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Review

Environmental risk factors for melanoma

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Abstract. Melanoma, a highly aggressive form of skin cancer, accounts for over 80% of deaths from cutaneous malignant tumors despite representing less than 10% of these cases. Early diagnosis is critical, as the prognosis is significantly better prior to metastasis. The incidence of melanoma has risen notably among fair-skinned populations, highlighting the importance of prevention. This article reviews the primary environmental risk factors for cutaneous melanoma, with a focus on ultraviolet radiation (UVR) and its role as a leading cause. UVR, particularly from intermittent sun exposure and artificial sources like sunbeds, is strongly linked to melanoma development through mechanisms involving DNA damage and immune system impairment. While regular sun exposure may have a protective effect due to skin adaptation, intermittent exposure significantly increases risk. The review also discusses the potential impact of diet, trauma, and smoking on melanoma risk, noting that while some dietary factors like caffeine may offer protection, others, such as citrus fruits and alcohol, may be harmful. Trauma and smoking do not show a clear causal relationship with melanoma, though interesting correlations exist that warrant further investigation. Overall, the article emphasizes the need for primary prevention strategies focused on reducing high-intensity UV exposure and promoting public awareness to mitigate the growing burden of melanoma.

Key Words: melanoma, risk factors, risk behaviours

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Introduction

Melanoma, the malignant tumour derived from melanocytes, is one of the most aggressive type of skin cancer. Although cutaneous melanoma represents only less than 10% of the total cutaneous malignant tumours, it is responsible for over 80% of the deaths caused by these tumours (Jemal et al 2011). The prognosis is, however, good if it is diagnosed early, before the metastatic stage (Touboul 2015). The incidence of melanoma has steadily increased over the past few decades, particularly among fair-skinned populations (Rigel 2010; Sung et al 2021; National Cancer Institute Melanoma of the Skin-Cancer Stat Facts, 2023).

Although significant progress has been made in the treatment of regionally advanced and metastatic melanoma, prevention continues to play a very important role, given the unpredictable evolution of melanoma. Melanoma is considered a multifactorial disease that results from the interaction between genetic susceptibility and exposure to environmental factors. Knowledge of avoidable risk factors plays an especially important role in primary prevention, while understanding genetic risk factors is crucial in designing screening campaigns for individuals at high risk.

This article aims to review the main environmental risk factors for the development of cutaneous melanoma.

Ultraviolet radiation and melanoma

Excessive exposure to ultraviolet radiation (UVR) from the sun is a leading environmental cause of skin cancer, with the World Health Organization (WHO) estimating that it results in approximately 65,161 deaths annually (6). UVR, comprising UVA, UVB, and UVC wavelengths, has been extensively studied for its carcinogenic effects. The International Agency for Research on Cancer (IARC) classifies the entire UVR spectrum as "carcinogenic to humans" (Group 1), a conclusion supported by robust evidence from laboratory, animal, and epidemiological research (Raimondi et al 2020).

Scientific studies have demonstrated that both UVA and UVB radiation contribute significantly to the development of skin cancer. These wavelengths induce DNA mutations, impair immune function, and disrupt cellular integrity and regulation. For example, experiments on human volunteers have shown that UVR can weaken the immune system through interacting and overlapping mechanisms, increasing susceptibility not only to skin cancer but also to other diseases (Raimondi et al 2020).

Epidemiological research further supports the link between UVR exposure and skin cancer. Studies consistently show that residing in areas with high ambient UVR—especially during early life—increases the risk of developing melanoma and non-melanoma skin cancers (NMSC) (Armstrong & Kricker 2001). Gandini et al (2005) conducted a systematic review and comprehensive meta-analysis of published observational studies on melanoma to better understand the disease's epidemiology by

exploring inconsistencies and variability in risk estimates. The analysis included relative risks (RRs) associated with sun exposure extracted from 57 studies published before September 2002. The results indicated that intermittent sun exposure and a history of sunburn were significant risk factors for melanoma, while high occupational sun exposure appeared to be inversely associated with the disease. The variability in risk estimates for intermittent sun exposure was significantly influenced by factors such as the country of the study and whether adjustments were made for phenotype and phototype (P = 0.024, 0.003, and 0.030, respectively). For chronic sun exposure, the inclusion of controls with dermatological diseases and the latitude of the study location also led to significant differences in the data (P = 0.05 and 0.031, respectively). Latitude was particularly important in studies examining a history of sunburn, with higher risks reported in studies conducted at higher latitudes (P = 0.031). Overall, the meta-analysis suggested that well-conducted research supports the hypothesis that intermittent sun exposure increases melanoma risk, while continuous high levels of sun exposure may have a protective effect.

The relationship between solar exposure and melanoma is complex, due in large part to the varying effects that sun exposure has on the skin. UVR, a key component of sunlight, interacts with the skin in diverse ways, and these interactions are modulated by the skin's natural protective mechanisms. Intermittent sun exposure is associated with a higher melanoma risk, likely because such exposure often occurs on relatively unprotected skin, allowing more UV radiation to penetrate deeply to the melanocytes—the cells responsible for melanin production. Conversely, regular sun exposure, which leads to tanning and skin thickening, may offer better protection by blocking UV radiation at the epidermal level. The risk is particularly elevated during a high-dose first exposure to the sun after a period of sun avoidance, as this can result in significant DNA damage in melanocytes. These cells, with their low capacity for DNA repair and reduced melanin content, are particularly susceptible to UV damage. Furthermore, while keratinocytes, another type of skin cell, may undergo apoptosis after severe UV damage, damaged melanocytes are typically retained, increasing the likelihood of mutations that can lead to melanoma (Gilchrest et al 1999).

O'Sullivan and al (2019) conducted a study to estimate the current attributable and future avoidable burden of melanoma in relation to UVR exposure and modifiable UVR risk behaviors, including sunburn, sunbathing, and indoor tanning. The population attributable risk (PAR) for UVR in 2015 was calculated by comparing the incidence rates of melanoma in Canada for that year with estimated incidence rates for a 1920 birth cohort, adjusting for changes in reporting and ethnicity. The analysis focused on 98.9% of melanomas occurring in Caucasians in Canada. The study found that adult sunburn and sunbathing were associated with increased melanoma risks, with relative risks of 1.28 (95% CI: 1.15, 1.43) and 1.44 (95% CI: 1.18, 1.76), respectively. In 2015, it was estimated that 62.3% of melanomas in Canada were attributable to UVR exposure, with 29.7% linked to the combination of sunburn (7.4%), sunbathing (17.8%), and indoor tanning (7.0%). The study further estimated that a 50% reduction in these modifiable UVR behaviors could prevent approximately 11,980 melanoma cases by 2042. The authors conclude that their findings highlight the importance of prevention strategies targeting modifiable UVR behaviors to reduce the increasing burden of melanoma.

Sunburns are a major risk factor for melanoma, with those experienced during childhood often seen as carrying the greatest risk. Dennis et al (2008) conducted a meta-analysis that compiled odds ratios (ORs) from 51 studies examining the relationship between melanoma and the occurrence of "ever" experiencing a sunburn. Additionally, their analyses explored linear dose-response data from 26 studies, which had not been previously reported. The findings indicate that an increasing number of sunburns correlates with a higher risk of melanoma, regardless of when the sunburns occur. The substantial ORs observed per decade for adult and lifetime exposure suggest that the quantity of sunburns, rather than the timing of exposure, elevates the risk of melanoma. However, Zhong et al (2023) conducted a Mendelian randomization study investigating the potential causal relationship between childhood sunburn and the risk of cutaneous melanoma using large-scale genetic data from genome-wide association studies (GWAS). The analysis provided evidence that childhood sunburn may significantly increase the risk of developing cutaneous melanoma, suggesting that the pathophysiological effects of early-life sunburn contribute to the development of skin malignancies. As the first study to explore this association using genetic data, it underscores the importance of heightened vigilance in individuals with a history of childhood sunburn and reinforces the need for public health initiatives to promote sun protection and reduce sunburn incidence during childhood as a strategy to prevent melanoma.

Sunbeds and melanoma

Sunbeds and sunlamps, commonly used for tanning, represent a significant source of intentional UVR exposure, especially in Northern Europe, the USA, and increasingly in sunnier countries like Australia. Modern tanning devices primarily emit UVA radiation, with a small fraction of UVB, essential for achieving a deep, long-lasting tan. However, both UVA and UVB contribute to DNA damage and immunosuppression. Notably, these tanning units can emit UVR levels 10–15 times stronger than the midday sun in the Mediterranean, subjecting the skin to intense UVR in short sessions of 10–20 minutes.. The term "sunbeds" generally refers to various tanning devices, including sunbeds, tanning beds, booths, canopies, and solariums (Raimondi et al 2020).

In 2012, an updated meta-analysis reviewed 27 epidemiological studies assessing the risk of cutaneous melanoma associated with artificial UVR tanning. The summary relative risk (SRR) for individuals who had ever used indoor tanning compared to those who had never used it was 1.20 (95% CI 1.08–1.34), with the risk being independent of skin sensitivity or population, and a clear dose-response relationship observed. When the analysis was limited to 18 studies that used population-based sampling of cases and controls, the SRR increased to 1.25 (95% CI 1.09–1.43). Moreover, analysis of 13 studies focusing on early exposure showed that individuals who began using sunbeds before the age of 35 had a significantly higher risk, with an estimated SRR of 1.59 (95% CI 1.36–1.85). There was no significant heterogeneity between studies and no evidence of publication bias (Boniol et al 2013).

Colantonio et al (2014) conducted a study to update and clarify the evidence connecting indoor tanning with melanoma, with a particular emphasis on the frequency of use and the effects of exposure to newer tanning bed models. The results reinforced the link between tanning bed use and an elevated risk of melanoma, especially with more frequent use. Importantly, the risk did not differ significantly between studies conducted before and after 2000, suggesting that newer tanning technologies do not offer increased safety compared to older models.

Some authors have hypothesized that indoor tanning might reduce the risk of melanoma by preventing sunburns. Recently, two publications have questioned the carcinogenic effects of indoor tanning (Burgard et al 2018; Reichrath et al 2020). Critics have pointed to the lack of randomized clinical trials—unethical to conduct in this context—to argue that the link between sunbed use and melanoma is not necessarily causal.

However, Suppa and Gandini (2019) conducted a comprehensive review of recent studies examining the association between sunbed use and melanoma risk. These studies reinforce earlier findings that early sunbed exposure, particularly in women, significantly increases the risk of melanoma. New insights have emerged, including the role of sunbed use in the development of additional primary melanomas and its association with melanoma on the lower limbs, which is the most common site in women. Additionally, sunbed use has been linked to other melanoma risk factors, such as a high count of nevi, the presence of atypical nevi, and sun damage. The economic impact of sunbed-induced melanoma is also substantial, with significant costs related to medical care and lost productivity The authors consider that their review demonstrates that the extensive data from observational studies provides sufficient evidence to establish that sunbed use does indeed cause melanoma. Applying all epidemiological criteria for causality to this relationship, they showed that indoor tanning significantly increases melanoma risk. Consequently, UVR is the most significant environmental risk factor for melanoma. Therefore, primary prevention strategies should prioritize reducing UV exposure, particularly the high-intensity, intermittent UVR that causes sunburns. UVB radiation peaks between 10 AM and 4 PM, making it essential to limit sun exposure during these hours to prevent sunburn. If exposure is unavoidable, it is recommended to wear protective clothing, wide-brimmed hats, sunglasses, and apply sunscreen for protection.

Diet and melanoma

Epidemiologic studies have suggested that some dietary factors and nutrients could influence melanoma risk, though the importance of many of these associations is still subject to debate. Diet might affect melanoma development through several potential mechanisms, such as decreasing melanoma risk by promoting UV-induced apoptosis and increasing the risk by enhancing photosensitivity (Yang et al 2018).

Yang et al (2018) conducted a narrative review to summarize recent epidemiologic studies of diet and melanoma based on published literature. They showed that current epidemiologic evidence largely indicates that caffeine intake may have protective effects against cutaneous melanoma, whereas the consumption of citrus fruits and alcohol may be detrimental. While experimental studies have suggested possible biological mechanisms for these associations, there is limited data from randomized controlled trials (RCTs) to confirm the effectiveness of dietary modifications in preventing melanoma. The relationships between polyunsaturated fatty acids, niacin/nicotinamide, folate, and vitamin D intake with melanoma are still inconsistent, requiring further investigation through prospective studies.

Trauma and melanoma

Current epidemiological, clinical, and scientific research does not support a link between single or repeated traumatic events and melanoma development. However, since many patients with acral melanoma or melanoma on the extremities have reported previous trauma, it highlights the need for public campaigns aimed at early detection of suspicious moles in these specific areas, along with public education on self-examination (Kaskel et al 2000).

Interestingly, De Giorgi et al (2020) reported a rare case of a patient with metastatic melanoma whose tumor recurred in a finger that had previously experienced direct but minor trauma. The authors suggest that tissue trauma and subsequent chronic inflammation might facilitate metastasis through two possible, though not mutually exclusive, pathways. The first pathway involves the initial injury triggering local proinflammatory and wound-healing responses, potentially enhancing the seeding of metastatic cells from distant sites. The second pathway suggests that dormant metastatic cells already present at the trauma site are stimulated to proliferate due to changes in the microenvironment, such as a macrophage-induced proinflammatory milieu, which includes cytokines, chemokines, and growth factors. Further research is necessary to identify which of these mechanisms is responsible, as such findings could significantly improve outcomes for melanoma patients over time.

Smoking and melanoma

Dusingize et al. investigated the association between cigarette smoking and the incidence of melanoma in a prospective cohort study involving more than 38,000 participants. Their findings did not indicate that smoking increases the risk of melanoma. In fact, the analysis suggests that former smokers may have a lower risk of melanoma compared to those who have never smoked, although this conclusion is made with caution. The inverse association was more evident among former smokers rather than current smokers. Although not always statistically significant, the reductions in risk among former smokers seemed greater with longer durations or higher intensity of smoking (Dusingize et al 2018). These findings align with previous cohort studies and meta-analyses, which have generally reported moderately lower risks of melanoma among smokers. The authors observed nonsignificant dose–response trends, with smoking intensity and duration associated with a decreased risk, while a longer time since quitting was linked to a relative risk of melanoma that was not significantly different from the null. These observations are consistent with earlier studies that have found reduced risks of invasive melanoma with longer smoking durations and higher quantities of tobacco smoked (Odenbro et al 2007; Song et al 2012).

Conclusion

Melanoma remains one of the most deadly forms of skin cancer, with its incidence steadily rising, particularly in fair-skinned populations. Despite advancements in the treatment of advanced melanoma, the unpredictable nature of the disease underscores the critical importance of prevention. This review highlights UVR as the most significant environmental risk factor for melanoma, emphasizing the dangers of both intermittent sun exposure and the use of artificial tanning devices. The complex relationship between UVR and melanoma development suggests that while regular sun exposure may induce protective skin adaptations, intermittent and intense exposure poses a substantial risk. Other factors such as diet, trauma, and smoking also play roles in melanoma risk, though their impacts are less clear and require further research. The findings stress the need for comprehensive public health strategies that prioritize reducing UV exposure, promoting protective behaviors, and increasing awareness of melanoma risk factors. Early detection and prevention efforts are essential to curbing the rising incidence of this aggressive cancer and improving patient outcomes.

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