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Chapter 1

Melanoma — Epidemiology, Risk Factors, and the Role of Adaptive Pigmentation

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Additional information is available at the end of the chapter

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1. Introduction

Malignant cutaneous melanoma is an aggressive form of skin cancer that affects well over 100,000 individuals world-wide each year. Melanoma results from uncontrolled proliferation of melanocytes and can occur throughout the body including skin, mucosal surfaces, and the retina. This chapter will focus on cutaneous melanoma because it is the most common site of the disease. Cutaneous melanoma has a high association with exposure to UV radiation and is most commonly found on sun exposed surfaces [5]. If diagnosed in its early stages, resection of cutaneous melanoma is associated with favorable five-year survival rates. As melanoma progresses, however, it has a tendency to metastasize beyond its primary site. It expands both radially and vertically through the skin and eventually spreads throughout the body via hematogenous or lymphatic routes. Long-term prognosis correlates strongly with the stage of disease, and after melanoma metastasizes, survival rates markedly decline. In general, five-year survival rates for metastatic melanoma are under 20%. Thus, early identification and treatment are essential clinical tools to minimize mortality.

For a variety of reasons, the incidence of melanoma has increased faster than any other cancer over the last several decades [6] (Figure 1), and the estimated healthcare cost in 2020 is predicted to be 4.58 billion dollars [7]. Considering the deadly nature of metastatic melanoma along with the steady increase in incidence throughout the past century, appropriate measures to prevent the development of the disease are important and will require a more complete knowledge of the risk factors associated with this disease. This chapter reviews the epidemiologic and genetic risk factors associated with the development of malignant cutaneous melanoma, with an emphasis on mechanisms of melanocyte resistance to UV damage in the skin.

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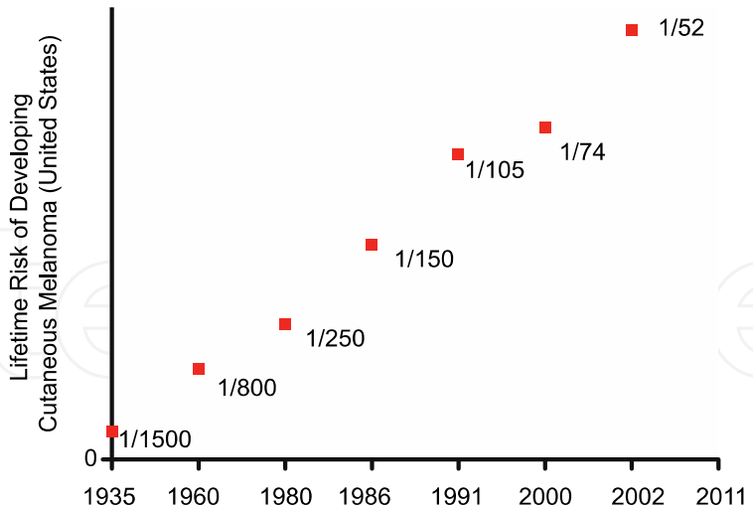


Figure 1. Lifetime risk of melanoma has increased in the United States from 1935-2011. (Adapted from [4]).

2. Epidemiology

This section will address the epidemiology of melanoma in reference to risk factors, incidence and mortality, gender differences, and variations between ethnicities.

2.1. Incidence and mortality

The Surveillance, Epidemiology, and End Results (SEER) database predicts a diagnosis of melanoma in over 76,000 individuals in the United States for 2014. Though it can affect patients of any age, melanoma traditionally affects older individuals with an average age at diagnosis and death of 62 and 69 years respectively. While many cancer incidence rates have plateaued over the last century, the incidence of melanoma has steadily increased [6]. In the early 1930's, the lifetime risk of developing melanoma for an American was 1 in 1500, while in 2002, it was reported to be 1 in 68 [8]. The melanoma incidence rate increased an additional 1.8% per year between 2002 and 2012, such that 21.3 per 100,000 individuals were diagnosed with melanoma between 2007 and 2011 [1]. Though some portion of this rise is due to enhanced awareness and improvements in diagnosis, the causes underlying the increased incidence may be diverse. An important factor may be that life span has increased during this time period. As melanoma incidence correlates with age, we would expect more cases in a population of individuals that live longer [9]. However, chief among the potential contributive factors is increased exposure to ultraviolet (UV) radiation, either solar or artificial. The popularization of a tanned physique in Western cultures beginning the early 1900's has led to intentional exposures to UV. Many individuals believe they look better, feel healthier, appear younger and are happier with tanned skin [10]. The desire for UV exposure coupled with increased recreational and occupational opportunities, results in significantly more time devoted to sun exposure or in artificial tanning beds.

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Although incidence rates have been increasing steadily, melanoma mortality rates have stabilized over the past 20 years due to advances in medical, surgical and supportive care [11]. The overall five-year survival rate is currently above 90%, likely related to diagnosis at curable stages for the majority of cases [1]. From 1975 until the 1990's, the mortality rate climbed 1.9% per year. From 2006-2010, there were 2.7 deaths per 100,000 individuals, and 9,700 individuals are predicted to die from melanoma in 2014 [1] (Figure 2). The mortality rate for women has actually decreased by 0.6% from 1989-2007. The mortality rate for men has increase 0.2% during the same time frame [1].

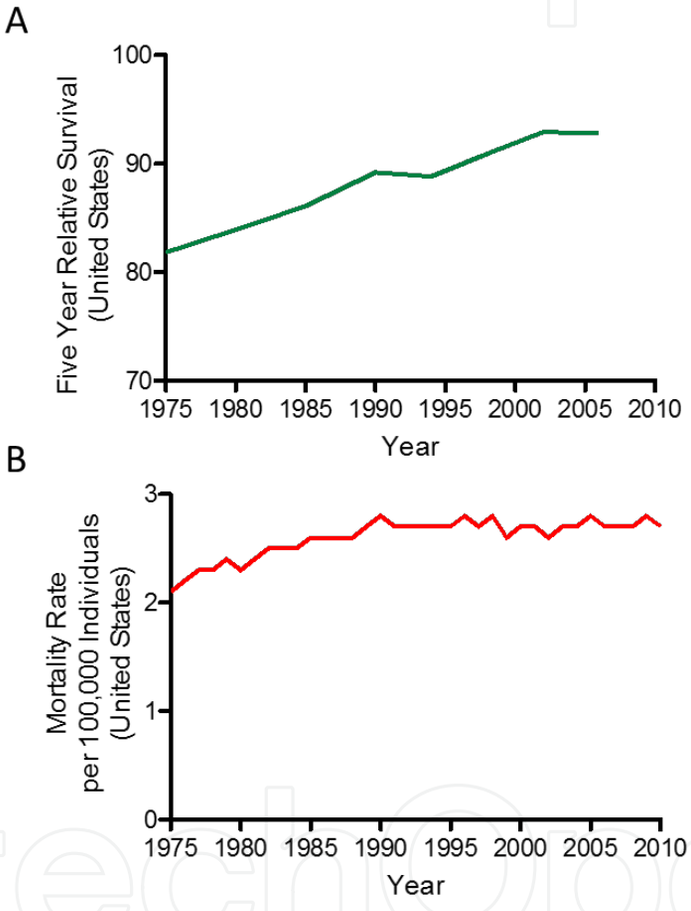


Figure 2. A. Five year relative survival rate for melanoma in the United States from 1975-2009. B. Mortality rate for melanoma in the United States from 1975-2009 (Adapted from [1]).

2.2. Gender

Melanoma affects men and women differently. Before the age of 40, women are more susceptible to melanoma (1 in 391 women versus 1 in 691 men diagnosed each year), however, after the age of 40, the rates reverse, and 1 in 35 men will develop melanoma versus 1 in 54 women [12]. Overall men are more susceptible to melanoma, with 27.7 new cases per 100,000 men versus 16.7 new cases per 100,000 women [1]. While the mortality rate for women is decreasing,

it is actually increasing for men [13]. Men account for 60% of deaths due to melanoma [14]. Although both genders are experiencing a rise in melanoma rates, there has been a massive increase in the incidence rate for women under 40, presumably due to recreational UV exposure and the popularization of having a tanned complexion [15]. In women between the ages of 20-29, melanoma is the 2nd most common cancer, trailing behind breast cancer [16]. In fact, there has been a 50% increase in melanoma incidence in young adult women since 1980 such that it is now the leading cause of cancer death among women ages 20 – 25 years old. Melanoma also is the second-most common cancer in adolescents and young adults (men and women) between the ages of 15 and 29 years. Melanoma presentation appears to differ somewhat between genders. In women, melanoma often presents on the extremities while in men, it most frequently presents on the trunk [17].

2.3. Ethnicity

The incidence, mortality rates, and presentation for melanoma differ markedly by ethnicity (Figure 3). Caucasians are the most likely to develop melanoma, however the overall five year survival is lower for African Americans than Caucasians (77% and 91% respectively) [13]. The initial diagnosis is generally at a later stage in individuals with darker skin pigmentation than in Caucasians [18] and tends to be a different subtype. Caucasians frequently present with superficial spreading melanoma while individuals with darker pigmentation often present with acral lentigenous melanoma[19]. In African Americans, Asians, Filipinos, Indonesians, and Native Hawaiians, melanoma often presents on areas that are not sun exposed including the palms and soles of hands and feet respectively, mucous membranes, and nail beds while melanoma in Caucasians generally presents on sun-exposed areas [20].

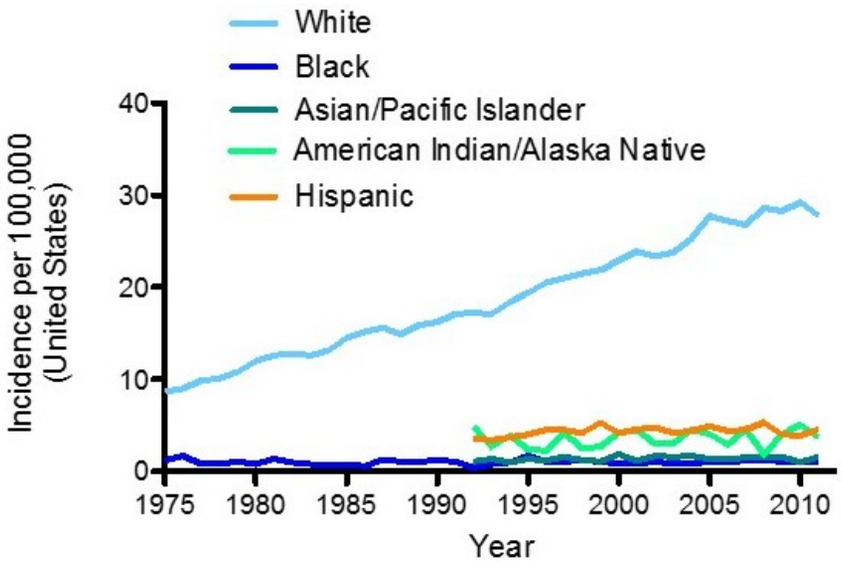


Figure 3. Melanoma incidence rate by ethnicity in the United States from 1975-2011. There is a discrepancy in the incidence rate between the different ethnicities. Ethnicities with fairer complexions have a higher incidence rate than ethnicities with darker complexions (Adapted from [1]).

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3. Risk factors

Risk factors for the development of melanoma can be divided into extrinsic and intrinsic factors and include exposure to UV radiation either via sunlight or indoor tanning salons, medications, chemical exposures, presence of nevi, family history of cancer, and pigment of skin [21] (Table 1).

Extrinsic Risk Factors		Intrinsic Risk Factors	
Ultraviolet Radiation	UV exposure, especially blistering sunburns in childhood, correlates with melanoma risk.	**History of Skin Cancer**	A family and personal history of melanoma and non-melanoma skin cancer increases risk of melanoma
	Countries located closer to the equator with increased sun exposure have a higher melanoma incidence rate	**Nevi**	A large number of congenital nevi, nevi with large diameter, and dysplastic nevi are all associated with an increased risk
	Indoor tanning bed use increases incidence and mortality rate of melanoma	**Medical History**	Immunosuppressive states and a past medical history of non-cutaneous skin cancer increase the risk of melanoma
Medication	Psoralen, UVA light therapy and neonatal blue light phototherapy are associated with an increased risk of melanoma	**Defective DNA Repair**	Individuals diagnosed with xeroderma pigmentosum cannot repair UV induced DNA damage
Environmental Exposure	Polyvinyl chloride, heavy metals and pesticides are associated with an increased risk of melanoma	**Skin Complexion**	Fair skin, inability to tan, and increased susceptibility to UV induced sunburn increase risk for melanoma

Table 1. Major melanoma risk factors.

3.1. Extrinsic

3.1.1. Ultraviolet radiation

Ultraviolet radiation, probably the single-most important environmental carcinogen with respect to melanoma, is found in natural sunlight and in artificial tanning sources. UV energy is conventionally divided into three wavelengths: UVA (320-400 nm), UVB (290-320 nm), and UVC (100-280 nm). Each type of UV energy has its own distinctive energy profile, biophysical characteristics, and effects on biologic tissue. Although solar energy contains all three UV subtypes, absorption of the higher-energy UV components by atmospheric ozone results in ambient sunlight being mainly (>90%) UVA and the remainder UVB. Both UVA and UVB are bioactive and cause DNA damage and cellular injury that contribute to carcinogenesis. In fact, exposure to UV radiation may be responsible for over 80% of all melanomas [22].

UVA and UVB contribute to the pathogenesis of melanoma via distinct but overlapping mechanisms [23]. UVA (and to a lesser extent UVB) causes DNA damage indirectly through the generation of highly reactive free radicals and oxidative injury [24, 25]. Free radicals change DNA in ways that ultimately affect base-pairing, which can lead to mutation. Oxidation of

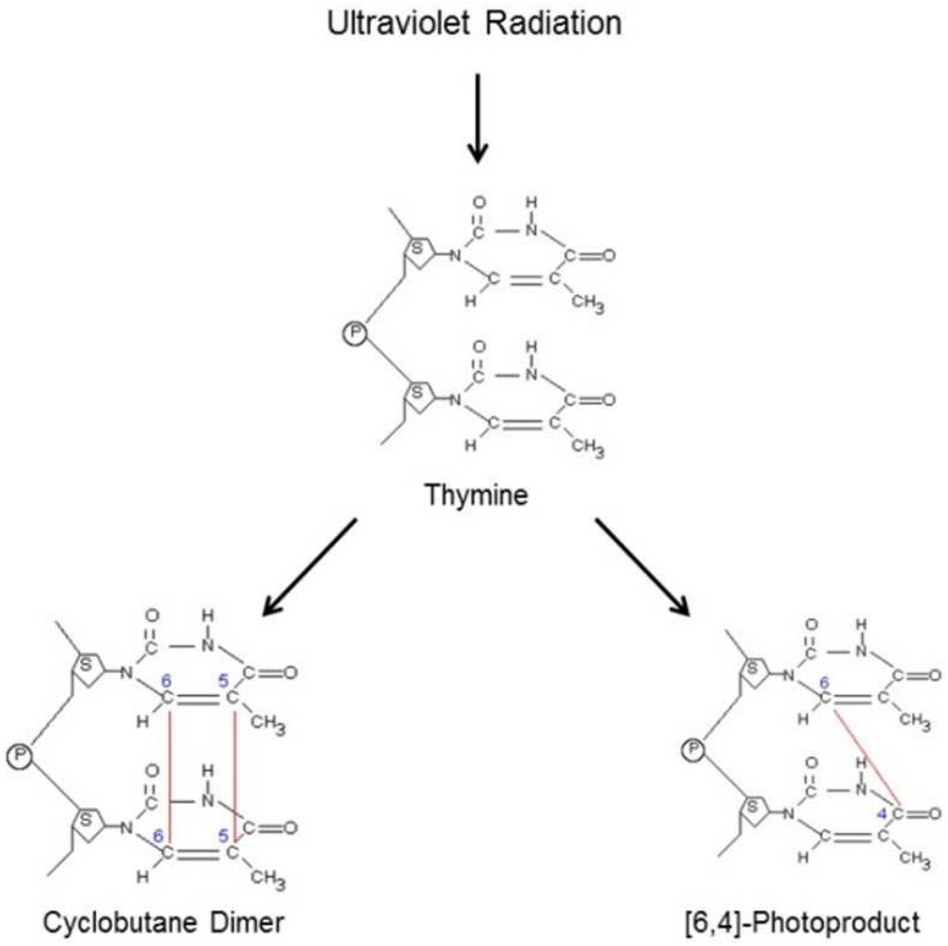


Figure 4. Generation of 6,4-photoproducts and cyclobutane dimers from adjacent pyrimidines. UVB radiation is absorbed by thymine and cytosine residues, resulting in the formation of mutagenic photoproducts that contribute to malignancy.

guanine, for example, is well-known to cause formation of 8-oxo-dG which base pairs with A instead of C; this change leads to transversion point mutations if not repaired in a timely manner. Indeed, some estimate that up to 80% of malignant cutaneous melanomas may result from indirect DNA damage, highlighting the importance of "lower UV energy" in the pathogenesis of melanoma [26]. UVB radiation, in contrast, is higher in energy and directly affects adjacent pyrimidines in the double helix to cause a photochemical reaction. Through direct absorption of UVB energy by pyrimidines, two major types of photoproducts are generated: cyclopyrimidine dimers (CPD's) and 6,4 photoproducts (6,4-PP) [27-30] (Figure 4). Both lesions distort the DNA double helix and, if left unrepaired, lead to characteristic "UV signature" transition mutations (G →T and G→C mutations) [30]. It is largely through the identification of these UV signature mutations that we know that UV is a major risk factor for skin cancer and melanoma [31]. Although UVC, the UV component with the highest energy per photon, can cause substantial damage to cells, the ozone layer absorbs the majority of UVC emitted by the sun, therefore this component is not thought to be a significant contributor to most cases of melanoma. Melanomas classically occur on sun exposed skin [32], and exposure to UV radiation corre-

lates with not only the risk for melanoma [33] but also mortality rates [34]. The correlation between melanoma risk is particularly strong with the UVA component, providing further evidence that UVA may be a significant causative factor in melanomagenesis [35].

3.1.1.1. Geographic factors

The global distribution of melanoma also demonstrates the importance of UV radiation in the pathogenesis of this disease. Countries that are located on latitudes closer to the equator have increased UV intensity and higher rates of melanoma among fair-skinned persons [4, 36]. Australia and New Zealand, which are near the equator, have the highest incidence of melanoma in the world with a risk of 1 in 50 individuals [21]. The World Heath Organization reports that Australia and New Zealand have an age adjusted incidence rate of 35.1 individuals per 100,000 individuals [2]. The incidence of melanoma in Australia has doubled from 1986-2006 [37]. Norway, despite also having a fair-skinned, UV-sensitive population predominantly of Scandinavian descent, has a relatively low incidence of melanoma, presumably due to its high latitude (with comparatively weak ambient solar energy) and low UV exposure [38]. High altitudes are also a risk factor for development of melanoma, presumably because UV strength is higher due to less interference between solar energy and particulate matter present in the atmosphere [39, 40] (Figure 5).

Although latitude and altitude do play a major role in melanoma risk, skin complexion is also an important component to explain the variations in melanoma incidence throughout the world. Central America, despite being closer to the equator than North America has a significantly lower age adjusted incidence rates (1.5 and 13.8 individuals per 100,000 individuals) presumably due to having a predominantly dark-skinned complexion [2].

3.1.1.2. UV exposure patterns

Intermittent sun exposure confers a higher risk for developing melanoma than continual exposure [41-43], but the age at which the exposure causes the greatest damage is still controversial. Some studies suggest that sun exposure for a younger individual is more likely to be associated with the development of melanoma [44], while others suggest age of exposure is less important than the cumulative dose of UV [45]. Regardless of age, sunburn is a major risk factor in the development of melanoma, and the risk doubles with more than 5 sunburns [45, 46] or one or more blistering sunburns [43].

3.1.1.3. Sunscreen

The effect of sunscreen on melanoma prevalence is also controversial for a variety of reasons. The widespread use of broad-spectrum sunscreen has not decreased the incidence despite blocking both UVA and UVB radiation. Early sunscreens were designed to prevent sunburn and only blocked UVB radiation. Individuals who used UVB blocking sunscreen were able to stay out in the sun for longer periods of time and were exposed to greater doses of UVA radiation. A delay may exist between the advent of broad-spectrum sunscreen and its effect on melanoma incidence due to the latency between sun exposure and development of

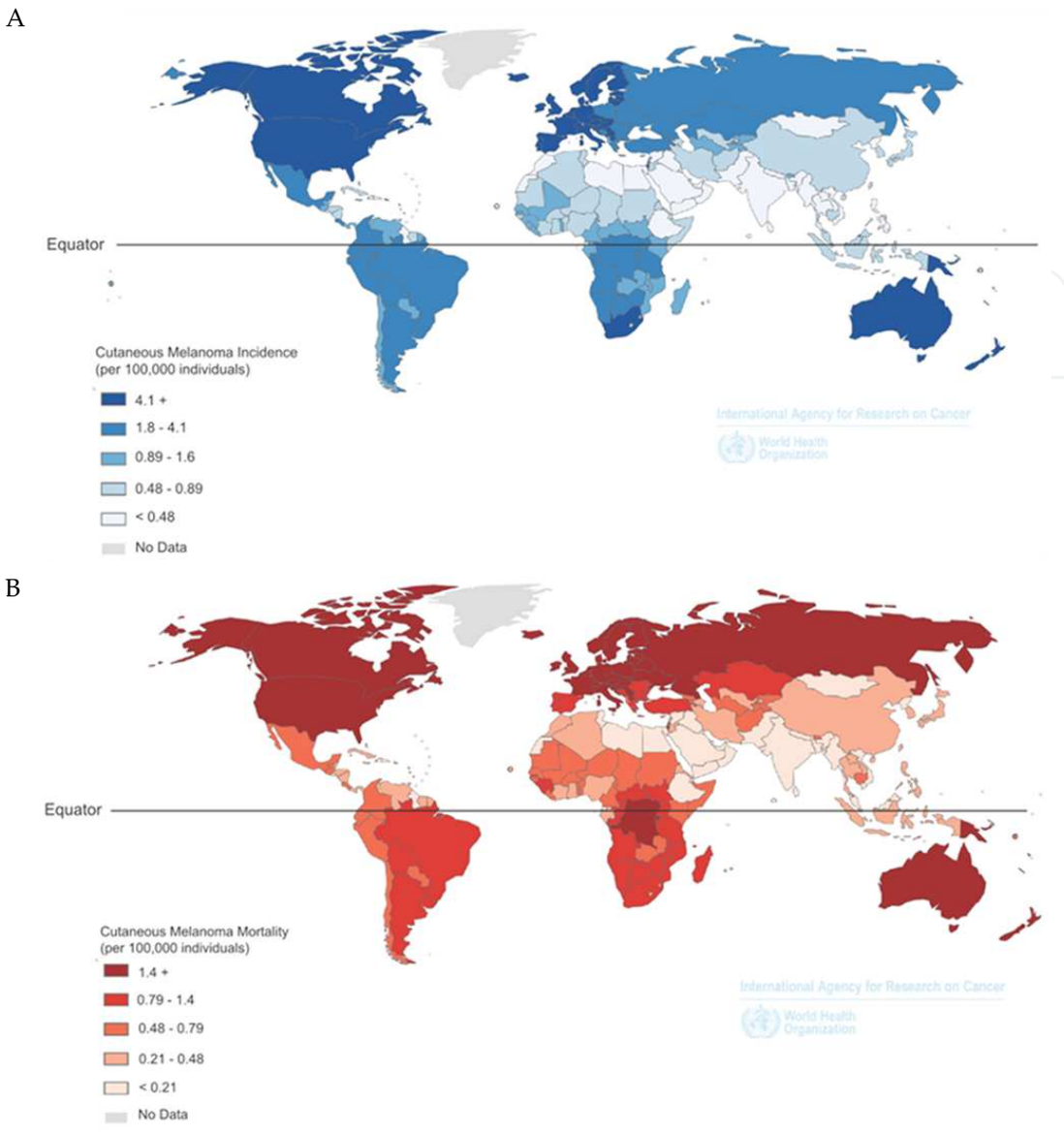


Figure 5. Geographical variation in melanoma incidence (A) and mortality (B). Melanoma incidence is highest in countries populated by fair-skinned persons living in high-UV environments (adapted with permission from [2]).

melanoma. In addition, the use of sunscreen can also promote cellular damage by increasing the reactive oxygen species [47] and if absorbed past the epidermis, can cause photosensitization in melanocytes [48]. Despite some negative effects, the American Society for Clinical Oncology states that the use of broad-spectrum sunscreen with an SPF of 15 or greater decreases an individual's risk of melanoma by up to 50% and should be worn daily to prevent damage from UV radiation [45, 49].

3.1.1.4. Indoor tanning bed use

There has been an explosive increase in the widespread use of indoor tanning beds since their invention in the early 1970's. Over 30 million individuals use indoor tanning salons [50] and

over 70% are female [51]. Overall, 2-3 million of salon-users are teenagers [52]. At age 17, 35% of American females admit to use of an artificial tanning device [53]. The prevalence of artificial tanning is concerning, especially among young adolescents. The earlier tanning begins, the more potential risk there is for carcinogenesis and malignant transformation. In individuals between 18-29 years of age, 76% diagnosed with malignant melanoma had previously used artificial tanning devices [54]. There is a strong positive correlation not only between the use of indoor tanning beds and the development of melanoma [55] but also with death due to melanoma [56]. One tanning session increases the chance an individual will develop melanoma by 20%, and each additional session per year increases risk by another 2% [54]. The International Agency for Research on Cancer classifies UV tanning devices in Group1, most dangerous oncogenic substances [57]. Among salon establishments, artificial tanning beds vary in their delivered dose, and the amount of UVA and UVB radiation is unregulated [10] making artificial tanning incredibly dangerous. State legislative statues vary as to whether minors have restricted access. Many experts hypothesize that the burgeoning use of artificial tanning salons over the last three decades may be a major contributing factor to the continued increase in melanoma incidence.

3.1.2. Medications

Many medications that have great benefit for disease treatment also increase patient susceptibility to cancer. Psoralen and ultraviolet A radiation (PUVA) is an effective treatment for psoriasis and other dermatologic conditions. Psoralen increases reactivity to UV radiation, therefore the combination of psoralen and UVA causes a substantial degree of cellular damage. Patients who receive PUVA have a 10 fold increase in risk of developing melanoma 15 years after treatment, and the risk increases with number of treatment sessions (>250) and time following treatments [58].

Neonatal blue light phototherapy (NBLP) is another example of light therapy that may lead to an increased risk for the development of melanoma. NBLP is a treatment for neonates with elevated bilirubin levels and risk of kernicterus. The therapy is associated with short term side effects that are treatable and/or reversible; however, it may also increase the risk of development of melanoma in later years. The blue lamps used for treatment generally emit a combination of blue light and wavelengths in the UVA region of the spectrum [59]. UVA is known to cause DNA damage as explained above, and some studies have demonstrated that visual light can also cause damage through increased activity along the cytokine and oxidant signaling pathways [60]. Reports disagree as to whether exposure to NBLP causes an increase in nevi number and melanoma susceptibility. Bauer et al. assessed 8112 Caucasian children and showed no correlation between nevi number and exposure to NBLP [61]. However, Matichard et al. and Csoma et al. demonstrated that treatment with NBLP correlated with size of nevus (nevi > 2mm in diameter significantly correlated with exposure to NBLP) [62] or with presence of atypical nevi respectively [63]. A study of twins in 2011 demonstrated that NBLP treatment correlated with a higher prevalence of both clinically normal and dysplastic nevi [64] suggesting that NBLP does increase the risk of development of melanoma in adulthood, and children who receive NBLP should be monitored throughout life.

3.1.3. Heavy metals and chemical exposure

Exposure to heavy metals and certain chemicals are associated with an increased risk of melanoma, presumably through mutagenic changes to DNA in melanocytes. Fortes and de Vries suggest that exposure to polycyclic hydrocarbons (for example, individuals who work in industries associated with petroleum, printing, and electronics), ionizing radiation, polyvinyl chloride (a substance present in clothing dye), heavy metals, and pesticides all increase the risk of developing melanoma [65]. Both polycyclic aromatic hydrocarbons [66] and heavy metals [67] react with UVA to generate free radicals which can subsequently damage DNA, but a variety of molecular mechanisms may be involved in carcinogenesis with these agents.

3.2. Intrinsic

3.2.1. History of skin cancer

Personal or family history of skin cancers is associated with higher melanoma risk. UV-initiated malignancies such as squamous cell carcinoma, basal cell carcinoma or actinic keratosis [68, 69] may indicate cumulative UV exposure, however other skin malignancies not thought to be UV-related (e.g. mycosis fungoides) also increase risk of melanoma [70]. Increased risk from skin cancers such as mycosis fungoides may be due to the immunosuppression associated with the disease (immunodeficiency discussed below). First degree relatives of an individual with melanoma also have a higher risk of developing melanoma than the general population [71], and if a first degree relative has had multiple melanomas, the relative risk of an individual developing melanoma is increased to 61.78 [72]. A past medical history of cutaneous melanoma also substantially increases the risk of subsequently developing another [73, 74]. Although the majority of melanomas are sporadic, 10% of diagnoses are in the setting of familial syndromes [75]. For example, individuals diagnosed with Dysplastic Nevus Syndrome, also known as the Familial Atypical Multiple-Mole Melanoma Syndrome, have a 48.9% risk of developing melanoma by age 50 and an 82% risk by age 72 [76]. One of the most common causes of a familial melanoma syndrome is a mutation in the cyclin dependent kinase inhibitor 2A (*CDKN2A*) gene [75] which regulates cell cycle progression. However it is important to note that increased melanoma prevalence within a family may also represent shared environmental factors such as geography and chemical exposure rather than genetic mutations.

3.2.2. Nevi

Nevi can foreshadow the development of melanoma [77-79]. In 1978 two independent studies reported an association between nevi and melanoma for individuals with familial melanoma syndromes. Reimer et al. reported there was "a syndrome of pigmented lesions in melanoma-prone families" [80] while Lynch et al. described melanomas that were linked to individuals with a large number of "moles of variable size and color" [81]. A majority of benign nevi and melanomas share a common mutation in the BRAF gene (V600E) which results in a gain of function in BRAF signaling [26, 82-84]. This mutation activates the mitogen activated protein kinase cascade leading to the deregulation of the cell cycle and an increase in cell division.

While the BRAF mutation may be sufficient for the formation of a benign nevus, additional mutations are needed (e.g. PTEN loss) for the nevus to convert to a malignant melanoma.

The number of nevi, the presence of atypical or large nevi, and the development of new nevi all correlate with melanoma risk [85, 86]. *De novo* nevi formation is a result of exposure to UV radiation, and sunscreen may not influence this process [87-89]. While the risk of melanoma rises with an increased number of total body nevi, malignant degeneration of any particular nevus is rare. Rather, melanomas generally arise from dysplastic nevi, [90], and the risk of a normal nevus converting to melanoma is very low [91]. The presence of only one dysplastic nevus increases risk by 2 fold, however, >10 dysplastic nevi can increase the risk up to 12 fold [92] [93]. Dysplastic nevi are present in 34-56% of melanoma cases [94].

Risk associated with congenital nevi varies with size and quantity. Small congenital nevi are not associated with an increase in risk [92] while large congenital nevi covering over 5% of the body surface area confers an increased risk [95]. Individual large congenital nevi >20 cm in diameter increase an individual's lifetime risk of melanoma to 10% [96]. Reports suggest that if a melanoma is going to arise from a congenital nevi, most will occur by the age of 10 pointing to the importance for screening the pediatric population [97].

3.2.3. Medical history

Medical conditions associated with immunodeficiency or that use immunosuppressive therapies can trigger melanoma. Patients diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome have an increased prevalence of melanoma with a 50% increased risk of the disease [98] [99]. Because antiretroviral treatment for HIV/AIDS has increased patient's lifespan, these individuals should be closely monitored and obtain regular screening throughout their life. Patients who receive an organ transplant not only have 2.4 greater risk of developing melanoma [100], they also have a more aggressive cancer [101] and a worse prognosis [102] than the general population. Transfer of melanoma from donor to recipient is possible if the donor was previously afflicted with the condition [103].

A previous medical history of noncutaneous skin cancer is also associated with an increased risk of developing melanoma. Individuals who were previously diagnosed with Kaposi sarcoma, breast cancer, lymphoma, prostate cancer, thyroid cancer, and leukemia had an increased risk of subsequently developing melanoma [104]. Childhood cancer survivors have a 2.5 fold increased risk of developing melanoma [105] and are diagnosed at a younger age than the general population (32 years) [106]. Studies speculate that the increased risk following malignancy may be due to either germline mutations in oncogenes or due to the chemotherapy and radiation to treat the prior malignancy [105].

Although melanoma is associated with the production of female hormones, no increased risk of melanoma-associated pathogenesis can be attributed to pregnancy [107]. A majority of women who are pregnant experience a phenomenon known as melasma, an increase in pigment due to increases in melanocyte activity [108]; however, the increase in pigment is not associated with an increase in melanoma incidence.

3.2.4. Nucleotide excision repair

Nucleotide excision repair (NER) is the molecular process by which bulky DNA lesions are recognized, excised, and repaired by the coordinated actions of multiple factors [109-111]. As described above, UVB radiation and to a lesser extent UVA radiation promote the formation of photoproducts that distort the double helix and prevent transcription [112, 113]. Without accurate repair, these photoproducts may cause transition mutations and lead to unregulated cellular proliferation and carcinogenesis.

There are two primary mechanisms of NER, global genome NER (GGR) and transcription coupled NER (TCR), which differ in their initiation site (Figure 6). GGR recognizes damage in non-transcribed regions of the genome. Xeroderma pigmentosum (XP) complementation group C (XPC) and HR23B heterodimerize, recognize distortions within the DNA double helix [114, 115], and recruit the TFIIH complex. TFIIH is a multiprotein complex composed of nine proteins including the helicases XPB and XPD. XPB and XPD unwind 20-30 nucleotides surrounding the damaged base in the 3′-5′ and 5′-3′ direction respectively [116]. The opened DNA structure is stabilized by recruitment of XPA and RPA [117, 118]. After the structure is stabilized, XPF and XPG endonucleases remove the damaged base [119, 120] and the gap is repaired by polymerase δ and ε [121].

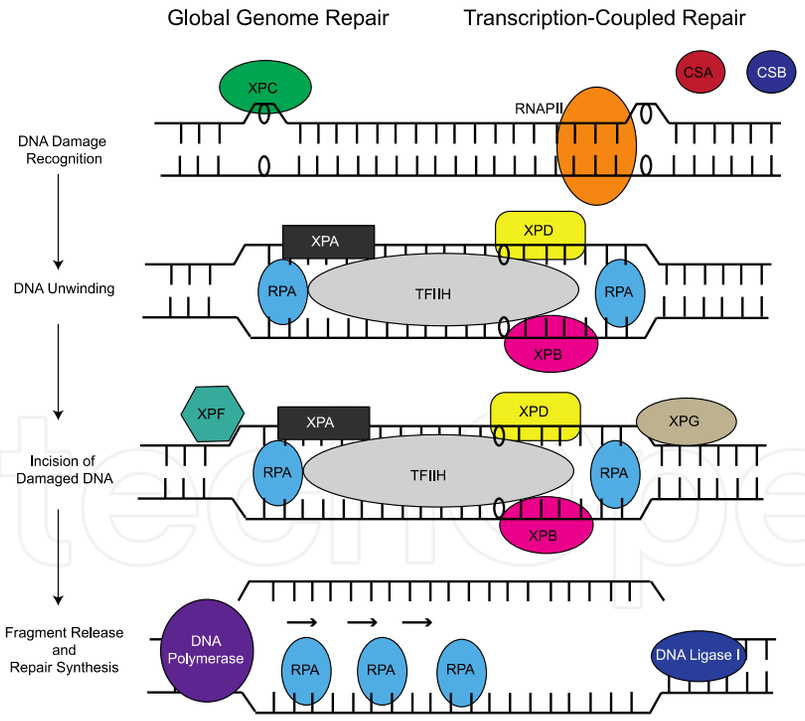


Figure 6. The nucleotide excision repair (NER) pathway is the major way cells rid themselves of bulky DNA lesions such as UV photoproducts. NER is accomplished through the cooperative action of a variety of proteins, working in concert to (1) recognize DNA damage, (2) access and unwind the DNA in the region of the lesion, (3) incise and remove the damage, and (4) repair the gap with a high degree of fidelity using the undamaged strand as a template. Without effective NER, UV mutations accumulate and skin cancers of all kinds occur with high incidence. (Adapted from [3]).

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TCR recognizes damage in transcribed regions of the genome after transcription by RNA polymerase II has stalled [122, 123]. Following exposure to UV radiation, Cockayne syndrome B (CSB), Cockayne syndrome A (CSA), and the core NER factors (excluding XPC) are recruited to the sites of stalled RNA polymerase II [124-126]. After damage recognition, either by GGR or TCR, many NER factors work in concert to unwind the double helix in the area of photodamage, excise the damaged strand, and repair the gap using the undamaged sister strand as a template. In this way, NER corrects UV photodamage with a high degree of fidelity and minimizes the chances for UV-induced mutagenesis..

The importance of DNA repair in preventing melanoma is evident in individuals diagnosed with xeroderma pigmentosum (XP) [127, 128]. They are highly sensitive to UV radiation and develop epidermal thinning, telangiectasias, and altered pigmentation in addition to increased prevalence of skin malignancies [129], with a large number of UV-induced mutations in oncogenes and tumor suppressors [130]. These patients have defective DNA repair due to mutations in one of 8 factors associated with NER [131]. Since DNA repair is not possible, patients with XP are encouraged to limit exposure to UV radiation in order to prevent cellular damage. Individuals diagnosed with XP have a 1000 fold increase in skin cancer risk compared to the average population and are often diagnosed with melanoma in the second decade (on average over 40 years before the general public) [132].

3.2.5. Skin complexion

The amount of melanin pigment present in the skin determines skin complexion, and low basal pigmentation (having a fair-skinned phenotype) constitutes a major risk factor for the development of melanoma. Melanin pigments, all derived from the amino acid tyrosine, are synthesized by melanocytes, transported to the keratinocytes where they absorb UV radiation, and prevent damage to the sensitive layers of the skin. In fact, melanocytes produce two distinct forms of melanin. Eumelanin is a dark brown/black chemically inert pigment that potently blocks penetration of UV energy into the skin. Pheomelanin, in contrast, is a lighter-colored pigment that is much less effective at blocking UV penetration and that may even potentiate oxidative UV damage [133] (Figure 7).

The amount of eumelanin in the epidermis largely determines skin complexion. The Fitzpatrick skin phototype was developed by a Harvard University Medical School dermatologist to classify an individual's UV susceptibility based on basal pigment levels, tendency to burn, and ability to tan [134]. Individuals with a lower Fitzpatrick score have fair skin (less pigment), red or blonde hair, burn easily and are unable to tan, while individuals with a higher Fitzpatrick score have a darker complexion (more pigment), do not burn, and tan easily (Table 2). Compared to individuals with a Fitzpatrick score of IV, individuals with a Fitzpatrick score of I have a relative risk of 2.09 developing melanoma [71]. A recent study demonstrated that pigment and race were not sufficient to predict an individual's Fitzpatrick score and sun sensitivity; this finding highlights the importance of physician-based counseling to all patients regarding sun safety and prevention of sun-induced malignancies [135].

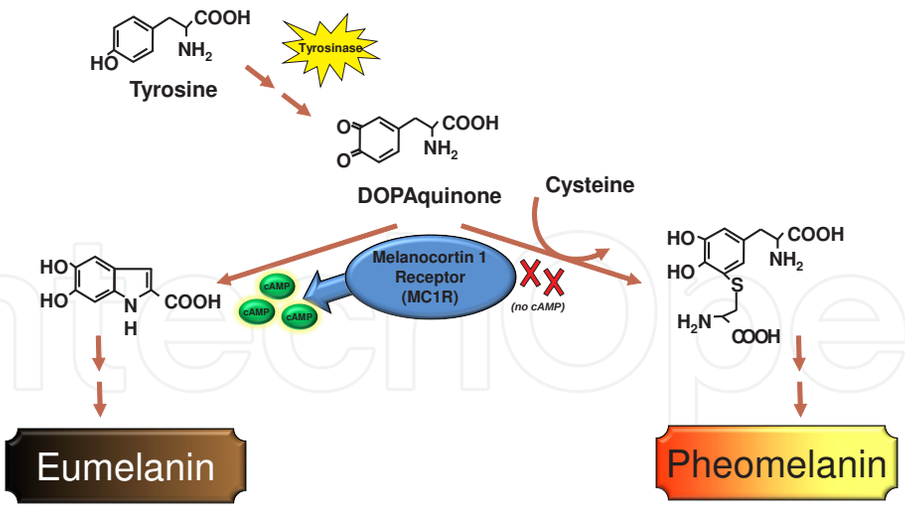


Figure 7. Synthesis of eumelanin and pheomelanin is regulated by the melanocortin 1 receptor (MC1R). Eumelanin, a dark brown/black pigment with excellent UV protective properties, is produced when melanocytes are stimulated through MC1R signaling and cytoplasmic cAMP levels are increased. In contrast, pheomelanin, a sulfated pigment with poorer UV-blocking properties is made when MC1R is inactive.

Phototype	Skin color	MED (mJ/cm^2 UV)	UV Response	Melanoma Risk
I	Ivory/pale white	15-30	Burns easily and strongly, never tans	++++
II	Very white	25-40	Burns easily, tans minimally with difficulty	+++/++++
III	White	30-50	Burns moderately, tans somewhat	+++/++
IV	Light brown, beige, olive	40-60	Burns minimally, tans moderately	++
V	Moderate brown	60-90	Rarely burns, tans well	+
VI	Dark brown/black	90-150	Never burns, tans profusely	+/-

Table 2. The Fitzpatrick scale of skin complexion. MED represents the minimal erythematous dose (the least amount of UV required to cause a sunburn).

4. Pigmentation and MC1R

The melanocortin 1 receptor (MC1R) is a major determinant of skin pigmentation and UV sensitivity. UV exposure activates the MC1R, which directly controls not only the adaptive tanning response (UV-induced pigmentation) but regulates melanocyte DNA repair and, thus, the mutagenic risk as well.

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4.1. Eumelanin versus pheomelanin

Melanocytes, derived from neural crest cells, produce pigment in the skin. As described above, lack of basal skin pigmentation is a major risk factor for the development of melanoma. The two major types of pigment produced by the melanocyte are eumelanin and pheomelanin. Pigmentation depends on the type and amount of melanin produced in addition to its cellular distribution rather than number of melanocytes present in the skin [136-138]. Eumelanin is a dark insoluble polymer that absorbs UV light [139, 140] and oxidants [141], protecting DNA from the damaging effects of these factors. Pheomelanin is a soluble red/yellow polymer containing cysteine, which provides little protection from UV light and reports demonstrate that pheomelanin can promote oxidative damage [133, 142]. Synthesis of both eumelanin and pheomelanin begins with the conversion of tyrosine to DOPA and then to DOPAquinone via the enzyme tyrosinase [143]. Incorporation of a cysteine into DOPAquinone molecule eventually leads to the production of pheomelanin rather than eumelanin. Individuals without a functional tyrosinase are unable to produce any pigment and have a condition known as albinism [140]. Control of the ratio of pheomelanin to eumelanin in a cell is determined by multiple factors including pH of the cellular milieu and levels of the tyrosinase enzyme [133, 144]. Higher levels of tyrosinase and neutral pH favor eumelanin production and darker pigmentation [144, 145]. In addition to pH and tyrosinase, the melanocortin 1 receptor is one of the major factors controlling the pigment ratio.

4.2. MC1R and pigment switch

The melanocortin 1 receptor (MC1R) is one of the major proteins controlling the switch between the production of eumelanin and pheomelanin, and therefore is a one of the major control points of pigment production. Increased activation of MC1R by melanotropic hormones leads to an increase in tyrosinase expression and eumelanin production [146]. MC1R is a G-coupled protein receptor that is activated by alpha-melanocyte stimulating hormone (α-MSH) leading to the activation of adenylate cyclase and an accumulation of cAMP. cAMP promotes two pathways: 1) it activates protein kinase A (PKA) and 2) it up-regulates cAMP responsible binding element (CREB) and microphthalmia transcription factor (MITF); these factors ultimately cause an increased expression of enzymes involved in pigment production [136, 140, 147-149]. MC1R is a highly polymorphic protein with over 100 variants reported [150-152]. Five specific variants, D84E, R142H, R151C, R160W, and D294H, are associated with a decrease in pigment production and the red hair/fair skin phenotype [153-155]. These individuals are more susceptible to melanoma due to a decrease in eumelanin production coupled with inefficient DNA repair; this latter point suggests that MC1R plays a role not only in pigment production, but also in nucleotide excision repair [156, 157].

Studies using agouti signaling protein (ASIP) confirm the role of MC1R in the production of eumelanin. ASIP is a competitive antagonist of MSH and binds to MC1R causing an increase in the production of pheomelanin [158]. The effects of ASIP on melanocyte pigment production require a functional MC1R [158, 159]. The reduction in eumelanogenesis and increase in pheomelanogensis accompanied by ASIP signaling is only partially due to inhibition of MSH binding to MC1R. Binding of ASIP to MC1R causes a decrease in tyrosinase activity as well as

tyrosinase related protein 1 and 2 protein levels, thus promoting pheomelanin synthesis [158-161]. ASIP also signals through a cAMP independent pathway via attractin and mahoguin to influence MC1R signaling and increase pheomelanin levels [162].

4.3. MC1R and adaptive pigmentation

The inability to have an adequate adaptive tanning response is a major risk factor for the development of melanoma. As explained above, the tanning response increases the production of pigment in the skin and serves as a protective barrier from the damaging effects of UV radiation. Adaptive pigmentation is dependent upon MC1R signaling [163]. UV radiation promotes cellular damage in keratinocytes, activating the damage response protein p53. p53 activation increases the transcription of proopiomelanocortin, which is processed and cleaved to MSH [164]. MSH is secreted from the keratinocytes and diffuses to the melanocyte membrane where it binds to and activates MC1R promoting the synthesis of eumelanin [146, 165]. Individuals with defective MC1R signaling, whether from inability of MC1R to bind to its ligands or from an inert response upon binding, cannot increase their pigment production following exposure to UV radiation and instead are highly susceptible to burning [163] (Figure 8).

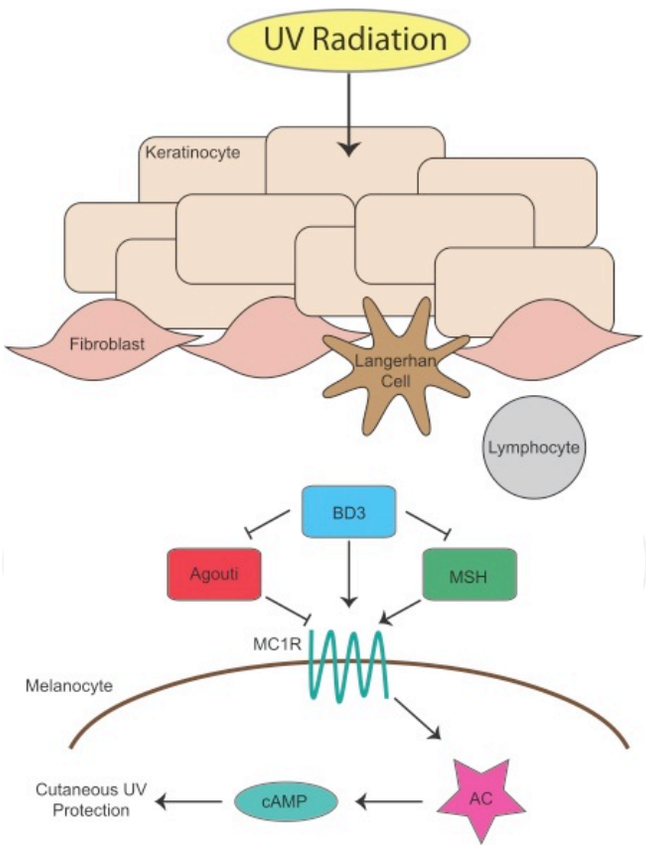


Figure 8. Cutaneous response to UV radiation. UV radiation induces the secretion of MSH and agouti signaling protein. MSH binds to MC1R and activates adenylyl cyclase (AC) which leads to the accumulation of cAMP. cAMP signaling to promote pathways responsible for cutaneous UV protection. Agouti signaling protein binds to MC1R and prevents activation of adenylyl cyclase inhibiting the adaptive tanning pathways.

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Current research is investigating pharmacological methods to increase the tanning response in order to prevent damage, particularly in those individuals who have defective MC1R signaling. Forskolin is an activator of adenylyl cyclase and functions downstream of MC1R leading to an increase in the production of cAMP. Forskolin applied to a transgenic mouse model with humanized skin promoted the synthesis of eumelanin and adaptive pigmentation [166]. Phosphodiesterase inhibitors including rolipram prevent cAMP degradation and is hypothesized to have similar effects to forskolin. Rolipram is currently an FDA-approved drug and may have clinical applications for this condition.

5. Conclusion

The incidence of melanoma has dramatically increased throughout the past century. Although the cause for the increase is unknown, it is clear there are a number of environmental and genetic factors responsible for melanoma risk. The major environmental risk factor is exposure to UV radiation via ambient sunlight or artificial tanning beds. The intensity of the ambient sunlight varies with geography throughout the world. Countries located on latitudes closer to the equator have a higher incidence rate compared to countries located further away from the equator. Exposure to UV radiation, however, does not entirely explain the increase in melanoma diagnoses. Other environmental factors also play a role including certain medications (PUVA, NBLP) and exposure to heavy metals. Genetic factors also play a major role in melanoma risk. As melanoma often originates from pre-existing nevi, the presence of a large number of nevi, nevi with large diameters, or the presence of dysplastic nevi increase the risk. A past medical history of cutaneous or non-cutaneous cancer also increases the risk of subsequently developing melanoma. Although there are many intrinsic factors which play a role in determining one's risk of developing melanoma, the most important is the ability to produce pigment. Eumelanin protects the skin from UV induced damage. Individuals with fair skin and a low Fitzpatrick phototype are highly susceptible to melanoma. A subset of individuals with fair skin also has defective MC1R signaling and is unable to promote the adaptive tanning pathway. Clearly, much is known about the risk factors for developing melanoma, and hopefully as we better understand the pathogenesis of the disease, we will develop therapeutics and strategies to prevent melanoma from occurring.

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