Genetic Predisposition, UV-Induced Damage, and Immunotherapeutic Treatments for Skin Cancer

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Abstract

Skin cancer has emerged as a pivotal area of research as dermatologists and oncologists strive toward more effective prevention, diagnosis, and treatment strategies. This research publication highlights the multifaceted causes, consequences, and treatments of skin cancer, addressing the interdisciplinary intersection of genetic predisposition, ultraviolet (UV) exposure, cellular damage, immunotherapy, and the ethical dimensions of affordability and accessibility. From an epigenetic lens, genetic mutations including BRAF, NRAS, p53, PTCH1, and CDKN2A are evaluated alongside immune-regulatory genes such as CTLA-4 and BRCA1/2. Clinical and experimental research findings are examined to characterize UV exposure as a primary physical carcinogen, while the efficacy of immunotherapies in improving survival outcomes for skin cancer patients is also critically assessed.

Introduction

Skin cancer — including melanoma and non-melanoma forms such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) — has increasingly emerged as a global health concern. Within the United States, the age-adjusted incidence of skin cancers rose between 1973 and 2005 at a rate of 2.8%, reflecting the growing prevalence of skin cancer across both fair-skinned and dark-skinned populations (Zhu et al., 2022). Correspondingly, total annual treatment expenditures in the United States increased from $3.6 billion to $8.1 billion over a relatively short period — underscoring the substantial and growing economic burden of the disease (Zhu et al., 2022).

In response, researchers have focused on identifying both genetic predisposition and the impact of UV exposure on susceptibility to melanoma and BCC. This review article examines key genetic biomarkers and hereditary risk factors while also analyzing UV exposure case studies to explore how sunlight exposure elevates melanoma risk. Additionally, personalized screening programs and

immunotherapies are evaluated to identify the most significant interventions available for ensuring that high-risk populations are diagnosed and treated in the most effective and equitable manner possible.

Discussion

Genetic Predisposition to Skin Cancer: Mutations in BRAF, NRAS, p53, and PTCH1

Researchers have established that genetic predisposition plays a central role in susceptibility to skin cancer, particularly basal cell carcinoma. Mutations in genes of the Hedgehog signaling pathway — specifically PTCH1, SMO, and SUFU — have been identified in up to 85% of BCC cases, with the disease presenting characteristic symptoms including pigmentation changes and erosion of affected areas (Ju et al., 2023). Mutations in PTCH1 are specifically responsible for Gorlin syndrome, a hereditary condition associated with a dramatically elevated risk of BCC, while defects in DNA repair genes such as XPA and XPC confer extreme UV sensitivity, further increasing the likelihood of melanoma, SCC, and BCC diagnoses.

The BRCA1/2 mutation has also been linked to extended susceptibility to both melanoma and BCC (Ju et al., 2023). Separately, researchers examining hereditary melanoma risk found that CDKN2A mutations represent the highest hereditary risk factor for melanoma, present in approximately 20–40% of familial melanoma cases, where they impair regulation of the cell cycle (Bonilla et al., 2016). CDK4 mutations, while rarer, are also associated with familial melanoma and disrupt the same genetic pathway as CDKN2A. Additionally, immune-regulatory gene variants such as specific polymorphisms in CTLA-4 have been associated with multiple BCC development, illustrating the interplay between immune regulation and skin cancer susceptibility.

Analysis of UV Exposure Studies: Clinical Trials and Case Studies

UV exposure studies are central to informing diagnostics, treatment protocols, and preventive interventions for skin cancer patients. One group of researchers analyzed UV exposure as a risk factor for cutaneous melanoma specifically in individuals with skin of color, finding that intermittent, high-intensity sun exposure — such as sunbathing or tanning bed use — carries considerably greater risk than chronic, low-level exposure (Lopes et al., 2021). Epigenetic and meta-analytic data further revealed that patients living closer to the equator or at higher altitudes face greater UV intensity and, consequently, elevated melanoma risk. Notably, tanning bed use initiated at a young age was found to significantly double melanoma risk, illustrating a clear dose-dependent effect (Lopes et al., 2021).

In quantitative terms, a total of 7,272 melanoma cases — representing 1.76% of the general population — were identified in skin-of-color populations across the studies reviewed. However, 11 of 13 studies found no significant association between UV exposure and melanoma in skin-of-color patients, highlighting important subgroup-specific variability and suggesting that melanoma etiology in minority populations may involve factors beyond UV exposure alone. Complementary research identified UV radiation as the "most prominent natural physical carcinogen," noting its role in inducing cyclobutane pyrimidine dimers and 6-4 photoproducts in DNA — lesions associated with significant genomic damage (Gruijl, 1999). UV exposure also suppresses immune responses, reducing the body's capacity to reject UV-induced tumors, which compounds its carcinogenic effect and heightens the risk of both SCC and BCC.

Effects of UV Damage on Skin: Cellular Development and Mitochondrial Dysfunction

Researchers have increasingly focused on the cellular-level consequences of UV radiation, which is capable of penetrating deep into the dermis of the skin. UVA radiation (320–400 nm) causes significant damage to deeper skin layers, while UVB radiation (280–320 nm) carries higher energy that is primarily absorbed in the epidermis (Yuan et al., 2024). Together, these two forms of radiation induce oxidative stress, inflammation, and genetic damage with compounding effects on skin health. Chronic UV exposure has additionally been linked to mitochondrial DNA (mtDNA) mutations, impairment of the electron transport chain (ETC), and an increase in 4,977 bp mtDNA deletions — a biomarker now widely used to assess the extent of photoaging.

At the cellular level, researchers have documented two key death pathways triggered by UV-induced mitochondrial damage: the intrinsic apoptotic pathway, marked by cytochrome c release and caspase-9 activation, and ferroptosis, a form of cell death in which UVB elevates lipid peroxidation markers and promotes ferroptotic cell death (Sreedhar et al., 2020). Quantitatively, repeated UVA exposure was found to increase the frequency of mtDNA deletions in dermal cells by 40%, with both the 4,977 bp "common deletion" and a 3,895 bp mtDNA deletion identified at unusually high rates in sun-exposed skin biopsies. These findings establish that UV radiation accelerates mtDNA deletion accumulation, driving oxidative stress, mitochondrial dysfunction, and accelerated skin aging — with oxidative stress increasing by approximately 40% and deletion accumulation rising 30–40-fold over time (Sreedhar et al., 2020).

Applications of Immunotherapies for Skin Cancer Treatment

Researchers have found skin cancers to be among the malignancies most sensitive to immunotherapeutic intervention. Recent research has reported an average response rate of

approximately 40% for anti-PD-1 (anti-programmed death-1) therapy across a range of cutaneous malignancies, including malignant melanoma, Merkel cell carcinoma, basal cell carcinoma, cutaneous squamous cell carcinoma, and Kaposi sarcoma (Paulson et al., 2019). The high mutational burden characteristic of many skin cancers enables the immune system to more readily identify and target malignant cells, making the tumor microenvironment particularly amenable to immunotherapy. However, many skin cancers are also capable of developing resistance to immunotherapy when defects arise in the complex mechanisms governing immune recognition.

Programmed Death-1 (PD-1) is a protein expressed on the surface of T cells that regulates their activity; when PD-1 binds to PD-L1, a complementary protein expressed on tumor cells, the resulting signal suppresses T-cell attack on the tumor (Jiang et al., 2019). Therapeutic drugs designed to block the PD-1/PD-L1 interaction restore T-cell function, enabling the immune system to more effectively eliminate the tumor. A meta-analysis of over 35 clinical trials encompassing more than 21,000 patients with various skin cancers found that PD-1/PD-L1 therapies significantly improved both overall survival (OS) and progression-free survival (PFS), with hazard ratios of 0.76 and 0.81 respectively. Specifically, patients receiving PD-1/PD-L1 therapy experienced a 24% lower risk of death (95% CI: 0.71–0.82) and a 19% lower risk of cancer progression (95% CI: 0.73–0.89) compared to controls — results that are statistically robust and unlikely to be attributable to chance alone.

Personalized Screening Programs for Skin Cancer: Focus on Minority Populations

As melanoma accounts for approximately 70% of skin cancer deaths and is most commonly associated with lighter skin tones, researchers have examined whether MC1R risk variants — prevalent in nearly half of all melanoma patients diagnosed — may help identify individuals at elevated risk, carrying a two- to threefold increase in melanoma susceptibility (Hay et al., 2017). To investigate this, researchers employed a randomized controlled trial design with 885 participants allocated in a 6:1 ratio to receive either personalized genomic testing for melanoma risk (n = 750) or placement on a waiting-list control (n = 135), with control participants offered testing after outcome measurement. Randomization was balanced by self-reported Hispanic versus non-Hispanic ethnicity, with baseline surveys conducted in person and follow-up assessments conducted by telephone.

Results revealed that participants identified as carrying higher-risk MC1R variants were more likely to adopt protective behaviors, including wearing long-sleeved clothing and reducing sun exposure, and were less likely to experience sunburn — outcomes attributed to heightened

awareness of their personal risk profile (Hay et al., 2017). This research, endorsed by the National Cancer Institute at the National Institutes of Health, forms part of an ongoing effort to evaluate the effectiveness of personalized screening programs in raising awareness and expanding access to skin cancer treatment options for both minority and non-minority populations.

Ethics, Discussion, and Limitations

In considering the implications of current skin cancer research, it is important to acknowledge that immunotherapies such as PD-1 inhibitors, while highly effective, carry significant financial costs that raise ethical concerns about affordability and equitable access. Similar concerns apply to personalized screening programs, as many minority and low-income patients — particularly those living below 200% of the federal poverty level — remain systematically underscreened (Hay et al., 2017). Minority and immigrant patients face a disproportionately higher susceptibility to advanced-stage melanoma diagnoses, with correspondingly elevated mortality rates, driven by low awareness and inadequate access to dermatological care. Researchers have noted a structural disparity in which wealthier and insured populations benefit substantially from established public health campaigns, while underserved communities in the United States lack equivalent affordable programs.

Addressing these inequities ethically requires the development of low-cost educational interventions that raise awareness of skin cancer risk and promote sun-protective behavior in underserved communities. Researchers have emphasized the importance of promoting skin self-checks and implementing knowledge-based educational sessions — particularly in Hispanic and other minority communities — prior to clinical consultations, as a means of expanding risk perception and health literacy. Bridging these access barriers is not only a public health imperative but an ethical responsibility, ensuring that the advances achieved in oncology and dermatology are made available equitably across all populations.

Conclusion

With rapid advancements in oncology and dermatology, the genetic, environmental, and immunological dimensions of skin cancer are becoming increasingly well understood, enabling more targeted and effective approaches to diagnosis and treatment. Genetic mutations including BRAF, NRAS, p53, PTCH1, and CDKN2A have been identified as significant contributors to elevated skin cancer susceptibility, while UV radiation has been established as a preventable carcinogen that causes damage on both cellular and molecular levels. PD-1/PD-L1 checkpoint

inhibitors have demonstrated meaningful improvements in survival outcomes for patients with advanced melanoma, with a 24% reduction in mortality risk across large-scale clinical meta-analyses.

From a public health perspective, bridging socioeconomic barriers and expanding health literacy remain essential to realizing the full potential of these scientific advances for all populations. The future of skin cancer care will depend on the development of low-cost educational campaigns, community-based screening programs, and genomic data-driven tools that together can democratize access to dermatological care and transformatively improve outcomes for patients across all communities.

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