Cutaneous ultraviolet exposure and its relationship to the development of skin cancer

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Skin cancer is becoming an increasingly important public health problem. Multiple studies have now demonstrated a relationship between ultraviolet exposure and increased risk of developing skin cancer. However, the specifics of that association are somewhat different for malignant melanoma, basal cell carcinoma, and squamous cell carcinoma. A better understanding of the mechanisms that allow cutaneous ultraviolet radiation to induce neoplasia will result in the development of better future sun-protection agents and strategies. (J Am Acad Dermatol 2008;58:S129-32.)

In this supplement of the *Journal of the American Academy of Dermatology*, a comprehensive review of the myriad of issues related to the development and use of broad-spectrum photoprotection has been presented. To put the importance of photoprotection into perspective and to better understand the key associated issues, an understanding of the cause of most skin cancers, the magnitude of the problem, and the rationale for ultraviolet (UV) protection is critical.

At current rates, 1 in 5 people in the United States will develop a skin cancer of some sort during their lifetime, with more than 1 million new cases appearing this year alone in the United States. The incidence of malignant melanoma is increasing faster than any other cancer in the United States. In 1935, the lifetime risk for a person in the United States developing invasive melanoma was 1 in 1500. In 2007, this risk is now 1 in 63 for invasive melanomas (Fig 1) and 1 in 33 if in situ melanomas are included. In addition, according to the World Health Organization, melanoma is increasing faster than any other malignancy worldwide. The economic magnitude of this public health problem is illustrated by the fact that costs associated with the treatment of skin cancers are more than $500 million annually in the United States alone.

Abbreviations used:

BCC: basal cell carcinoma
SCC: squamous cell carcinoma
UV: ultraviolet

Yet skin cancer is one of the few cancers where the cause of the majority of cases is known—excessive sun exposure[1]—and it would be expected that lowering an individual's UV exposure should similarly improve later skin cancer development risk. However, much of the data relating UV exposure to skin cancer risk are circumstantial and indirect.

RELATIONSHIP OF UV EXPOSURE TO SKIN CANCER DEVELOPMENT

The skin is the most exposed organ to environmental UV and to the associated sequellae.[2] Exposure to UV radiation on the skin results in clearly demonstrable mutagenic effects. The p53 suppressor gene, which is frequently mutated in skin cancers, is believed to be an early target of the UV radiation—induced neoplasm.[3] Although there is no direct way that the active wavelengths for the development of skin cancer in human beings can be determined, there is ample indirect evidence demonstrating probable ranges. In terms of squamous cell carcinoma (SCC) in albino hairless mice, the action spectrum has been determined to have a strong peak at 293 nm with secondary peaks at 354 and 380 nm.[4] The primary wavelength influencing melanoma risk appears to be in the UVB (290-320 nm) range. However, studies in fish and opossums have also shown a small effect on melanoma development as a result of exposure to UVA

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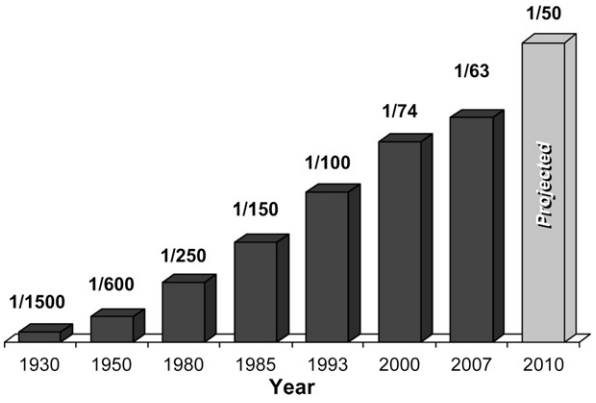

Fig 1. Estimated lifetime risk of person in United States developing invasive melanoma. (New York University Melanoma Cooperative Group, 2007.)

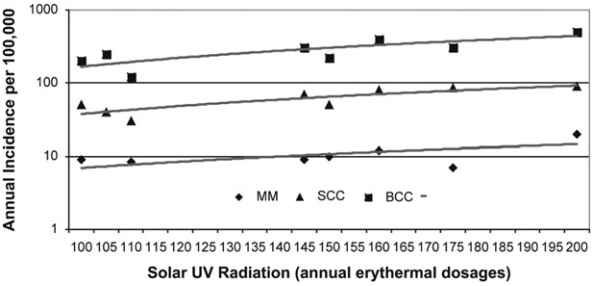

Fig 2. Relationship of incidence rates of basal cell carcinoma (*BCC*), squamous cell carcinoma (*SCC*), and melanoma (*MM*) to estimated ambient erythemal ultraviolet (*UV*) radiation in United States. (Adapted from Armstrong and Kricker.[9])

wavelengths.[5,6] Fair-skinned individuals who are more sensitive to the effects of exposure at these wavelengths are at higher risk for the development of skin cancer.[7] In addition, skin cancer rates are also increased in persons with increased artificial UV exposure through tanning salons.[8]

The amount of average annual UV radiation correlates with the incidence of skin cancer[9] (Fig 2). There is a direct relationship between the incidence of nonmelanoma skin cancer and latitude. The closer an individual is to the equator, the greater the UV energy to which they are exposed. It has been demonstrated that there is a direct correlation with basal cell carcinoma (BCC) and SCC incidence and latitude.[10] Scotto et al[11] demonstrated a strong inverse correlation between latitude and incidence of BCC and SCC for both men and women.

In terms of melanoma, the relationship is not as clear-cut. Incidence rates for melanoma correlate in a lesser way with latitude as that for nonmelanoma skin cancer, but other factors may also be involved.[12] Melanoma mortality in the United States and Canada have also been shown to directly correlate with ambient UV exposure.[13] The correlation of melanoma incidence to UV radiation exposure is greater when ambient UVA (320-400 nm) radiation is also included.[14] High-altitude regions tend to have a higher melanoma rate that may be related to the higher UV fluences (J/cm^2) noted at these sites.[15] Melanoma risk has also been noted to be directly related to annual UV exposure. Fears et al[16] demonstrated that when lifetime residential history was coupled with levels of mid-range UV radiation (UVB flux) to provide a measure of individual exposure to sunlight, a 10% increase in annual UVB flux was associated with a 19% increased risk of melanoma. Even in women who could develop a deep tan, a 10% increase in hours outdoors was associated with 5.8% increase in melanoma incidence. The association between melanoma risk and average annual UVB exposure was strong and consistent for men and women. However, the studies examining a latitudinal gradient for melanoma risk have been somewhat inconclusive.[10] Although worldwide studies have only shown a weak correlation, the association of melanoma mortality in 1950 to 1967 to estimates of annual erythemal solar UVB dose across the United States and Canada demonstrated a stronger relationship.[17]

The anatomic areas that skin cancer develops on appear to be somewhat related to the average amount of UV exposure to those sites.[18] The density of skin cancer is highest on the sites that are virtually constantly exposed to UV, namely, the head and neck. Skin cancer rates are low in rarely UV-exposed areas such as the scalp in women and the buttocks in both sexes.[19] Melanoma tends to be found more frequently in women on the legs where more average UV exposure may occur than in men.[20]

The timing and periodicity of the UV exposure appears to be important in its effect on subsequent skin cancer risk. In terms of nonmelanoma skin cancer, the long-term chronic UV exposure appears to increase the chance of developing this cancer. Acute intermittent UV exposure elevates the risk of developing melanoma in the future.[21] Migration studies have demonstrated sun exposure early in life appears to have a greater influence on subsequent skin cancer risk than does that at a later age. Persons born in the high UV insolation environment of Australia have an increased risk for developing skin cancer compared with those born in Northern Europe who migrated at age 10 years or older[22] (Fig 3). Several additional studies from other countries have also found that risk of developing melanoma was less in those who migrated to the country 10 or more years after birth than were those who were born there.[23,24] However, a recent study has now demonstrated that excessive UV exposure later in life

may be equally important to that acquired earlier. Pfahlberg et al[25] found a very similar upward gradient of melanoma risk in exposure categories related to the frequency of sunburns comparing UV exposure occurring before and after age 15 years. More than 5 sunburns doubled the melanoma risk, irrespective of their timing in life. The results of this study did not provide supporting evidence for the existence of a critical age interval but rather suggested that the hazardous impact of UV exposure seems to persist lifelong.

Studies have shown that a simple behavioral change, protection from UV exposure, can lower subsequent skin cancer risk.[26] What has become recently more apparent is the need for that protection to provide adequate UVB and UVA protection. Broad-spectrum sunscreens provide better protection from UV-induced neoplasia.[27] Seite and Fourtanier[28] have demonstrated that daily use of broad-spectrum photoprotection can significantly reduce UV-induced skin damage.

The development of potential precursors to invasive skin cancer such as actinic keratoses and dysplastic nevi has been shown to be inhibited by the regular use of sunscreen.[29-31] Personal nevus count is related to the risk of developing melanoma.[32] Lower nevus counts were found in children who regularly used sunscreens than those who did not, suggesting that sun protection early in life might lower subsequent melanoma risk.[33]

Primary prevention programs for skin cancer that are focused on lowering UV exposure appear to be having a positive effect in lowering skin cancer incidence.[34] Persons with a history of BCC had fewer subsequent BCCs develop if they protected themselves from UV exposure.[35]

Reduction in sun exposure by daily use of a sunscreen may reduce risk of SCC.[36] A meta-analysis of 11 studies of melanoma risk and sunscreen use showed only a small protective advantage.[37] However, when evaluating only the more recent studies where high sun-protection factor sunscreens were available, there appeared to be a protective effect, and other inherent flaws associated with retrospective studies may be responsible for protection not being noted.[38]

The standard measurement of sun-protective effect for sunscreens (sun-protection factor) measures only UVB protection. UVA protection in high sun-protection factor sunscreens can be variable.[39] Some studies evaluating the protective effects of sunscreen include the use of earlier sunscreens that may have not had adequate UVA coverage to provide appropriate protection, which may have contributed to a lack of efficacy.[40] For all of these reasons, it is important that development of future sunscreens incorporate a full range of UV protection.[41] In addition, the message of UV protection should include the triad of wearing protective clothing,[42] avoiding the midday sun when the UV intensity is greatest, and regularly using sunscreen to have the greatest impact in lowering skin cancer risk. This is, in fact, the approach promoted by the American Academy of Dermatology and other interested organizations[43] and is also the recommendation best supported by existing data.

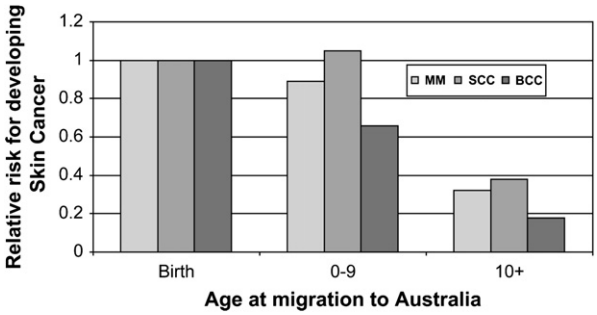

Fig 3. Relationship of age (in years) at arrival in Australia versus risk of developing basal cell carcinoma (*BCC*), squamous cell carcinoma (*SCC*), and melanoma (*MM*). (Adapted from Armstrong and Kricker.[9])

SUMMARY

There are now many studies that provide a firm basis for the association of UV exposure with the development of skin cancer. Yet, a variety of questions remain regarding the exact basis for this relationship. Hopefully, we will have even more definitive answers to questions related to the optimization of effectiveness of UV photoprotection and for reducing the risk from exposure to UV radiation as improved photoprotective agents, strategies, and methods are developed in the future.

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