Melanoma Epidemiology and Prevention

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Epidemiology

Introduction

The incidence of melanoma is continuing to increase throughout the world in fair-skinned populations. In the United States, melanoma incidence has risen from 8.2 to 9.4 cases per 100,000 within the white population in 1975 (females and males, respectively) to 38.9 and 24.2 cases in 2013. Increased incidence has occurred mainly for thin lesions, those less than 1 mm in Breslow's depth. Reasons for the increased incidence include excessive tanning, potential exposure to chemicals, and a more effective application of diagnostic criteria. Mortality rates have also increased among white males, rising from 2.9 per 100,000 in 1975 to 4.6 in 2013. They have risen very little for white females during the same time period, from 1.7 to 1.9 per 100,000 between 1975 and 2013 [1]. This chapter reviews both causes for and prevention of melanoma.

Risk Factors for Melanoma

The relationship between risk factors and incidence is complex, but increased exposure to UV radiation (UVR) is the major factor responsible for the development of melanoma. In conjunction with UVR, host factors as well as phenotypic and genetic factors are also responsible for an individual's likelihood of developing melanoma.

Phenotypic Factors

Fair Skin Phenotype

It is well established that fair-skinned individuals have an increased risk for melanoma compared to those with darker skin. Phenotypic characteristics such as light eyes, light or red hair, and fair skin color are host factors known to increase the risk of developing melanoma. There appears to be an inverse relationship between darker skinned individuals and the decreased risk of melanoma. In a meta-analysis of 60 studies, individuals with red hair were compared to those with dark hair, finding a relative risk of 3.64 (95% CI, 2.56, 5.37) for developing melanoma. Individuals with blue eyes had a relative risk of 1.47 (95% CI,

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1.28, 1.69) compared to those with brown eyes and fair-skinned individuals had a 2.06-fold (95% CI 1.68, 2.52) increased risk [2]. As there is no commonly accepted standard for assessing skin color between studies and populations, some authors feel that a reported inability to tan may be a better risk marker for melanoma and increases risk approximately twofold [3, 4]. Some have developed more quantitative approaches to measure pigmentation such as the extraction and quantification of pheomelanin and eumelanin from undyed hair [5], but these have not been widely adopted due to the difficult assays required.

Freckling

Freckles are benign, ranging in diameter from a few millimeters to a few centimeters, pigmented skin spots that appear with increased sun exposure commonly in fair-skinned individuals. Increased freckling is associated with higher risks of melanoma (RR = 2.10, 95% CI 1.80–2.45) in many studies, and in the meta-analysis by Gandini et al. [2]. Phenotypic characteristics and freckling tendency can be used to identify those at high risk and can be targeted for surveillance.

Nevi

Nevi are a strong risk factor for the development of melanoma. Nevi are benign collections of melanocytes that may be congenital or acquired [6]. The relationship between sun exposure, nevus development, and melanoma risk is still not fully understood. It is theorized that melanocytes within a nevus may be more likely to undergo malignant transformation [2]. A number of studies have shown that melanoma may have arisen from preexisting melanocytic nevi in 30% of cases [7].

Some studies have hypothesized that multiple nevi may be a marker for previous sun exposure suggesting that sun exposure and number of nevi have a multiplicative effect on the risk for melanoma. Children and adolescents who practice sun-protective behaviors have decreased numbers of new developing nevi [8–10]. Sun exposure plays a role in the development of nevi [11]. The risk for melanoma increases as the number of nevi increases, from a risk of 1.47 (95% CI 1.36, 1.59) for fewer than 15 total nevi to a relative risk of 6.89 (95% CI 4.63, 10.25) for more than 100 nevi [12].

The Divergent Pathway to Melanoma Development

Whiteman et al. [13] suggested that melanomas from varied body sites arise through different pathways with different associations with either solar keratosis or nevi. Melanomas located in the head and neck regions are associated with chronic sun exposure, fewer nevi, and more solar keratoses. Melanoma located on the trunk with similar histological features was associated with more intermittent sun exposure, many nevi, and fewer solar keratoses. This suggests that individuals with a greater genetic tendency to form nevi have a lower threshold to UV exposure to induce the melanocytes to proliferate and become neoplastic. In contrast, people with a low genetic tendency to develop nevi require a higher threshold of sun exposure to induce melanocytes to proliferate.

Exposures

Sun Exposure

The cause of melanoma is multifactorial and complex but sun exposure plays a primary role in the development of melanoma. Ultraviolet radiation exposure has been recently classified as a Class I carcinogen [14]; ultraviolet radiation includes UVC (200–280 nm), UVB (280–320 nm), and UVA (320–400 nm). UVC is highly toxic, but very little of it reaches earth as it is screened by the stratospheric ozone layer. UVB rays directly damage DNA through the production of DNA-damaging photoproducts and cyclobutane pyrimidine dimer formation, while UVA indirectly damages DNA through reactive oxygen species production [15]. Analyses in the United Kingdom suggest that 90% of melanoma cases in men and 82% in women are attributable to excess solar irradiation [16] and 68% worldwide [17]. The rising incidence may be due to early detection, increased surveillance, and

changes in diagnostic criteria, but the majority are thought to be linked to increased sun exposure through altered patterns of behavior, such as the choice of clothing [18] and outdoor activities.

Sun exposure is classified as "total, intermittent, or chronic" with "sunburn history" as an important component. Intermittent sun exposure refers to intense, short periods of sun exposure experienced on weekends or on vacations in sunny locations. Chronic sun exposure is continuous with less intensity and mostly seen in occupational settings. Total sun exposure is the sum of intermittent and chronic exposures.

A meta-analysis examined 57 studies of sun exposure and melanoma and reported relative risks of 1.34 (95% CI, 1.02, 1.77) for total sun exposure, 1.61 for intermittent sun exposure (95% CI, 1.31, 1.99), 0.95 for chronic sun exposure (95% CI, 0.87, 1.04), and 2.03 for a history of sunburn (95% CI, 1.73, 2.37) [19]. It is unclear whether, in fact, chronic sun exposure decreases the risk for melanoma. Certainly, those with chronic sun exposure have adapted to the UV and thus are less likely to be harmed by it. Similar results have been found when looking at the risk of sun exposure on multiple primary melanomas [20].

Current evidence does not clearly show a critical period during life where risk from sun exposure is highest [21, 22]. For example, the increased risk for more than five sunburns during childhood was 2.0 (95% CI, 1.2, 3.5) and during adulthood was 2.1 (95% CI, 1.4, 3.3) [21]. Sunburns during any period of life, whether it is childhood, adolescence, or adulthood, increase the risk for melanoma. Due to the fact that sunburns are based on self-report and memory is fallible, there is no strong evidence for any specific "number" of sunburns and increased risk for melanoma. Although many experts purport that various specific numbers increase risk, there is no validity to a specific number.

Indoor Tanning

Approximately 7.8 million women and 1.9 million men use tanning beds each year [23], and the International Agency for Research on Cancer [14] has identified ultraviolet radiation (UVR) emitted from tanning beds as carcinogenic. Indoor tanning beds emit both UVA and UVB rays in amounts 2–4 times stronger than the midday sun during the summer in Washington, DC [24]. The longer a person uses indoor tanning beds and the earlier that someone begins using them, the more likely that one is to develop melanoma in the future [25]. A dose-response relationship was also noted between total hours ($P < 0.0001$), number of sessions ($P = 0.0002$) or years ($P < 0.006$), and melanoma risk [26]. Shifting trends in anatomic location of melanoma also appear to demonstrate the influence of indoor tanning on the risk for melanoma. There was a significant rise in truncal melanomas in women after 2002 in Iceland that coincided with rapidly expanding sunbed use after 1985 [27].

Occupation and Melanoma

Most studies of melanoma have focused on the relationship between host factors, UV radiation, and melanoma risk, but a number of relatively small studies have found links to polycyclic aromatic hydrocarbons, benzene, and other chemicals used in the printing industry [28–32]. Studies of electrical and electronics workers have demonstrated an increased risk for melanoma [33]. It must be noted that not all studies have shown positive associations. It is likely that the various occupational workers are also exposed to additional agents and many of the studies did not have appropriate control for confounders. For example, cosmic radiation, such as that received by pilots and airline attendants, has often been associated with increased melanoma risk. However, the lifestyle of these occupations may confound the association [34, 35]—whether due to circadian rhythm disruption [36] or opportunities for intense intermittent sun exposure. Multiple small studies have looked at issues related to occupation and due to the small number of subjects and incomplete control for confounding they are unable to determine strong links.

Polychlorinated Biphenyls

PCBs may affect melanomagenesis. PCBs are chlorinated compounds previously used as coolants in electrical apparatus and which, as

now discarded, leak into the environment. When that happens, meat, fish, milk, and water often contain PCBs [37–39]. There has been little research in dietary PCB exposure and melanoma risk, but one cohort study reported that exposure to dietary PCBs was associated with a fourfold increased risk of malignant melanoma [40]. A small pilot study conducted in British Columbia found strong associations between the risk of melanoma and plasma levels of non-dioxin-like PCBs (OR 7.02, 95% CI, 2.30, 21.43) [41]. This study is now being validated in a larger cohort.

Chromium

Chromium may play a major role in the pathogenesis of cutaneous melanoma [42]. Textile industries, which can often contain chemicals that are potentially harmful to skin, are known to contain the following chemicals: formaldehyde, nickel, and hexavalent chromium [43]. Cells exposed to chromium changed their shape and developed chromosomal abnormalities. Hexavalent chromium is a toxic form of the element, chromium. It can be used in electroplating, steel production, and metal plating. Tantalizing data [44–46] demonstrate an association between risk or mortality and melanoma after hip replacement with metal implants.

Genetic Factors

Melanoma is a heterogeneous disease with multiple signaling pathways associated with its pathogenesis. Insight into the pathways responsible for melanoma initiation and progression has come from current next-generation sequencing studies. It is beyond the scope of this chapter to fully elucidate the exciting developments in genetics that are leading to new understanding of the mechanisms of melanoma development. Excellent reviews of inherited and somatic mutations are by Hill et al. and Zhang et al. [47, 48].

Family History

A family history of melanoma is a strong risk factor for the development of melanoma, accounting for 10% of all melanoma cases [49]. Individuals with a first-degree relative with melanoma have a twofold increased risk for developing melanoma compared with those without a family history [50]. This assessment can be somewhat complex, as several family members with melanoma may have acquired the tumor due to genetic susceptibility or to common exposures, or possibly both. Mutations in the CDKN2A gene are the most common genetic mutations among families, with CDK4 occurring very much less frequently. Population-based studies have demonstrated the rarity of CDKN2A mutations among sporadic cases of melanoma [51]. Patients with a genetic predisposition acquire melanoma at a younger age, generally have thinner melanomas, and often have a history of dysplastic nevi or precursor lesions [52]. They also have a significantly higher risk for developing multiple primary melanomas [53]. It is not well known that melanoma can also arise in conjunction with familial cancer syndromes such as Li-Fraumeni, familial retinoblastoma, and Lynch syndrome type 2 [49].

Inherited Genetic Factors, Single-Nucleotide Polymorphisms

Pigmentation pathways clearly contribute to the risk of developing melanoma, with genetic loci at MC1R (melanocortin-1 receptor) and OCA2 identified in relation to facial freckling and total nevi [54] as well as red hair and fair skin [55]. MC1R mediates pigmentation and is expressed on the surface of melanocytes as a G protein-coupled receptor. It signals to downstream effectors to regulate skin pigmentation and control apoptosis and cell proliferation [56]. MC1R has also been shown to initiate the DNA repair process, increase phosphorylation of DNA repair proteins, and activate survival pathways [57, 58]. Mutations in the MC1R gene are therefore linked to inefficient DNA repair and melanocyte apoptosis [59]. Several recent studies have examined the role of MC1R in melanoma risk, finding that carriers of MC1R variants are at a significantly higher risk of melanoma, independent of sun exposure [60, 61].

Somatic Mutations

The Cancer Genome Atlas (TCGA) is currently the largest analysis of somatic aberrations in melanoma to date, including 333 cutaneous mel-

anomas (80% of which were metastatic), and providing valuable insight into mutations that drive melanoma [48]. Whole-exome sequencing studies have shown that melanoma carries one of the highest mutation burdens compared to most other cancers [62, 63]. Identifying the specific mutations involved with the development of melanoma may not only improve our understanding of molecular pathogenesis, but also recognize therapeutic options as well as link clinical characteristics to genetic subtypes. To date, most studies have generally been small and come up with different sets of somatic mutations associated with survival.

Tumor Subtypes

Melanoma has a variety of histological subtypes with multifaceted epidemiology. Different patterns have been noted including differences in anatomical site and age-specific incidence, leading to the idea that more than one pathway may be responsible for the development of melanoma. Different genotypes have been associated with various clinical and histological subtypes. Previous evidence indicates that melanoma arising from chronically sun-exposed skin compared to non-chronically sun-exposed skin differs in terms of location of primary tumor, histological and clinical presentation, age at onset, and speed of progression. BRAF gene mutations were commonly found in tumors arising from intermittently sun-exposed skin. These mutations tend to be found more commonly in melanoma arising from the trunk, which is exposed during intermittent sun exposure [64]. Data show that the BRAF V600E mutation occurred in significantly younger patients who had increased nevi and fewer actinic keratoses and were more likely to have a family history of melanoma [65]. BRAF V600E mutations have been significantly associated with the presence of ulceration, increased tumor thickness, and reduced survival [66]. NRAS mutations occur more commonly in melanoma arising from chronically sun-exposed sites such as the head and neck and extremities [47].

Hacker et al. [65] conducted a study analyzing 414 patients with newly diagnosed cutaneous melanoma and found mutually exclusive mutations in BRAF V600E (26%), BRAF V600 K (8%), BRAF wild type (5%), and NRAS (9%), as did Thomas et al. [67]. Data shows that BRAF V600E mutations occurred in significantly younger patients, those with increased nevi, fewer actinic keratoses, and those with a family history of melanoma [65]. Both Hugdahl et al. [66] and Thomas et al. [67] found that BRAF V600E mutations significantly associated with the presence of ulceration, increased tumor thickness, and reduced survival. BRAF V600 K and NRAS gene mutations occurred more commonly with increased nevi, increasing age, and less overall sun exposure [67].

Prevention of Melanoma

Melanoma is caused by a set of different combinations of excessive sun exposure and genetic factors. Until we understand the genetic factors and interactions more precisely, preventing melanoma generally means preventing excessive sunburn. Genetic testing can give us some indication of risk, but such testing is not yet ready for general population use. New studies are evaluating the use of chemopreventive agents. These are, however, still in the pipeline and are not quite ready for use by the general population [68]. Vitamin D supplements have been proposed as a way to reduce melanoma incidence and mortality, but there is little direct evidence that these will be effective [69].

Prevention of Excessive Sun Exposure: Primary Prevention

As sunburn at any life stage, including childhood, increases the risk of melanoma [70], there are multiple prevention programs that aim to prevent sunburns. Most individuals, particularly children, may not use adequate sun protection [71–73]. There has been a very strong emphasis on the use of sunscreens to prevent sunburns and skin cancer of all types. Green et al. [74] performed a randomized trial demonstrating that in Queensland, over a long period of time, the use of sunscreen decreased the

incidence of melanoma. Additionally, a population-based case–control study showed that the use of sunscreens was significantly more common among the control group [75]. However, the same study has found that other forms of sun protection, such as seeking shade and wearing long sleeves and hats, had an even stronger effect on risk reduction of melanoma. The Ontario Sun Safety Working Group [76] recently developed an update to recommendations for sun safety and recommended, in this order: protecting your skin, seeking shade or bring your own, wearing clothing and a wide-brimmed hat, and using sunscreen labeled "broad spectrum" and "water resistant" with a sun protection factor (SPF) of 30. Apply and reapply frequently. Don't use UV tanning equipment and avoid getting a sunburn while protecting your eyes with sunglasses.

Educational Efforts at Prevention Around the World and Within the United States

Recently, school-based sun safety educational programs and policies have been developed to teach sun safety, which when taught at an early age can influence a lifetime of healthy habits. The caveat is that such educational efforts must be implemented frequently and over a long period of time [77–79]. In 2012, the Community Prevention Services Task Force at CDC [78] reviewed 33 sun safety educational and policy interventions within schools between 1966 and 2011. They concluded that such programs "increased sun-protective behaviors and decreased ultraviolet exposure, sunburn incidence, and formation of new moles" [80].

As Australia and New Zealand have the highest rates of melanoma in the world, Australia developed the 1988 "Slip! Slop! Slap!" campaign that evolved into a comprehensive, multi-setting, multi-approach program that includes a voluntary "Sun Smart" school accreditation program [81]. Resources are provided for early childhood, primary and secondary schools, as well as workplaces, local government, sports groups, events, festivities, and families.

Examples of Sun Smart criteria include mandatory hat wearing, encouraging shade seeking, avoiding peak UVR hours, and positive sun-protective behavioral role modeling. A total of 90% of schools in Victoria, Australia, are registered with Sun Smart, reaching an estimated 430,000 children. Only 17% of Victorian primary schools had sun protection policies in 1993; 20 years later, 89% have policies in place. Australia's "no hat, no play" policy (recently promoted in Hawaii, USA) was shown to significantly increase hat wearing among children on the playground [82]. Only 2% of Victorian preschools reported hats available to preschoolers in 1988; 20 years later, 91% now have hats available [83].

In the United States and other countries like Sweden, Norway, and the UK, projected melanoma incidence will continue to rise [84]. Multiple skin cancer prevention programs are available on the Web [85]. In 2008, the SunWise program in the United States was estimated to prevent more than 11,000 cases of skin cancer and 50 premature deaths by 2015 and found that "every federal dollar invested in SunWise would save $2-4 in public health costs" [86]. Critically, the implementation of policy leads to increased practice [87]. Sun safety education campaigns have also been developed and adopted by a number of other countries such as South Africa, New Zealand, Canada, France, Germany, Northern Ireland, and Israel [85], although later in time compared to the Australian Sun Smart campaign and more sporadic implementation [84].

The success of sun safety education programs is in large part dependent upon the comprehensive nature of their implementation. Extracurricular programs such as aquatic centers, summer camps, and parks have been excellent scaffolding for the dissemination of sun safety knowledge and encouragement of sun safety behaviors. For example, the CDC-funded "Pool Cool" campaign was developed in order to increase UVR risk awareness and teach sun-protective behaviors before swimming lessons. The program was designed to target children, parents, patrons, and staff. The eight-lesson curriculum consists of a 5-min lesson on sun safety by lifeguards and/or

instructors before swim practice. As part of the program, centers receive shade structures, signage, and sunscreen dispensers for the promotion of a sun safe pool environment. An increase in sun-protective behaviors was reported in one randomized study and a decrease in sunburns reported in another observational study [88, 89].

Effectiveness of Skin Cancer Screening by Individuals and Physicians: Secondary Prevention

Skin cancer screening is still considered controversial, despite the seemingly intuitive advantages of being able to visually identify a skin cancer in its early stages by performing a full-body skin exam. In 2016, the United States Preventive Services Task Force (USPSTF) concluded that evidence was still insufficient for the recommendation of clinical skin cancer screening guidelines for asymptomatic adults without a history of prior malignant or premalignant skin conditions [90]. In 2003, a melanoma screening program piloted in the state of Schleswig-Holstein after intensive public awareness campaigns and skin cancer detection training for general health practitioners. The initial 5-year results showed an almost 50% reduction in melanoma rates compared to surrounding states [91]. Unfortunately, after nationwide implementation, 5-year data has yet to show any measurable reduction; in fact, mortality has since returned to baseline levels in Schleswig-Holstein [92, 93]. After reviewing tumor-stage distribution and malignant melanoma survival in Germany between 2002 and 2011, neither Schoffer et al. nor Boniol et al. found any direct influence on mortality from the introduction of this national skin cancer screening program [94, 95].

Preliminary data from a University of Pittsburgh screening program [96] and a Queensland study [97] have shown that finding a melanoma with decreased tumor thickness was associated with the screened group versus unscreened population. Most recently, a 2017 systematic review of 15 studies found the most current evidence, though low, showing some benefit to a skin cancer screening program [98]. Specialized surveillance for high-risk individuals has also been shown to result in lower treatment costs and fewer invasive procedures compared to standard community care [99] and has been recommended by a group of melanoma experts at the Society for Melanoma Research [100].

A study from Belgium found "lesion-directed skin exams" to have similar detection rates as total-body skin exams, which are six times more time consuming [101]. Public education on warning features and proper self-exam techniques are building blocks for successful lesion-directed skin exams, as these factors prompt physician follow-up for concerning moles [102]. There is insufficient data to elucidate the long-term effects of skin cancer screening on mortality. However, primary physician skin exams, particularly lesion directed, could be beneficial. These, in conjunction with specialized exams for high-risk populations, may offer the most potential for capturing benefits such as decreased tumor thickness and cost savings.

Guidelines and Recommendations for Melanoma Prevention and Screening

Multiple groups have made valuable recommendations for the prevention and screening for melanoma. Most suggest that effective prevention lies in the general population awareness of their skin and any changes. For example, Berwick and Paddock reported that among those who reported being aware of their skin, defined as aware of it for medical or cosmetic reasons, there was a 50% reduction in mortality from melanoma [103]. Furthermore, there is a need to assess the benefits of targeted screening to those at highest risk, such as males that are older than 50 years of age. In the meantime, the messages that may help to reduce melanoma incidence include the following: (1) protect the skin when the UV index is 3 or higher, (2) seek shade, (3) wear clothing and (4) a wide-brimmed hat as well as (5) generously apply

sunscreen labeled “broad spectrum” and reapply after 2 h in the sun to skin not covered by clothing, and finally (6) see your healthcare provider if you notice any suspicious-looking lesions.

Conclusions

Understanding the basic biology of melanoma has recently led to new therapies. Clearly, more work in this area is critical to understanding fully how melanoma develops and how to prevent it. Furthermore, there is a great deal more research needed to refine the definition of high-risk individuals for targeted education and screening in order to prevent melanoma.

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