

Ultraviolet Radiation and Melanoma

Holly E. Kanavy, DO, and Meg R. Gerstenblith, MD

Melanoma is a particularly aggressive type of skin cancer, and its incidence has been increasing steadily since the 1970s. This article will review the extensive epidemiologic data demonstrating that ultraviolet radiation (UVR) exposure, from the sun or artificial tanning beds, is the most important environmental risk factor for melanoma; the multiple detrimental effects of UVR on human skin, including DNA damage through the formation of dimeric photoproducts, gene mutations, oxidative stress, inflammation, and immunosuppression, all of which contribute to melanomagenesis; and the evidence that protection from UVR exposure, whether by melanin or by sunscreen, reduces the risk of developing melanoma.

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Since the 1970s, the incidence of melanoma has increased by 3%-7% per year, and from 1975 to 2008, the age-adjusted annual incidence nearly tripled from 7.89 to 22.52 cases per 100,000 individuals.¹ It is estimated that 70,230 new melanoma cases will be diagnosed in 2011.² The mortality rate also increased by about 60% during the same period, from 1.6 to 2.7 per 100,000 individuals.¹ Although melanoma accounts for <5% of all skin cancers in the United States, it is responsible for the most skin cancer-related deaths because of its high mortality when identified at an advanced stage.² The etiology of melanoma is multifactorial, with environmental, host, and genetic factors contributing to its development. Ultraviolet radiation (UVR) exposure is the most important environmental risk factor. This article will review the epidemiologic and basic science evidence supporting the role of UVR in the pathogenesis of melanoma.

Central Role of UVR in Melanoma Development: Epidemiologic Evidence

Geographic and Migration Studies

UVR has been studied extensively as a risk factor for melanoma. Ultraviolet light emitted by the sun ranges in wave-

length from 100 nm to 400 nm and is divided into 3 bands: UVA (320 nm-400 nm), UVB (280 nm-320 nm), and UVC (100 nm-280 nm). The ozone layer absorbs wavelengths shorter than ~310 nm, so the UVR that actually reaches human skin is approximately 90%-95% UVA and 5%-10% UVB.³ The geographic distribution of melanoma supports the importance of UVR exposure in its pathogenesis. Investigators have found that living closer to the equator, where there is the greatest ambient solar radiation, is consistently associated with increased melanoma risk. A study conducted in New Zealand, which together with Australia has the greatest incidence of melanoma worldwide, reported a 5% increase in melanoma risk for each degree decrease in latitude closer to the equator.⁴ Similar trends were reported for Norway, Sweden, and Finland, in which a North-South gradient of increasing melanoma incidence was observed.⁵ In the United States, the greatest incidence of melanoma is in Hawaii.⁶ According to the Surveillance, Epidemiology, and End Results Program data from cancer registries of 11 cities throughout the United States from 1992 to 2001, the incidence of melanoma is significantly correlated with lower latitude and a greater mean UVR index in non-Hispanic whites.⁷

Migration studies also provide evidence for the effect of ambient UVR exposure levels on melanoma risk. A case-control study of Australian immigrants, in which the authors controlled for ethnicity, found that individuals arriving after the age of 15 had one-fourth the risk of developing melanoma compared with those arriving before the age of 10, whose risk was similar to that of native-born Australians.⁸ Similarly, in a case-control study from Germany, France, and Belgium melanoma risk was 9 times greater in white individuals who were born in, or migrated before the age of 10 to, sunny areas compared with individuals who never lived in sunny areas, defined as geographic areas including European cities prox-

Department of Dermatology, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, Cleveland, OH.

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Address reprint requests to Meg R. Gerstenblith, MD, Department of Dermatology, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 3rd Floor, Cleveland, OH 44106. E-mail: Meg.Gerstenblith@UHhospitals.org

imal to the Mediterranean, Africa, the Southern United States, Australia, Asia, and Central and South America.⁹ Additional studies of Northern European immigrants to Israel revealed similar results.¹⁰

Several factors influence the amount of UVR to which humans are effectively exposed. The height of the sun in the sky is one such factor and depends on the time of day and year, being greatest midday during the summer months. Latitude and altitude are also important; the closer to the equator and the higher the altitude, the higher levels of UVR. Cloud cover density, fog, haze, and pollutants can significantly decrease UVR exposure levels, whereas surface reflection of sunlight, such as from snow, sand, and metal can reach up to 90% of ambient levels.¹¹ Depletion of the ozone layer has also impacted the exposure of human skin to UVR, with studies showing that a decrease in the ozone layer by 1% corresponds to a 1% to 2% increase in melanoma mortality.¹²

Sun Exposure and Sunburns

Many investigators have examined the association of sun exposure with melanoma risk, and the results demonstrate a complex relationship. Across studies, intense, intermittent sun exposure is significantly associated with melanoma risk.^{13,14} In migration studies, melanoma risk displays a linear relationship with high UVR exposure time.^{15,16} The authors of a comprehensive meta-analysis performed in 2005 pooling 57 studies on sun exposure and melanoma expanded these results.¹⁷ “Intermittent,” defined largely as recreational, exposure, “chronic,” or primarily occupational sun exposure, and “total” sun exposure, defined as intermittent plus chronic sun exposure, were examined. In men and women (combined), intermittent sun exposure conferred the greatest risk of melanoma, and total sun exposure was associated with the next greatest risk. Perhaps surprisingly, chronic sun exposure was not significantly associated with melanoma in this meta-analysis. However, there was heterogeneity among the studies; for example, at greater latitudes, chronic sun exposure and melanoma were significantly associated. The heterogeneity was attributed to study differences in the definition of intermittent exposure, country of origin of participants, and inclusion of phenotypes of participants. In other studies, chronic or occupational sun exposure was protective against melanoma.¹⁸⁻²⁰ In part, these studies have limitations, such as recall bias, difficulty with assessment of sun exposure history, and variable incorporation of confounding factors, such as host phenotype and latitude, but the finding that intermittent sun exposure and chronic sun exposure may differentially influence melanoma risk is one example of the complex relationship between UVR and melanoma.

In the same meta-analysis by Gandini et al,¹⁷ sunburns in childhood (<15 years) and sunburns in adulthood (>19 years) were examined separately and both were associated with an increased risk of melanoma. In a meta-analysis by Dennis et al²¹ the relationship of UVR exposure and melanoma risk was dose-dependent, whereby an increased risk of melanoma was seen with an increasing number of sunburns

for all time-periods, including childhood, adolescence, adulthood, and lifetime.

Artificial UVR Exposure

Artificial UVR has been used since the end of the 19th century as a therapy for several diseases, including psoriasis and eczema.²² A common treatment for psoriasis is a combination of oral psoralen, a plant-derived photosensitizer, and UVA radiation (PUVA). Patients exposed to PUVA can develop irregularly pigmented macules characterized by large, cytologically atypical melanocytes.^{23,24} Stern et al²⁵ conducted a prospective study of 1380 patients with psoriasis who were first treated with PUVA in 1975 or 1976 and assessed for melanoma risk. Approximately 15 years after the first exposure, melanoma risk increased substantially, especially in individuals exposed to high doses of PUVA therapy (>250 treatments).

During the last 40 years, recreational artificial UVR exposure through commercial tanning beds has become popular. In studies of commercial tanning beds, which emit mostly UVA radiation, investigators reported a significant association with melanoma. The International Agency for Research on Cancer (IARC), part of the World Health Organization, performed a meta-analysis of 19 epidemiologic and biological studies from 1981 through 2005 on artificial UVR exposure and melanoma risk, which included 7355 melanoma cases.²⁶ In this meta-analysis, which was adjusted for confounding factors, including sun sensitivity and sun exposure history, ever-use of sunbeds was significantly associated with melanoma risk, and people who began using tanning devices before 30 years of age were 75% more likely to develop melanoma.

On the basis of these findings, the IARC, which classified sun exposure as carcinogenic to humans in 1992, added tanning beds to this list in 2009.²⁷ In 2010, Lazovich et al²⁸ confirmed this association in a population-based case-control study in Minnesota, demonstrating that melanoma risk significantly increased among those using either UVB- or UVA-emitting devices. Risk also significantly increased with frequency of use, measured in years of tanning (multivariate odds ratio [OR] 1.47; confidence interval [CI] 1.06-2.02) for 1 year vs OR 2.45 [CI 1.83-3.28] for 10+ years; *P* for trend 0.006); hours of tanning (OR 1.46 [CI 1.15-1.85] for 1-9 hours vs OR 3.18 [CI 2.28-4.43] for 50+ hours; *P* for trend <0.0001); and number of tanning sessions (OR 1.34 [CI 1.00-1.81] for ≤10 sessions vs OR 2.72 [CI 2.04-3.63] for >100 sessions; *P* for trend 0.0002). Furthermore, the increased melanoma risk was present irrespective of the age at which indoor tanning commenced.

Anatomic Distribution of Melanoma

The anatomic distribution of melanoma also offers insight into the pathogenesis of the disease and the role of UVR. Overall, the most common sites for melanoma are the trunk

Table 1 The Heterogeneity of Melanoma: Distinct Somatic Mutations are Associated with Divergent Types of Melanoma^{33-35,87}

Somatic Mutations Commonly Found	BRAF (these mutations are also detected in benign acquired melanocytic nevi)		GNAQ (these mutations are also detected in blue nevi)	
	C-KIT	C-KIT	C-KIT	C-KIT
Tendency for nevus development	Few nevi	Many nevi*	No clear association	No clear association
UVR exposure Melanoma histopathologic subtype	Continuous LLM	Intermittent SSM NM	No clear association Acral lentiginous Mucosal	No clear association Uveal
Melanoma location	Chronic-sun exposed sites	Intermittently-sun exposed sites	Palms/soles Conjunctiva/sinuses Oropharynx/anogenital	Uvea
Age at occurrence of melanoma	Relatively older age	Relatively younger age	No clear association	No clear association

Note: LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma; UVR, ultraviolet radiation.

*These melanomas are also often associated with a preexisting nevus.

in men and the lower legs in women, areas of high levels of acute, intermittent sun exposure. The authors of one study in England and Wales reported a greater incidence of melanoma of the head and neck in outdoor workers and the reverse distribution of melanoma in indoor workers.²⁹ Furthermore, melanoma incidence rates on sun-exposed and unexposed body areas have different age peaks.³⁰⁻³² For example, lentigo maligna melanoma is a type of melanoma that arises on chronically sun-exposed sites in older individuals on a background of chronic sun damage.

Heterogeneity of Melanoma

The aforementioned data suggest that melanomas arising on body surfaces that receive chronic sun exposure may differ from those arising on body surfaces that receive intermittent sun exposure, supporting the notion that melanomas are heterogeneous and arise through different mechanisms. There are some types of melanoma for which UVR is not implicated as a risk factor, such as those that occur on the palms, soles, and mucosal surfaces. Studies of somatic mutations in melanoma also support the concept that melanomas are heterogeneous, and may explain the varied etiology. Melanomas have been found to contain distinct oncogenic mutations, and sun exposure patterns may vary among these different subtypes of melanoma. For example, melanomas with mutations in *BRAF*, found in approximately 30%-50% of melanomas, typically arise on skin that is intermittently exposed to the sun.³³ *C-KIT* mutations are commonly found in lentigo maligna melanomas, a subtype of melanoma associated with chronic UVR exposure, and acral and mucosal melanomas, subtypes of melanoma that do not implicate UVR exposure as a risk factor.^{34,35} Therefore, UVR exposure likely plays distinct roles in the development of melanoma depending on the body site, dose of UVR, and other incompletely understood factors (Table 1).

Mechanisms of Melanoma Development Induced by UVR Exposure

Many studies have advanced our understanding of the mechanisms by which intermittent or chronic exposure to UVR can cause melanoma, and the carcinogenic, inflammatory, and immunosuppressive properties of UVR are all considered important pathogenic factors.

DNA Damage by UVB and UVA Radiation

UVR-induced DNA damage is a fundamental event in photocarcinogenesis. Evidence to support this concept initially came from experiments conducted with bacteria in the 1920s. Gates³⁶ reported on a series of experiments in which plated bacteria were exposed to UVR at differing wavelengths until a lethal dose was determined. It was found that damage to nuclear DNA was responsible for this UVR effect.³⁷

The specific mechanisms by which DNA is altered by UVR are well-characterized. Alternating single and double bonds, known as conjugated bonds, in the ring structures of organic molecules absorb wavelengths of UVR in the range of 250 nm to approximately 300 nm (UVC-UVB range). The bases in DNA contain such ring structures with conjugated bonds, making DNA a major chromophore for UVR, with a maximum absorption of 260 nm.^{38,39} DNA bases directly absorb incident UVB photons, producing 2 types of DNA lesions. The most prominent is the cyclobutane pyrimidine dimer between adjacent thymine (T) or cytosine (C) residues.^{40,41} In *Xiphophorus* hybrid fish models, exposure to UVR of wavelengths in the range of 290 nm to 400 nm led to melanoma development; and removal of pyrimidine dimers resulted in decreased tumor formation.^{41,42} In addition, 6-4 photoproducts form between adjacent pyrimidine residues and are then converted to Dewar isomers.^{37,40,43,44}

Both types of DNA lesions can lead to genetic alterations, such as C (cytosine)-T (thymine) or CC-TT transitions; the latter mutation is considered the hallmark of UVR-induced mutagenesis, often called the “signature UVB mutation.”⁴⁵ DNA regions containing 5-methylcytosine are recognized as preferential targets, so-called “hotspots,” for UVB radiation.⁴⁶ Mutations affecting genes that encode proteins or enzymes involved in cell cycle control, apoptosis, or DNA repair, may result in carcinogenesis.⁴⁷

In addition to UVB radiation-induced DNA damage, UVA radiation causes oxidative DNA damage by generation of reactive oxygen species (ROS), including hydrogen peroxide, hydroxyl radicals, superoxide, singlet oxygen, and peroxy radicals. These molecules target guanine residues in particular, converting them to 8-hydroxydeoxyguanosine (8-OHdG). The presence of 8-OHdG causes G (guanine)-T (thymine) transversion mutations, DNA single-strand breaks, protein-DNA cross-links, and thymine glycol formation.^{40,48-50} The effects of UVA and UVB are not exclusive; studies in which animal models are used and in vitro human systems demonstrate that UVA can generate cyclobutane pyrimidine dimers and 6-4 photoproducts, and UVB can cause DNA damage through ROS formation.^{51,52} Both UVA and UVB also activate nitric oxide synthase in endothelial cells. Nitric oxide reacts with superoxide to form peroxynitrite, a molecule that directly causes DNA strand breaks.⁵⁰

DNA damage may also result in carcinogenesis by affecting genes regulating cell-cycle control. Somatic alterations at several specific loci have been implicated in UVR-induced melanoma, including tumor suppressors *TP53*, *CDKN2A*, and *PTEN*, and oncogenes *BRAF* and *NRAS*.⁵³⁻⁵⁶ Tumor protein 53 (*TP53*), on chromosome 17, activates cellular stress response pathways when DNA is damaged, inducing cell-cycle arrest, DNA repair, and apoptosis.⁵³ Cyclin-dependent kinase inhibitor 2A (*CDKN2A*), on chromosome 9, inhibits the cell cycle through its effector proteins p16 and p14ARF and when altered may result in unregulated cell division.⁵⁴ Mutations in phosphatase and tensin homolog (*PTEN*), a tumor suppressor gene on chromosome 10 whose product functions in cell-cycle control and apoptosis, have also been identified in melanomas.⁵⁵ Somatic mutations of the oncogenes *NRAS* and *BRAF* are seen in a high proportion of melanomas; these mutations result in constitutive activation of the mitogen-activated protein kinase signaling pathway involved in cell-cycle control, promoting oncogenesis.³³ Hocker and Tsao⁵⁶ summarized the rate of UVB signature mutations, including G: C > A (adenosine):T transitions and GG: CC > AA: TT mutations, at these 5 loci.

Several biological systems exist to repair the DNA damage caused by UVR, including nucleotide excision repair and mammalian mismatch repair. Nucleotide excision repair (NER) operates by 2 distinct pathways, depending on the type of DNA damage and how quickly it needs to be repaired. Transcription coupled repair operates on the transcribed strand of active genes, and global genome repair works more slowly to remove lesions within the entire genome. Oxidative damage to DNA, such as an 8-OHdG base change, is repaired by the base excision repair system.⁵⁷ Under normal circum-

stances, photoproducts produced after UVR exposure are eliminated, and the integrity of the genome is maintained. Unsuccessful repair can lead to mutations and ultimately skin cancer, as seen in the autosomal recessive disorder, xeroderma pigmentosum.⁵⁸ Affected individuals harbor mutations in one of the several genes encoding NER proteins and carry a 1000-fold increased risk for melanoma compared with the general population.⁵⁹

Mammalian mismatch repair (MMR) is also instrumental in repair of UVR-induced DNA damage. Responding to DNA damage, MMR facilitates cell-cycle arrest in the G2-M transition, suppressing potential mutagenesis, including that induced by UVR.⁶⁰ Loss of MMR therefore results in loss of cell-cycle control and/or resistance to apoptosis, both of which can lead to neoplastic transformation. MMR also seems to be necessary for proper functioning of NER because human cells with mutations in mismatch repair genes have a decreased ability to repair UVR-induced pyrimidine dimers.⁶¹

Inflammation

There are several proinflammatory effects of UVR that contribute to carcinogenesis. UVR causes increased blood flow and vascular permeability, leading to edema, erythema, and recruitment of neutrophils and macrophages. Damage to cellular membranes through ROS-induced peroxidation reactions and nitric oxide synthase activation lead to increased production of proinflammatory cytokines, including tumor necrosis factor (TNF- α), IL-1 α , and prostaglandins, such as prostaglandin E₂.⁶² Platelet-activating factor is released by keratinocytes in response to UVR exposure and promotes expression of inflammatory cytokines and mediators, including TNF- α , IL-6, IL-8, IL-10, COX-2, vascular endothelial growth factor, and inducible nitric oxide synthase. Platelet-activating factor also has a proangiogenic effect and is implicated in melanoma development and progression.⁶³ The inflammatory cascade furthers production of reactive oxygen species, perpetuating DNA damage.⁶⁴

Immunosuppression

UVA and UVB radiation have both local and systemic immunosuppressive effects on skin. Although the precise mechanism by which UVR induces immunosuppression is not fully elucidated, DNA damage is regarded as a fundamental inciting event, which then leads to depletion of Langerhans cells from the epidermis and interference with antigen presentation.⁶⁵ Systemically, release of immunosuppressive cytokines activates suppressor T cells; the cytokine that appears to be most influential is IL-10.⁶⁶ Other soluble factors include TNF- α , IL-4, prostaglandin E₂, calcitonin gene-related peptide, α -melanocyte-stimulating hormone, and platelet-activating factor.^{65,67} The immunosuppressive effects of UVR are well recognized, as evidenced by its use to treat inflammatory skin disorders, such as psoriasis.⁶⁸ Immunosuppression induced by UVR is thought to diminish immune surveillance and thus allow evasion of tumors. Immunosuppressed transgenic mice more readily developed cutaneous melanomas.⁶⁹

Studies of individuals on chronic immunosuppression exemplify the importance of an intact immune system in preventing cutaneous malignancies. In solid-organ transplant recipients, there is an increased risk of UVR-induced skin cancers, including melanoma.⁷⁰ In addition, the more UVR exposure a transplantation recipient has had, the greater the rate of skin cancer development.⁷¹

Protection from UVR Damage: Prevention of Melanoma

Melanin

One of several host factors that determine an individual's capacity to protect against the detrimental effects of UVR exposure is melanin, which is produced by melanocytes, the cell of origin for melanoma. Melanin plays a critical role in protecting keratinocytes from the damaging effects of UVR. Exposure to UVR stimulates melanin synthesis in melanocytes through the action of α -melanocyte-stimulating hormone on its receptor, the melanocortin 1 receptor (*MC1R*). Melanin forms supranuclear caps in keratinocytes and functions as a chromophore, absorbing UVR photons and scavenging reactive oxygen species, thereby protecting DNA from pyrimidine base formation and oxidative damage.^{72,73} The type of melanin and size and shape of melanosomes ("packets" of stored melanin) vary among individuals with different skin, hair, and eye pigmentation; individuals with dark pigmentation have large, elliptic melanosomes, whereas those with light pigmentation have small, round melanosomes. The *MC1R* gene is responsible for determining the type of melanin produced and thus accounts for variation in human pigmentation, with wild-type *MC1R* associated with high ratios of eumelanin (brown-black color) to pheomelanin (red-yellow color), and *MC1R* polymorphisms associated with low ratios of eumelanin to pheomelanin. Although eumelanin can absorb UVR and transform the energy into heat, preventing it from damaging DNA, pheomelanin is unable to function in this way.⁷⁴ Therefore, individuals with wild-type *MC1R*, who predominantly produce eumelanin, have better photoprotection from UVR compared with those with *MC1R* variants, who often have red hair, fair skin, and freckling and predominantly produce pheomelanin.⁷⁵

The low incidence of melanoma in populations with darker skin attests to the photoprotective role of eumelanin.⁷⁶ Observational studies consistently demonstrate that the incidence of melanoma is much greater in individuals with light pigmentation than in those with dark pigmentation.^{7,13} The age-adjusted melanoma incidence rate per 100,000 in the United States from 1975 to 2007 was 1.1 for black and 25.3 for white Americans.⁷⁷ Furthermore, the most common types of melanoma that develop in populations with lighter skin pigmentation, predominantly occurring on body sites receiving intermittent or chronic UVR exposure, rarely arise in populations with darker skin pigmentation, whereas acral lentiginous and mucosal melanoma, which are not tightly associated with UVR exposure, occur with similar incidence across populations with variations in skin pigmentation and

account for the majority of melanomas that occur in populations with darker pigmentation.

Case-control studies have shown a significantly increased risk of melanoma in those with *MC1R* variants, even after adjustment for pigmentation traits. Potential hypotheses to explain this independent association of *MC1R* variants with melanoma are that in addition to the diminished UVR filtering effect of pheomelanin compared with eumelanin, there may be further increased DNA damage associated with the production of reactive oxygen species as well as alterations of the immune system or inflammation.^{75,78-82}

Sunscreen for Prevention of Melanoma

UVR is further implicated as a cause of melanoma by studies in which authors demonstrate that the use of sunscreens can prevent melanoma. In a study in which HGF/SF transgenic mice were used, those treated with sunscreen displayed significantly less UVR-induced DNA damage, as measured by TT dimer concentration, and fewer UVR-induced melanomas compared with control mice.⁸³ Epidemiologic studies of sunscreen use and melanoma prevention in humans have been inconclusive because of recall bias, insufficient statistical power, and variations in measurements of UVR exposure and sunscreen use across studies.⁸³⁻⁸⁵ The first randomized controlled trial in humans of sunscreen use and melanoma recently confirmed that sunscreen indeed protects from melanoma. In this study, after 10 years of observation, there was a substantial reduction in invasive melanomas in subjects who used sunscreen with a sun protection factor (ie, SPF) of 16 daily for 5 years compared with those who used it on a discretionary basis for 5 years.⁸⁶ These findings not only further strengthen the association of UVR and melanoma but demonstrate that prevention of melanoma is possible.

Conclusions

In summary, UVR exposure is an important cause of melanoma, particularly in Caucasians. As the only known environmental risk factor for melanoma, avoidance of UVR exposure and use of sunscreen and other sun protective measures should be encouraged. Melanoma is a heterogeneous disease, however, and continued investigation can further elucidate the pathways by which UVR can induce melanoma, as well as the pathways to melanoma development that may not involve UVR exposure.

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