Clinical Epidemiology of Melanoma

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Contents

Abstract

Melanomas are common cancers among people of European ancestry, and incidence has been rising in most populations where fair-skinned people predominate. The principal environmental risk factor for cutaneous melanoma is solar ultraviolet radiation, although the association is nonlinear and modified by host factors. While overall, fair-skinned populations residing in regions of high ambient insolation have higher rates of melanoma than those residing in regions receiving less sunlight, it is also generally observed that outdoor workers have lower risks of melanoma than indoor workers. A suite of host phenotypic characteristics confer increased relative risks

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of melanoma including fair complexion, skin that burns and does not tan, red hair, freckling, and blue eyes. Those with a propensity for developing large numbers of melanocytic nevi also have markedly increased risks of melanoma. Recently, algorithms have been developed that combine information about various phenotypic characteristics to derive an overall summary risk score. Such tools are being tested as decision aids to stratify individuals into potential screening programs according to their future risk of melanoma.

Introduction

Melanoma constitutes 1.6% of all estimated new cancer cases worldwide (42,084 cases in 2012, excluding non-melanoma skin cancer), and the burden is similar for men (1.5%) and women (1.6%) (Ferlay et al. 2010; Ferlay et al. 2013a). Globally, melanoma ranks as the 15th most common cancer in women and 16th most common in men (Ferlay et al. 2013a). In both Australia and New Zealand, however, melanoma ranks as the third most common cancer in both men (7639 and 1358 cases in 2015, respectively) and women (5320 and 1066 cases in 2015, respectively), after prostate and colorectal cancer in men and breast and colorectal cancer in women (Australian Institute of Health and Welfare 2014; New Zealand Ministry of Health 2018). In Northern Europe melanoma is the fourth most common cancer in both men and women, while in the USA, it ranks as the fifth most common cancer in men (40,035 cases in 2012) and sixth in women (28,990 cases in 2012) (Ferlay et al. 2013a).

Worldwide Incidence and Mortality Patterns

Global Distribution

The burden of cutaneous melanoma is highest in the predominantly white-skinned populations of Europe and North America and is lowest in Africa (Fig. 1) (Ferlay et al. 2013a). The highest incidence rates occur in populations of white European ancestry residing in geographic areas with high UV exposure (typically at low latitudes). The age-standardized rate (ASR) [world standard (Segi 1960)] is 35.1/100,000 for Australia/New Zealand compared with 13.8/100,000 for North America, 14.6/100,000 for Northern Europe, 12.1/100,000 for Western Europe, 8.1/100,000 for Southern Europe, 1.6/100,000 for South America, 1.1/100,000 for Africa, and 0.5/100,000 for Asia (Ferlay et al. 2013a). Rates are generally higher in men compared with women and in older compared with younger age groups.

Highest Rates

The countries with the highest rates are New Zealand and Australia (Erdmann et al. 2013; Whiteman et al. 2016; Ferlay et al. 2013a) (Figs. 2 and 3). The estimated ASR in New Zealand in 2012 using the world standard population was 35.8/100,000 and 47.0/100,000 in 2011 using the US 2000 standard population [US 2000 (Anderson and Rosenberg 1998)] (Ferlay et al. 2013a; Whiteman et al. 2016). The corresponding rates in Australia were 34.9/100,000 and 49.2/100,000. The differences in incidence according

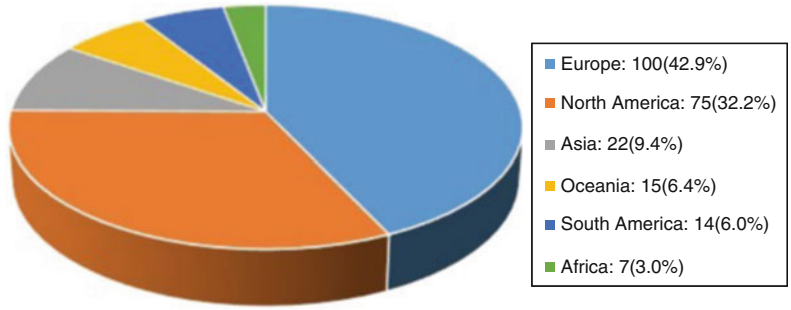

Fig. 1 Estimated number of cases of melanoma (×1000) across the world, by continent. (Source: Globocan 2012 (IARC))

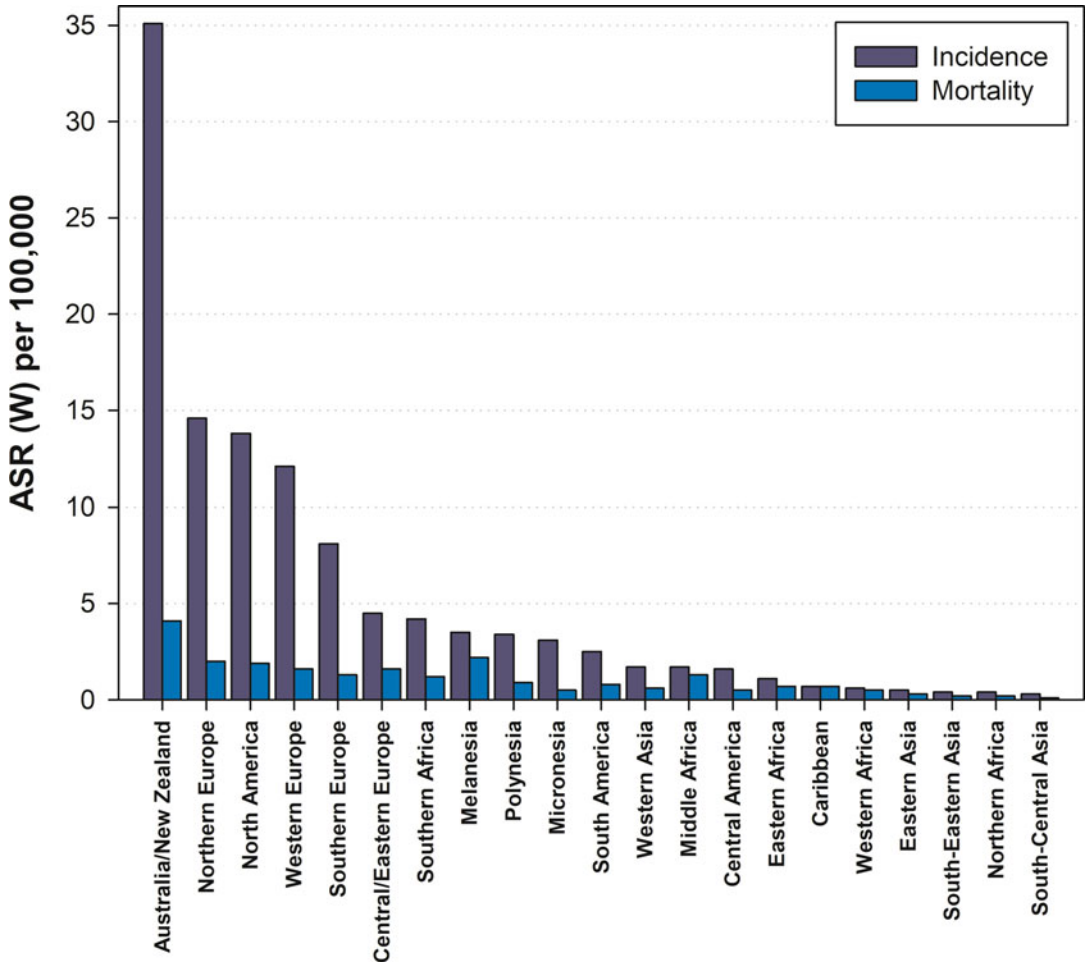

Fig. 2 Estimated incidence and mortality from invasive melanoma in regions of the world. (Source: Globocan 2012 (IARC))

to standard populations arise because the "world standard population" gives greater weight to young age groups and less weight to older age groups than the "US 2000 standard population"; for regions with greater proportions of the population in older age groups (such as Australia, Europe, and North America), the incidence rate standardized to the world standard population is always lower than the rate standardized to the US population.

In Europe, rates are highest in the northern populations of Switzerland, Denmark, Norway, and Sweden (Fig. 3) and are lowest in Eastern and Central Europe (Ferlay et al. 2013b). While this trend in Europe of decreasing incidence with decreasing latitude (and ambient UV levels) is the inverse of what is expected for a cancer caused by UV exposure, the disparate trend reflects differences in both skin phototypes and behavior in relation to sun exposure across populations.

Temporal Trends in Incidence

The incidence of cutaneous melanoma has steadily increased worldwide since the 1960s (Erdmann et al. 2013). In recent years, rates have continued to rise in most European countries, whereas in Australia, New Zealand, North America, Israel, and Norway, rates appear to be

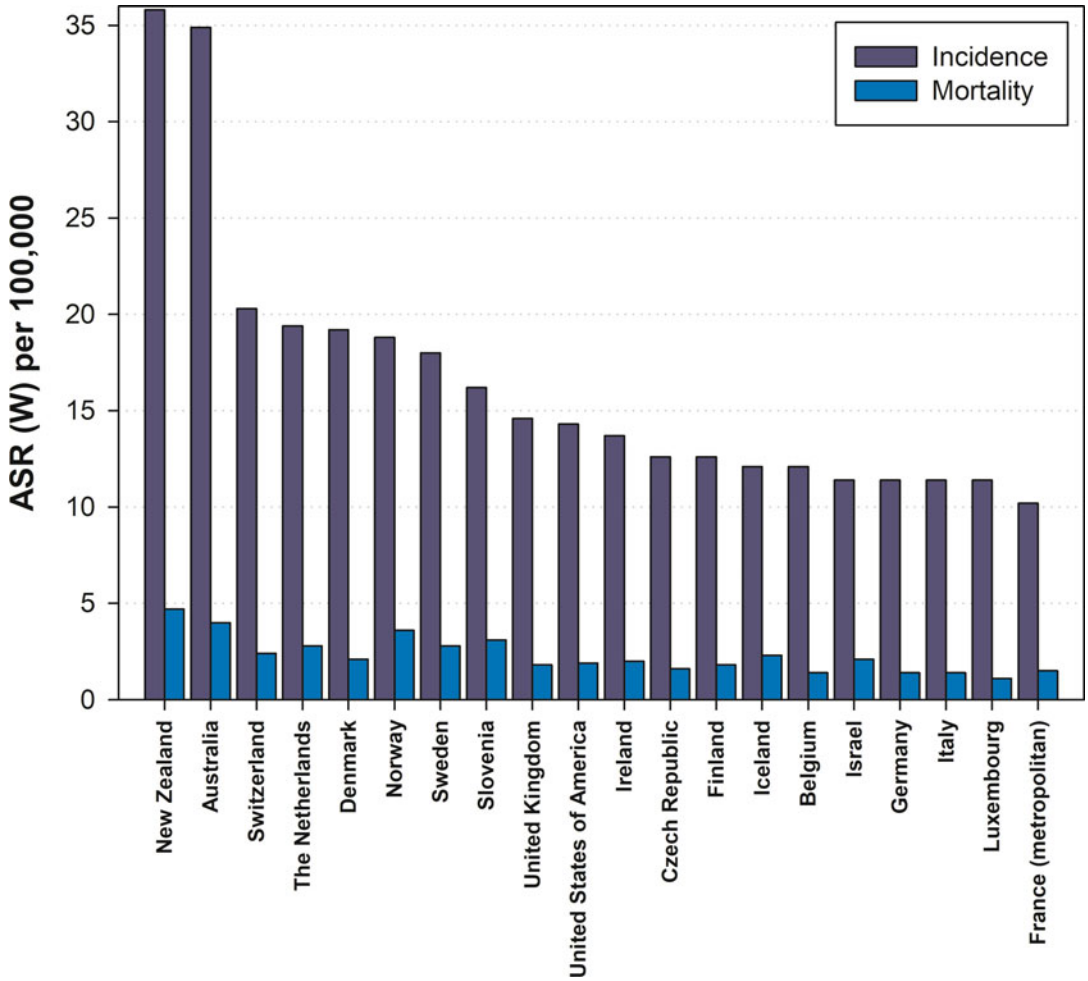

Fig. 3 Estimated incidence and mortality from invasive melanoma in the 20 countries with highest incidence worldwide. (Source: Globocan 2012 (IARC))

stabilizing in adults under 50 years (Erdmann et al. 2012). A comparison of melanoma incidence to 2011 and projected incidence to 2031 for six countries showed significant annual increases in incidence of more than 3% between 1982 and 2011 in the UK, Norway, Sweden, and US whites (Whiteman et al. 2016). Incidence was projected to continue increasing in these populations up to at least 2022. A second study of the US white population also predicted significant increases in incidence to 2019 (Guy et al. 2015). In Australia, incidence stabilized in 2005 and is projected to decline, while in New Zealand, rates have continued to rise but are projected to decline soon (Whiteman et al. 2016).

Erdmann et al. (2013) examined incidence rates for successive birth cohorts in eight countries (US whites, Canada, Norway, Denmark, the Czech Republic, England, Australia, and New Zealand) and reported a strong cohort effect with uniform increases in cohorts born up to the late 1940s followed by a stabilization or decline in more recent birth cohorts in Australia, New Zealand, US whites, Canada, and Norway only.

An examination of data from 18 European cancer registries over the period 1995–2012 suggested that the increase in incidence of invasive melanoma was driven largely by thin melanomas; the incidence of thick melanomas also increased, but more slowly (Sacchetto et al.

2018). The incidence of in situ melanomas increased over the time period at a rate almost double that of invasive melanoma, and this phenomenon has been reported in other regions including the USA (Criscione and Weinstock 2010) and Australia (Aitken et al. 2018). Some argue that the trend of increasing incidence of in situ and thin invasive melanoma reflects the overdiagnosis of indolent lesions, with increased detection of early-stage disease without decreasing mortality (Weinstock et al. 2017; Welch and Black 2010).

Mortality

Estimated mortality rates for melanoma vary internationally and are highest in Australia and New Zealand (ASR (W) 6.9/100,000) (Ferlay et al. 2013a). In Europe, mortality rates are highest in Northern Europe (2.5/100,000), slightly lower in Central and Eastern Europe (2.0/100,000), and lowest in Southern Europe (1.6/100/000). Mortality rates in North America are comparable to those of Northern Europe (2.6/100,000). Of the Northern European populations, mortality rates are highest in Norway (4.7/100,000) and Sweden (3.5/100,000). Worldwide, melanoma mortality rates are generally lower in women than in men and in younger compared with older age groups.

In the Nordic countries, mortality rates have increased steadily over a 40-year period between 1964 and 2003, but not to the same extent as incidence rates (Tryggvadottir et al. 2010). In the detailed analysis of mortality trends for six countries (UK, US whites, Norway, Sweden, Australia, and New Zealand), Whiteman et al. (2016) reported rising mortality rates in all six countries between 1982 and 2011, again less marked than incidence and with different rates of increase across countries. In the most recent decade, the rate of increase has been highest in Sweden [annual percentage change (APC) 1.8%], Norway (APC 1.5%), and the UK (APC 1.6). The rate of increase in Australia and New Zealand was 1.4% and 1.0%, respectively, and has been much lower in US whites (APC 0.20%). The higher mortality rate in Norway in comparison with other European countries may be due to more advanced stage of disease, on average, at diagnosis (Robsahm et al. 2018).

Melanoma Risk Factors

Demographic

Age

In susceptible populations, melanoma is one of the commonest cancers in young people. Incidence increases steadily with increasing age, and the highest rates are seen in people over the age of 74 years (Fig. 4).

Sex and Age by Sex

In most countries where melanoma is common, overall incidence is generally higher in men than women; however, up until middle age, rates in men and women are similar, or even slightly higher in women, but diverge thereafter with the male excess most notable in high-incidence populations (e.g., Australia, New Zealand) (Fig. 5). The body site distribution of melanoma also differs between men and women, with melanoma more likely to arise on the trunk in men and on the limbs in women, particularly the legs (Cho and Rosner 2005).

Socioeconomic Status

High socioeconomic status (SES) has been consistently associated with increased risk of melanoma, whereas low SES is associated with increased mortality from melanoma (Idorn and Wulf 2014; Jiang et al. 2015; McNally et al. 2014).

Ethnicity

Consistent with the global pattern of melanoma burden, incidence is highest in people with predominantly white European ancestry and is lowest in Asian and African populations (Ferlay et al. 2013a). These population differences can be attributed to the degree of skin pigmentation related to ethnic background. Variation in skin pigmentation in indigenous populations across

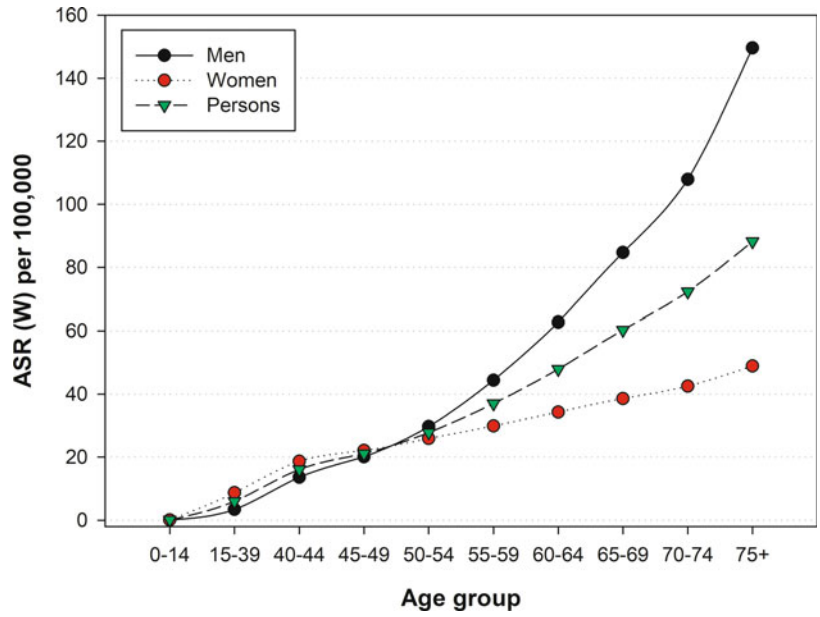

Fig. 4 Age-specific invasive melanoma rates for men, women, and persons in the USA. (Source: Globocan 2012 (IARC))

the globe correlates strongly with levels of ambient UVR exposure (Chaplin 2004); however, large-scale global migrations during the past several centuries have led to marked changes in the composition of populations. Thus, migrants (and their descendants) from high-latitude, low ambient UV environments to low-latitude, high ambient UV environments (e.g., from Europe to Australia or the Americas) developed melanomas at much higher incidence than those from the same populations who remained in their ancestral homelands. The USA has an especially diverse racial mixture dispersed across a wide range of latitudes. The highest rates of melanoma are observed in non-Hispanic whites, followed by Hispanic whites, Asians, Pacific Islanders, and Blacks; the exception is melanoma of the acral lentiginous melanoma subtype, for which the incidence rates are similar across races (Wang et al. 2016). Globally, acral melanoma is the predominant subtype in non-Caucasians (Chang 2013); however, its incidence is similar among races (Liu et al. 2015).

Constitutional

Many of the constitutional phenotypes associated with melanoma are genetically determined; this information relating specifically to genetics is reviewed in the molecular/genetic epidemiology chapter.

Phenotypic

The phenotypic characteristics most strongly associated with melanoma are melanocytic nevi (both common and atypical) and several factors relating to pigmentation. A nevus is a benign localized overgrowth of melanin-forming cells of the skin. Studies comparing nevus counts among identical and nonidentical twins suggested that the propensity for nevi is strongly determined by genetics (Bataille et al. 2000; Zhu et al. 1999). Most melanocytic nevi are acquired during childhood, and sun exposure, particularly in early childhood, promotes nevus development (Kelly et al. 1994). Thus, a person's nevus phenotype is determined by both their genetic constitution and their history of sun exposure.

The presence of large numbers of common acquired melanocytic nevi confers the highest risk of melanoma (Gandini et al. 2005a), with meta-analyses indicating a significant increase in risk of melanoma as nevus counts increase (RR for an increase in nevus count by one 1.02; 95% CI 1.01–1.02); the RRs for 10, 50, and 120 nevi compared with having no common nevi are 1.2,

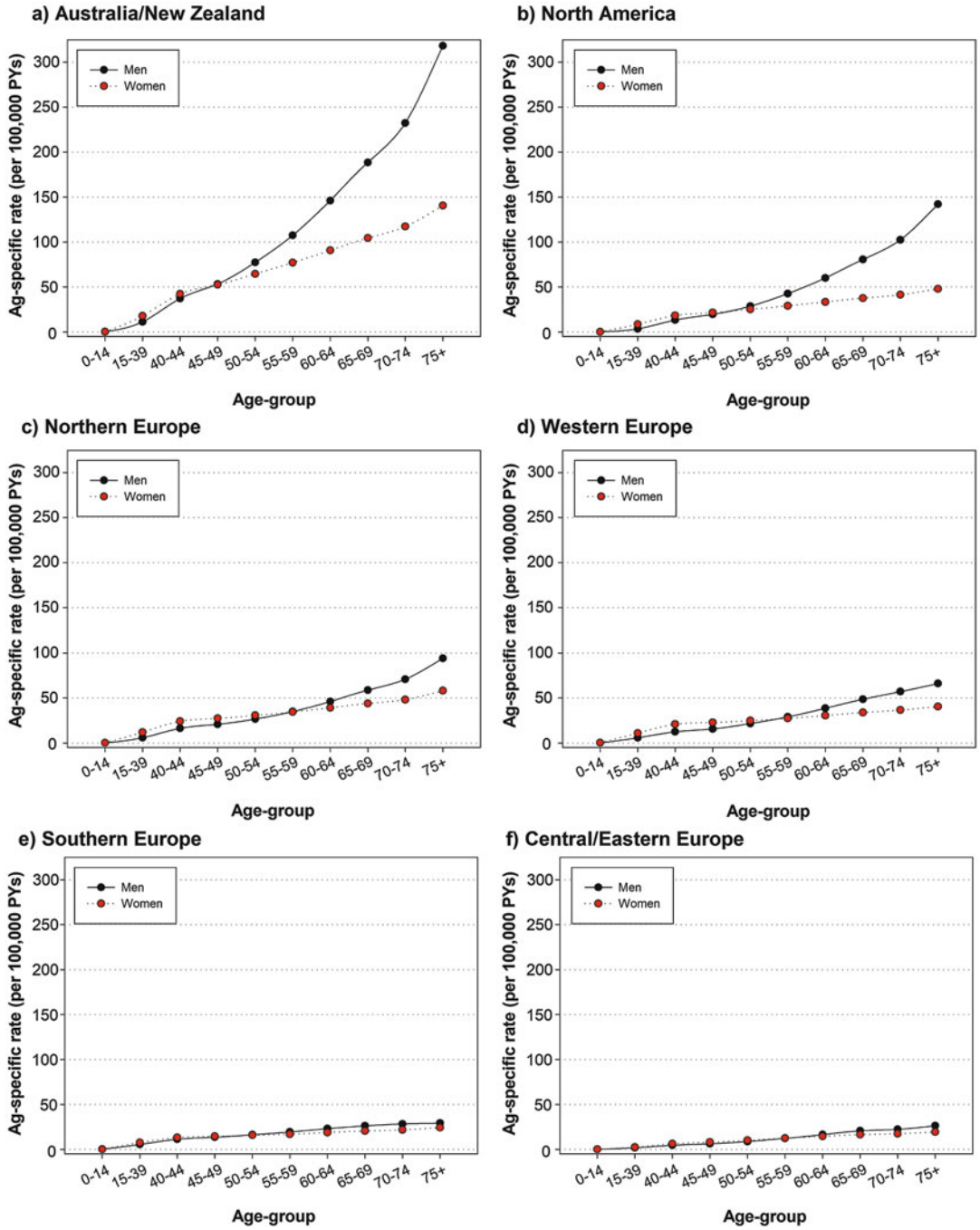

Fig. 5 Age-specific invasive melanoma rates for men and women in six different regions. (Source: Globocan 2012 (IARC))

2.3, and 7.6, respectively (Gandini et al. 2005a; Olsen et al. 2010a). The association between nevus density and melanoma risk varies according to body site, with high nevus counts more strongly associated with melanoma occurring on the trunk and limbs compared with the head and neck (Olsen et al. 2009). Atypical nevi, which are larger than common nevi and more variable in color/

surface/border, have repeatedly been shown to be an independent risk factor for melanoma (Bauer and Garbe 2003). Summary estimates from large meta-analyses have reported an almost fourfold increased risk of melanoma for people with at least one compared with no atypical nevi (Olsen et al. 2010a) and risk increases with increasing number (Gandini et al. 2005a). People with familial atypical multiple-mole syndrome (FAMM syndrome), characterized by the presence of multiple nevi, have a very high risk of developing melanoma (Marghoob et al. 1994). Similarly, people with congenital melanocytic nevi, a proliferation of benign melanocytes that are present at birth or develop shortly after birth (Viana et al. 2013), have an increased risk that varies according to the severity of the congenital phenotype, with lifetime risk ranging from 1% to 15% (Kinsler et al. 2017). A systematic review of melanomas occurring in congenital melanocytic nevi showed that 73% occur in patients with large congenital nevi (Krengel et al. 2006). Both FAMMS and congenital melanocytic nevi are rare.

Melanoma incidence is 10–20 times higher in white-skinned populations compared with darker-skinned populations (Hu et al. 2009) who mostly develop melanomas on non-sun-exposed sites (i.e., palmar and acral sites) (Cress and Holly 1997). Among people of European descent, higher rates of melanoma occur among those who have fair skin color compared with those with darker complexions. In a meta-analysis of 66 studies, the strongest pigmentary risk factors were fair hair color (red/blond) and skin phototypes I and II, that is, skin types that are susceptible to sunburn, compared to those that rarely burned/tanned with ease (Olsen et al. 2010b). The presence of freckling, which reflects both susceptibility to and extent of sun exposure (Sturm 2009; Tucker 2009), was associated with a twofold increased risk compared with absence of freckling (Olsen et al. 2010b). Light eye color (blue/blue-gray and green/hazel) was also associated with a modest increased risk, although the magnitude was less than for other pigmentary characteristics (Olsen et al. 2010b). In an earlier meta-analysis of 30 studies, a twofold increased risk of melanoma was associated with "light" versus "dark" skin color (Gandini et al. 2005c). Measures of pigmentation are highly correlated, however, and their independent effects have rarely been quantified. Recently published data from a large prospective study with risk factor information collected at baseline reported that of all phenotypic factors, those most strongly correlated were nevus density, tanning ability, and red hair color (Olsen et al., 2018).

The pigmentary characteristics responsible for the greatest burden of melanoma globally, taking into account both the prevalence of the phenotypic characteristics in the population and the magnitude of the risk associated with the phenotype, are skin phototype I/II (population attributable fraction [PAF] 0.27), presence of freckling (PAF 0.23), and blond hair color (PAF 0.23), followed by blue/blue-gray eye color (PAF 0.18), green/hazel eye color (PAF 0.13), and red hair color (PAF 0.10) (Olsen et al. 2010b).

Anthropometric Measures

Greater attained adult height has been consistently shown to be positively associated with melanoma (Dennis et al. 2008; Gallus et al. 2006; Kabat et al. 2014; Kvaskoff et al. 2014; Lahmann et al. 2015; Olsen et al. 2008; Shors et al. 2001; Wiren et al. 2014). Birthweight and height in childhood (7 years, 13 years) have also been positively associated with melanoma (Meyle et al. 2017). A genetic study which estimated predicted height based on genotype score reported a significant association between greater attained adult height and melanoma [OR per 1SD increase in height (1SD = 9.27 cm) 1.06 (95% CI 1.02–1.12)] (personal communication Dusingize et al. 2018). The use of genetic predictors of height rather than height itself has advantages over observational studies reporting on the association, since genetic variants are determined at birth and are therefore generally not associated with other factors, for example, environmental factors such as diet/nutrition, that could confound the association between height and melanoma.

Two meta-analyses have reported that overweight and obesity are associated with a 30% increased risk of melanoma among men but not women (Renehan et al. 2008; Sergentanis et al. 2013), although there was marked variation in the magnitude of effect across the included studies. High body mass index (BMI) has also been associated with greater Breslow thickness at diagnosis (de Giorgi et al. 2013; Stenehjem et al. 2018). A more recent meta-analysis which included over 17,000 melanoma cases reported a null association for both sexes, and a genetic study which estimated predicted BMI based on genotype score similarly reported a null effect; OR for risk of melanoma per 1 SD increase in genetically predicted BMI (1 SD = 4.6 kg/m^2) 1.00 (95% CI 0.91–1.11) (personal communication Dusingize et al. 2018).

Environmental

Ambient UVR and Exposure to Sun

Ultraviolet radiation (UVR) in sunlight is the principal environmental cause of melanoma (IARC 2012), estimated to account for between 63% and 90% of melanoma cases (Armstrong and Kricker 1993; Olsen et al. 2015c). Evidence for the association is derived from numerous sources and study designs including ecological, migrant, observational, and molecular studies. In predominantly white-skinned populations, there is a strong latitudinal gradient such that melanoma incidence rates increase with proximity to the equator. Migrant studies indicate an increased risk of melanoma in people who spent their childhood in regions with high ambient UVR. Interestingly, people who migrate from regions of low ambient UVR to regions with high ambient UVR at older ages had lower risks than those who migrate at younger ages, suggesting that sun exposure in early life is particularly important (Holman and Armstrong 1984; Whiteman et al. 2001). Genomic sequencing studies which have identified extremely high burdens of "UV signature" mutations (C to T and CC to TT transitions) in the majority of cutaneous melanomas (Shain et al. 2015), including driver mutations in key genes, provide further strong support that UVR is the principal mechanism of carcinogenesis in melanoma.

The relationship between UVR and melanoma is complex, however, and exposure effects are highly modified by host factors (see Constitutional section above) and behaviors. For example, higher melanoma rates among indoor than outdoor workers (Elwood and Jopson 1997) may be explained, at least in part, by self-selection bias whereby people with sun-sensitive skin are less likely to choose an outdoor occupation (Green et al. 1996; Green and Williams 2007). Moreover, individual exposure to UVR is difficult to measure, and the various sun exposure measures used in observational studies have low reproducibility (English et al. 1998), which may lead to misclassification bias. All of these factors should be considered in interpreting the observational data. In aggregate, case-control and cohort studies, as reported by a large meta-analysis (57 studies), show significant associations between measures of an intermittent pattern of sun exposure (e.g., recreational exposure such as sunbathing, vacations to sunny locations) and with a history of sunburns, but inverse associations with high occupational exposure and a high continuous pattern of sun exposure (Gandini et al. 2005b). There is evidence to suggest that sun exposure in childhood is a strong determinant of melanoma risk (Whiteman et al. 2001).

Two decades ago, a "divergent pathway" model was proposed to explain the epidemiologic associations of melanoma with both chronic and intermittent patterns of sun exposure (Whiteman et al. 1998, 2006, 2003). This model posited that people who have an inherently high propensity for nevus development requires sun exposure to initiate carcinogenesis, after which host factors drive the development of melanoma. The model predicted that such people develop cutaneous melanomas on relatively sun-protected anatomic sites. In contrast, the model hypothesized that people with a low propensity to develop nevi tend to develop melanomas associated with cumulative sun exposure and arising on sun-exposed body sites such as the head and neck.

In support of this hypothesis, multiple studies have shown that the relationship between exposure to UVR and melanoma varies by anatomic site of melanoma, with stronger associations seen for the more exposed body sites. People with melanoma of the trunk are more likely to have many nevi than people with melanoma occurring on the head and neck (Kvaskoff et al. 2013; Whiteman et al. 2003), while people with head and neck melanoma are more likely to have many solar keratoses and to report high levels of sun exposure in adulthood (Olsen et al. 2011, 2009; Whiteman et al. 2006). Melanomas on the trunk are more likely to arise from a preexisting nevus (Carli et al. 1999; Hacker et al. 2010; Pandeya et al. 2018; Skender-Kalnenas et al. 1995).

More recently, studies investigating the prevalence of driver mutations in *BRAF* have shown differences in the prevalence of somatic mutations in melanomas arising on sun-exposed and non-exposed skin that are also consistent with melanomas arising through different causal pathways. *BRAF* mutations are more likely to occur on non-sun-exposed body sites (Curtin et al. 2005; Hacker et al. 2013; Liu et al. 2007; Maldonado et al. 2003) in people with high nevus counts (Hacker et al. 2010) and are less likely to be associated with solar keratoses (Garcia-Casado et al. 2015; Lee et al. 2011) or high cumulative sun exposure (Hacker et al. 2010), while *NRAS* mutations occur more frequently in melanomas arising in chronic sun-damaged skin (Lee et al. 2011).

There is also emerging evidence of heterogeneity with respect to the causal role of sunlight among the different classes of *BRAF*-mutant melanoma. Whereas $BRAF^{V600K}$ mutant melanomas are associated with higher levels of sun exposure (Jewell et al. 2012) and occur more commonly in older persons and on the head and neck (Menzies et al. 2012), $BRAF^{V600E}$ mutant melanomas occur more commonly in people under the age of 50 years with higher nevus counts and are more common in melanomas arising on intermittently sun-exposed body sites (i.e., the trunk) (Liu et al. 2007; Viros et al. 2008). The interaction between genotype/phenotype and melanoma development will become delineated more clearly when ongoing sequencing efforts are mature, permitting the combined analysis of thousands of tumor samples.

UVR has little, if any, role in the development of acral melanomas, the predominant subtype in non-Caucasians. Acral melanomas occur on the non-sun-exposed palmar and plantar body sites and have an absence or low frequency of UV-induced genetic mutations (Beadling et al. 2008; Krauthammer et al. 2012) and a higher incidence of *KIT* mutations (Curtin et al. 2005; Handolias et al. 2010), similar to mucosal melanomas (Bello et al. 2013). Whole genome sequencing of acral and mucosal melanomas has revealed a much lower mutation burden compared with cutaneous melanoma and one that is dominated by large-scale structural variants rather than UV signature mutations (Hayward et al. 2017). Among acral melanomas, variation in clinical, histologic, and molecular features has been reported according to the degree of sun exposure (i.e., dorsal vs. volar and subungual/interdigital) (Haugh et al. 2018).

Other Environmental Exposures

Ionizing Radiation

Numerous studies have investigated the incidence of melanoma in people highly exposed to ionizing radiation, including atomic bomb survivors (Sugiyama et al. 2014) and nuclear workers (Cardis et al. 2007; Muirhead et al. 2009), and have found no evidence of increased risk. Survivors of childhood cancer have an elevated risk of melanoma compared with the general population (SIR 2.42, 95% CI 1.77–3.23), and this increased risk is presumed to be due to radiation treatment for the first cancer (Guerin et al. 2003), although the role of radiotherapy in melanomagenesis remains controversial (Fink and Bates 2005). An increased risk of melanoma has been reported in pilots/flight crews who are exposed to cosmic radiation (Sanlorenzo et al. 2015), even though average annual exposure as measured by dosimetry is below levels considered "hazardous" (Grajewski et al. 2011). It has been speculated that the increased risks of melanoma observed in this occupational group may be due to higher levels of recreational sun exposure rather than cosmic radiation (Shantha et al. 2015).

Artificial Sources of UVR

Tanning beds are the predominant source of artificial UV radiation, especially among young women residing in mid- to high-latitude regions of the world (IARC 2007). A meta-analysis conducted by the International Agency for Research on Cancer (IARC) Working Group on Artificial Ultraviolet Light and Skin Cancer reviewed data from 19 studies and reported a modest increase in the risk of melanoma (summary RR 1.15; 95% CI 1.00–1.31) for "ever" compared with "never" exposure to indoor tanning equipment and a higher risk if first exposure occurred before age 35 years (summary RR 1.75, 95% CI 1.35–2.26) (IARC 2007). The IARC concluded that there was sufficient evidence that UV-emitting tanning devices cause melanoma (El Ghissassi et al. 2009). A more recently published meta-analysis of 32 studies confirmed that use of indoor tanning facilities is associated with the development of melanoma (Boniol et al. 2012). A significantly raised risk was observed for ever use (summary RR 1.20, 95% CI 1.08–1.34) and for first exposure before age 35 years (summary RR 1.87, 95% CI 1.41–2.48), and the association remained significant when the analysis was restricted to studies that had adjusted for confounders related to sun exposure and sun sensitivity. A significant 42% increased risk was found among those who were classified as "high users" (defined by duration of use), and risk increased with number of sunbed sessions at a rate of 1.8% (95% CI 0–3.8%) for each additional session of sunbed use per year.

Sunbed use during adolescence and early adulthood was associated with a significantly increased risk of early-onset melanoma (i.e., melanoma diagnosed when aged 18–29 years; OR for more than 10 lifetime sessions 6.6, 95% CI 1.4–30.5) in an Australian case-control study (Cust et al. 2011). Among sunbed users with a diagnosis of melanoma between the ages of 18 and 29 years, 76% of melanomas were attributable to sunbed use. A large Norwegian prospective study in women similarly reported a significant dose-response relationship with number of sessions of sunbed use, and among cases, women who first used sunbeds when aged under 30 years were on average 2.2 years younger at diagnosis than never users (Ghiasvand et al. 2016).

Finally, an ecological study conducted in Iceland reported a marked increase in the incidence of melanoma in women aged under 50 years following the widespread introduction of sunbeds in the early 1990s, followed by a decline once public health interventions to decrease sunbed use were implemented (Hery et al. 2010). Although inferences about causality cannot be made from ecological studies, the observed trends strongly suggest that the widespread availability and use of sunbeds in that population contributed to the spike in melanoma incidence.

Less common sources of artificial UV radiation exist in medicine and industry, including psoralen and UVA radiation (PUVA) treatment for psoriasis, vitiligo, and other skin conditions. Long-term exposure to PUVA is associated with an increased risk of melanoma (Stern 2001).

Occupational

A recent systematic review and a European multicenter case-control study have reported increased risks of melanoma among employees in specific occupational groups including in the agricultural, airline, electrical, nuclear, oil, pulp, tannery, and teaching industries (Jiang et al. 2015; Pukkala et al. 2014; Suarez et al. 2007). These increased risks have not been clearly related to specific exposures with the possible exception of arsenic, polychlorinated biphenyls (PCBs) (IARC 2015), and polyvinyl chloride (PVC) (Langard et al. 2000). The systematic review also synthesized the evidence for an association between occupational UV exposure and melanoma incidence; five studies reported a significant association with outdoor occupational UVR and two with indoor occupation (Jiang et al. 2015).

Numerous epidemiological studies have reported on associations between type of work (indoor vs. outdoor) and risk of melanoma. Overall, these studies have tended to report that indoor workers have higher risks of melanoma than outdoor workers. When analyzed according to the anatomical location of the melanoma however, outdoor workers have higher risks of melanoma

on the face, ears, and neck, but lower risks of melanoma on the trunk. A correlational study of melanoma notifications in England and Wales reported that outdoor workers had an excess of melanomas of the face, head, and neck (+9%) and a significant deficit of melanomas (−22%) at other body sites when compared with the general population (Beral and Robinson 1981). In contrast, office workers were found to have a significant excess of melanomas (+31%) at sites other than the face, head, and neck. A comparable study conducted in Sweden reported similar findings (Vagero et al. 1990); outdoor workers had an elevated risk of melanoma at uncovered body sites (such as the face) (+7%) and a lower risk (−19%) of developing melanomas on covered body sites (such as the trunk), whereas office workers had a significantly increased risk of melanoma at covered sites (+34%). Another record linkage study compared the rates of melanoma among Swedish men in various industries over a 19-year period, reporting no elevated risk of melanoma overall among farmers, but an excess of melanomas on the scalp, face, and neck in this group (Linet et al. 1995). Among a cohort of Swedish construction workers (1971–1993), the incidence of melanoma occurring on the head, face, and neck among workers with the highest reported levels of occupational sun exposure was twice that of those with the lowest levels of occupational sun exposure (Hakansson et al. 2001).

The observation of higher incidence of melanoma in indoor workers on usually covered body sites is most likely explained by higher levels of recreational sun exposure observed among indoor workers compared with outdoor workers (Nelemans et al. 1993). Similarly, an increased risk of melanoma reported for airline pilots and cabin crew (Sanlorenzo et al. 2015) most likely reflects behavior in relation to recreational sun exposure rather than cosmic radiation exposure (dos Santos Silva et al. 2013).

Reproductive Factors and Exogenous Hormone Use

Men and women have different age-specific patterns of melanoma incidence, and women diagnosed with melanoma have a survival advantage over men (Joosse et al. 2011). These observations led to the hypothesis that sex steroids may be important in the development of melanoma; however, there is a lack of supportive epidemiological evidence. A meta-analysis reported that higher parity was associated inversely with melanoma while late age at first pregnancy significantly increased risk (Gandini et al. 2011), although the authors concluded that confounding by socioeconomic factors may explain the observed associations. They found no association between age at menarche, age at menopause, or menopausal status and melanoma (Gandini et al. 2011). A later meta-analysis confirmed an association between older age at first birth and melanoma risk, but only among case-control and not cohort studies (Li et al. 2014). The meta-analysis by Gandini and colleagues found no evidence that use of oral contraceptives or menopausal hormone therapy increased risk (Gandini et al. 2011).

Data from two large population-based cohort studies suggest that women treated with assisted reproductive technology (ART) do not have a significantly elevated risk of melanoma compared with the general population (Luke et al. 2015) or, among parous women, compared with women never treated with ART (Reigstad et al. 2015). Among women treated with ART, a subset of women with a diagnosis of a uterine abnormality were at increased risk (HR 2.86, 95% CI 1.15–7.22).

In summary, there is no evidence that exogenous hormone use is associated with melanoma.

Health History

Parkinson's disease has been associated with an increased risk of melanoma (Bajaj et al. 2010; Huang et al. 2015; Liu et al. 2011). Compared with the general population, melanoma incidence rates are 1.5–3.5 times higher than expected in Parkinson's disease patients (Inzelberg et al. 2016). A bidirectional relationship has been observed (Dalvin et al. 2017; Liu et al. 2011), suggesting the presence of shared genetic risk factors (Inzelberg et al. 2016). A meta-analysis of 12 studies reported a pooled OR for melanoma after a diagnosis of Parkinson's disease of 3.6 (95% CI 1.49–8.77) and for Parkinson's disease

after melanoma of 2.11 (95% CI 1.26–3.54). A large study conducted in the USA confirmed these findings; patients with Parkinson's disease had a 3.8-fold increased likelihood of having pre-existing melanoma as compared with controls (95% CI 2.1–6.8), while patients with melanoma had a 4.2-fold increased risk of developing Parkinson's disease (95% CI 2.0–8.8) (Dalvin et al. 2017).

An increased risk of melanoma in patients with Type II diabetes has been reported, with a meta-analysis of nine cohort studies reporting a pooled RR of 1.15 (95% CI 1.00–1.32) (Qi et al. 2014). There was evidence of significant heterogeneity across studies, however, and the finding was not confirmed in a large population-based cohort study conducted in Taiwan (Tseng et al. 2016).

Several studies have reported that use of phosphodiesterase inhibitors, which suppress phosphodiesterase enzyme 5A (Gray-Schopfer et al. 2007), is associated with a modest increased risk of melanoma; however, despite biological plausibility, a recent evaluation of the evidence suggests that the relationship is unlikely to be causal (Loeb et al. 2017).

Diet

Although laboratory-based experimental studies have indicated a possible role for dietary factors including antioxidants and polyunsaturated omega-3 fatty acids (PUFAs) in melanoma etiology, the findings from observational studies have been inconsistent, and data from RCTs are limited. Systematic reviews of observational and interventional studies have reported no clear relationship between diets high in antioxidants (retinol; vitamins A, C, and E; carotenoids; and selenium) (Miura and Green 2015), vitamin D (Gandini et al. 2009; Tang et al. 2011), and omega-3 PUFAs (Noel et al. 2013; Veierod et al. 1997) or fish, vegetable, or fruit consumption and melanoma (de Waure et al. 2015). There is limited evidence for an association with other dietary components including selenium, grape-seed proanthocyanidins, epigallocatechin-3-gallate, and resveratrol (Tong and Young 2014). A modestly increased risk of melanoma associated with citrus consumption was observed in two large cohort studies of health professionals (Wu et al. 2015); however, a causal relationship has not been established (Berwick 2015).

Smoking

There is evidence from observational epidemiologic studies that melanoma is inversely associated with tobacco smoking. A meta-analysis of 23 studies reported a significant 30% reduced risk of melanoma among current smokers and a 10% reduced risk among former smokers (Li et al. 2015), and the pooled findings from cohort and case-control studies were similar. Five large prospective studies have examined the association (DeLancey et al. 2011; Dusingize et al. 2018; Freedman et al. 2003; Song et al. 2012). Three of these studies have reported a significant inverse dose-response relationship: one overall across men and women (Freedman et al. 2003), one for men only (Song et al. 2012), and one for former but not current smokers and for number of cigarettes smoked but not duration of smoking (Dusingize et al. 2018). The mixed evidence regarding the dose-response relationship argues against a causal association, which may be due to residual confounding and/or surveillance bias (Dusingize et al. 2018).

Alcohol

A systematic review and meta-analysis of 30 studies examining the association between alcohol consumption and melanoma reported a modest positive association (summary RR for highest vs. lowest intake 1.29, 95% CI 1.14–1.45) with a significant dose-response relationship (summary RR for a 10 g increment in daily intake 1.07, 95% CI 1.03–1.11) (Gandini et al. 2018). Of the included studies, only 11 had adjusted for a measure of phenotype and 9 for a measure of sun exposure. Subgroup analyses relating to beverage type (wine, beer, liquor) all reported nonsignificant associations. An earlier meta-analysis of 16 studies similarly reported a modest association between alcohol consumption and melanoma that was similar for case-control and cohort studies (Rota et al. 2014). Among the subset of studies that had adjusted for a measure of sun exposure, however, the association was null. Overall, the

evidence relating to alcohol and melanoma is inconsistent and the reported associations are weak.

Trauma

There is no strong evidence that acute trauma is a risk factor for cutaneous melanoma (Wallingford et al. 2011). Two large population-based cohort studies reported no association between thermal or chemical burns and melanoma after a mean follow-up time of 16 years (Lindelof et al. 2008; Mellemkjaer et al. 2006).

There is some evidence that trauma may be associated with melanomas occurring on palmar and plantar sites. A case-control study conducted in Paraguay reported a significant association between injury and plantar melanoma (Rolon et al. 1997), and a second case-control study conducted in Australia and Scotland reported a significant association between penetrative trauma and acral melanoma (Green et al. 1999).

Immunosuppression

Melanoma is an immunogenic cancer (Kubica and Brewer 2012), likely due to high loads of somatic mutations, which in turn, results in the expression of more neoantigens than are present for other cancers (McArthur and Ribas 2013). It is speculated that immune surveillance recognizes neoantigens and tends to suppress early melanomas; if so, then suppression of the immune system would likely result in immune escape (Marconcini et al. 2018).

There is some empirical support for this hypothesis. Populations with compromised immunity are at increased risk of developing cutaneous melanoma, including organ transplant recipients (Green and Olsen 2015; Grulich et al. 2007) and those diagnosed with HIV/AIDS (Grulich et al. 2007; Olsen et al. 2014a), and certain lymphoproliferative disorders including non-Hodgkin's lymphoma and chronic lymphocytic leukemia (Brewer et al. 2014; Famenini et al. 2014; Morton et al. 2010; Olsen et al. 2015a; Pirani et al. 2011). Patients treated with biologic therapies for rheumatoid arthritis (Olsen and Green 2017; Olsen et al. 2016; Wolfe and Michaud 2007) and inflammatory bowel disease (McKenna et al. 2014; Singh et al. 2014) are also at increased risk.

In transplant recipients, the risk of melanoma is two to three-fold higher than the general population (Green and Olsen 2015), and higher risks are observed when the state of immunosuppression is greatest; that is, in the period immediately following transplantation (Bilmon et al. 2014; Vajdic et al. 2009). There is also evidence that the degree of immunosuppression is important for HIV/AIDS patients; a large cohort study reported a statistically significant trend of higher relative risks of melanoma with decreasing recent CD4 counts (Silverberg et al. 2011).

Screening

The aim of screening is to detect melanoma at an early stage, thereby reducing morbidity and mortality. Early detection efforts have focused on four strategies: skin self-examination (SSE) by individuals (or their partners), opportunistic screening by physicians (or "case-finding"), population-based screening, and screening of "high-risk" subgroups of the population (or "targeted screening"). The US Preventive Services Task Force (USPSTF) evaluated SSE in their 2009 statement, concluding that the evidence of potential benefit was insufficient to recommend SSE for the general population (Wolff et al. 2009); the USPSTF did not include a statement on SSE in their more recent recommendation (USPSTF 2016). The USPSTF also evaluated visual skin examination by a clinician to screen for skin cancer in asymptomatic adults and concluded that there was insufficient evidence and that the balance of benefit and harms cannot be determined.

There has been no randomized controlled trial to evaluate the effectiveness of skin examination for reducing melanoma morbidity or mortality, although a pilot study of population-based screening conducted in Queensland, Australia, commenced in 2002 (Aitken et al. 2002). Forty-four communities, each including at least 1000 adults aged 30 years or older, were randomized into intervention or control groups to compare the effects of a 3-year, community-based melanoma

screening intervention or usual medical care; skin checks were conducted by primary care physicians. Due to financial constraints, the full trial was not completed; however, some differences in outcome were noted between the intervention and control groups, including an increased overall rate of skin cancer detected in intervention communities, and melanomas detected by the screening intervention were on average thinner than those detected in the general population of Queensland.

The only country to initiate population-based screening for skin cancer is Germany. A 1-year pilot project (the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany, or SCREEN) was conducted in the northern state of Schleswig-Holstein and involved a population-based skin cancer awareness campaign, clinician training, and clinical visual skin examination (Breitbart et al. 2012; Katalinic et al. 2012). Almost 20% of the population undertook the free screening examinations, and in the five following years, an increase in melanoma incidence and a significant decrease in melanoma mortality were observed. Based on these findings, a biannual skin cancer screening program was introduced nationwide for all insured people aged over 34 years. The trend of reduced melanoma mortality in the Schleswig-Holstein region was not sustained with longer-term follow-up, however, and there was no appreciable decline in mortality in Germany 5 years after the initiation of the national screening program (Katalinic et al. 2015).

Most medical and public health organizations in North America, the UK, Australia, and New Zealand do not advocate skin screening for people of average risk, but do recommend surveillance for individuals who are at high risk (American Cancer Society 2016; Cancer Council Australia 2017; Lebwohl 2015; Australian Cancer Network Melanoma Guidelines Revision Working Party 2008; Cancer Research UK 2017). Targeted screening of those at very high risk for melanoma (i.e., family history and/or personal history and/or dysplastic nevus syndrome) has been shown to be both effective (Masri et al. 1990; Moloney et al. 2014) and cost-efficient (Watts et al. 2017). Since the majority of melanomas occur in people who do not have the abovementioned phenotypic traits, however (Weinstock 2000), various melanoma risk prediction algorithms have been developed to assist in the identification of people who might benefit from surveillance (Olsen et al. 2014b; Vuong et al. 2014) (see Sect. 5).

Current controversies in relation to the early detection of melanoma include the phenomenon of "overdiagnosis" of indolent lesions (Welch and Black 2010) and the role of whole-body photography (Rayner et al. 2018) and artificial intelligence (Esteva et al. 2017; Haenssle et al. 2018). Overdiagnosis refers to the detection of lesions that would not otherwise have been detected in a person's lifetime (Carter et al. 2015b; Welch and Black 2010). It differs from misdiagnosis, or the "incorrect diagnosis of symptomatic person with a condition they do not have" (Carter et al. 2015b), which can result from differences in interpretation by pathologists (Elmore et al. 2017). In the context of a screening program, overdiagnosis can result in unnecessary treatment and follow-up surveillance, with psychosocial consequences for the patient and financial considerations for health systems. These are threats to population-based screening efforts, as the benefits from screening should outweigh any potential harms (Wilson and Jungner 1968). Attempts have been made to quantify the degree of overdiagnosis of breast and prostate cancer (thought to be largely driven by screening and early detection programs) (Force et al. 2016; Gulati et al. 2013; Welch and Passow 2014; Zahl et al. 2013); these methods require data from well-conducted ecological or cohort studies (Carter et al. 2015a). A comprehensive review of screening for melanoma is provided in the chapter on screening.

Risk Prediction

Various statistical tools have been developed to quantify individual risk of melanoma, either current or future, and these were reviewed separately by Vuong et al. (2014) and Usher et al. (2014) in 2014. The primary aim of such tools is to aid

targeted surveillance, that is, to identify those individuals at highest risk who are most likely to benefit personally from screening.

The performance of risk prediction tools is evaluated using three criteria: (1) how well the model-predicted probabilities concord with the observed probabilities (calibration), (2) the ability of the model to distinguish subjects with different outcomes (discrimination), and (3) the ability of the model to improve the decision-making process (clinical usefulness). The key measure of discrimination is the area under the receiving operating characteristic curve (AUC; also called the c-index, or concordance index), which is a plot of the sensitivity versus 1-specificity (Freedman et al. 2005). The AUC is the chance that given two people, one who will develop the disease and the other who will not, the model will assign a higher probability of an event to the former. The AUC can range in value from 0 to 1, with a perfectly discriminating model having an AUC of 1; this would occur for a test whereby all risk scores generated for cases were higher than those generated for all non-cases, with no overlap. AUCs for risk prediction tools in cancer typically fall between 0.6 and 0.8 (Gail and Pfeiffer 2005; Pfeiffer et al. 2013).

The two reviews identified 28 melanoma prediction models published up to 2013, which, in aggregate, considered over 140 possible risk factors (Usher-Smith et al. 2014; Vuong et al. 2014). The factors most frequently included in final models were number of nevi, age, presence of freckles, history of sunburn, hair color, and skin color. Most of the tools were developed in case-control studies, which are prone to various inherent biases, and model discrimination, where reported, ranged from fair to very good (AUC, 0.62–0.86) (Vuong et al. 2014). Only a subset of the melanoma risk prediction tools have been validated in an external population (Fortes et al. 2010; Olsen et al. 2015b). An independent validation of six risk prediction models in an Australian population showed generally high discrimination but poor calibration, suggesting that models may need to be calibrated specifically for different target populations (Olsen et al. 2015b). There are currently no published data on the performance of the various melanoma risk prediction tools in clinical settings, including assessment of usefulness in clinical decision-making.

Two new risk models were published subsequent to the two reviews, both using Australian data, one developed in a case-control study (Vuong et al. 2016) and one in a prospective cohort study (Olsen et al. 2018). The model by Vuong and colleagues included five terms – hair color, nevus density, first-degree family history of melanoma, previous non-melanoma skin cancer, and lifetime sunbed use – and showed good discrimination (AUC 0.70) and calibration. The model by Olsen and colleagues included seven terms – age, sex, tanning ability, number of nevi at age 21, hair color, number of previous non-surgical treatments for actinic lesions, and sunscreen use – and showed high discrimination (AUC 0.79) and reasonable calibration. Both of these models incorporated self-assessed risk factor information and would be suitable for use in the general population. Both models showed good discrimination when validated using other data (AUC in the range 0.6–0.7).

Several studies have examined the contribution of genetic information (MC1R; polygenic risk score) to risk models incorporating traditional risk variables, reporting a modest improvement (0.7–3%) in the AUC when genetic data were included (Cho et al. 2018; Cust et al. 2014, 2018). Clearly, knowledge is expanding very rapidly in this area, and it is likely that prediction tools will improve in the years ahead (Table 1).

Summary and Conclusions

Melanoma is a common cancer in fair-skinned populations, and incidence rates have been rising around the world since the early 1960s. In some high-incidence populations, it appears incidence rates may have peaked and may soon decline. Risk factors include demographic, constitutional, environmental, and clinical factors. Screening for melanoma is not currently advocated in most

Table 1 Epidemiology of cutaneous melanoma: risk factor summary

Risk factor/exposure	Direction of association	Magnitude of effect[a]	Strength of evidence
Demographic			
Older age	↑	++	Strong
Male sex[b]	↑	++	Strong
Caucasian ancestry	↑	++	Strong
Constitutional			
High number of common nevi	↑	++	Strong
One or more atypical nevi	↑	++	Strong
Sun-sensitive skin (including inherited syndromes)	↑	++	Strong
Inability to tan	↑	++	Strong
Red or blond hair color	↑	++	Strong
Fair eye color	↑	++	Strong
Attained adult height	↑	+	Strong
Environmental			
Ultraviolet radiation exposure	↑	++	Strong
Immunosuppression	↑	+	Strong
Glucocorticoid use	↑	+	Strong
Chemical exposures (PCBs, PVC)	↑	+	Strong
Arsenic	↑	+	Strong
Ionizing radiation exposure	↑	+	Probable relationship, based on substantial data
Parkinson's disease	↑	+	Probable relationship, based on substantial data
Alcohol use	↑	+	Inconsistent findings; limited study to date
Dietary factors	–	NA	Weak, if any, relationship, based on substantial data
Cigarette smoking	↓	+	Probable relationship, based on substantial data
Women only:			
Older age at first birth	–	NA	Weak, if any, relationship, based on substantial data

PCB polychlorinated biphenyls; *PVC*, polyvinyl chloride
[a]+ indicates the approximate magnitude of the association: ++ moderate to large increase in risk, + slight to moderate increase in risk, NA no association.
[b]overall rates (note incidence in some regions is higher among women up to middle age)

countries, although different schemes have been discussed. In the future, risk prediction algorithms may be used to target screening and surveillance to high-risk subgroups of the population.

Cross-References

- ▶ Molecular Epidemiology of Melanoma
- ▶ Melanoma Prevention and Screening

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