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Mini-review

Non-melanoma skin cancer: Importance of gender, immunosuppressive status and vitamin D

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Abstract

Ultraviolet light B (UVB) is responsible for the majority of cutaneous damage and is believed to be the single most important etiologic agent in the development of non-melanoma skin cancers (NMSC). These skin tumors are by far the most common form of cancer in humans, with over 1 million new cases identified in the United States each year. Several risk factors exist, which increase the chance of a patient developing NMSC including gender, immunosuppressive status and more controversially vitamin D levels. The present review provides an overview of each of these areas.

Keywords: Ultraviolet light; Solid organ transplants; Male; Female; Vitamin D

1. Introduction

Sunlight that reaches the earth's surface and ultimately our skin is the single most important risk factor for the development of non-melanoma skin cancer (NMSC). Solar radiation is made up of three wavelengths UVA, UVB, and UVC light although UVC is currently filtered out by our earth's atmosphere. It has been well documented that UVA and UVB function as initiators and promoters in the cutaneous carcinogenesis process [1]. However, numerous additional factors including gender, immunosuppressive status, and vitamin D levels all contribute to the development of this most common cancer. The present review will examine what is currently known about how these factors influence NMSC development.

2. Ultraviolet light and inflammation

Ultraviolet light B (UVB; 290–320 nm) is a major environmental carcinogen that has been implicated in the development of both basal cell carcinoma (BCC) and squamous cell carcinomas (SCC), collectively known as NMSC. These skin tumors are by far the most common form of cancer in humans. In 2002, an estimated 1 million Americans were diagnosed with NMSC. According to statistics from the American Cancer Society non-melanoma skin cancer has the highest incidence of all cancers and approximately equals all other cases of human cancers combined [2]. Epidemiological as well as basic research studies have demonstrated that the

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inflammatory response seen following both brief periods of high intensity sun exposure as well as chronic sun exposure plays a critical role in the formation of NMSC [3–6]. This exposure induces functional changes in both resident skin cells as well as infiltrating cells of the immune system, which may ultimately contribute to the development of skin cancer [7–10]. Exposure to UVB light is initially associated with an inflammatory response characterized by increased blood flow and vascular permeability which results in edema and erythema, the infiltration of neutrophils into the dermis, the induction of pro-inflammatory cytokines and the production of reactive oxygen species (ROS) [9,11,12]. It is now clear that inflammatory cells have significant effects on tumor development. Early in the tumor development process inflammatory cells such as neutrophils can be powerful tumor promoters. Neutrophils and other phagocytic cells induce DNA damage in proliferating cells through their generation of reactive oxygen and nitrogen species, which in normal circumstances are produced by these cells to fight infection [13]. In addition these cells mediate damage through the generation of arachidonic acid derivatives, including prostaglandins and leukotrienes, which are capable of producing an intense inflammatory response [14]. Exposure of epidermal cells to UVB light both *in vivo* and *in vitro* has been associated with increased release of arachidonic acid (AA) from membrane phospholipids [15,16] as well as increased biosynthesis of prostaglandins from AA via the induction of the cyclooxygenase-2 (COX-2) enzyme [17]. These prostaglandins are now believed to contribute to the damage associated with the UVB induced inflammatory response in the skin. It is known that the production of prostaglandin E_2 (PGE_2) by the COX pathway contributes to ROS generation in two ways: first, oxygen radical generation during the catalytic conversion of prostaglandin G_2 to H_2 and second, prostaglandin-mediated oxidative alterations of the inflammatory process. As a byproduct of prostaglandin synthesis, reactive oxygen species that can induce the formation of oxidative DNA adducts such as 8-oxo-deoxyguanosine (8-oxo-dG) are formed [18]. A number of recent studies including our own demonstrated that 8-oxo-dG is one of the major modified DNA base products after UVB irradiation and suggested that 8-oxo-dG may be associated with UVB-induced skin carcinogenesis [19–22]. Recent studies also suggest that reactive intermediates such as those produced following UVB exposure may also contribute to the mutation of genes such as p53, a tumor-suppressor gene that has been shown to play an important role in multistep carcinogenesis, particularly in UV-induced tumorigenesis. [23,24]. Therefore an increase in PGE_2 production and function appears to be critical to the observed damaging effects of UVB light on the skin [25–29]. Having said that, certain other risk factors play key roles in determining the numbers of skin tumors that develop in different populations.

3. Gender and skin cancer

With the increased focus on individualized medicine, there is growing interest and attention being paid to gender differences in physiological processes.

Gender differences have been reported in the development of a number of diseases including tobacco-induced lung cancer [30], myeloid leukemia [31], multiple sclerosis [32], and diabetic cardiomyopathy [33]. Additionally, there is a male gender bias with respect to enhanced morbidity and mortality following trauma and sepsis [34]. Males have also been found to display enhanced phenotypic and innate immune responses to endotoxin [35] and gender differences in the inflammatory pain response have also been identified [36,37]. In addition, females demonstrate enhanced immune responses following hemorrhagic shock compared to males [38,39]. There appears to be a gender related difference in the development of cancer as well. Previous studies, as well as a recent report of the "Surveillance, Epidemiology and End Results" (SEER) program of the National Cancer Institute, revealed that the cancer incidence for all sites are greater in males compared to females, and that the cancer mortality rate is similarly higher in males [40,41]. These gender differences appear to hold true for NMSC as well. Epidemiological studies have reported the development of significantly more NMSC in men than women [42–45], with the American Cancer Society reporting approximately twice the incidence of NMSC development in men compared to women and a threefold greater incidence of cutaneous squamous cell carcinoma (SCC) in males compared to females [2]. Skin cancer is less common in darkly pigmented persons than in light-skinned Caucasians but is often associated with increased morbidity and mortality [46]. A recent population-based study assessed trends in mortality rates for NMSC reported that in the United States the rate among men was twice that among women. Furthermore, mortality rates among white men exceeded that of black men by a factor of two; the same was observed among women, but to a lesser extent [47]. It is currently believed that lifestyle choices play a major role in this gender disparity. Historically men tended to have occupations that required them to spend more time out in the sun and overall men are less likely to use sun protection than women [48,49]. Occupational exposure to ultraviolet light does show a strong relationship between cumulative sunlight exposure and SCC risk [50]. However, no clinical studies have examined gender differences in the development of NMSCs following exposure to equivalent UV doses. Recent studies from our laboratory using the Skh-1 mouse model have demonstrated that while male mice exhibited less UVB-induced inflammation compared to female mice, they displayed higher levels of epidermal oxidative DNA damage and lower total antioxidant activity levels both prior to and 48 h following a single UV exposure. Long-term studies showed that when exposed to equal doses of UVB, male Skh-1 mice developed tumors earlier, in greater number and with a more advanced grade than female mice [51]. These results suggest that skin cancer development in males may be influenced more by inherent antioxidant capacities and the resultant oxidative DNA damage, in contrast to female skin, where the magnitude of the UVB-induced inflammatory appears to play a more important role. Clearly gender related hormonal differences may play key roles in the observed responses to acute UVB exposure as well as in UV-induced tumor development. The skin locally synthesizes significant amounts of sexual hormones with intracrine or paracrine actions. The local level of each sexual steroid depends upon the expression of each of the androgen- and estrogen-synthesizing enzymes in each cell type within the skin [52]. Surprisingly little work has been carried out examining the contribution of the sex hormones to skin cancer development. Further studies exploring these differences in both murine models and human skin are necessary (Fig. 1).

4. Immunosuppression and skin cancer

4.1. Solid organ transplantation and skin cancer

According to the United Network for Organ Sharing, 28,930 solid organ transplantations were carried out in the United States in 2006 and approximately 140,000 organ transplant recipients are living in the United States [53]. Patient and organ

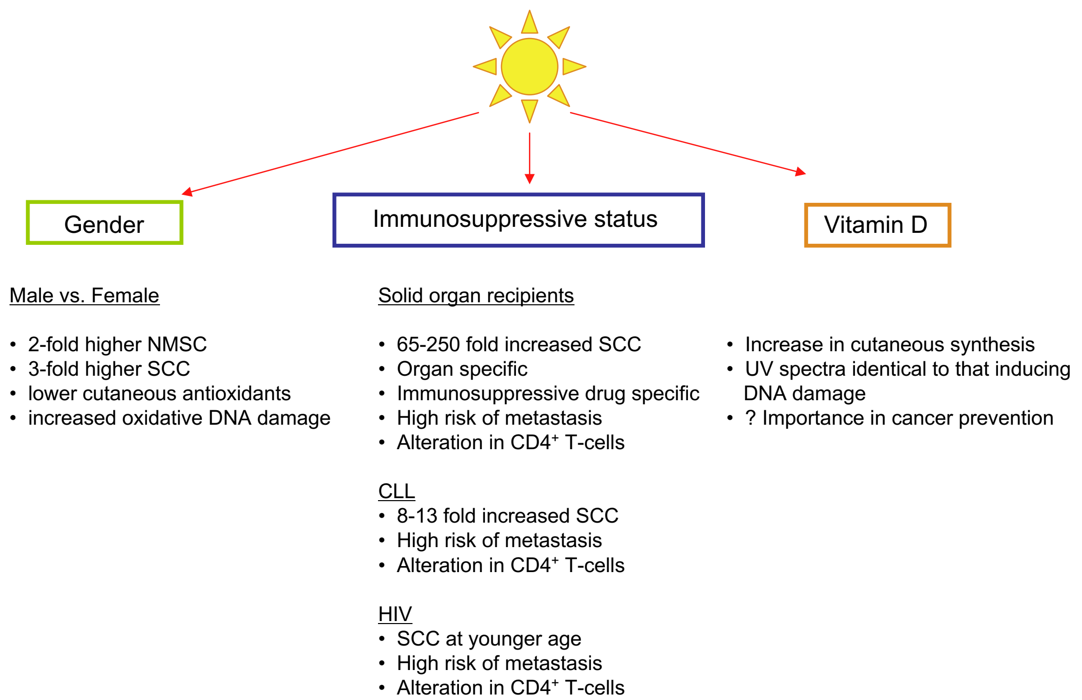

Fig. 1. Differential effects of UVB on gender, immunosuppressed patients and vitamin D.

survival following transplantation have increased substantially over the past 20 years as a result of better surgical techniques and more efficient immunosuppressive regimes. This increased survival rate has lead to the realization that the lifelong immunosuppressive treatment and the resulting modification of the immune system is associated with an increased risk of developing various cancers, with NMSC being the most common post-transplant malignancy [54,55]. The risk of UV-induced NMSC in these patients is between 65- and 250-fold higher than that seen in the general population, with a 27–44% incidence of NMSC after 10–25 years of immunosuppressive therapy [56–60]. While the general population more commonly develops the more benign BCC as compared to the more invasive SCC (1:3) this ratio is inverted to a 4:1 ratio in favor of SCC in transplant recipients [59]. These patients develop an excess of SCC at a relatively young age compared to the general population, with increased risk of local recurrence, regional and distant metastasis and significant morbidity and mortality [61–66]. More than one hundred NMSC, with high risk of metastasis and death, may develop in a high-risk patient in one year [56]. In fact SCC has been reported to account for 27% of deaths in Australian heart transplant patients surviving more than 4 years after transplantation [67]. The percentage of patients who have had skin cancer increases dramatically with time after transplantation and also with increased latitude [58]. For example 45% of patients in Australia develop a skin tumor within ten years of receiving a solid organ transplant but only 10–15% of patients in Italy or Holland did so [58,67–69]. In the United States a study carried out in heart transplant patients found a 35% incidence of skin cancer at 10 years post transplant [70]. The organ that is transplanted also appears to result in observed differences in skin cancer incidence. Heart transplant recipients develop skin cancer at rates two to three time higher than in age-matched recipients of kidneys [59,71,72]. This increase appears to correlate to an older age at transplantation as well as the levels of immunosuppressive therapy necessary to prevent rejection [71]. The presence of signature p53 mutations, a hallmark of UV exposure, in skin tumors arising in transplant patients indicates that as tumors arising in the immunocompetent population, UV light is also an important etiologic factor for these tumors [73].

In addition to UV exposure, age and organ type, the risk of developing NMSC in transplant recipients appears to depend on the type and duration of immunosuppressive therapy being administered and appears to be associated with a decreased $CD4^+$ lymphocytic response [59,74]. The link between this decrease and the development of skin cancer is suggested by the fact that in the NMSC of normal individuals, $CD4^+$ lymphocytes are the predominant inflammatory cell, while in immunosuppressed transplant recipients, $CD4^+$ and $CD8^+$ cells are present in equal numbers [75]. Continued prolonged immunosuppressive therapy results in a significant decrease in the number of dermal $CD4^+$ lymphocytes while Langerhans cells in the epidermis remain unchanged [59,74,76]. In addition to both directly and indirectly damaging DNA, UV light suppresses the cutaneous immune system as a result of a decrease in the density of epidermal Langerhans cells inhibiting antigen presentation and recognition in an already immunocompromised host [77,78]. This decrease in $CD4^+$ T-cells combined with the decrease in Langerhans cells as a result of UVB exposure may be an important component of the increased skin cancer risk in these patients. Furthermore, transplant patients with NMSC have been found to have significantly reduced numbers of $CD4^+$ lymphocytes compared with transplant patients without NMSC [79,80]. In fact recent studies have demonstrated that stopping immunosuppressive therapy and thus reversing the CD4 inhibition has resulted in a decrease in the development of SSC in transplant patients [81,82]. Clearly the treatment must be balanced with risk of organ rejection.

4.2. Leukemia and skin cancer

Chronic lymphocytic leukemia (CLL), the most common form of leukemia in the United States, affects approximately 81,000 patients per year in the US resulting in a prolonged immunocompromised status [83]. This immunocompromised status contributes to the increased risk in these patients of developing other cancers, the most common of which is NMSC cancer [84]. These tumors, associated with chronic UV exposure, are potentiated by the immunodeficiency and the immune dysregulation associated with CLL [85,86]. An estimated 8–13-fold increased incidence in developing skin cancer has been described in these patients [84]. Similar to transplant patients, CLL patients have an altered ratio of BCC to SCC [87]. The increase in the ratio of SCC to BCC implies that SCC development may be more controlled by intact immunosurveillance mechanisms than in many other cancers. Therefore a decrease in immunosurveillance may be permitting uncontrolled proliferation of UV damaged cells. Studies have also showed an increased incidence of skin cancers in patients diagnosed with non-Hodgkin's lymphoma [86]. Lymphoma and leukemia associated SCC tends to behave more aggressively and have substantially higher rates of recurrence and metastasis [87,88] than in non-immunocompromised patients. This higher rate may result from the underlying T-cell defects [84,89] or could be as a result of prolonged treatment with alkylating agents and other immunosuppressant therapies. This may also explain the increased incidence of SCC in transplant patients [90,91].

4.3. HIV and skin cancer

As is seen with solid organ transplant patients, improved immunosuppressive therapies have had a significant impact on HIV infected individuals, transforming the once terminal illness to a chronic disease. The development of highly active anti-retroviral therapy in the mid 1990s reduced the incidence of AIDS and mortality in HIV-infected people [92,93]. A result of this increased life span is the increased incidence of a variety of non-AIDS-defining cancers in HIV-infected adults including SCC of the skin. As seen in transplant patients and in patients with CLL, it appears that these tumors have a more aggressive clinical course in HIV-infected people than in the general population [94]. Patients with HIV have been found to develop rapidly growing SCCs at a young age (median age, 44 compared with 70 years in the general population) with a 20% risk of local recurrence and a high risk for metastasis [95–97]. Available data suggests that anti-tumor response and survival in HIV-infected people with malignancy are improved in people with higher $CD4^+$ counts [98]. However, the possible mechanisms for the increased incidence and altered clinical course of SCC development in HIV-infected people remain unclear.

5. Vitamin D

Exposure to UVB is known to have adverse effects on our skin including inducing tumor formation as well as photoaging. However, one beneficial effect of UV exposure is the production of vitamin D. 1,25-dihydroxyvitamin D3 [1,25(OH)(2)D(3)], the biologically active vitamin D metabolite, has a variety of important physiological effects. It has been shown to be important in preventing a number of diseases including bone diseases, cancers, autoimmune diseases, as well as cardiovascular diseases [99–103]. Our body can acquire vitamin D both by UVB induced conversion of 7-dehydrocholesterol in the skin and in smaller amounts through the intake of supplemented foods or nutritional supplements. Unfortunately, the UV action spectra for vitamin D photosynthesis, DNA damage and skin cancer are identical [104]. Questions have arisen in recent years as to how much UVB exposure is needed for adequate vitamin D synthesis, how to balance this with the risk of skin cancer development and how much vitamin D is really needed for maintenance of health.

While for a majority of people, exposure to UVB light may be the primary source of vitamin D [105], oral supplementation has been found to adequately increase circulating vitamin D levels to recommended doses [106] suggesting that unnecessary intentional UVB exposure can be prevented [107]. The balance between UVB exposure necessary for adequate vitamin D synthesis vs. the increased risk of developing skin cancer has resulted in controversy since repeated exposures to UVB have been linked with the development of not only NMSC in immunocompetent and immunocompromised individuals but also with melanoma development [56,108]. The daily production of vitamin D in the skin occurs after a short UVB exposure, less than one minimal erythemic dose [109,110]; however, the probability is that the public will spend more time in the sun than the minutes needed for vitamin D production. Further UV exposure results only in more extensive conversion of the pro-vitamin D to inactive metabolites but increases DNA damage, which over time leads to increases in tumor development [25,110,111].

The effects of UVB on the skin in terms of both vitamin D synthesis and DNA damage directly correlate with individual skin types (I–VI). These skin types are defined by the extent that the individuals skin, following a period of little or no exposure, sunburns vs. tans in response to moderate sun exposure [112]. For example a type I individual who burns easily and rarely tans will achieve maximal vitamin D synthesis in a matter of minutes during sun exposure in the spring or summer and burn at longer exposures where as an individual with darker type VI skin will not sunburn but will also have less vitamin D synthesis per sun exposure [113]. Therefore it appears that for at least some individuals, adequate vitamin D levels will not be easily achievable solely through UVB exposure.

A link between UVB induced vitamin D synthesis and health has been touted based upon the reported inverse association between increased risk of dying of a number of cancers such as colon and breast and the distance of the patient from the equator [100]. A review by Garland et al [114] of relevant epidemiological studies reported that 20 out of 30 studies on colon cancer, 9 out of 13 on breast cancer, 13 out of 26 on prostate cancer and 5 out of 7 on ovarian cancer reported a significant benefit of vitamin D, its serum metabolites, sunlight exposure or another marker of vitamin D status on cancer risk or mortality. A potential flaw in epidemiological studies however is that a majority of these studies linking low UV exposures to higher incidence of internal cancers used latitude as a surrogate for exposure rather than measuring personal UV dose. In reality, the health benefit in increasing serum vitamin D levels suggested by epidemiological studies has only recently begun to be investigated in prospective randomized studies. A recent prospective randomized placebo-controlled trial of vitamin D supplementation involving post-menopausal women, found no relationship between colorectal cancer risk and vitamin D intake, sun exposure or baseline serum vitamin D levels [115]. However, Lappe et al. [116] reported that improving calcium and vitamin D nutritional status substantially reduced all-cancer risk in postmenopausal women, suggesting that supplementation provides the desired protective effect without increased skin cancer risk. A more recent study showed a moderate, non-significant inverse association between serum vitamin D levels and reduced risk for colorectal adenoma recurrence, particularly among women [117]. An additional confounding variable is that it still is not clear exactly how much vitamin D is needed to protect against cancer and other diseases. Recommendations for vitamin D are provided in the Dietary Reference Intakes developed by the Institute of Medicine of the National Academy of Sciences. The US Recommended Dietary Allowance of vitamin D is 200 IU (5 μg), which many experts now feel is too low [118–121]. A recent report suggests that the most advantageous serum concentration for a number of health endpoints begins at 30ng/ml with the optimal concentration falling between 36 and 40 ng/ml [122]. Taken together, these studies demonstrated the need for further controlled prospective studies to determine if there truly is a relationship between vitamin D levels and the incidence of cancer and other diseases [107] and to determine if increased skin cancer risks are balanced by positive effects resulting from increased cutaneous vitamin D synthesis.

6. Conclusions

Non-melanoma skin cancer (NMSC) is the most common malignancy occurring in white populations. It is currently becoming an important challenge in terms of public health management since the increasing incidence rates will have an impact on healthcare costs. A clear understanding of the risk factors for individuals in the development of this cancer, further research into preventing and treating this cancer and more effective tracking records may help to begin to reverse the current trend of 1 million new cases being reported in the United States alone each year.

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