Photodermatology, Photoimmunology & Photomedicine

WILEY

Photodermatology, Photoimmunology & Photomedicine

REVIEW ARTICLE OPEN ACCESS

Assessment of the Influence of UVR in Cutaneous Melanoma

Graeme J. Walker | Kiarash Khosrotehrani

Experimental Dermatology Group, The University of Queensland Frazer Institute, Woolloongabba, Queensland, Australia

Correspondence: Kiarash Khosrotehrani (k.khosrotehrani@uq.edu.au)

Received: 10 October 2024 | **Revised:** 9 April 2025 | **Accepted:** 15 April 2025

Funding: The authors received no specific funding for this work.

Keywords: genome-wide association study | melanin | melanoma | pyrimidine dimer | single-nucleotide variant | ultraviolet radiation

ABSTRACT

Background: Although a role for ultraviolet radiation (UVR) in cutaneous malignant melanoma (CMM) development is accepted, there is debate over the magnitude and mechanisms given its association with intermittent but not chronic exposure.

Objectives: To assess new ideas and data on the subject, review some debated topics, bringing a molecular view to epidemiological observations.

Methods: We reviewed some recent advances in the field of epidemiology and genetics, including phenome-wide association studies, evolutionary genetics related to skin cancer, and mechanisms of UVR-induced DNA adduct formation.

Results: High rates of CMM are strongly correlated with light colored skin across the globe. CMM shares risk factors associated with UVR sensitivity with keratinocyte cancer (KC). CMM risk is dominated by *MC1R*, a gene regulating the proportions of black and red melanin produced. An emerging mutagenic mechanism involves reactive melanin, particularly red pheomelanin, that can itself induce DNA adducts.

Conclusion: Demographically, epidemiologically, and mechanistically, pigmentation status is central to CMM risk and a shared genetic susceptibility, comprising several pigmentation genes, between CMM and KCs. In the general population, CMM risk is associated with pale skin and poor tanning ability, mechanistically due to a relative lack of protection against UVR adduct formation, or perhaps via an alternate manner in individuals with abundant pheomelanin. Overall, evidence suggests that UVR exposure impacts CMM risk.

1 | Introduction to the Question Being Addressed

We attempted to put in perspective some recent advances in UVR carcinogenesis in cutaneous melanoma (CMM), including some perhaps not often discussed conundrums. Put simply, there has been debate over the strength of the association between sun exposure and CMM. In many ways, it does not behave like a UVR-induced cancer as does squamous cell carcinoma (SCC) and, to a lesser extent, basal cell carcinoma (BCC). In assessing this, we found it helpful to compare innate and environmental risk factors for the three skin cancers.

2 | Strength of Association Between UVR Exposure and Melanoma

The relative risk (RR) for CMM development conferred by chronic sun exposure is small, ~1.3, but higher for a history of

Abbreviations: BCC, basal cell carcinoma; CMM, cutaneous malignant melanoma; CPD, cyclobutene pyrimidine dimer; KC, keratinocyte cancer; LMM, lentigo malignant melanoma; Mb, megabase; PheWAS, phenome-wide association study; PRS, polygenic risk score; SCC, squamous cell carcinoma; TF, transcription factor; TFBS, TF binding site.

sunburns (RR = ~2) [1]. RRs vary between studies. Table 1 summarizes the skin cancer risk factors associated with UVR exposure across a large cohort [2]. Higher than average daily hours of bright sunlight increased the risk of all skin cancers, ranging from a RR of 1.45 for BCC to 1.92 for CMM and 5.2 for SCC. SCC was much more associated with chronic UVR indicators like actinic keratoses than CMM. Pale skin was a risk factor for all three cancers. Importantly, the strongest risk factor for CMM overall is the presence of many naevi; for those carrying > 100 naevi, the RR is ~6.9, and for multiple atypical naevi, ~10.5 [3].

CMM can be viewed as developing via two generalized pathways. The first tends to involve naevi, truncal location, somatic ^{V600E}*BRAF mutation*, and intermittent sun exposure, and the second pathway lesions on sun-exposed anatomical sites but without naevi [4]. It is odd that outdoor work does not increase CMM risk. At least in part, outdoor work may select for those who tan and do not burn, hence are at relatively lower risk for CMM anyway. But CMM subtype is important to consider. In meta-analysis, CMM risk depended upon whether lentigo maligna melanoma (LMM) was included [5]. The RR for any CMM (excluding eye, acral, and mucosal) associated with lifetime UVR exposure was ~1.45, but with LMM excluded, it dropped to 1.16. LMM is strongly associated with chronic sun exposure [6]. Perhaps there is a form of skin adaptation to chronic UVR exposure that mitigates against the development of some forms of CMM, for instance, *BRAF*-mutant lesions.

3 | Age of UVR Exposure and CMM Risk

Childhood sunburns are thought to increase CMM risk. While this may be so, meta-analyses of case–control studies do not provide a consistent significant correlation [1, 7]. Whiteman and colleagues [7] suggest that this is mainly due to differences in reporting and ways of measuring past exposures. More convincing evidence comes from ecological studies assessing age at migration to a country with different UVR levels. These studies almost invariably show that CMM risk for white-skinned individuals is influenced by where they spend their childhood, in both low-to-high UVR and high-to-low UVR migration studies (decreased CMM risk in the former case compared to the destination population and increased risk in the latter) [7]. Childhood sunburns similarly increase SCC and BCC risk [8, 9]. In the 23andMe cohort, sun exposure before the age of 30 was more associated with KC risk than CMM risk [10].

Although all skin cancer risk is dramatically higher in old age, CMM can occur at a younger age than KCs, especially SCC. In Australia, 7.9% of CMMs were in individuals under 40 [11]. In contrast, < 5% of BCCs and < 0.3% of SCCs were in persons under 40 [11], perhaps fitting with the idea that cutaneous SCC, especially, is a UVR-driven cancer, needing many years of cumulative exposure to develop, not always the case for CMM.

TABLE 1 | Estimated relative risk for the development of all three major skin cancers along with various risk factors.

	CMM	BCC	SCC
Naevi	2.7	1	0.8
Freckles	1.5	1.8	1.6
Fair skin	3.1	1.5	2.3
Outdoor worker	0.86	1.19	1.64
Intermittent UVR exposure	1.71	1.38	0.91
History of sunburn	1.91	1.4	1.23
Childhood (< 9) in low UVR country	0.89	1.05	0.66
Unable to tan	3.5	3.7	6.9
Actinic keratoses	1.9	3.9	15.4

Note: Adapted from Armstrong and Kricker [2]. RR < 1 denotes a protective effect, RR close to zero little or no risk, and increasingly > 1 indicates the highest risk.

4 | Genetic Susceptibility to CMM

Familial CMM is associated with rare high-penetrance genes such as *CDKN2A*, *CDK4*, *BAP1*, and *POT1* [12]. Outside the familial context, decades of CMM genome-wide association studies (GWAS) have uncovered common risk variants (Figure 1). Naevus risk is dominated by the *IRF4* variant rs12203592 and variants at *MTAP/CDKN2A*. *IRF4* is surprisingly not generally associated with CMM, although it is reported to be linked to CMMs associated with solar keratoses in some datasets [21]. Instead, CMM risk is dominated by *MC1R*. It is difficult to explain why *IRF4*-rs12203592, strongly linked to light-colored skin and poor tanning ability, would not increase CMM risk. One might suspect that naevus risk might somewhat mask the effect of UVR in exacerbating CMM in general, but the IRF4 effect on naevus count but not CMM argues against this. There are some other complexities with respect to IRF4. Naevus GWAS interpretations are complicated since naevus count reduces with age and rs12203592 is linked mostly in younger people [22], and IRF4 is experimentally linked to both pigment production [23] and immune function, controlling macrophage polarization [24]. Notwithstanding these conundrums, ostensibly the same pigmentation genes confer susceptibility to all major skin cancers, actinic keratoses (AK), poor tanning ability, sensitive skin, and accelerated aging (Figure 1).

5 | CMM Phenome-Wide Association Study (PheWAS)

GWAS techniques have now been extended to polygenic risk score (PRS) analysis, which begins with a specific trait and considers many SNPs in order to improve genetic risk prediction. A PheWAS tests a SNP (or SNPs) across multiple phenotypes to identify associations with a range of traits. After constructing the PRS, a PheWAS is performed to see how the PRS SNPs associate with multiple phenotypes. Large datasets like the UK Biobank contain genetic information and phenotype data for thousands of diseases, traits, clinical lab values, and lifestyle factors. PheWAS analyses across the UK biobank show that CMM associates most strongly with other KCs, AK, and skin dermatoses (presumably sun-associated) than any other phenotype (Figure 2), [25]. SCC diagnosis

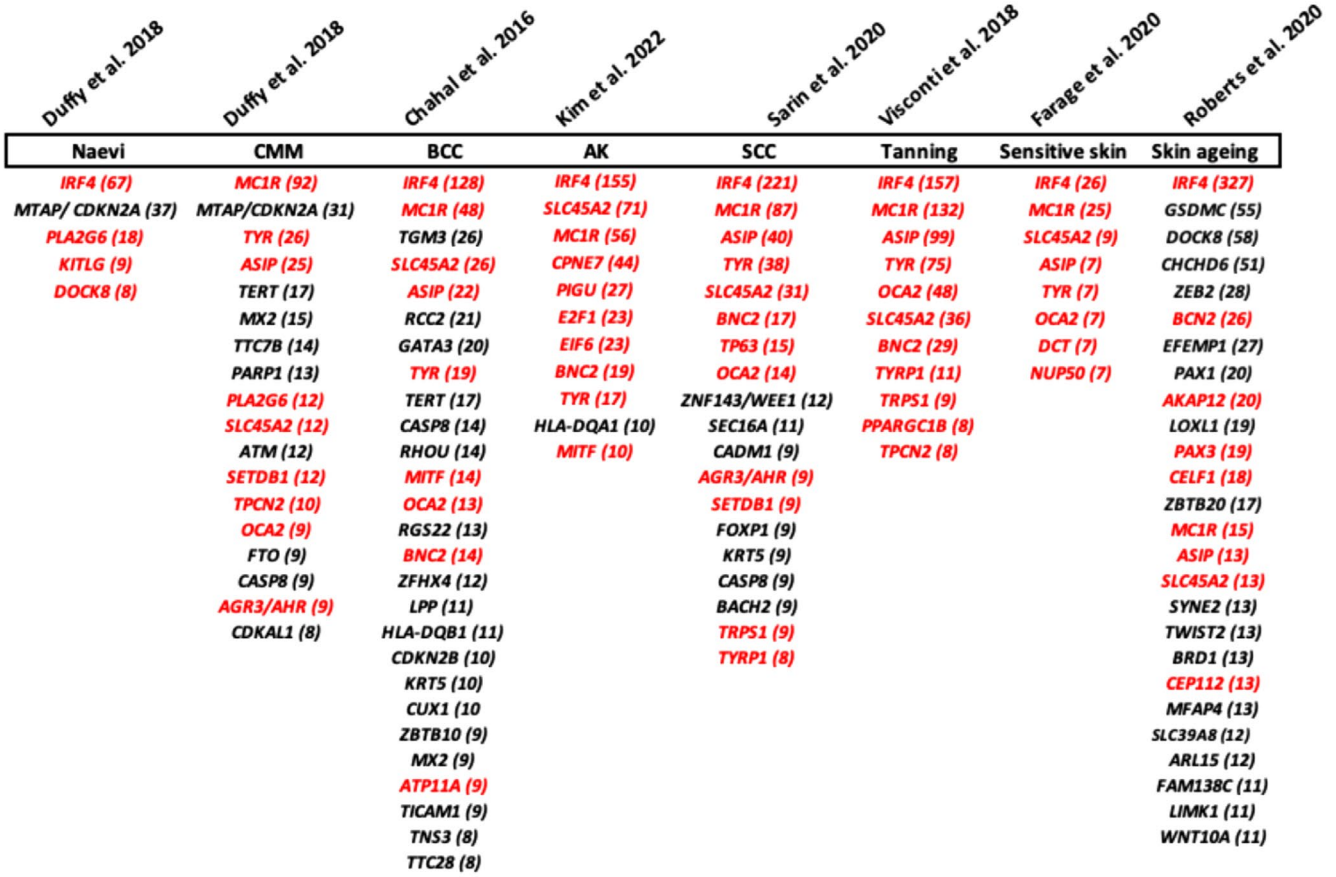


FIGURE 1 | Summary of GWAS genes for skin cancer and related phenotypes. $-\text{Log}_{10}\text{P}$ (LOD) scores are shown in italics (values > 8 are shown but LOD > 7 listed for skin sensitivity). Genes in red are skin pigmentation-related, those in black are not. Genes were defined as pigmentation-related by a LOD score > 8 for association with skin color across the UK Biobank (https://geneatlas.roslin.ed.ac.uk/) and/or listed in Ju and Mathieson [13]. AK, actinic keratosis; BCC, basal cell carcinoma; CMM, cutaneous malignant melanoma; SCC, squamous cell carcinoma. References in brackets are; Duffy et al. [14], Chahal et al. [15], Kim et al. [16], Sarin et al. [17], Visconti et al. [18], Farage et al. [19], Roberts et al. [20].

(Figure 2b) most strongly associates with actinic keratosis, BCC, and CMM.

This may reflect a shared environmental risk, i.e., UVR exposure, between KCs and CMM.

Others have shown that KC is the most common second cancer after a CMM diagnosis [27, 28].

But putting the PheWAS results in perspective, 82.3% of individuals with CMM reported CMM alone, 10.6% reported CMM and BCC, only 3.4% reported CMM and SCC, and 3.7% reported all three skin cancers [26]. The PheWAS secondary phenotype associations could be biased since the detection of a first skin cancer leads to subsequent intensified screening. One can mitigate this by performing an "exclusion PheWAS" [25], essentially a PheWAS with the skin cancer cases excluded (Figure 2). Because of the PRS construction, secondary phenotypes with shared genetic PRS risk with the primary phenotype will remain associated, but those dependent upon the primary diagnosis may not. For CMM, after exclusion, only dermatoses, AK, and benign skin neoplasms remain significant, suggesting that these have shared genetics with CMM. Many of the remaining secondary phenotype associations (e.g., KCs) may be explained by intensified screening or other bias. However, CMM, SCC, and BCC do apparently share an overlapping risk SNP set: *MC1R*, *IRF4*, *OCA2*, *ASIP*, *TYR*, *SLC45A2* [25], genes strongly associated with skin color and tanning. Overall, PheWAS analysis suggests the co-occurrence of UVR-sensitive phenotypes and CMM.

To gain a better picture of the function of the genes conferring skin cancer risk, we interrogated the UK Biobank (Figure 3). For each significant skin cancer GWAS gene, we tested its association with solar keratoses, tanning, and skin color to assess the influence of these phenotypes. Clearly, such genes are very important in skin cancer risk. For CMM, the pigmentation-related genes conferring risk are *MC1R*, *TYR*, *ASIP*, *SLC45A2*, *SETDB1*, *TPCN2*, *OCA2*, and *AGR3/AHR*. Yet other genes are unrelated to solar keratoses, tanning, and skin color (*MTAP*, *TERT*, *MX2*, *TTC7B*, *PARP1*, *ATM*, *FTO*, *CASP8*). Hence, pigmentation genes are important but do not explain all CMM (or BCC and SCC) risk.

Most of the above genetic analyses are based on European populations. Other lighter-skinned populations like East Asians do not carry *IRF4*-rs12203592 SNP or *MC1R* red hair variants; other pigmentation gene variants confer lighter skin color. An East Asian-specific *OCA2* paler skin variant evolved separately from the European migratory wave out of Africa [29]. Such variants

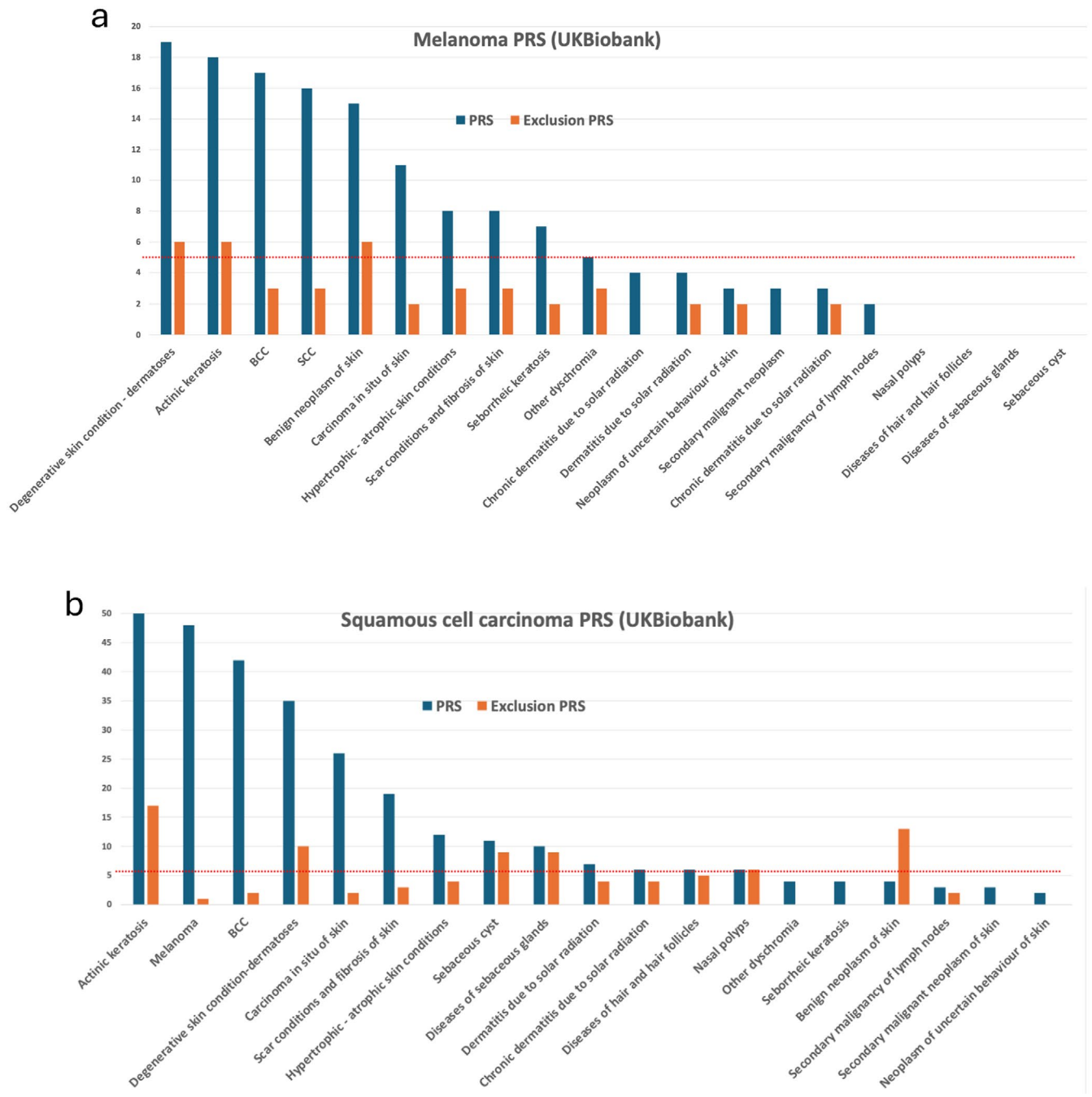


FIGURE 2 | PRS-PheWAS scores for (a), CMM and (b), SCC, across the UKBiobank. *y* axis shows $Log_{10}P$ values for phenotypes on the *x* axis. The dotted red horizontal line indicates phenome-wide significance. Blue bars from PRS-PheWAS and orange bars from exclusion PRS-PheWAS. Graphs are constructed from data taken from Fritsche et al. [25, 26]. Analysis based upon 417,321 individuals of European ancestry which includes 4496 with CMM and 18,285 with KC. Presumably dermatoses are sun exposure related.

are associated with lower tanning ability and increased skin cancer risk (albeit relatively low) in Asians [30].

6 | CMM Risk and Geography

Further highlighting the importance of skin pigmentation are geographical trends across the world. The Global Cancer Observatory (https://gco.iarc.fr) summarizes skin cancer incidence in 185 countries (Figure 4) [31]. Studies have shown that globally CMM is negatively correlated with average ambient UVR dose per country ($r = -0.52$), but positively correlated with the proportion of light-skinned individuals in a population ($r = 0.61$, $p < 0.001$) [32, 33] (Figure 5). As discussed previously [7] this is skewed because high ambient UVR countries harbor "resistant" dark-skinned populations, whereas susceptible light-skinned populations are in both high-UVR countries (e.g., Australasia) and lower-UVR countries (e.g., Scandinavia, Netherlands, UK). CMM incidence is positively correlated with KC incidence across the globe; the latter is also negatively correlated with UVR proxies (Figure 5). This is a critical point and suggests that the negative correlation with UVR is due to

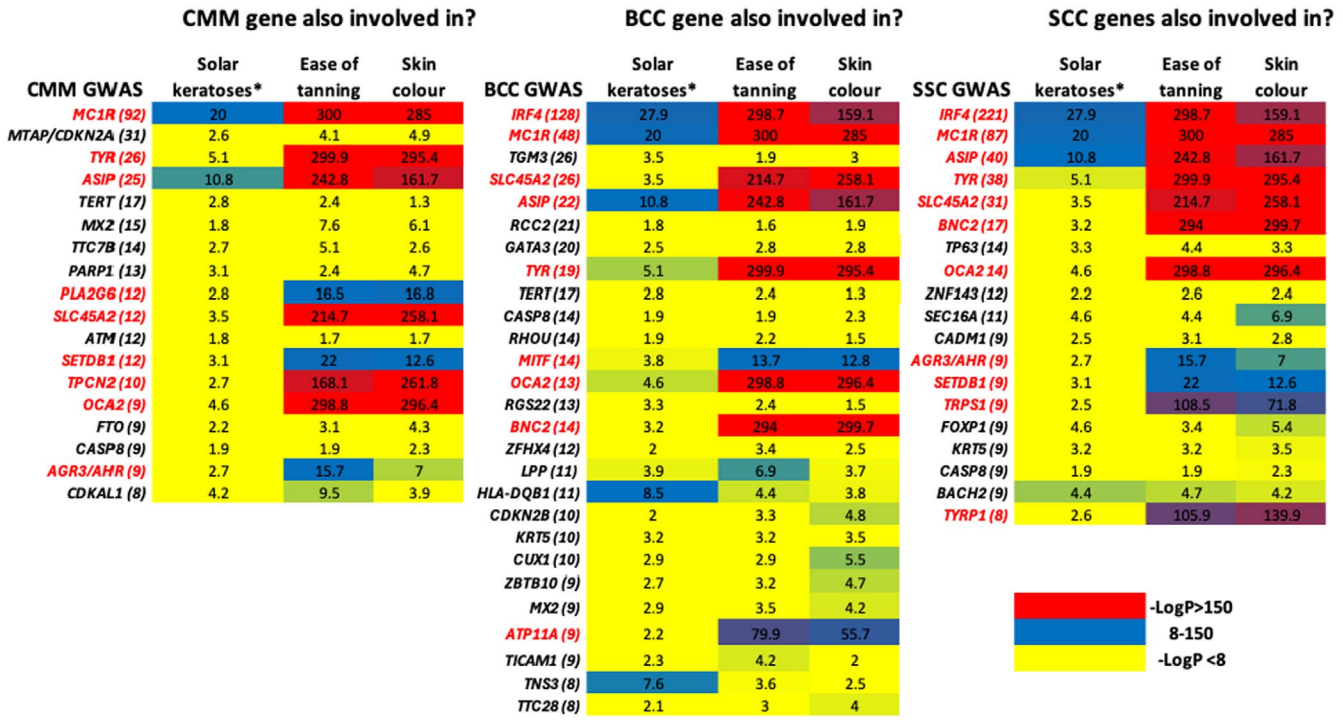


FIGURE 3 | Phenotypic action of skin cancer GWAS genes. To the left of each panel we list skin cancer gene with LOD score ($-\text{Log}_{10}p$) in brackets. For each of these GWAS genes we used the GeneATLAS browser (https://geneatlas.roslin.ed.ac.uk/) to assess whether they are statistically associated with scores for solar keratosis, tanning ability, and skin color. Numbers listed are the maximum LOD for each phenotype. *In terms of "solar keratoses", we substituted this for the phenotype UK Biobank grouping "skin changes associated with chronic exposure to non-ionizing radiation", since 92% of these cases were actinic keratoses. The remainder were overwhelmingly "radiodermatitis" (7.2%), it is not clear if these were radiation treatment associated.

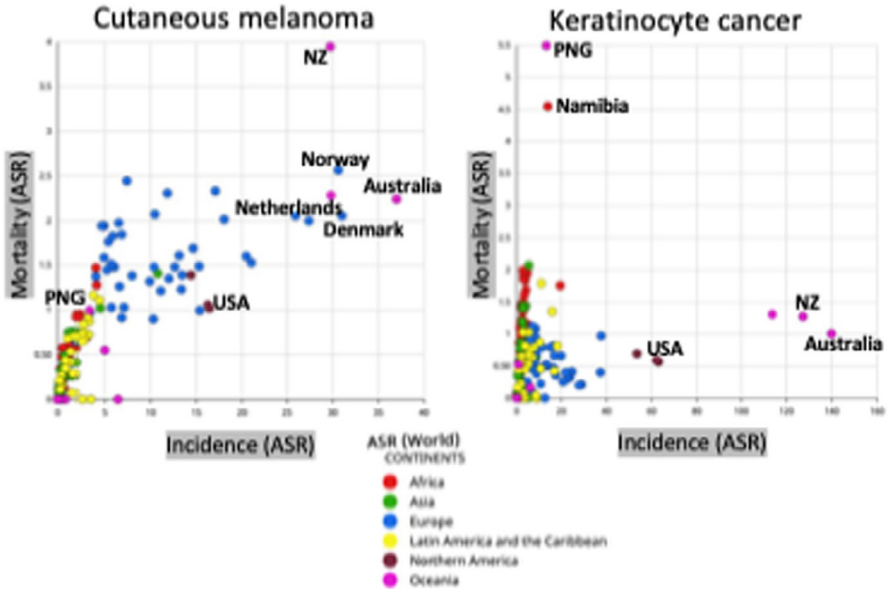
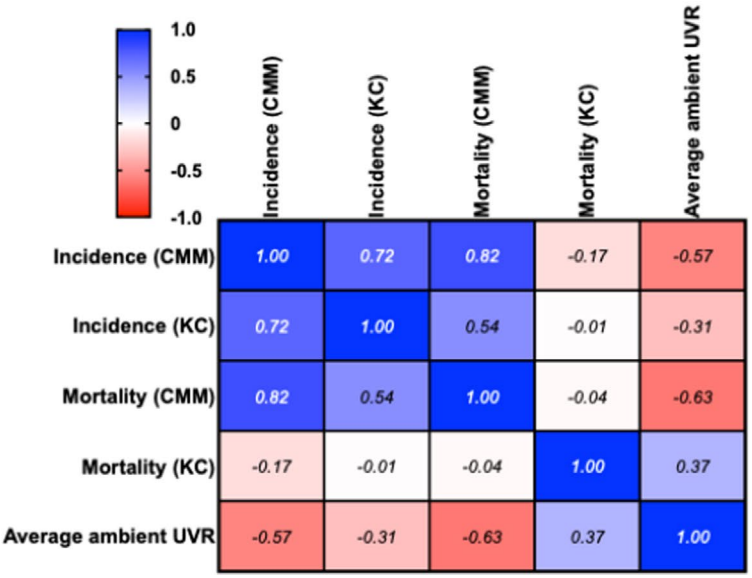


FIGURE 4 | Global skin cancer incidence and mortality from the Global Cancer Observatory (https://gco.iarc.fr). ASR = age standardized rate per 100,000. Datapoints represent each country and are color-coded by regions. Note strikingly high KC incidence in Australia/NZ.

pale-skinned populations in low UVR settings rather than a lack of a role for UVR in these skin cancers, unless one argues that SCC is not UVR-induced.

Given the importance of *MC1R* in CMM risk, we collected population frequencies of "R" (red hair) variants where available (Figure 6). CMM risk, as expected, follows closely the presence of these *MC1R* variants across the selected countries, but is dissociated from average UVR levels (Figure 6). Perhaps the unexpectedly high incidence of CMM in some Northern European countries is partially due to the high frequencies of red-haired MC1R variants?



	Incidence (CMM)	Incidence (KC)	Mortality (CMM)	Mortality (KC)	Average ambient UVR
Incidence (CMM)		1.28E-26	3.53E-39	0.03	1.77E-14
Incidence (KC)	1.28E-26		2.57E-13	0.86	0.0001
Mortality (CMM)	3.53E-39	2.57E-13		0.66	7.77E-18
Mortality (KC)	0.031	0.86	0.66		3.87E-06
Average ambient UVR	1.77E-14	0.0001	7.77E-18	3.87E-06	

FIGURE 5 | Numbers denote Spearman's correlation coefficient, *r*, for the various worldwide measures, calculated using GraphPad PRISM. Columns denote Incidence of CMM (ASR = age standardized rate), Incidence of keratinocyte cancer (KC), Mortality from CMM, Mortality from KC, UVR = average daily ambient UVR level (in J/m^2) for the years 1997–2003 (https://apps.who.int/gho/data/view.main.35300), calculated from satellite data or a proxy such as latitude. *p*-values for each calculation are shown below the figure.

A limitation of these analyses is the inadequacies of UVR exposure proxies per country [38]. In Australia, for instance, there is a gradient of CMM risk, higher in the high-UVR northern parts than in the lower-UVR south [39]. There can be group skin color diversity within countries also. But global comparisons are helpful, not least for underlining the effects of modern migration and childhood UVR exposure [7].

7 | Ambient UVR, Population Skin Cancer Incidence and Mortality

Another possibly confounding factor in assessing UVR causality in CMM is overdiagnosis in some settings, i.e., a rise in incidence due to increased screening but little change in mortality [40]. CMM incidence across US counties correlates with measures of diagnostic scrutiny, but not proxies for UVR exposure [41]. One might better assess UVR causality using global mortality (Figures 4 and 5). CMM mortality positively correlates with CMM incidence and KC incidence, but negatively with UVR proxy. Notably, across the Cancer Observatory dataset, 84.6% of CMM cases and 58.2% of CMM deaths worldwide are from Europe, North America, and Australasia (together comprising only 14.8% of the world's population) [31], suggesting that the concentration of CMM in these countries is not due to overdiagnosis alone, but perhaps also due to risk factors like pale skin and UVR exposure.

Unlike CMM mortality, KC mortality is positively correlated with higher UVR levels. Papua New Guinea (PNG), Namibia, Mozambique, and Tanzania have the highest KC mortality. This is difficult to explain. First, these countries may have limited cancer registries and relatively underdeveloped medical systems. KC mortality is negatively correlated with regional GDP in Spain (whereas CMM is positively correlated) [42]. Secondly, the above African countries have among the highest incidence of albinism worldwide [43]. Such individuals frequently develop aggressive KCs. The incidence of albinism in PNG is not documented, but individuals with albino-like skin and KC susceptibility have been described [44]. Thirdly, SCC developing in chronic ulcers occurs in tropical PNG and might explain the relatively high SCC mortality, rather than UVR carcinogenesis. Chronic skin ulceration with subsequent scarring (including from UVR-induced damage to the lesion) and localized depigmentation is characteristic of such SCCs [45].

8 | Historical Migrations, Evolutionary Selection for Lighter Skin, and CMM Variants?

Paler skin following the gradient from Africa to northern Europe resulted from selective pressure against dark skin in low ambient UVR environments, hypothesized due to selection against low vitamin D levels affecting bone health [46, 47]. Only a few genes (*SLC45A2*, *TYR*, *OCA2*, and *SLC24A5*) explain most of the selective sweep of light-skin alleles out of Africa into Europe [13]. For example, the *SLC45A2*-rs35395 light-skin allele exhibits a very strong selective sweep (i.e., increases in light-skin variants with ancestry effects corrected for) in Europe, increasing in frequency from nearly zero 13,000 years ago to virtually 100%

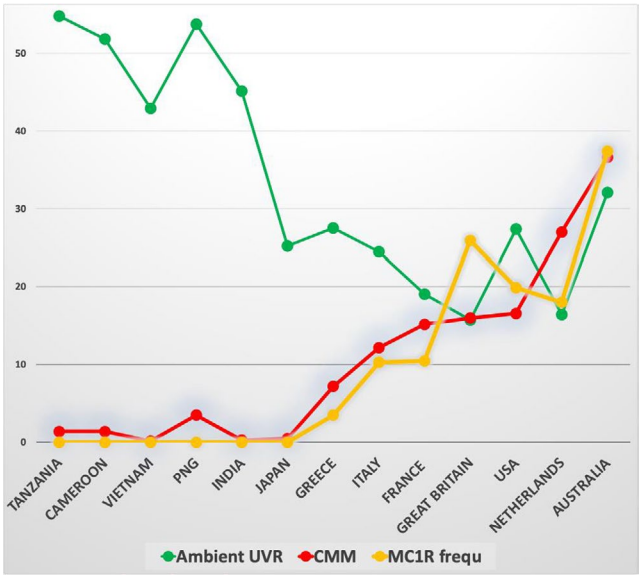


FIGURE 6 | Horizontal axis shows countries in order of increasing CMM incidence. (Red line is age standardized rate per 100,000) from the Global Cancer Observatory. Green line is estimated ambient UVR exposure (see legend to Figure 5). Yellow line is population frequency of at least one "R" red hair *MC1R* variant [obtained from Savage et al. [34], Gerstenblith et al. [35], and the Allele Frequency database (https://alfred.med.yale.edu)]. These R variants confer considerable risk for CMM, the odds ratio (OR) with one "R" variant is ~2, but with two copies is 3.43 (for CMM), 6.0 (LMM), and ~2.5 (KC) [36, 37]. (Values were adjusted for the shared y axis).

2000 years ago and today [48]. There seems to be less selection for the strong skin cancer variants (*IRF4* and *MC1R*) recently within Europe [13, 49]. *MC1R* red hair variants Arg151Cys (rs1805007) and Arg160Trp (rs1805008) are projected to be ~80,000 years old [50], perhaps arising early in the out-of-Africa migration. Similarly, *IRF4*-s12203592 exhibited strong inter-ancestry frequency differences > 40,000 years ago but has been under weaker selection since (high frequency in early hunter-gatherers but much lower frequency in modern Europeans) [13]. Another light-skin *IRF4* SNP, rs3778607, only weakly associated with skin cancer, exhibits greater evidence for recent selection than *IRF4*-rs12203592.

It would be intriguing to understand the reasons for the appearance of *MC1R* red hair and *IRF4*-rs12203592 SNPs. Why do they exhibit a larger effect on skin cancer than, say, *SLC45A2*, and why does *MC1R* but not *IRF4* strongly increase CMM risk? Are they associated with other phenotypes? PheWAS analyses across the UKBiobank for *MC1R-rs18050087*, *MC1R-rs1805008*, and *IRF4-rs12203592* showed some effects on reticulocyte biology, standing height, and lymphocyte biology, but the associations are dwarfed by their effect sizes on skin color. PheWAS analysis of *SLC45A2*, *OCA2*, *SLC24A5*, and *TYR* revealed similar findings. Hence, evidence is not strong for skin cancer risk variants evolving for any reason other than lighter pigmentation. Why did red melanin develop? *Mc1r* is strongly selected for in animal species due to adaptation to environmental pressures [51]. The various mechanisms include sexual selection, selection for camouflage, or other reasons for specific coloration, possibly immunity and metal homeostasis. In an evolutionary sense, eumelanin is hypothesized to be the ancestral form, appearing first as a reactive oxygen species scavenger, later co-opted for photoprotection [52]. But the reasons for the selection of pheomelanin in humans are still unclear given the trade-offs of free radical production and the fact that it can be degraded by UVR.

9 | The Mutational Consequences of UVR Exposure

Somewhat contradictory findings regarding the causal factors of UVR in CMM do not apply to KC, particularly SCC, which appears driven by cumulative UVR-induced DNA damage. Could there be differences in UVR-induced mutation formation? Carcinogens leave tell-tale signatures in DNA. For instance, lung cancers are dominated by C>A and C>T single-nucleotide variants (SNVs). The same signature is seen in cells treated with benzopyrene, a component of tobacco smoke [53], confirming benzopyrene's carcinogenicity.

Of 33 tumor types in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (https://cancer.sanger.ac.uk), the highest average SNV counts per tumor are in BCC (47.3 SNVs/Mb), SCC (45.2 SNVs/Mb), and CMM (14.4 SNVs/Mb). These SNVs are overwhelmingly at C>Ts, ensuing from misrepaired UVR-induced cyclobutane pyrimidine dimers (CPDs). Even sun-exposed normal human epidermis carries 2–6 SNVs/Mb [54], with over 50 SNVs/Mb in Australian forearm skin samples [55]. Such C>T burden is higher with age and light-skin color [56]. Melanocyte DNA in normal back skin carries up to 30 SNVs/Mb [57]. Mouse CMM models tell us that a few or even perhaps a single intense UVB exposure can leave significant mutational imprints in CMMs [58]. Tumors from murine CMMs induced by a single UVB exposure contain ~12 SNVs/Mb in the exome, spontaneous tumors ~2–8 SNVs/Mb [58, 59].

While C>T and tandem CC>TT mutations are accepted markers of UVR damage, Drobetsky et al. [60] showed that UVR adduct formation was "context-dependent", limited by the nucleotides adjacent to the mutated cytosine. The strongest UVR signature is defined in the COSMIC catalogue [61], (SBS7a), is represented by C>Ts at the triplet motifs TCC (mutated base underlined), or TCA. In CMMs, the SBS7a SNV pattern represents ~10 mutations/Mb. A second UVR signature, SBS7b, comprises C>Ts at TCC or CCC (10 mutations/Mb). Minor UVR signatures SBS7c (T>A) and SBS7d (T>C) represent less than one SNV/Mb. The SBS signatures of CMMs, SCCs, BCCs, and normal UVR-exposed skin cells are virtually identical; CMM cannot be separated in this respect. Predictably, SBS7 is much less prominent in acral and mucosal melanoma (Table 2). Here, the dominant mutation signature is SBS1 (C>Ts at NCG, N = any nucleotide), due to spontaneous deamination of methylated cytosines that are mutated (SBS1 is observed in all TCGA tumor types) [64].

If one stratifies CMMs in terms of high and low chronic sun damage (severe solar elasticity vs. very little) [65], the former carries many more C>Ts, although both groups exhibit a dominant SBS7 signature [66]. Hence, SBS7 seems a sensitive indicator of previous UVR exposure, whereas mutation load better indicates chronicity of exposures (Table 2) [55]. Perhaps the differences in the epidemiology of CMM and KC (associated

TABLE 2 | Summary of UVR exposure association and mutation landscape of major melanoma subtype.

Subtype	Anatomical site	Frequency in of subtype in Australia	Contribution of UVR	Average Mutation load	Proportion SBS7 signature
Cutaneous MM (SSM/NM)	Tend to be truncal but also other sites	65%–75%	Intermittent	~36 per Mb	> 90%
Lentigo Maligna MM	Head, neck, arms	10%–15%	Chronic	> 100 per Mb	> 90%
Desmoplastic MM	Head, Neck	1%–5%	Chronic	> 100 per Mb	> 90%
Acral MM	Fingers, Toes	1%–2%	Little or None	~2.1 per Mb	~60%
Mucosal MM	Internal mucosal surfaces	1%–2%	None	~2.3 per Mb	~48%

Note: Mutation statistics estimated from Newell et al. [62], and the frequency of subtypes in Australia from the Cancer Council of Australia [63].

with intermittent versus chronic exposure respectively) are explained by the efficiency of removal of CPDs. In mice, after a single intense UVR exposure, CPDs are removed ostensibly completely after a few days. But when the same dose is fractionated into very small doses, "chronic" irradiation over a much longer period, CPDs persist for weeks, particularly in clonal deposits [67, 68].

10 | UVA Mutation Signature

Attempts at defining a UVA signature mostly involve irradiated cultured cells. UVA can induce 8-oxo-guanine adducts formed by reactive oxygen species, resulting in G>T (C>A) changes [69], while others suggest that UVA mainly induces CPDs [70]. Jin et al. [70] outline the problems in defining a UVA signature, including that similar adducts can be formed by both UVA and UVB, and that the mutagenic effects of UVA in melanocytes are largely unknown. The C>A dominated mutation signatures in non-melanocytic cells treated with UVA [69] are SBS18 (damage due to reactive oxygen species) and SBS36 (defective DNA base excision repair). The former is not significantly enriched in skin cancers, while SBS36 is enriched in CMM but not in SCC or BCC. Perhaps this could represent a melanocyte-specific mode of mutation formation by UVA, although this is unresolved.

11 | Non-Canonical UVR-Induced SNVs and BRAF Mutations

Mutations upregulating oncogenic *BRAF* and *NRAS* in CMM are thought not to have been UVR-induced since they do not occur at canonical C>Ts. *BRAFV-600E*, the most common *BRAF* mutation, results from a T>A (in the GTG context) mutation at nucleotide 1799 and is present in ~26% of CMMs. Recent experimental work with yeast suggests that T>A can be induced by UVR at GTG [71], and so can AC>TT changes producing less common *BRAF-V600R* and *BRAF-V600K* mutations. Similarly, recurrent *NRAS* mutations (Q61R and Q61L) can result from T>C and T>A changes induced by UVR in yeast [71], matching signatures SBS7c (T>A and T>C at TTT), SBS7d (T>A at ATT, and T>C at GTT), predicted UVR signatures based upon co-occurrence with SBS7a/b. In experimental mouse CMM models also, T>A and T>C, with adjacent pyrimidines, are significantly increased in UVR-induced compared to spontaneous melanomas [58, 72]. Although rare non-canonical changes have been somewhat ignored because of the preponderance of C>Ts in CMM, they may form oncogenic mutations. There is still, however, the anomaly that the *BRAF-V600E* variant is observed in many internal cancer types [73, 74].

12 | Canonical UVR-Like Mutation Signatures in Some Internal Cancers

The two major UVR signatures (SBS7a and SBS7b) are detected at low rates in breast cancer, pancreatic adenocarcinoma, lung and parotid gland SCCs (Sanger COSMIC database), and renal cell carcinomas [75]. Conceivably, such CPDs may have occurred via a non-UVR-related "chemical" induction ("dark CPDs"). Some reactive chemicals can induce CPDs on contact with DNA without any need for UVR exposure. One of these is dioxetane, a strained heterocyclic organic compound generated by particular metabolic processes [76]. Signature SBS7a, including CC-TTs, has been observed in pediatric B cell acute lymphoblastic leukemia [77], and in normal lymphocytes (memory B-cells) [78]. Possibly, such lymphocytes have been exposed to UVR during skin residency. In sum, it should be noted that the SBS7 signature occurs in apparently non-UVR contexts; hence, its presence does not necessarily signal UVR causality in cancer.

13 | Mechanisms of UVR-Induced Adduct Formation

The most common UVR-induced DNA adducts are CPDs. UVR also induces 6–4 pyrimidone photoproducts (6-4PPs) and oxidative adducts to a lesser extent. CPDs form between adjacent pyrimidines that become covalently linked. There are two basic mechanisms: one via direct interaction of UVR photons (particularly UVC and UVB) with DNA, and the second indirect method whereby other molecules absorb UVR photon energy and themselves interact with pyrimidines.

Photon energy directly interacting with DNA leads to excited electron states within pyrimidine bonds, which then undergo

a photochemical reaction within milliseconds to form CPDs and/or 6-4PPs. Depending upon the energy of the excited electron states within the pyrimidine bonds, CPDs form directly, whereas 6-4PP formation depends more upon an intermediate reactive oxetane species, permitting covalent bond formation [79].

The second indirect mechanism requires photosensitizers, one of which is melanin. Adducts formed as such are termed "dark" CPDs, formed maximally at about an hour post-UVR. They may account for 30%–50% of all CPDs produced [80]. The process is not simple, with UVR exposure inducing superoxides and nitric oxide, causing a large increase in peroxynitrite that can degrade melanin into reactive fragments [81], which can enter the cell nucleus where DNA interaction occurs. Dark eumelanin is less likely to degrade and/or become photoactivated than the reddish pheomelanin [82]. Dark CPDs are also induced by other photosensitizers in the skin, particularly those with tricyclic, heterocyclic, or porphyrin ring structures with conjugated double bonds (*pi*-electron system). They include acetone, acetophenone, and para-aminobenzoic acid [83]. These act via slightly different mechanisms and molecular intermediates than melanin but similarly ultimately induce CPDs [83]. Notably, dark CPDs are produced not only in melanocytes, but also in keratinocytes and even fibroblasts, which contain no melanin [81]. Since DNA is not the chromophore, the UVR action spectrum for dark CPD formation will be different than the currently defined spectrum for "ultrafast" dimer formation, which peaks at UVB. But both UVB and UVA induce dark CPDs in human skin [84]. There is considerable interest in mitigating the formation of dark CPDs. In vitro work suggests that post-UVA application of antioxidants can reduce their development [80].

14 | Further to the Role of Melanin and Possibly UVA in CMM Carcinogenesis

The most parsimonious explanation for the strong correlation between skin pigmentation and CMM incidence is the protection afforded by melanin against UVR-induced damage [85]. The level of protection against CPD formation is up to 59-fold higher in the basal epidermis (where melanocytes reside) in African compared to Caucasian skin [86]. This must be a factor in the preponderance of skin cancers in white compared to black-skinned individuals. But while dark melanin (eumelanin) is UVR-protective, the red/yellow melanin (pheomelanin) is less so, tends to degrade/disperse in inflamed skin, is more prone to forming DNA-damaging reactive intermediates, and is less able to scavenge reactive oxygen species [87]. In cell culture, pheomelanin was 3–5 times more effective at inducing dark CPDs than eumelanin [87]. These may be important factors explaining increased CMM risk in carriers of *MC1R* R variants, since the cardinal function of MC1R is pigment switching between black eumelanin and red pheomelanin synthesis.

Despite the recent discovery that melanin can induce CPDs [81], the existence of reactive melanin and its possible mutagenic activity has been known for almost 50 years [88]. Wood et al. [89] showed in the *Xiphophorus* fish melanoma model that the action spectrum for tumor induction overlapped with that of photosensitized melanin production by UVA. Subsequent work [90] suggested a pyrimidine dimer rather than a melanin radical-based mechanism in UVA-based melanoma induction in *Xiphophorus*. Noonan et al. [91] used pigmented and albino *Mt-Hgf* transgenic mice to show that UVA-accelerated CMM development required the presence of melanin. More oxidative damage was detected in UVA-treated mice than in UVB-treated mice, but only in the presence of pigment. Very few CPDs were induced in the pigmented mouse skin, but as the tissue was fixed immediately post-UVR, "dark" CPDs would not have been detected. As adults and neonates, these mice have extrafollicular melanocytes that do not transmit melanin to adjacent keratinocytes (possibly analogous to naevi). The irradiation of such melanin deposits perhaps leads to melanin-induced UVA mutagenesis. The pigmented *Mt-Hgf* mice also have a far higher incidence of spontaneous CMM than otherwise identical albino transgenics, further suggesting a role for activated melanin [84, 92].

UVA does not exacerbate CMM in all mouse models. This may be due to the substantially higher levels of melanin in the *Mt-Hgf* model than in other published models [59, 93], while perhaps some differences in UVA lamps may also explain the disparities. Phenotypic differences between engineered mouse models can be due to both the identity of engineered transgene/mutation and how it was engineered. These can influence both temporal and spatial expressions of the transgene, particularly in neonatal mice [92], and phenotypic outcomes including tumor initiation [94].

15 | Lack of CMM in Albinism

Another argument for the role of melanin is the rarity of CMM in Africans with albinism, although they frequently develop aggressive SCCs in their 20s [95]. They can succumb to invasive KC at a young age, although where sun protection is practiced, mortality is similar to that of non-albino Africans [95]. This form of albinism is due to *OCA2* gene mutation, but presumably all other pigmentation genes, including *MC1R* and *IRF4* are functional. A systematic review of skin cancers in Africans with albinism showed that only 1.7% (12/715) were CMMs [96]. Given that 1/3 of these were acral melanoma, which we disregarded because it is not UVR-associated [97], only ~1% of all skin cancers were CMM. To gain some context for this, we asked what might be an estimated proportion of skin cancer types detected in a high-UVR population like Australia? The Australia Institute for Health and Welfare Report [11] catalogued new CMMs in 2021. As a proxy for KC incidence, we used the number of paid Medicare treatments for their removal in 2014 [98]. Based on these data ~1.3% of all skin cancers reported annually in Australia are CMM. Although such estimates for both African albinos and the general Australian population are probably subject to bias (low numbers in the case of albinism, and possibly many unaccounted-for KCs in Australia), it is still unclear whether the proportion of CMM in African albinos is lower than that of the general African population. Ravichandran et al. [99] reviewed all cases of CMM worldwide in individuals with albinism and came to similar conclusions. But clearly, even enormous levels of UVR-induced damage, such as that incurred

in Africa, are insufficient to induce CMM with any great frequency in albinism.

16 | Vitiligo and CMM Risk

Vitiligo provides perhaps another "natural experiment" that might provide clues to CMM development. Autoimmune vitiligo is a condition of depigmentation, usually in patches, due to the local death of melanocytes. Such individuals are not at increased CMM risk because of the lack of pigment; instead, they have a substantially lower-than-normal risk, in fact, for all the major skin cancers [100]. In the context of CMM growth and spread, a tendency for immune-related death of melanocytes may be a good thing [100]. Vitiligo GWASs have identified many genes, the strongest being the *HLA-DRB1* and *DQA1* immune loci, and *TYR*, *OCA2*, *ASIP*, *MC1R*, and *IRF4*. For the pigmentation loci, the specific SNPs conferring increased skin cancer risk conferred decreased vitiligo risk [101, 102]. Thus, vitiligo patients tend to have the same skin/pigmentation phenotype as relatively skin cancer-protected darker-skinned individuals who tan and do not burn (Figure 1). Even the immune gene SNPs show an inverse relationship: increased vitiligo risk but decreased skin cancer risk [102]. Despite caveats such as individuals with very fair skin might not report vitiligo, or that easily burnable vitiliginous skin may favor enhanced sun protection behavior, vitiligo is protective for CMM. Is this due to the immune effect or the pigmentation effect? A pilot study of DNA from lesional and non-lesional skin in vitiligo suggested that lesional skin may carry fewer mutations, a non-SBS7 mutation signature, and potential upregulation of DNA repair activity [103]. One could speculate that in vitiligo, there may be a "genetic" protective effect against UVR overriding the pigmentation defect.

17 | Conclusion

In assessing the influence of UVR on CMM, it is helpful to compare innate and environmental risk factors for all skin cancers. First, CMM, BCC, and SCC have in common light-skin color, poor tanning phenotype, correlated worldwide incidence, overwhelming preponderance of SBS7 somatic mutations, and increased risk from childhood sun exposure, consistent with a role for UVR in exacerbating them all. Important differences are that CMM is associated with naevi, intermittent vs. chronic exposure, is extremely rare in African albinism, and is sometimes of earlier onset than SCC, which almost invariably occurs in over 40s. These differences possibly argue for less of a role, or perhaps a somewhat different role for UVR in CMM. The lack of association of *IRF4* variants with CMM in GWASs, while it is the largest-effect risk gene for KC, is an anomaly, curiously differentiating naevus and CMM risk. Strikingly, across large scale GWASs, *IRF4* is the strongest risk gene for naevus count, BCC, SCC, AK, tanning ability, sensitive skin, and skin aging.

Genome-wide sequencing has collated millions of somatic mutations in skin cancer. But SNV signatures per se do not discriminate CMM and KCs apart from a marginally higher SNV load in KCs (differences in specific somatic mutations are not covered here). The preponderance of C>Ts in CMM seems due to the initial transformed cell or lesion at some time encountering UVR. The discovery of "dark" CPD formation in which melanin can act as a photosensitizer suggests a possible role for chemiexcitation in UVR carcinogenesis in CMM, especially in individuals producing pheomelanin. Evolutionarily, depigmentation has resulted from adaptive evolution over time in differing UVR contexts, but the trade-off has been skin cancer risk, particularly in the case of *MC1R* red hair variants and *IRF4*-rs12203592. Natural experiments related to pigmentation come from African albinism and vitiligo. Both conditions potentially confer lower-than-normal risks of CMM. Notwithstanding the notion that melanin can be pro-mutagenic, one could speculate a "genetic" protective effect in both conditions since, despite the specific pigmentation defect, such individuals carry "good" SNPs in *MC1R, IRF4*, and other CMM risk genes.

Author Contributions

G.J.W. did the bulk of the writing and preparation of the manuscript. G.J.W. and K.K. contributed to the writing, the conception and design of the paper, the definition of intellectual content, editing, and both authors take overall responsibility for the work. Both authors read and approved the final manuscript.

Acknowledgments

The authors are grateful to Frances Noonan and Rick Sturm for helpful discussions. Open access publishing facilitated by The University of Queensland, as part of the Wiley - The University of Queensland agreement via the Council of Australian University Librarians.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in (The Global Cancer Observatory) at (https://gco.iarc.fr), the GeneATLAS database (https://geneatlas.roslin.ed.ac.uk), COSMIC Catalogue of Somatic Mutations in Cancer (https://cancer.sanger.ac.uk), The GNOMAD database (https://gnomad.broadinstitute.org), The Global Cancer Observatory Exposure to solar ultraviolet (UV) radiation Data by country (https://apps.who.int/gho/data/view.main.35300), The Allele Frequency Database (https://alfred.med.yale.edu).

References

1. S. Gandini, F. Sera, M. S. Cattaruzza, et al., "Meta-Analysis of Risk Factors for Cutaneous Melanoma: II. Sun Exposure," *European Journal of Cancer* 41, no. 1 (2005a): 45–60.

2. B. K. Armstrong and A. Kricker, "The Epidemiology of UV Induced Cancer," *Journal of Photochemistry and Photobiology. B* 63 (2001): 8–18.

3. S. Gandini, F. Sera, M. S. Cattaruzza, et al., "Meta-Analysis of Risk Factors for Cutaneous Melanoma: I. Common and Atypical Naevi," *European Journal of Cancer* 41, no. 1 (2005b): 28–44.

4. D. C. Whiteman, P. Watt, D. M. Purdie, M. C. Hughes, N. K. Hayward, and A. C. Green, "Melanocytic Nevi, Solar Keratoses, and Divergent Pathways to Cutaneous Melanoma," *Journal of the National Cancer Institute* 95, no. 11 (2003): 806–812, https://doi.org/10.1093/jnci/95.11.806.

5. M. S. Paulo, B. Adam, C. Akagwu, et al., "WHO/ILO Work-Related Burden of Disease and Injury: Protocol for Systematic Reviews of Occupational Exposure to Solar Ultraviolet Radiation and of the Effect of Occupational Exposure to Solar Ultraviolet Radiation on Melanoma and Non-Melanoma Skin Cancer," *Environment International* 126 (2019): 804–815.

6. M. Kvaskoff, V. Siskind, and A. C. Green, "Risk Factors for Lentigo Maligna Melanoma Compared With Superficial Spreading Melanoma: A Case–Control Study in Australia," *Archives of Dermatology* 148, no. 2 (2012): 164–170.

7. D. C. Whiteman, C. A. Whiteman, and A. C. Green, "Childhood Sun Exposure as a Risk Factor for Melanoma: A Systematic Review of Epidemiologic Studies," *Cancer Causes & Control* 12 (2001): 69–82.

8. I. Savoye, C. M. Olsen, D. C. Whiteman, et al., "Patterns of Ultraviolet Radiation Exposure and Skin Cancer Risk: The E3N-SunExp Study," *Journal of Epidemiology* 28, no. 1 (2018): 27–33.

9. Y. Li, J. Wu, and Z. Cao, "Childhood Sunburn and Risk of Melanoma and Non-Melanoma Skin Cancer: A Mendelian Randomization Study," *Environmental Science and Pollution Research* 30 (2023): 122011–122023.

10. P. Fontanillas, B. Alipanahi, N. A. Furlotte, et al., "Disease Risk Scores for Skin Cancers," *Nature Communications* 12, no. 160 (2021): 5.

11. Australian Institute of Health and Welfare, *Report, Skin Cancer in Australia* (AIHW, 2016).

12. S. Pellegrini, L. Elefanti, L. Dall'Olmo, and C. Menin, "The Interplay Between Nevi and Melanoma Predisposition Unravels Nevi-Related and Nevi-Resistant Familial Melanoma," *Genes* 12, no. 7 (2021): 1077.

13. D. Ju and I. Mathieson, "The Evolution of Skin Pigmentation-Associated Variation in West Eurasia," *Proceedings of the National Academy of Sciences of the United States of America* 118, no. 1 (2021): e2009227118.

14. D. L. Duffy, G. Zhu, X. Li, et al., "Novel Pleiotropic Risk Loci for Melanoma and Nevus Density Implicate Multiple Biological Pathways," *Nature Communications* 9, no. 1 (2018): 4774.

15. H. S. Chahal, W. Wu, K. J. Ransohoff, et al., "Genome-Wide Association Study Identifies 14 Novel Risk Alleles Associated With Basal Cell Carcinoma," *Nature Communications* 7 (2016): 12510.

16. Y. Kim, J. Yin, H. Huang, E. Jorgenson, H. Choquet, and M. M. Asgari, "Genome-Wide Association Study of Actinic Keratosis Identifies New Susceptibility Loci Implicated in Pigmentation and Immune Regulation Pathways," *Communications Biology* 5, no. 1 (2022): 386.

17. K. Y. Sarin, Y. Lin, R. Daneshjou, et al., "Genome-Wide Meta-Analysis Identifies Eight New Susceptibility Loci for Cutaneous Squamous Cell Carcinoma," *Nature Communications* 11, no. 1 (2020): 820.

18. A. Visconti, D. L. Duffy, F. Liu, et al., "Genome-Wide Association Study in 176,678 Europeans Reveals Genetic Loci for Tanning Response to Sun Exposure," *Nature Communications* 9, no. 1 (2018): 1684.

19. M. A. Farage, Y. Jiang, J. P. Tiesman, P. Fontanillas, and R. Osborne, "Genome-Wide Association Study Identifies Loci Associated With Sensitive Skin," *Cosmetics* 7, no. 2 (2020): 49.

20. V. Roberts, B. Main, N. J. Timpson, and S. Haworth, "Genome-Wide Association Study Identifies Genetic Associations With Perceived Age," *Journal of Investigative Dermatology* 140, no. 12 (2020): 2380–2385.

21. D. C. Gibbs, I. Orlow, J. I. Bramson, et al., "Association of Interferon Regulatory Factor-4 Polymorphism rs12203592 With Divergent Melanoma Pathways," *Journal of the National Cancer Institute* 108, no. 7 (2016): djw004, https://doi.org/10.1093/jnci/djw004.

22. D. L. Duffy, M. M. Iles, D. Glass, et al., "IRF4 Variants Have Age-Specific Effects on Nevus Count and Predispose to Melanoma," *American Journal of Human Genetics* 87, no. 1 (2010): 6–16, https://doi.org/10.1016/j.ajhg.2010.05.017.

23. C. Praetorius, C. Grill, S. N. Stacey, et al., "A Polymorphism in IRF4 Affects Human Pigmentation Through a Tyrosinase-Dependent MITF/TFAP2A Pathway," *Cell* 155, no. 5 (2013): 1022–1033.

24. J. Lu, T. Liang, P. Li, and Q. Yin, "Regulatory Effects of IRF4 on Immune Cells in the Tumor Microenvironment," *Frontiers in Immunology* 6, no. 14 (2023): 1086803.

25. L. G. Fritsche, L. J. Beesley, P. VandeHaar, et al., "Exploring Various Polygenic Risk Scores for Skin Cancer in the Phenomes of the Michigan Genomics Initiative and the UK Biobank With a Visual Catalog: PRSWeb," *PLoS Genetics* 15, no. 6 (2019): e1008202.

26. L. G. Fritsche, S. B. Gruber, Z. Wu, et al., "Association of Polygenic Risk Scores for Multiple Cancers in a Phenome-Wide Study: Results From the Michigan Genomics Initiative," *American Journal of Human Genetics* 102, no. 6 (2018): 1048–1061.

27. T. E. Robsahm, M. R. Karagas, J. R. Rees, and A. Syse, "New Malignancies After Squamous Cell Carcinoma and Melanomas: A Population-Based Study From Norway," *BMC Cancer* 14 (2014): 210.

28. A. Loya, D. S. Gombos, and S. P. Patel, "Second Primary Malignancies in Patients With Melanoma Subtypes: Analysis of 120,299 Patients From the SEER Database (2000–2016)," *Frontiers in Oncology* 12 (2022): 853076.

29. Z. Yang, H. Zhong, J. Chen, et al., "A Genetic Mechanism for Convergent Skin Lightening During Recent Human Evolution," *Molecular Biology and Evolution* 33, no. 5 (2016): 1177–1187.

30. K. Shido, K. Kojima, K. Yamasaki, et al., "Susceptibility Loci for Tanning Ability in the Japanese Population Identified by a Genome-Wide Association Study From the Tohoku Medical Megabank Project Cohort Study," *Journal of Investigative Dermatology* 139, no. 7 (2019): 1605–1608.

31. M. Arnold, D. Singh, M. Laversanne, et al., "Global Burden of Cutaneous Melanoma in 2020 and Projections to 2040," *JAMA Dermatology* 158, no. 5 (2022): 495–503.

32. S. J. Merrill, S. Ashrafi, M. Subramanian, and D. E. Godar, "Exponentially Increasing Incidences of Cutaneous Malignant Melanoma in Europe Correlate With Low Personal Annual UV Doses and Suggests 2 Major Risk Factors," *Dermato-Endocrinology* 7, no. 1 (2015): e1004018.

33. W. You, R. Henneberg, B. J. Coventry, and M. Henneberg, "Cutaneous Malignant Melanoma Incidence Is Strongly Associated With European Depigmented Skin Type Regardless of Ambient Ultraviolet Radiation Levels: Evidence From Worldwide Population-Based Data," *AIMS Public Health* 9, no. 2 (2022): 378–402.

34. S. A. Savage, M. R. Gerstenblith, A. M. Goldstein, et al., "Nucleotide Diversity and Population Differentiation of the Melanocortin 1 Receptor Gene, MC1R," *BMC Genetics* 9 (2008): 1–8.

35. M. R. Gerstenblith, A. M. Goldstein, M. C. Fargnoli, K. Peris, and M. T. Landi, "Comprehensive Evaluation of Allele Frequency Differences of MC1R Variants Across Populations," *Human Mutation* 28, no. 5 (2007): 495–505.

36. E. Tagliabue, M. C. Fargnoli, S. Gandini, et al., "MC1R Gene Variants and Non-Melanoma Skin Cancer: A Pooled-Analysis From the M-SKIP Project," *British Journal of Cancer* 113, no. 2 (2015): 354–363.

37. S. Caini, S. Gandini, F. Botta, et al., "MC1R Variants and Cutaneous Melanoma Risk According to Histological Type, Body Site, and Breslow Thickness: A Pooled Analysis From the M-SKIP Project," *Melanoma Research* 30, no. 5 (2020): 500–510.

38. D. E. Godar, "UV Doses Worldwide," *Photochemistry and Photobiology* 81, no. 4 (2005): 736–749.

39. P. Baade, X. Meng, D. Youlden, J. Aitken, and P. Youl, "Time Trends and Latitudinal Differences in Melanoma Thickness Distribution in Australia, 1990–2006," *International Journal of Cancer* 130, no. 1 (2012): 170–178.

40. H. G. Welch, B. L. Mazer, and A. S. Adamson, "The Rapid Rise in Cutaneous Melanoma Diagnoses," *New England Journal of Medicine* 384, no. 1 (2021): 72–79.

41. A. S. Adamson, H. Welch, and H. G. Welch, "Association of UV Radiation Exposure, Diagnostic Scrutiny, and Melanoma Incidence in US Counties," *JAMA Internal Medicine* 182, no. 11 (2022): 1181–1189.

42. A. Del Alcalá Ramírez Puerto, J. C. Hernández-Rodriguez, M. Sendín-Martín, J. Ortiz-Alvarez, J. Conejo-Mir Sánchez, and J. J. Pereyra-Rodriguez, "Skin Cancer Mortality in Spain: Adjusted Mortality Rates by Province and Related Risk Factors," *International Journal of Dermatology* 62, no. 6 (2023): 776–782, https://doi.org/10.1111/ijd.16618.

43. J. G. R. Kromberg, K. A. Flynn, and R. A. Kerr, "Determining a Worldwide Prevalence of Oculocutaneous Albinism: A Systematic Review," *Investigative Ophthalmology & Visual Science* 64, no. 10 (2023): 14.

44. R. J. Walsh, "A Distinctive Pigment of the Skin in New Guinea Indigenes," *Annals of Human Genetics* 34, no. 4 (1971): 379–388.

45. H. M. Foster and S. J. Webb, "Skin Cancer in the North Solomons," *Australian and New Zealand Journal of Surgery* 58, no. 5 (1988): 397–401, https://doi.org/10.1111/j.1445-2197.1988.tb01087.x.

46. N. G. Jablonski, "The Evolution of Human Skin Pigmentation Involved the Interactions of Genetic, Environmental, and Cultural Variables," *Pigment Cell & Melanoma Research* 34, no. 4 (2021): 707–729.

47. M. D. Lucock, "The Evolution of Human Skin Pigmentation: A Changing Medley of Vitamins, Genetic Variability, and UV Radiation During Human Expansion," *American Journal of Biological Anthropology* 180, no. 2 (2023): 252–271.

48. E. K. Irving-Pease, A. Refoyo-Martínez, W. Barrie, et al., "The Selection Landscape and Genetic Legacy of Ancient Eurasians," *Nature* 625, no. 7994 (2024): 312–320.

49. R. A. Sturm and D. L. Duffy, "Human Pigmentation Genes Under Environmental Selection," *Genome Biology* 13 (2012): 248.

50. R. M. Harding, E. Healy, A. J. Ray, et al., "Evidence for Variable Selective Pressures at MC1R," *American Journal of Human Genetics* 66, no. 4 (2000): 1351–1361.

51. H. I. Ahmad, G. Liu, X. Jiang, C. Liu, Y. Chong, and H. Huarong, "Adaptive Molecular Evolution of MC1R Gene Reveals the Evidence for Positive Diversifying Selection in Indigenous Goat Populations," *Ecology and Evolution* 7, no. 14 (2017): 5170–5180.

52. M. E. McNamara, V. Rossi, T. S. Slater, et al., "Decoding the Evolution of Melanin in Vertebrates," *Trends in Ecology & Evolution* 36, no. 5 (2021): 430–443, https://doi.org/10.1016/j.tree.2020.12.012.

53. C. Mingard, J. N. D. Battey, V. Takhaveev, et al., "Dissection of Cancer Mutational Signatures With Individual Components of Cigarette Smoking," *Chemical Research in Toxicology* 36, no. 4 (2023): 714–723.

54. I. Martincorena, A. Roshan, M. Gerstung, et al., "High Burden and Pervasive Positive Selection of Somatic Mutations in Normal Human Skin," *Science* 348, no. 6237 (2015): 880–886, https://doi.org/10.1126/science.aaa6806.

55. H. Y. Wong, R. C. Lee, S. Chong, et al., "Epidermal Mutation Accumulation in Photodamaged Skin Is Associated With Skin Cancer Burden and Can Be Targeted Through Ablative Therapy," *Science Advances* 9, no. 19 (2023): 2384.

56. C. D. Robles-Espinoza, N. D. Roberts, S. Chen, et al., "Germline MC1R Status Influences Somatic Mutation Burden in Melanoma," *Nature Communications* 7, no. 1 (2016): 12064.

57. J. Tang, E. Fewings, D. Chang, et al., "The Genomic Landscapes of Individual Melanocytes From Human Skin," *Nature* 586, no. 7830 (2020): 600–605.

58. P. Mukhopadhyay, B. Ferguson, H. K. Muller, H. Y. Handoko, and G. J. Walker, "Murine Melanomas Accelerated by a Single UVR Exposure Carry Photoproduct Footprints but Lack UV Signature C>T Mutations in Critical Genes," *Oncogene* 35, no. 25 (2016): 3342–3350.

59. R. L. Bowman, R. C. Hennessey, T. J. Weiss, et al., "UVB Mutagenesis Differs in Nras- and Braf-Mutant Mouse Models of Melanoma," *Life Science Alliance* 4, no. 9 (2021): e202101135.

60. E. A. Drobetsky, A. J. Grosovsky, and B. W. Glickman, "The Specificity of UV-Induced Mutations at an Endogenous Locus in Mammalian Cells," *Proceedings of the National Academy of Sciences of the United States of America* 84, no. 24 (1987): 9103–9107.

61. L. B. Alexandrov, J. Kim, N. J. Haradhvala, et al., "The Repertoire of Mutational Signatures in Human Cancer," *Nature* 578, no. 7793 (2020): 94–101, https://doi.org/10.1038/s41586-020-1943-3.

62. F. Newell, P. A. Johansson, J. S. Wilmott, et al., "Comparative Genomics Provides Etiologic and Biological Insight Into Melanoma Subtypes," *Cancer Discovery* 12, no. 12 (2022): 2856–2879.

63. Cancer Council of Australia skin cancer statistics, "Skin Cancer Incidence and Mortality," (2025), accessed January 5, 2025, https://www.cancer.org.au/about-us/policy-and-advocacy/prevention/uv-radiation/related-resources/skin-cancer-types.

64. N. K. Hayward, J. S. Wilmott, N. Waddell, et al., "Whole-Genome Landscapes of Major Melanoma Subtypes," *Nature* 545, no. 7653 (2017): 175–180.

65. V. J. Mar, S. Q. Wong, J. Li, et al., "BRAF/NRAS Wild-Type Melanomas Have a High Mutation Load Correlating With Histologic and Molecular Signatures of UV Damage," *Clinical Cancer Research* 19, no. 17 (2013): 4589–4598.

66. P. Mukhopadhyay, J. A. Roberts, and G. J. Walker, "Further Assessment of Exome-Wide UVR Footprints in Melanoma and Their Possible Relevance," *Molecular Carcinogenesis* 56, no. 6 (2017): 1673–1679.

67. D. L. Mitchell, R. Greinert, F. R. De Gruijl, et al., "Effects of Chronic Low-Dose Ultraviolet B Radiation on DNA Damage and Repair in Mouse Skin," *Cancer Research* 59, no. 12 (1999): 2875–2884.

68. A. van Schanke, M. J. Jongsma, R. Bisschop, G. M. van Venrooij, H. Rebel, and F. R. de Gruijl, "Single UVB Overexposure Stimulates Melanocyte Proliferation in Murine Skin, in Contrast to Fractionated or UVA-1 Exposure," *Journal of Investigative Dermatology* 124, no. 1 (2005): 241–247, https://doi.org/10.1111/j.0022-202X.2004.23551.x.

69. M. Zhivagui, A. Hoda, N. Valenzuela, et al., "DNA Damage and Somatic Mutations in Mammalian Cells After Irradiation With a Nail Polish Dryer," *Nature Communications* 14, no. 1 (2023): 276.

70. S. G. Jin, F. Padron, and G. P. Pfeifer, "UVA Radiation, DNA Damage, and Melanoma," *ACS Omega* 7, no. 37 (2022): 32936–32948.

71. M. F. Laughery, A. J. Brown, K. A. Bohm, et al., "Atypical UV Photoproducts Induce Non-Canonical Mutation Classes Associated With Driver Mutations in Melanoma," *Cell Reports* 33, no. 7 (2020): 108401.

72. A. Viros, B. Sanchez-Laorden, M. Pedersen, et al., "Ultraviolet Radiation Accelerates BRAF-Driven Melanomagenesis by Targeting TP53," *Nature* 511, no. 7510 (2014): 478–482.

73. AACR Project GENIE Consortium, "AACR Project GENIE: Powering Precision Medicine Through an International Consortium," *Cancer Discovery* 7, no. 8 (2017): 818–831, https://doi.org/10.1158/2159-8290.CD-17-0151.

74. J. Durślewicz, "Detection of BRAF V600E Mutation in Ganglioglioma and Pilocytic Astrocytoma by Immunohistochemistry and Real-Time PCR-Based Idylla Test," *Disease Markers* 2020, no. 1 (2020): 8880548.

75. D. Novacescu, T. G. Cut, A. A. Cumpanas, F. Bratosin, R. A. Ceausu, and M. Raica, "Novel Expression of Thymine Dimers in Renal

Cell Carcinoma, Demonstrated Through Immunohistochemistry," *Biomedicine* 10, no. 11 (2022): 2673.

76. A. A. Lamola, "Production of Pyrimidine Dimers in DNA in the Dark," *Biochemical and Biophysical Research Communications* 43, no. 4 (1971): 893–898, https://doi.org/10.1016/0006-291x(71)90701-7.

77. V. Thatikonda, S. M. A. Islam, R. J. Autry, et al., "Comprehensive Analysis of Mutational Signatures Reveals Distinct Patterns and Molecular Processes Across 27 Pediatric Cancers," *Nature Cancer* 4, no. 2 (2023): 276–289.

78. H. E. Machado, E. Mitchell, N. F. Øbro, et al., "Diverse Mutational Landscapes in Human Lymphocytes," *Nature* 608, no. 7924 (2022): 724–732, https://doi.org/10.1038/s41586-022-05072-7.

79. A. Banyasz, T. Douki, T. Improta, et al., "Electronic Excited States Responsible for Dimer Formation Upon UV Absorption Directly by Thymine Strands: Joint Experimental and Theoretical Study," *Journal of the American Chemical Society* 134, no. 36 (2012): 14834–14845.

80. G. J. Delinasios, M. Mahsa Karbaschi, M. S. Cooke, and A. R. Young, "Vitamin E Inhibits the UVAI Induction of "Light" and "Dark" Cyclobutane Pyrimidine Dimers, and Oxidatively Generated DNA Damage, in Keratinocytes," *Scientific Reports* 8, no. 1 (2018): 423.

81. S. Premi, S. Wallisch, C. M. Mano, et al., "Chemiexcitation of Melanin Derivatives Induces DNA Photoproducts Long After UV Exposure," *Science* 347, no. 6224 (2015): 842–847.

82. K. Mokrzyński, M. Sarna, and T. Sarna, "Photoreactivity and Phototoxicity of Experimentally Photodegraded Hair Melanosomes From Individuals of Different Skin Phototypes," *Journal of Photochemistry and Photobiology. B, Biology* 243 (2023): 112704.

83. C. Lu, N. E. Gutierrez-Bayona, and J. S. Taylor, "The Effect of Flanking Bases on Direct and Triplet Sensitized Cyclobutane Pyrimidine Dimer Formation in DNA Depends on the Dipyrimidine, Wavelength and the Photosensitizer," *Nucleic Acids Research* 49, no. 8 (2021): 4266–4280.

84. K. P. Lawrence, T. Douki, R. P. E. Sarkany, S. Acker, B. Herzog, and A. R. Young, "The UV/Visible Radiation Boundary Region (385–405 Nm) Damages Skin Cells and Induces "Dark" Cyclobutane Pyrimidine Dimers in Human Skin In Vivo," *Scientific Reports* 8, no. 1 (2018): 12722.

85. N. Kobayashi, A. Nakagawa, T. Muramatsu, et al., "Supranuclear Melanin Caps Reduce Ultraviolet Induced DNA Photoproducts in Human Epidermis," *Journal of Investigative Dermatology* 110, no. 5 (1998): 806–810.

86. D. Fajuyigbe, S. M. Lwin, B. L. Diffey, et al., "Melanin Distribution in Human Epidermis Affords Localized Protection Against DNA Photodamage and Concurs With Skin Cancer Incidence Difference in Extreme Phototypes," *FASEB Journal* 32, no. 7 (2018): 3700–3706.

87. S. Premi and D. E. Brash, "Chemical Excitation of Electrons: A Dark Path to Melanoma," *DNA Repair (Amst)* 44 (2016): 169–177.

88. H. Z. Hill, "The Function of Melanin or Six Blind People Examine an Elephant," *BioEssays* 14, no. 1 (1992): 49–56.

89. S. R. Wood, M. Berwick, R. D. Ley, R. B. Walter, R. B. Setlow, and G. S. Timmins, "UV Causation of Melanoma in Xiphophorus Is Dominated by Melanin Photosensitized Oxidant Production," *Proceedings of the National Academy of Sciences of the United States of America* 103, no. 11 (2006): 4111–4115.

90. A. A. Fernandez, L. Paniker, R. Garcia, and D. L. Mitchell, "Recent Advances in Sunlight-Induced Carcinogenesis Using the Xiphophorus Melanoma Model," *Comparative Biochem and Physiol Part C: Toxicology & Pharmacology* 155, no. 1 (2012): 64–70.

91. F. P. Noonan, M. R. Zaidi, A. Wolnicka-Glubisz, et al., "Melanoma Induction by Ultraviolet A but Not Ultraviolet B Radiation Requires Melanin Pigment," *Nature Communications* 3, no. 1 (2012): 884.

92. H. Y. Handoko, N. F. Box, and G. J. Walker, "Modeling Epidermal Melanoma in Mice: Moving Into New Realms but With Unexpected Complexities," *Journal of Investigative Dermatology* 132, no. 9 (2012): 2299–2302.

93. L. D. Trucco, P. A. Mundra, K. Hogan, et al., "Ultraviolet Radiation–Induced DNA Damage Is Prognostic for Outcome in Melanoma," *Nature Medicine* 25, no. 2 (2019): 221–224.

94. B. Ferguson, H. Y. Handoko, P. Mukhopadhyay, et al., "Different Genetic Mechanisms Mediate Spontaneous Versus UVR-Induced Malignant Melanoma," *eLife* 8 (2019): e42424.

95. J. Kromberg, "Albinism in Africa, Chapter 2—Clinical Features, Types of Albinism, and Natural History. InAlbinism in Africa," in *Historical, Geographic, Medical, Genetic, and Psychosocial Aspects* (Academic Press, 2018), 27.

96. N. T. Onyishi and S. R. Ohayi, "Cutaneous Melanoma in African Albinos: A Systematic Review," *Journal of Clinical and Diagnostic Research* 15, no. 11 (2021): WE01–WE06.

97. S. S. Bernardes, I. Ferreira, D. E. Elder, et al., "More Than Just Acral Melanoma: The Controversies of Defining the Disease," *Journal of Pathology. Clinical Research* 7, no. 6 (2021): 531–541.

98. Australian Institute of Health and Welfare & Cancer Australia, "Skin Cancer in Australia," (2024), accessed August, 20, 2024, https://www.aihw.gov.au/getmedia/0368fb8b-10ef-4631-aa14-cb6d55043e4b/18197.pdf.

99. S. Ravichandran, P. Funchain, and J. Arbesman, "Characterizing Melanoma in the Setting of Oculocutaneous Albinism: An Analysis of the Literature," *Archives of Dermatological Research* 315, no. 8 (2023): 2413–2417.

100. Y. J. Ju, H. Kang, J. H. Han, J. H. Lee, S. Lee, and J. M. Bae, "All-Cause and Cause-Specific Mortality Among Patients With Vitiligo: A Nationwide Population-Based Study in Korea," *Journal of Investigative Dermatology* 144, no. 1 (2023): 125–132.

101. Y. Jin, G. Andersen, D. Yorgov, et al., "Genome-Wide Association Studies of Autoimmune Vitiligo Identify 23 New Risk Loci and Highlight Key Pathways and Regulatory Variants," *Nature Genetics* 48, no. 11 (2016): 1418–1424.

102. W. Wu, C. I. Amos, J. E. Lee, et al., "Inverse Relationship Between Vitiligo-Related Genes and Skin Cancer Risk," *Journal of Investigative Dermatology* 138, no. 9 (2018): 2072–2075.

103. I. Gupta, S. Shankrit, K. Narta, et al., "Whole-Exome Sequencing of Vitiligo Lesions Indicates Lower Burden of Somatic Variations: Implications in Risk for Nonmelanoma Skin Cancers," *Journal of Investigative Dermatology* 143, no. 6 (2023): 1111–1114.