin D in reducing the risk of skin cancer is required, which may open up novel opportunities for its diagnosis and treatment. Also, not all the tumour-suppressor actions of vitamin D receptor appear to be ligand-mediated, and there are a few studies where the vitamin D receptor can function in the absence of a ligand. However, such studies are limited and require more elaborative work.

Conclusion

The synthesis of vitamin D via the vitamin D pathway plays a significant role in maintaining the levels of circulating vitamin D in the body. Also, the same pathway is crucial for the pathogenesis and the progression of cutaneous melanoma, illustrating the gene–environment interactions. However, to understand these intricate mechanisms linking vitamin D and skin cancer, there is an increased need for well-designed prospective studies that will include information about genotypes and phenotypes of vitamin D metabolism and open up novel opportunities to establish a possible link between vitamin D and skin cancer. In summary, recent advances in vitamin D, skin biology and pharmacology are providing new and exciting opportunities in skin healthcare for treating different pathologies.

Acknowledgement

The authors would like to thank Dr. Utpreksha Vaish and Dr. Monika Chauhan for their valuable suggestions in the completion of this manuscript.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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