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Review Article

Determining how Vitamin D Affects the Microenvironment of Tumors and Skin Malignancies: A Review

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Abstract

As the fourth most frequent disease worldwide and the cause of 6.2% of all cancer cases combined, skin cancer poses a serious health risk. Though skin cancer death rates are lower than those of other cancers, they are noticeably higher in the Asian population (43%). The prognosis of skin cancer is associated with genetic, environmental, and DNA abnormalities; nonetheless, prolonged exposure to ultraviolet (UV) radiation continues to be one of the major contributing factors globally. In addition to being a vital source of vitamin D, exposure to the sun poses a significant environmental risk for skin cancer. However, research examining the connection between vitamin D levels and the risk of skin cancer has produced inconsistent, if not contradictory, findings. To shed light on the relationships, this study examines the function of vitamin D and skin carcinogenesis. Moreover, it has been shown that vitamin D controls the development and metastasis of tumors in addition to inhibiting cancer stem cells. In summary, to fully comprehend the complex mechanisms behind the function of vitamin D in skin carcinogenesis, well-designed studies on the metabolism of vitamin D from a genotypic and phenotypic perspective must be included. These new discoveries will create new avenues for addressing the illness and present fresh possibilities for its remediation.

Keywords: *Skin Cancer, DNA, Vitamin D, Remediation.*

Introduction

Since Edwin Smith Papyrus's discovery of the earliest known case of breast cancer in 1600 BC, cancer, the emperor of all diseases, has coexisted alongside humans. **[**1**]**. Since then, the illness has progressed alongside humans and has greatly increased global burden. Nearly every organ in the body is affected by cancer, including the skin, liver, lungs, breasts, colon, and rectum. As per the 2020 worldwide cancer statistics, 6.2% of newly diagnosed cases of cancer are skin cancer incidences. **[**2**]**. Skin cancer is brought on by mutations that result from unrepaired DNA damage and aberrant cell proliferation in the epidermis. The head and neck region typically accounts for the majority of skin cancer cases. As seen in Figure 1, skin cancer can be roughly divided into non-melanoma and melanoma. Squamous cell carcinoma (SCC) and

basal cell carcinoma (BCC) are examples of non-melanoma skin malignancies (NMSC). The basal cells of the lower epidermis are typically home to basal cell cancer. Even though HPV rarely spreads to other areas of the body and grows slowly, it can spread to the surrounding tissues if it is not identified and treated. **[**3**]**.

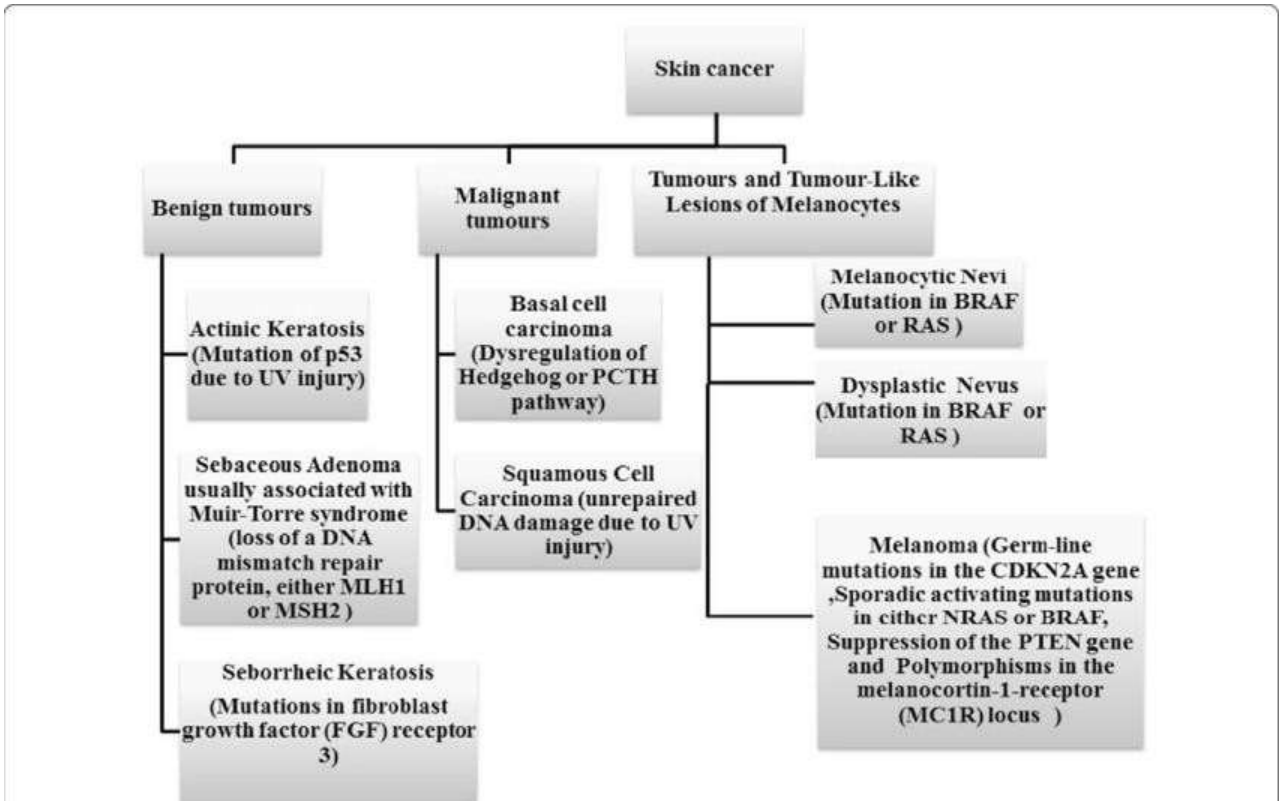

Fig: 1 Classification of Skin Cancer

However, one kind of cancer that appears in the squamous cells is called squamous cell carcinoma. The outermost layer of the epidermis's cell layer and the classification of skin malignancies are depicted in Figure 2. Cancers known as melanomas originate in the melanocytes, which are the pigment-producing cells (melanin) found in all skin cells.4. One of the main causes of this kind of cancer is ultraviolet radiation.

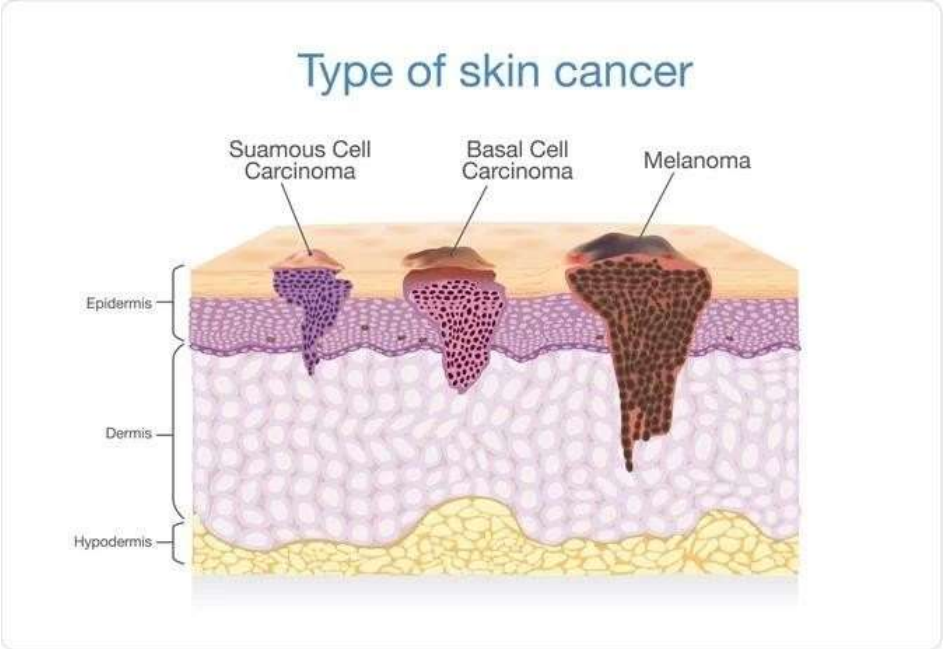

Fig 2: Types of Skin Cancers

Reasons and Risk Factors

Skin cell DNA abnormalities that result in unchecked proliferation and tumor formation are the primary cause of skin cancer. However, the likelihood of getting skin cancer is a result of a confluence of hereditary and environmental variables. Continuing exposure to UV radiation is still one of the most frequent causes. Chronic UV exposure has been linked to 65% of cases of cutaneous melanomas and 90% of cases of cutaneous squamous cell carcinoma and basal cell carcinoma.**[**5**]**.

Current methods of therapy

The primary physical examination is the gold standard for diagnosing skin malignancies other than melanoma, and it is followed by a biopsy and histopathologic examination.**[**6**]** But because squamous cell carcinoma can spread to nearby tissues, a comprehensive lymph node examination is also necessary for a definitive diagnosis. Many non-invasive diagnostic techniques, such as dermoscopy, multiphoton microscopy, confocal microscopy, Raman spectroscopy, cross-polarized light and fluorescence photography, and coherence tomography with high-frequency ultrasound, have been developed in order to avoid intrusive procedures.**[**7**]** Prior to using the biopsy approach, these technologies aid in characterizing

the characteristics of skin tumors that are not melanoma. Dermoscopy screens for basal cell carcinomas and squamous cell carcinomas in addition to being used to identify melanocytic lesions.**[**8, 9**]** With the best cure rate of any currently available therapy, surgical excision of the lesion is the most often utilized procedure for treating non-melanoma skin malignancies.**[**10, 11**]** Additional techniques used to treat non-melanoma skin cancer patients include photodynamic treatment (PDT), radiation therapy, medication, cryotherapy, and laser therapy.**[**12**]** However, the scope of this study does not allow for a full examination of the current approaches to treatment or care.

Calciferol, another name for vitamin D, is a member of the fat-soluble vitamin family that supports the absorption of calcium, controls the metabolism of bone minerals, and preserves muscle mass.**[**13**]** There are two main forms of vitamin D found in nature: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), which can be obtained from plants or animals. Since vitamin D2 cannot be synthesized by the human body, it is typically given to diet. On the other hand, endogenous 7-dehydrocholesterol is converted into vitamin D3 in the human skin via a photochemical reaction triggered by ultraviolet light. It can also be taken, though, by eating particular foods.**[**14**]** Furthermore, vitamin D3 is typically chosen as a therapeutic option for vitamin D deficiency due to its pharmacological potency above that of the D2 form.**[**15**]**

Synthesis and Metabolism

The first step in the endogenous synthesis of vitamin D3 is skin exposure to UV-B radiation with a wavelength of between 295 and 315 nm.20 Provitamin D3 (7-dehydrocholesterol), a substance found in skin, photo-isomerizes into previtamin D3 (precholecalciferol), which then undergoes a heat-dependent reaction to become vitamin D3. Later, vitamin D3 is hydroxylated in the liver by 25-hydroxylase, which results in the formation of 25-hydroxy-vitamin D3 (25(OH)D), or calcidiol. With the aid of the 1-α-hydroxylase enzyme, the calcidiol undergoes further hydroxylation in the kidneys to generate calcitriol, an active metabolite in the hormonal form displays the flow chart for the synthesis and metabolism of vitamin D. **[**16**]**

Vitamin D and the Development of Skin Cancer

Determining the function of vitamin D in the etiology of human skin cancer is important and difficult because sun exposure is necessary for the creation of vitamin D, which may also be the cause of skin cancer

in certain cases. Understanding the connection between sun exposure, vitamin D, and skin cancer has been accomplished through a variety of research that have been produced from in vitro and in vivo trials as well as epidemiological and genetic investigations in humans.[17] Certain vitamin D pathway gene anomalies may be related to vitamin D, as suggested by genetic investigations conducted on both malignant and normal skin cells. While there are clinical data that link vitamin D levels to the occurrence or progression of skin cancer, it can be challenging to distinguish between the sun exposure, which is a major factor in determining vitamin D levels, makes it more difficult to distinguish between the effects of vitamin D and sun exposure.[18]

A growing body of research indicates that the growth and behavior of cancer cells may be governed by endogenous vitamin D production, metabolism, and transcripts regulated by vitamin D receptors.[19] Vitamin D has been shown to have inhibitory effects on non-melanoma skin cancer as well as beneficial benefits in the prevention of skin cancer in a number of clinical trials and in vitro research. It is unclear, nevertheless, exactly how the vitamin D receptor and certain metabolic enzymes (CYP27A1, CYP27B1, and CYP24A1) relate to the development and course of non-melanoma skin cancer.[20]

An essential component of the general balance of cholesterol is the mitochondrial protein enzyme CYP27A1. The inner mitochondrial membrane contains the enzyme CYP27B1, which is involved in the hydroxylation of 25(OH)D at the 1-alpha location.

Defects in the Hedgehog pathway, another important signaling system, can also lead to basal cell carcinomas. Forty Sonic Hedgehog (Shh) triggers the nuclear activation transcription factor Gli, which raises the expression of cyclin and anti-apoptotic proteins while suppressing the genes involved in keratinocyte development.[21] When UV-B rays are exposed to epidermal cells and chemical carcinogenesis occurs, the components of the Sonic Hedgehog pathway are activated.[22] Sonic hedgehog is upregulated in the epidermis, utricles of dysplastic hair follicles, and the outer rim of cells that comprise the lipid-laden cells in dermal cysts in vitamin D receptor-null mice, per a study.[23] These results suggest that the vitamin D receptor has important antagonistic effects on the Sonic Hedgehog signaling pathway and may be protective against the development of basal cell carcinoma.

Daily Intake of Vitamin D

Age determines how much vitamin D is needed daily, yet there has been debate over the recommended concentration needed for daily use. Data on vitamin D intake per day for various age groups have been published by the independent, non-profit Institute of Medicine, as Table 2.18 illustrates. An individual's age affects how much vitamin D they should consume each day. For instance, adults over 70 years of age should consume 800 IU of vitamin D3/day, while babies need 400 IU. All other age groups require between 600 and 700 IU.

The validity of circulating levels of vitamin D as a gauge of vitamin D status in the human body was confirmed by Seamans et al. (24). Vitamin D deficiency is defined as serum levels less than 20 ng/mL by the American Endocrine Society. On the other hand, serum levels above 30 ng/mL are thought to be necessary for preserving good health, whereas those between 20 and 30 ng/mL are seen to be inadequate.**[**25**]**

A few little adjustments to daily routine could assist the body maintain enough amounts of vitamin D and avoid vitamin D insufficiency. This entails consuming foods high in vitamin D on a daily basis, obtaining adequate sun exposure—as this is the main way to synthesize vitamin D—and taking proactive measures to preserve general health. On the other hand, vitamin D supplementation may be used as a substitute for prudent sun exposure for individuals with skin cancer who are unable to obtain the recommended daily intake.

Selected food sources of vitamin D		Food sources of calcium	
food	**IU per serving**	**food**	**milligrams**
Cod liver oil	1,360	yogurt	415
Tuna fish	154	Milk 1 cup	300
Orange juice	137	Orange juice	300
Milk, grains	115-124	broccoli	21
Margarine	60	Cottage cheese	138
Egg	41	sardines	324
cheese	6	Cheddar cheese	204

Effects of vitamin D on tumor microenvironment

Studies have also shown that vitamin D is crucial for controlling the tumor microenvironment and suppresses the proliferation of cancer cells and cancer stem cells. According to a number of studies, vitamin D may control the development and spread of tumors by affecting interactions between cells and their surroundings.**[**26**]** The stromal microenvironment contains a high concentration of tumor cells and a small percentage of cancer stem cells, as well as extracellular components, immune cells, cancer-associated fibroblasts, and the vasculature for nutrition. The primary cause of tumor start has been amply established to be chronic inflammation. It is well recognized that vitamin D has anti-inflammatory properties that are particular to individual tumors.

It is also known that vitamin D3 inhibits the pro-inflammatory pathway in prostate cancer cells that is

mediated by p38 MAPK.[27] It has also been observed that vitamin D3 inhibits the pro-inflammatory nuclear factor kappa B (NFκB) pathway and inhibits Akt in macrophages.65 It was also shown that vitamin D3 modifies the phenotypes of immune cells and cancer by inhibiting pro-inflammatory cytokines including TNF-α and IL-6.66 Mice lacking the vitamin D receptor experienced worse cutaneous wound healing, which was caused by the recruitment of F4/80+ macrophages to the wound site.[28] It is unknown if the compromised innate immune response seen in the skin might potentially affect the tumor microenvironment.

Future Perspective

The actions of certain vitamin D derivatives made by the human body are compatible with the pleiotropic properties of vitamin D, as well as its ability to regulate calcium homeostasis and have anti-carcinogenic properties. The involvement of vitamin D in photoprotection and the prevention or attenuation of skin malignancies other than melanoma was documented by reviewing both in vivo and in vitro studies. [29] While it is widely known that vitamin D lowers the incidence of skin cancer, its exact mode of action is yet unknown. Further research is needed to determine the exact mechanism by which vitamin D lowers the incidence of skin cancer, as this could lead to new developments in the detection and management of the disease. Furthermore, not all of the vitamin D receptor's tumor-suppressive effects seem to be ligand-mediated, and some research suggests that the vitamin D receptor can still function in the absence of a ligand. These investigations are constrained, though, and more thorough research is needed. [30]

Conclusion

The body's ability to produce vitamin D through the vitamin D route is crucial for preserving the amount of vitamin D that is in circulation. Additionally, the pathophysiology and advancement of cutaneous melanoma are significantly influenced by the same route, demonstrating the interplay between genes and environments. However, in order to fully comprehend the complex mechanisms underlying the relationship between vitamin D and skin cancer, more well-designed prospective studies are required. These studies should provide data on the genotypes and phenotypes of vitamin D metabolism as well as present fresh approaches to investigating the possibility of a relationship between vitamin D and skin cancer. In conclusion, new and exciting possibilities in skin healthcare are being presented by developments in vitamin D, skin biology, and pharmacology for the treatment of various diseases.

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