

1.2.1 Introduction

Melanomas are common cancers arising from the pigment cells of the skin. While in situ and locally invasive melanomas are curable by surgery, advanced disease is difficult to treat and can be lethal, as reflected in the rising mortality rates for these cancers [1]. Population-based strategies to control the disease have largely focused on primary prevention and early detection. For such strategies to be implemented, it is imperative that the underlying epidemiology of melanoma is understood. Emerging evidence from diverse disciplines suggests that melanomas may arise through several different causal pathways; characterizing these pathways is crucially important to developing rational approaches for preventing and treating cutaneous melanoma. The aim of this chapter is to briefly describe the patterns of melanoma occurrence, before reviewing recent discoveries that have changed our understanding of the way in which melanoma arises.

1.2.2 Patterns of Melanoma Incidence and Mortality

1.2.2.1 Geographic Variation

Cutaneous melanoma is a cancer mostly afflicting fair-skinned Caucasian populations; however, the incidence of the disease varies enormously depending upon the geographic location of the population under study. Indeed, the variation in melanoma incidence across populations is among the greatest observed for any cancer [2], and this single fact remains the most

persuasive evidence regarding the role of the environment (notably, sunlight) in the causation of this cancer.

The “latitude gradient” for melanoma was first reported by Lancaster [3, 4], and has been a consistently observed feature of melanoma since reliable cancer registrations commenced around the world. Summaries of national melanoma notifications provided to the International Agency for Research on Cancer (IARC) (2002) demonstrate that the highest reported national incidence rates for melanoma occurred in the populations of Australia (39:100,000 per year) and New Zealand (34:100,000 per year). The next highest national melanoma rates were observed in the USA (17:100,000 per year) followed by the Scandinavian countries with rates around 12–15:100,000 per year. Other European populations (e.g., the UK, Germany, Netherlands, Austria, France) reported melanoma rates in the range 4–10:100,000 per year. The predominantly non-Caucasian populations of Africa, Asia, and the Pacific and the mixed populations of Central and South America consistently reported melanoma rates less than 3:100,000 per year.

National figures provide a basis for global comparisons of melanoma incidence, but do not reveal the extremes in melanoma incidence within populations having large subgroups that are heterogeneous for melanoma risk (e.g., within the USA, New Zealand, Israel, and South Africa), nor do they reveal variations in melanoma incidence observed in those nations that span many degrees of latitude (e.g., Australia). In all such jurisdictions, melanoma rates are the highest among the fair-skinned residents with European ancestry (e.g., “non-Hispanic whites” in the USA; “Europeans” in New Zealand) and considerably lower among those with darker skin (e.g., “Hispanics” and “Blacks” in the USA; “Maoris” in New Zealand) [5, 6]. With respect to latitude, those residing at low latitudes tend to experience higher rates of melanoma than those residing at higher latitudes. For example, within Australia, residents of predominantly tropical Queensland (capital city Brisbane, latitude 27°S) have higher melanoma rates (65:100,000 per year) than those residing in New South Wales (capital city Sydney, latitude 34°S; 47:100,000 per year) or Victoria (capital city Melbourne, latitude 38°S, 36:100,000 per year)

D. Whiteman (✉) and A. Green
Cancer and Population Studies, The Queensland Institute
of Medical Research, Royal Brisbane Hospital,
Brisbane, Queensland 4029, Australia
e-mail: david.whiteman@qimr.edu.au; adele.green@qimr.edu.au

[7]. Similar gradients have been observed within the USA, New Zealand, Scandinavia, and other nations [8–10].

A latitude gradient for melanoma is not observed in all regions however; for example, the Caucasian populations of southern Europe (southern Spain, Italy, the Balkans) experience lower rates of melanoma than those prevailing in northern Europe. This phenomenon has been described and explored previously [11], and is widely assumed to reflect the overall darker pigmentary characteristics that predominate within the populations of southern compared with northern Europe.

1.2.2.2 Temporal Trends

1.2.2.2.1 Incidence

During recent decades, the incidence of melanoma has risen rapidly around the world, with increases in the age-standardized incidence of at least 4–6% per annum reported in many fair-skinned populations including Queensland [12], New South Wales [13], the USA [14], Canada [15], Scotland [16], Germany [17], Finland [18], France [19], and most other European nations [20].

The rates of increase have not been uniform across populations however, and even within populations, there have been notable differences in rates of change across anatomical sites, age groups, and birth cohorts. These changes potentially mask some important developments that may herald a turning point in the “epidemic” of melanoma. Thus, in many populations the rates of melanoma have risen more rapidly in men than in women, particularly in older age groups [14, 16, 17]. There are encouraging signs, however, that the incidence of melanoma among young people (<40 years) has stabilized or even declined in several high-incidence populations.

An analysis of US SEER data reported annual percentage changes (APC) for melanoma of +2.4% for men younger than 40 years in the period 1974/75 through to 1988/89, but –2.1% in the period 1990/91 through to 1996/97 [14]. By way of comparison, for men aged more than 60 years, the changes in melanoma incidence for the corresponding periods were +7.0% per annum and +5.2% per annum respectively. These data indicate that while melanoma continues to increase in older men, it would appear that the incidence may be declining in younger men. Notably, melanoma incidence in young US women increased in both time periods.

Melanoma incidence rates across Europe have changed markedly during the past five decades. Recent analyses of European data have identified up to tenfold increases in melanoma incidence in the Scandinavian countries in the five decades since the 1950s, with lesser but still sizeable increases in western European nations [20]. It appears that

these trajectories have now leveled off in most northern and western European nations, particularly among more recent birth cohorts. In contrast, while the countries of southern and eastern Europe have experienced relatively small increases in incidence during the past five decades, there is no evidence that the rate of increase has stabilized [20].

Similar to the recent experiences reported from the USA and western Europe, registry data from Queensland and New South Wales in Australia suggest that melanoma incidence has plateaued among young people of both sexes [12, 21], and may be declining [13].

Another notable feature of recent melanoma trends has been the widespread observation of rapid rises in the incidence of in situ, thin, and early-stage melanomas [12, 14, 16, 17, 19, 22]. Such increases have raised concerns about the “over-diagnosis” of melanoma and resurrected the hypothesis that much of the observed increase is due to the increasing rates of diagnosis of a prevalent pool of “non-metastasizing” or clinically indolent melanomas [19, 23] (for a full discussion of the concept, see Burton et al. [24, 25]).

1.2.2.2.2 Mortality

As melanoma incidence has risen rapidly in many parts of the world, so has melanoma mortality, albeit at a slower pace. For example, in the USA, melanoma incidence increased by about fivefold between 1950 and 1990, whereas mortality increased by slightly less than twofold during the same period [26]. Similar observations have been made in western and northern Europe [20, 27, 28].

There are data to suggest that melanoma mortality may have peaked in the USA and parts of Europe [20, 26]. In Australia, an analysis conducted in the mid-1990s demonstrated that melanoma mortality was still climbing overall, but that among the youngest birth cohorts, there were early signs of a decline in mortality [29]. The most recent data [30] suggest that between 1989 and 2002, overall melanoma mortality stabilized in Australian males and declined in females (–0.8% per annum). When examined by age, it was found that mortality had declined significantly among those less than 54 years and had stabilized among those aged 55–79 years, but continued to rise among those aged 80 years and older.

1.2.2.3 Age and Sex Distributions

In all populations, melanoma is uncommon before the age of 40 years; thereafter the age-specific incidence climbs steadily and peaks in the seventh and eighth decades [12, 14, 16, 31, 32]. When examined according to the anatomical site of the

melanoma, consistent differences emerge, the implications of which are discussed in more detail in Sect. 1.2.4.1 below. In summary, most studies reveal that the peak incidence of melanomas on the trunk occurs at younger ages (fifth to sixth decades) than melanomas arising on the head and neck (eighth decade) [31–35].

The sex distribution of melanoma has varied by population, with high-latitude, low-incidence populations (e.g., Scotland, Canada) historically reporting substantially higher rates among females (of up to twofold in Scotland) [15, 36]. Recently, the patterns of occurrence of melanoma have undergone striking change (see below), and the excess of melanomas observed among females in previous generations in these populations has been ameliorated owing to rapid increases in melanoma incidence among men [15, 16]. In contrast, in most mid- to low-latitude populations (e.g., Australia, the USA), melanoma incidence appears always to have been higher among men and remains so in spite of recent increases in both sexes. In New Zealand, however, melanoma incidence among women was previously higher than men [37], but rapid rises in melanoma incidence among men have resulted in similar rates for men and women.

1.2.2.4 Incidence by Anatomical Site

Early studies reporting on the anatomical distribution of melanoma reported an excess of melanomas on the back and shoulders in men and the lower limbs in women [38–41]. These data were often interpreted as evidence that melanoma was associated predominantly with intermittent patterns of sun exposure. Another approach to compare the incidence of melanoma at different body sites is to adjust for the surface areas of the sites being compared. In so doing, one is comparing the propensity for melanomas to arise *per unit area of skin*. When this is done, the area-adjusted incidence of melanoma is found to be highest on the face in both sexes, and then on the shoulders and back in males and the shoulders, upper arms, and back in females [42]. Negligibly low rates of melanoma are observed on the buttocks and the female scalp [38, 43].

1.2.3 Analytical Epidemiology: Risk Factors for Melanoma

During more than three decades of epidemiologic research, investigators have identified a range of factors that have been associated consistently with melanoma. For comparative

purposes, these are classified as environmental factors and host factors.

1.2.3.1 Environmental Factors

Sunlight (and most particularly the ultraviolet (UV) spectrum of sunlight) is the only environmental factor that has been compellingly implicated as a cause of melanoma. Data from human studies may be summarized as follows:

1. Melanoma incidence is 10–20-fold higher among the fair-skinned than the dark-skinned people [44].
2. Among fair-skinned people, melanoma incidence generally increases with proximity to the equator (some exceptions occur, particularly in continental Europe, where the association is confounded by pigmentation).
3. Fair-skinned migrants from high- (e.g., the UK) to low-latitude countries (e.g., Australia) have lower melanoma rates than native-born residents, and vice versa [45].
4. People with xeroderma pigmentosum (XP) (a disorder in which sufferers have a single gene mutation that abolishes their ability to repair sunlight-induced DNA damage) have 1,000-fold higher risks of melanoma than the average population [46].
5. People with a past history of other types of skin cancer (basal cell carcinomas and squamous cell carcinomas) caused by high doses of solar UV radiation have threefold higher risks of melanoma than the average population [47, 48].
6. Phenotypic measures of sun sensitivity (such as fair skin, freckling, and tendency to burn) confer approximately twofold raised risks of melanoma in all populations [49].

In addition, there is mounting evidence from animal studies that UV radiation is intimately involved in melanoma development ([50]).

1.2.3.1.1 Opposition to the Sunlight Hypothesis

Despite these persuasive findings, the question continually arises as to whether sunlight plays a role in melanoma development (reviewed by Tucker [51]), with some concluding that sunlight plays little, if any, role [52]. Opponents of the “sunlight hypothesis” cite two observations which they claim negate the role of sunlight in melanoma.

Firstly, opponents argue that since the majority of melanomas develop on body sites that are habitually covered by clothing (such as the back and shoulders in males and the lower limb in females), as opposed to sun-exposed sites (such as the face or hands), it follows that most melanomas cannot be caused by sunlight. As described above, the rank order and

magnitude of area-adjusted incidence rates for melanoma at specific anatomical sites (see Sect. 1.2.2.4 above) would affirm rather than preclude a role for sunlight in their causation.

The second line of argument against sun exposure as a cause of melanoma has been that case–control studies have typically reported modest associations between measures of past sun exposure and melanoma risk, and a number of meta-analyses have reported inverse associations between measures of chronic or occupational sun exposure and melanoma risk [53].

To interpret the findings of case–control studies, it is important to acknowledge that participants in such studies need to be sampled from within a defined geographic area, which implicitly matches cases and controls on their background level of exposure to ambient solar UV radiation. Thus each separate case–control study is constrained to discriminate across limited ranges of sun exposure when assessed on a global scale (the only exception being if the population has a very high incidence of migration into the study area from other latitudes). This problem is compounded by the lack of reliable, objective methods to assess past exposure to the sun, with consequent misclassification.

Because of these design limitations, a strong argument can be made that ecological studies (demonstrating, for example, the five to tenfold higher rates of melanoma in Queensland than in the ethnically similar population of Scotland [54], or that migrants from low to high solar environments have substantially higher rates of melanoma than pertain in their place of origin [55, 56]) constitute higher-quality evidence than case–control studies for assessing the relationship between sunlight and melanoma. In summary, the case–control method is a strong design for identifying markers of *susceptibility* for melanoma, but it has limited utility for assessing those factors which are strongly determined by the geographic location of the study. (Analogous observations regarding the limitations of the case–control design have been made for studies attempting to identify dietary factors associated with cancer. As for sunlight, the dietary range within each population is small relative to the range across populations [57].)

Accepting that solar UV is a determinant of melanoma, several issues have been the subject of recent inquiry and debate. These include the question of a “critical period” for the development of melanoma, the role of different patterns of sun exposure, and the role of artificial sources of UV radiation.

1.2.3.1.2 The “Critical Period” Hypothesis for Sun Exposure

There has been longstanding speculation that children may be particularly susceptible to the carcinogenic effects of

sunlight, and that UV exposure during this time may have more potent effects on the cells of origin for melanoma than sun exposure at older ages. A recent systematic review of the literature assessed the issue of childhood sun exposure by compiling data on two separate groups of studies, ecological (or descriptive) studies and analytical studies [45]. In the former, 20 studies were identified that assessed melanoma risk in relation to measures of ambient sun exposure at different ages; the latter comprised 13 case–control studies that assessed melanoma risk according to recall of sun exposure patterns at different ages. The two groups of studies yielded strikingly different conclusions. Those studies comparing measures of ambient sun exposure consistently reported that the incidence of melanoma was significantly lower among those whose childhoods were spent in environments of low ambient insolation.

Most informative were the studies of fair-skinned migrants from areas of high to low solar irradiance (e.g., from Africa or Pacific Islands to northern Europe). For these migrants, lifetime risks of melanoma remained significantly higher than for native-born residents, despite decades of residence in a low solar environment [58]. In contrast to the consistent and clear findings from the ambient exposure studies, case–control studies relying on recall of individual sun exposure habits differed widely in their findings, and no consistent associations with childhood sun exposure were observed. These discrepant sets of results highlight the difficulties that can arise when interpreting epidemiologic data from different types of studies. In this instance, the studies of ambient exposure were considered more reliable, and hence more likely to reflect a true association, than the studies which measured sun exposure through recall of time outdoors.

While these findings were compatible with childhood being a period of particular susceptibility to sunlight, they could not rule out an independent effect of adult sun exposure. Indeed, adult migrants to Australia still develop melanoma at higher rates than if they had remained in their place of birth. Moreover, melanoma incidence is higher among migrants settling in low-latitude environments (such as Queensland, Australia) compared with higher latitudes (such as Victoria, Australia), and their risk of melanoma continues to increase with longer durations of residence [59]. Each of these observations suggests that sun exposure during adulthood confers additional melanoma risks, over and above any risks accrued through childhood exposure.

1.2.3.1.3 Patterns of Exposure

A prevailing view in the melanoma literature is that “intermittent” exposure to sunlight confers higher risks of melanoma than “chronic” (or occupational) sun exposure [11, 60, 61]. At least three high-quality systematic reviews have

addressed this issue, each deriving summary estimates of melanoma risk associated with measures of intermittent and chronic sun exposure [53, 62, 63]. Nelemans et al. [62] reviewed 25 published case–control studies and calculated pooled odds ratios of 1.57 (95% CI 1.29–1.91) and 0.73 (95% CI 0.60–0.89) for “intermittent” and “chronic” sunlight exposures respectively. Elwood and Jopson [53] reviewed 29 case–control studies, and calculated an adjusted summary odds ratio of 1.87 (95% CI 1.67–2.09) for “intermittent” sun exposure and 1.18 (95% CI 1.02–1.38) for total sun exposure.

The most recent meta-analysis [63] separately estimated summary relative risks for melanoma associated with measures of “intermittent,” “chronic,” and “total” sun exposure, and sunburn. Importantly, the authors identified significant heterogeneity of risk estimates for each of these measures of sun exposure, with differences in risk estimates variously associated with country, latitude, and choice of controls. In particular, there was an inverse correlation between latitude and the magnitude of the risk estimate for chronic sun exposure, indicating that chronic patterns of sun exposure are more strongly associated with melanoma risk with increasing proximity to the equator. Given the inherent limitations of retrospective assessments of solar exposure, the heterogeneity of study findings, and the absence of experimental data, definitive statements about the relative carcinogenicity of different patterns of sun exposure cannot be made. Moreover, newly emerging evidence suggests that the relationship between sun exposure and melanoma differs by anatomical site and genotype [64–67], raising new questions about the mechanisms through which sunlight causes melanoma. Since very few individual studies (and no meta-analyses) have assessed the site-specific risk of particular patterns of sun exposure, the epidemiological evidence for a specific effect of exposure pattern must be considered inconclusive at this time.

1.2.3.1.4 Artificial Sources of Ultraviolet Radiation

Because of the ecological and analytical studies linking sun exposure to melanoma and the conclusion that the carcinogenic component of sunlight is UV radiation, one would infer that artificial sources of UV radiation exposure (such as sunbeds and tanning lamps) are also potential causes of melanoma [68]. In a recent systematic review, ten studies were identified (nine case–control; one cohort) that addressed this hypothesis and provided relevant estimates of risk [69]. While there were differences in methodology, the simplest measure of exposure (ever/never exposed) was associated with a summary relative risk of 1.25 (95% CI 1.05–1.49). Young age at first use of sunbeds was associated with significantly increased risk of melanoma (summary OR 1.69, 95% CI 1.32–2.18).

A similar exercise was undertaken by The IARC Working Group on Artificial Sources of Ultraviolet Radiation [70]. That review identified 23 informative studies including 1 cohort study, 14 population-based case–control studies, and 8 hospital-based case–control studies. Similar to the earlier review, the summary risk estimate for ever/never use of sunbeds was 1.15 (95% CI 1.00–1.31), although significant heterogeneity in the risk estimates was noted. Sunbed use before the age of 35 years was associated with a 75% increased risk of melanoma (OR 1.75, 95% CI 1.35–2.26). On the basis of these findings, the IARC Working group concluded that there was evidence of a causal relationship between sunbed exposure and melanoma of sufficient strength to merit changes in policy regarding public access to these sources of UV exposure.

1.2.3.2 Host Factors for Melanoma

Epidemiological studies have consistently shown that a suite of host characteristics are associated with significantly increased risks of melanoma, including numbers of nevi (systematically reviewed by Gandini et al. [71]), tanning ability (systematically reviewed by Bliss et al. [49]), red hair or freckling (systematically reviewed by Bliss et al. [49]), and family history (systematically reviewed by Ford et al. [72]).

Of these factors, the numbers of nevi on the skin confer the highest relative risks for melanoma, with risks increased by up to sevenfold for people with >100 nevi compared with <15 nevi [71]. The role of nevi as risk markers, and possible precursors, for melanoma is discussed in more detail below (Sect. 1.2.4.3).

1.2.3.3 Genes and Melanoma

A brief discussion of the genetic determinants of melanoma is warranted in this chapter since much new information has been generated recently which has direct relevance to our understanding of the interplay of causal factors of this cancer. What follows is a brief account of notable developments and the current state of play with respect to epidemiological risk assessment.

1.2.3.3.1 High-Risk Genes

The clinical observation that up to 10% of people with melanoma had a family history of the disease hinted at an underlying genetic cause and prompted initial efforts to identify kindreds in which melanoma occurred in multiple family

members. Using such approaches, genetic epidemiologists identified a region on the short arm of chromosome 9 associated with melanoma [73–75] which was found to map to a region that was also commonly deleted in cancer cell lines (9p21). The deleted locus was later identified as harboring the *CDKN2A* gene. Germline mutations in this gene have since been reported in “melanoma-prone” families worldwide [76–78]. Two other genes have since been identified within the same locus, one of which, *P14ARF*, overlaps *CDKN2A* and shares some coding regions, albeit in a different reading frame. The other candidate high-risk gene, *CDKN2B*, lies very close to *CDKN2A* and shares a similar mechanism of action. The three proteins encoded by these genes (namely, p16^{INK4a}, p14^{ARF}, and p15^{INK4b}) are each potential tumor suppressors, and each plays a role in cell-cycle arrest [79]. Another, very rare, high-penetrance familial melanoma gene, *CDK4* [80], encodes the primary target of p16^{INK4a}. Currently, it appears that each of these genes may play a role in melanoma development, although the weight of evidence favors mutations in *CDKN2A* as the most prevalent germline event in the development of familial melanoma in humans [79].

Early estimates suggested that the penetrance of melanoma among *CDKN2A* carriers was up to 90%; however, recent studies have reported considerably lower risk estimates. For example, a population-based study estimated melanoma penetrance among *CDKN2A* mutation carriers to be 14% at the age of 50 years, 24% at 70 years, and 28% at 80 years [81]. These estimates were derived by comparing the incidence of melanoma among relatives of *CDKN2A* mutation carriers with the incidence of melanoma among relatives of non-carrier probands in a large, multinational cohort of patients with multiple primary melanomas. But even these estimates may be higher than the “true” population penetrance, since they were derived from the experience of relatives of carriers who themselves have had melanoma.

A population-based study in Iceland reported the prevalence of disease-related variants of *CDKN2A* among “healthy” controls in the range 0.08–0.38%, underscoring the notion that penetrance is far from universal, even for “high-risk” genes [82]. There have been reports that the penetrance of melanoma among *CDKN2A* mutation carriers increases with proximity to the equator, suggesting a gene–environment interaction [83], although this conclusion has since been challenged [81]. This is an issue of fundamental importance and clearly warrants further investigation in carefully designed, population-based studies.

Outside of melanoma kindreds, the prevalence of germline *CDKN2A* mutations among patients with “sporadic” melanoma is low. A large, population-based study in Queensland, Australia, found no germline *CDKN2A* mutations among 201 cases of sporadic melanoma [84]. A Canadian study of 254 patients reported an overall prevalence of germline *CDKN2A* mutations of 3.2% [85], although this may be an

overestimate because the patients in that study included those likely to have a genetic basis, including patients with a strong family history of melanoma, early-onset disease, multiple primaries, and atypical nevus syndrome. The best estimate to date probably comes from the Icelandic study, which reported frequencies of disease-related variants of around 0.7–1.0% among “sporadic” melanoma cases [81].

Several other genes have been associated with a high risk of melanoma as part of an overall cancer syndrome. Patients with XP have one of several very specific mutations which render them unable to repair UV-damaged DNA. These patients develop cutaneous melanoma at more than thousand times the rate of the normal population [46, 86]. Cowden disease is another autosomal dominant syndrome which is caused by mutation in the *PTEN* gene. Affected individuals develop breast and thyroid cancer predominantly, but also melanoma. There is no evidence that germline *PTEN* mutations account for cases of melanoma outside of this syndrome however [87].

1.2.3.3.2 Low-Risk Genes

Until the recent advent of high-throughput genome-wide scans, the search for “low-risk” melanoma genes had been through the candidate gene approach. Typically these candidates were genes associated with pigmentation, or which encode DNA repair enzymes.

Most interest has focused on the melanocortin-1-receptor gene (*MC1R*), first identified in 1992 as the gene encoding a receptor for the melanocyte-stimulating hormone (MSH) [88]. This complex mediates the production of melanin by melanocytes. Variant *MC1R* genotypes are associated with red hair color and freckling on the skin [89–91]. More than 77 variants of the human *MC1R* gene have been identified [92], of which 3 (Arg151Cys, Arg160Trp, and Asp294His) are designated as “red hair genes.” The prevalence of *MC1R* variants is high (50%), even among southern European populations in whom red hair is uncommon [93].

Because *MC1R* genotypes are associated with both red hair and skin type, and because these characteristics are both associated with increased risks of melanoma, a logical extension was to test for an association between *MC1R* genotype and melanoma. Numerous studies have tested this hypothesis; a systematic review and meta-analysis of 11 studies reported risks for melanoma on the order of 1.5–2.5 for seven of the nine *MC1R* variants tested [94]. Highest risks were associated with the Asp294His variant (OR 2.40; 95% CI 1.50–3.84). Unfortunately, that meta-analysis could not assess the effects of *MC1R* independently of the effects of other pigmentation characteristics, and so the magnitude of the risk estimates must be interpreted with caution. One recent study did estimate the extra risk conferred by *MC1R*

genotype, over and above the contribution of skin color [95], and found a very modest increment. This suggests that the association of *MC1R* with melanoma is mediated almost entirely through the effects of this gene on pigmentation and not through other pathways.

Other “low-risk” candidate genes that have been investigated for possible associations with melanoma include polymorphisms in various DNA repair genes (e.g., from the XP gene family, *XPC* [96–99], *XPB* [98–100], and *BrCa2* [102] among others). At least one study has reported on risks associated with polymorphisms of the Vitamin D receptor [103]. From an epidemiologic perspective, all published studies to date have been underpowered, and most of the reported associations have been modest. Moreover, any positive associations have generally been observed within subgroups of populations, increasing the likelihood of type 1 error. It is therefore impossible to draw firm conclusions about the role, if any, of the low-risk candidates tested. This is a rapidly moving area however, and it is likely that very soon genome-wide association studies will provide new layers of information. All identified associations (including those already in the literature) will require formal testing in properly designed validation studies with large sample sizes before they can be accepted.

1.2.4 Multiple Causal Pathways to Melanoma?

The preceding sections have described the overall patterns of occurrence and risk factors for melanoma as they have been presented historically. That is, studies have been designed and data have been analyzed under the implicit assumption that all cutaneous melanomas are a single homogeneous group. Parallel lines of inquiry across a range of disciplines have resulted in findings that challenge this assumption, consistent with the view that melanomas are heterogeneous and may arise through several different causal pathways. A brief overview of those earlier findings is presented here, leading to the recently described divergent pathway hypothesis for melanoma.

1.2.4.1 Variations in Site-Specific Incidence of Melanoma with Age

The proposition that melanomas on different body sites might differ in their etiology has been around for at least three decades [104] and was initially based on the observation that people with melanomas of the face were generally older than patients with melanomas at other body

sites. Following those anecdotal observations, two descriptive studies independently explored this hypothesis using reliable cancer data in populations with very different underlying rates of melanoma, namely in Canada [33] and New Zealand [37]. Importantly, both studies used similar methodology by adjusting the incidence of melanoma at different body sites for the relative surface area of each site. Both studies found that the area-adjusted incidence of melanomas in young adults was considerably higher on the trunk than the head and neck. Thereafter, melanoma on the trunk continued to rise steadily in adulthood, peaked in late middle age, and then declined slightly in older age groups. In contrast, the area-adjusted incidence of head and neck melanoma was low among the young and middle-aged, but then rose very rapidly among older age groups to far exceed the rate of melanoma on the trunk. These concordant findings from disparate populations suggested that the age dependence of melanoma by anatomical site is a real effect, possibly reflecting different subsets of tumors.

1.2.4.2 Risk Factors for Melanoma at Different Anatomical Sites

Several analytic studies conducted during the 1980s and 1990s performed post hoc analyses in which risk factors for melanoma were examined according to the anatomical site of the tumor. While the studies were not specifically designed to assess site-specific differences in melanoma risk, they nevertheless consistently reported that melanomas on the trunk or legs were statistically associated with high nevus counts, whereas melanomas on the head and neck were not [105–108]. In a case-control study in New South Wales, Australia, Bataille et al. [109] observed that patients with melanomas of the head and neck had substantially fewer nevi and more solar keratoses than patients with melanomas of the trunk or legs.

At about the same time, an immunohistochemical analysis of melanoma was reported which hinted at quite distinct patterns of risk factors based on the presence or absence of p53 immunoexpression [110]. Melanomas over-expressing p53 protein were found to occur more frequently on the head and neck than melanomas without evidence of p53 expression, and were associated with older age and high counts of solar keratoses. Further, p53 immunonegative melanomas occurred more commonly on the trunk, and were associated with greater numbers of nevi. These data suggested that the molecular profile of melanomas, at least in relation to p53 expression, may reflect their causal origins and provided a novel basis by which melanomas might be classified beyond their histological appearances.

1.2.4.3 *Nevus-Associated Melanomas Differ from Other Melanomas*

At about the same time as the risk factor studies, dermatopathologists began to note that melanomas with evidence of neval remnants had different characteristics from melanomas without such remnants. Depending upon the series, around 25% of cutaneous melanomas have remnants of neval tissue upon histological examination [106, 111–114]. The co-occurrence of these two histological entities (melanoma and nevus) is substantially higher than expected assuming a random distribution of melanomas and nevi on the skin surface [115, 116], and is certainly higher than the co-occurrence of nevi with other tumors of the skin [116]. Green first proposed the concept that melanomas arising from nevi may reflect a distinct pathway for the origins of these cancers, and suggested that the propensity for malignant progression was determined, at least in part, by the anatomical site of the target cell [117]. An analysis of pathology reports provided support for this theory [42]. Several other groups also investigated the anatomical distribution of melanoma with contiguous neval remnants (hereafter “CN+ melanoma”) compared with other melanomas without neval remnants (CN– melanoma). Each study found that CN+ melanomas occur more commonly on the trunk than on the head and neck [106, 114, 116]. Further, patients with CN+ melanomas were significantly more likely to have high nevus counts and to report episodes of severe sunburn than controls [115]. In contrast, CN– melanoma patients were significantly more likely than controls to have red or blond hair, but had similar histories of sunburn and only modestly higher nevus counts. These observations suggest that CN+ melanomas differ from CN– melanomas in their association with phenotypic and environmental risk factors, and provided new insights into the likely multiplicity of pathways through which melanomas can arise [117].

In a histological review of 943 melanoma specimens from three study sites in Ontario and British Columbia (Canada) and New South Wales (Australia), 36% had contiguous neval remnants [118]. Patients with CN+ melanomas were significantly more likely to have high nevus counts and their tumors were more likely to arise on the trunk. In contrast, CN– melanomas were more likely among older people, among LMM subtypes, among those with melanomas arising on the head and neck, and those with pronounced solar elastosis. Very similar patterns of association for CN+ and CN– melanomas were also reported in another independent study [119], thereby confirming earlier reports.

1.2.4.4 *Population Heterogeneity in Nevus Burden*

Because of the close epidemiologic and histologic association between nevi and melanoma, there has been much

research into the origins of these benign melanocytic tumors. Studies in environments of low ambient sunlight [120–123] and high ambient sunlight [124–127] have reported that children exposed to high levels of sunlight, however measured, have greater numbers of nevi than those who report lower levels of exposure. Moreover, studies which have used common protocols to count nevi on children from similar ethnic backgrounds residing in areas of differing ambient UVR consistently report significantly higher nevus counts among those children residing in higher solar environments [128, 129].

A strong genetic contribution to nevus burden is also apparent, based on the findings of twin studies conducted in high- and low-solar environments [130, 131]. Because monozygotic (MZ, or identical) twin pairs share all of their genes, whereas dizygotic (DZ, or fraternal) twin pairs share only half of their genes on average, comparisons of the within-pair correlations of nevus counts for MZ and DZ twins permit inferences about heritability. The heritability estimates for nevus counts among twins residing in Australia and the UK were strikingly similar (MZ twins $r \sim 0.94$; DZ twins $r \sim 0.60$), despite the very large differences in insolation between Australia and the UK, and the systematically higher nevus counts among Australian twins.

Taken together, these studies demonstrate the importance of both sunlight and genes as determinants of nevi. They show that within fair-skinned populations, there exist some people with a high propensity to develop nevi, while others have a low propensity, and that this propensity is genetically determined. The degree of expression of the phenotype (“nevus burden”) is then determined by the ambient solar radiation of the environment in which an individual resides and modified by their outdoor exposure.

1.2.4.5 *The Hypothesis of Divergent Causal Pathways to Melanoma*

By the close of the 1990s, the collected findings from studies across the epidemiologic spectrum suggested that cutaneous melanomas were not a single homogeneous entity. Moreover, the nevus heritability studies indicated that a person’s tendency for nevus development (a putative proxy for melanocytic proliferative capacity, and hence melanoma susceptibility) was under strong genetic control. These observations led to the “divergent pathway hypothesis” for melanoma, which proposes that people with an inherently low propensity for melanocyte proliferation (identified by low nevus counts) develop melanoma through chronic exposure to sunlight [110, 132]. In contrast, among people having an inherently high propensity for melanocyte proliferation (identified by high nevus counts), the hypothesis predicts that sun

exposure is required only to initiate melanoma development, after which inherited host factors supervene to drive progression of the tumor. Among this latter group, melanomas are expected to develop on body sites with unstable melanocyte populations such as the trunk, and will do so at younger ages. In the relatively brief interval since the hypothesis was first proposed, there have been numerous studies that tested melanomas using a variety of approaches.

1.2.4.5.1 Ecological Studies

A number of studies have tested the divergent pathway model by comparing the age-specific incidence of melanoma by anatomic site. Lachiewicz et al. [31] compared the age-specific incidence curve for melanomas arising on the trunk with those arising on the head and neck for 48,673 melanoma patients notified to the US SEER registries between 2000 and 2004. Strikingly different curves were observed by body site, with the age distribution of melanomas of the trunk peaking 10 years before those of the face and ear (64 vs. 74 years).

A Swiss study compared the relative melanoma density (RMD) by anatomical site and age group [133] (the RMD is the ratio of the “observed” to the “expected” number of melanomas at any given anatomical site, and where the “expected” number is that which would be anticipated at that site assuming an even distribution of tumors over the whole body surface). Among those aged less than 50 years, melanomas occurred most densely on the trunk in both males and females whereas in those aged more than 65 years, RMD was highest on the face and lowest on the thighs and buttocks. Similar analyses with ostensibly the same findings have since been reported from Sweden [35], Scotland, and Australia [54]. Overall, these studies provide strong evidence that melanomas tend to arise on the trunk at younger ages and on the face and head at older ages, and that this phenomenon occurs in all populations.

1.2.4.5.2 Risk Factor Studies

Several studies have directly tested the divergent pathway hypothesis for melanoma by comparing the prevalence of risk factors within subgroups of melanoma patients. Using data from 178,153 eligible participants followed up within three large, prospective studies, Cho et al. assessed risk factors for melanoma across anatomical sites [134]. Significant differences in melanoma risk across anatomical sites were seen, especially for associations with nevi (test for heterogeneity $p=0.04$). High nevus counts were more strongly associated with melanomas of the trunk (OR 4.67) than the head (OR 3.45) or upper (OR 2.50) or lower limbs (OR 2.00).

Two publications arising from a large, hospital-based case-control study in Italy concluded that they did not find evidence of differences in risk factors by anatomical site. The first publication estimated the relative risks associated with various measures of past sun exposure (numbers of sunburns etc.) and phenotype (hair color, eye color, numbers of nevi) for melanomas at different anatomical sites [135]. Some modest variations in the magnitude of association were noted for some exposures, but overall, there was no statistically significant evidence of heterogeneity by body site. The second publication assessed the risks of site-specific melanomas associated with nevus counts at specific anatomical sites [136] and reported that people with higher nevus counts had higher risks of melanomas of the trunk than other sites. So, while the authors concluded that their data did not support differences in melanoma risk by site, their data confirm the findings of earlier studies that people with large numbers of nevi are more likely to develop melanomas on the trunk than on the head and neck.

1.2.4.5.3 Somatic Mutation Studies

Much work has been undertaken to document the molecular phenotypes of melanoma since the original observations of Maldonado [66] that *BRAF* mutations are more strongly associated with melanomas from non-sun-exposed sites than from sun-exposed sites. Those original findings have been confirmed in subsequent studies [137, 138] and it is now clear that *BRAF* mutant melanomas are associated with particular phenotypic and sun-exposure attributes, including high nevus counts, truncal location, and young age [139, 140]. Interestingly, both studies have also reported that *BRAF* mutant melanomas have stronger associations with early life sun exposure than wild-type melanoma, consistent with a role for sunlight in initiating these tumors in early life. Such a pathway is supported by the finding that *BRAF* mutations are also more likely in melanomas with histological evidence of contiguous neval remnants [141, 142]. The supposition that *BRAF* mutations in nevocytes are acquired following sun exposure in early life has been given indirect support from an intricate study comparing *BRAF* mutations in two types of “congenital” nevi. The investigators reported that none of 32 nevi that were present at birth were found to harbor *BRAF* mutations [143]. In contrast, 20 of 28 (71%) of the melanocytic nevi with a “congenital pattern” but that were known to have arisen in childhood showed the common *BRAF* V600E mutation.

Recently, interest has focused on identifying possible genetic modifiers of *BRAF* mutation, with some evidence that constitutional *MC1R* variants confer a substantially increased risk of such mutations among people with only limited amounts of sun exposure [144]. Such findings await

confirmation in large, population-based studies however, since the numbers of participants examined to date have been small and the resultant risk estimates have been imprecise. With the advent of high-throughput technologies, molecular studies of this type are being reported with increasing frequency, and it is inevitable that these gene–gene and gene–environment associations will be clarified in due course. For the moment, the emerging picture appears largely congruent with the concept that distinct subsets of melanomas can be defined on the basis of their molecular phenotype, and that these phenotypes are associated with different risk factors.

1.2.5 Conclusions

Melanomas are epidermal cancers arising predominantly in fair-skinned people. The incidence of melanoma has risen rapidly in many populations during recent decades, and rates continue to rise in most populations. Encouraging trends in Australia and the USA suggest that melanoma rates may have stabilized among younger people, and these trends will be closely monitored. Such trends might be anticipated in northern and western Europe; continued surveillance in these areas is required.

The principal environmental determinant of cutaneous melanoma is sunlight, with incidence rates varying more than tenfold between ethnically similar populations residing in environments with different levels of ambient sunlight. Epidemiological studies have identified a number of phenotypic risk factors for melanoma, many of which appear to be genetically determined. Recent studies suggest that epidermal melanocytes develop into malignant tumors through more than one pathway, as evidenced by differing molecular profiles, anatomical distributions, and risk factor profiles for subgroups of melanomas. This field is moving rapidly, and it is likely that in the near future, a clearer understanding of the molecular origins of melanomas will be delivered. It is hoped that such knowledge will be of value in designing interventions to control this cancer.

References

1. Ries, L.A.G., Eisner, M.P., Kosary, C.L., Hankey, B.F., Miller, B.A., Clegg, L., et al.: SEER Cancer Statistics Review, 1973–1997. National Cancer Institute, Bethesda (2000)
2. Fraumeni Jr., J.F.: Genes and the Environment in Cancer Causation. National Cancer Institute, Washington (2007)
3. Lancaster, H.O.: Some geographical aspects of the mortality from melanoma in Europeans. *Med. J. Aust.* **1**, 1082–1087 (1956)
4. Lancaster, H.O., Nelson, J.: Sunlight as a cause of melanoma: a clinical survey. *Med. J. Aust.* **1**, 452–456 (1957)
5. Deapen, D., Bernstein, L., Liu, L., Kerford, D., Balcius, P., Morrell, D., et al.: Cancer incidence in Los Angeles county. In: Curado, M.P., Edwards, B., Shin, H.R., Storm, H., Ferlay, J., Heanue, M. (eds.) *Cancer Incidence in Five Continents*, vol. IX. IARC Scientific, Lyon (2007)
6. Ministry of Health: Cancer in New Zealand: Trends and Projections. Ministry of Health, Wellington (2002)
7. Australian Institute of Health and Welfare (AIHW). ACIM (Australian Cancer Incidence and Mortality) Books. AIHW. Canberra (2010)
8. Crombie, I.K.: Variation of melanoma incidence with latitude in North America and Europe. *Br. J. Cancer* **40**, 774–781 (1979)
9. Bulliard, J.L., Cox, B., Elwood, J.M.: Latitude gradients in melanoma incidence and mortality in the non-Maori population of New Zealand. *Cancer Causes Control* **5**, 234–240 (1994)
10. Magnus, K.: Incidence of malignant melanoma of the skin in Norway, 1955–1970: Variations in time and space and solar radiation. *Cancer* **32**, 1275–1286 (1973)
11. Armstrong, B.K.: Epidemiology of malignant melanoma: intermittent or total accumulated exposure to the sun. *J. Dermatol. Surg. Oncol.* **14**, 835–849 (1988)
12. Coory, M., Baade, P., Aitken, J., Smithers, M., McLeod, G.R., Ring, I.: Trends for in situ and invasive melanoma in Queensland, Australia, 1982–2002. *Cancer Causes Control* **17**(1), 21–27 (2006)
13. Marrett, L.D., Nguyen, H.L., Armstrong, B.K.: Trends in the incidence of cutaneous malignant melanoma in New South Wales, 1983–1996. *Int. J. Cancer* **92**(3), 457–462 (2001)
14. Jemal, A., devesa, S.S., Fears, T.R., Hartge, P., Tucker, M.A.: Recent trends in cutaneous melanoma incidence among whites in the United States. *J. Natl. Cancer Inst.* **93**, 678–683 (2001)
15. Ulmer, M.J., Tonita, J.M., Hull, P.R.: Trends in invasive cutaneous melanoma in Saskatchewan 1970–1999. *J. Cutan. Med. Surg.* **7**(6), 433–442 (2003)
16. MacKie, R.M., Bray, C.A., Hole, D.J.: Incidence and survival from malignant melanoma in Scotland. *Lancet* **360**, 587–591 (2002)
17. Lasithiotakis, K.G., Leiter, U., Gorkiewicz, R., Eigentler, T., Breuninger, H., Metzler, G., et al.: The incidence and mortality of cutaneous melanoma in Southern Germany: trends by anatomic site and pathologic characteristics, 1976 to 2003. *Cancer* **107**(6), 1331–1339 (2006)
18. Stang, A., Pukkala, E., Sankila, R., Soderman, B., Hakulinen, T.: Time trend analysis of the skin melanoma incidence of Finland from 1953 through 2003 including 16,414 cases. *Int. J. Cancer* **119**(2), 380–384 (2006)
19. Lipsker, D., Engel, F., Cribier, B., Velten, M., Hedelin, G.: Trends in melanoma epidemiology suggest three different types of melanoma. *Br. J. Dermatol.* **157**(2), 338–343 (2007)
20. de Vries, E., Bray, F.I., Coebergh, J.W., Parkin, D.M.: Changing epidemiology of malignant cutaneous melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. *Int. J. Cancer* **107**(1), 119–126 (2003)
21. Whiteman, D.C., Bray, C.A., Siskind, V., Green, A.C., Hole, D.J., Mackie, R.M.: Changes in the incidence of cutaneous melanoma in the west of Scotland and Queensland, Australia: hope for health promotion? *Eur. J. Cancer Prev.* **17**(3), 243–250 (2008)
22. Garbe, C., McLeod, G.R., Buettner, P.G.: Time trends of cutaneous melanoma in Queensland, Australia and Central Europe. *Cancer* **89**(6), 1269–1278 (2000)
23. Welch, H.G., Woloshin, S., Schwartz, L.M.: Skin biopsy rates and incidence of melanoma: population based ecological study. *Br. Med. J.* **331**(7515), 481 (2005)
24. Burton, R.C., Coates, M.S., Hersey, P., Roberts, G., Chetty, M.P., Chen, S., et al.: An analysis of a melanoma epidemic. *Int. J. Cancer* **55**, 765–776 (1993)
25. Burton, R.C., Armstrong, B.K.: Recent incidence trends imply a nonmetastasizing form of invasive melanoma. *Melanoma Res.* **4**(2), 107–113 (1994)

26. Jemal, A., Devesa, S.S., Fears, T.R., Hartge, P.: Cancer surveillance series: changing patterns of cutaneous malignant melanoma mortality rates among whites in the United States. *J. Natl. Cancer Inst.* **92**(10), 811–818 (2000)
27. de Vries, E., Bray, F.I., Eggermont, A.M., Coebergh, J.W.: Monitoring stage-specific trends in melanoma incidence across Europe reveals the need for more complete information on diagnostic characteristics. *Eur. J. Cancer Prev.* **13**(5), 387–395 (2004)
28. de Vries, E., Coebergh, J.W.: Cutaneous malignant melanoma in Europe. *Eur. J. Cancer* **40**(16), 2355–2366 (2004)
29. Giles, G.G., Armstrong, B.K., Burton, R.C., Staples, M.J., Thursfield, V.J.: Has mortality from melanoma stopped rising in Australia? Analysis of trends between 1931 and 1994. *Br. Med. J.* **312**, 1121–1125 (1996)
30. Baade, P., Coory, M.: Trends in melanoma mortality in Australia: 1950–2002 and their implications for melanoma control. *Aust. N. Z. J. Public Health* **29**(4), 383–386 (2005)
31. Lachiewicz, A.M., Berwick, M., Wiggins, C.L., Thomas, N.E.: Epidemiologic support for melanoma heterogeneity using the surveillance, epidemiology, and end results program. *J. Invest. Dermatol.* **128**(5), 1340–1342 (2008)
32. Stang, A., Stabenow, R., Eisinger, B., Jockel, K.H.: Site- and gender-specific time trend analyses of the incidence of skin melanomas in the former German Democratic Republic (GDR) including 19351 cases. *Eur. J. Cancer* **39**(11), 1610–1618 (2003)
33. Elwood, J.M., Gallagher, R.P.: Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int. J. Cancer* **78**, 276–280 (1998)
34. Bulliard, J.-L.: Site-specific risk of cutaneous malignant melanoma and pattern of sun exposure in New Zealand. *Int. J. Cancer* **85**, 627–632 (2000)
35. Perez-Gomez, B., Aragonés, N., Gustavsson, P., Lope, V., Lopez-Abente, G., Pollán, M.: Do sex and site matter? Different age distribution in melanoma of the trunk among Swedish men and women. *Br. J. Dermatol.* **158**(4), 766–772 (2008)
36. MacKie, R., Hunter, J.A., Aitchison, T.C., Hole, D., McLaren, K., Rankin, R.: Cutaneous malignant melanoma, Scotland, 1979–89. The Scottish Melanoma Group. *Lancet* **339**, 971–975 (1992)
37. Bulliard, J.L., Cox, B.: Cutaneous malignant melanoma in New Zealand: trends by anatomical site, 1969–1993. *Int. J. Epidemiol.* **29**(3), 416–423 (2000)
38. Osterlind, A., Hou-Jensen, K., Møller-Jensen, O.: Incidence of cutaneous malignant melanoma in Denmark 1978–1982. Anatomic site distribution, histologic types and comparison with non-melanoma skin cancer. *Br. J. Cancer* **58**, 385–391 (1988)
39. Magnus, K.: Habits of sun exposure and risk of malignant melanoma: an analysis of incidence rates in Norway 1955–1977 by cohort, sex, age and primary tumor site. *Cancer* **48**, 2329–2335 (1981)
40. Popescu, N.A., Beard, C.M., Treacy, P.J., Winkelmann, R.K., O'Brien, P.C., Kurland, L.T.: Cutaneous malignant melanoma in Rochester, Minnesota: trends in incidence and survivorship, 1950 through 1985. *Mayo Clin. Proc.* **65**, 1293–1302 (1990)
41. Masback, A., Westerdahl, J., Ingvar, C., Olsson, H., Jonsson, N.: Cutaneous malignant melanoma in South Sweden 1965, 1975, and 1985. A histopathologic review. *Cancer* **73**, 1625–1630 (1994)
42. Green, A., MacLennan, R., Youl, P., Martin, N.: Site distribution of cutaneous melanoma in Queensland. *Int. J. Cancer* **53**, 232–236 (1993)
43. Chen, Y.T., Zheng, T., Holford, T.R., Berwick, M., Dubrow, R.: Malignant melanoma incidence in Connecticut (United States): time trends and age-period-cohort modeling by anatomic site. *Cancer Causes Control* **5**, 341–350 (1994)
44. Armstrong, B.K., Kricke, A.: How much melanoma is caused by sun exposure? *Melanoma Res.* **3**, 395–401 (1993)
45. Whiteman, D.C., Whiteman, C.A., Green, A.C.: Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. *Cancer Causes Control* **12**, 69–82 (2001)
46. Kraemer, K.H., Lee, M.M., Andrews, A.D., Lambert, W.C.: The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. *Arch. Dermatol.* **130**, 1018–1021 (1994)
47. Green, A.C., O'Rourke, M.G.E.: Cutaneous malignant melanoma in association with other skin cancers. *J. Natl. Cancer Inst.* **74**, 977–980 (1985)
48. Levi, F., Randimbison, L., La-Vecchia, C., Erler, G., Te, V.C.: Incidence of invasive cancers following squamous cell skin cancer. *Am. J. Epidemiol.* **146**(9), 734–739 (1997)
49. Bliss, J.M., Ford, D., Swerdlow, A.J., Armstrong, B.K., Cristofolini, M., Elwood, J.M., et al.: Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. *Int. J. Cancer* **62**, 367–376 (1995)
50. Noonan FP, Recio JA, Takayama H, et al. Neonatal sunburn and melanoma in mice. *Nature*. Sep 20 2001;413(6853):271–272.
51. Tucker, M.A.: Is sunlight important to melanoma causation? *Cancer Epidemiol. Biomarkers Prev.* **17**(3), 467–468 (2008)
52. Shuster, S.: Is sun exposure a major cause of melanoma? *No. Br. Med. J.* **337**, a764 (2008)
53. Elwood, J.M., Jopson, J.: Melanoma and sun exposure: an overview of published studies. *Int. J. Cancer* **73**(2), 198–203 (1997)
54. Whiteman, D.C., Bray, C.A., Siskind, V., Hole, D., MacKie, R.M., Green, A.C.: A comparison of the anatomic distribution of cutaneous melanoma in two populations with different levels of sunlight: the west of Scotland and Queensland, Australia 1982–2001. *Cancer Causes Control* **18**(5), 485–491 (2007)
55. Cooke, K.R., Fraser, J.: Migration and death from malignant melanoma. *Int. J. Cancer* **36**(2), 175–178 (1985)
56. Khat, M., Vail, A., Parkin, M., Green, A.: Mortality from melanoma immigrants to Australia: variation by age at arrival and duration of stay. *Am. J. Epidemiol.* **135**, 1103–1113 (1992)
57. Wynder, E.L., Stellman, S.D.: The “over-exposed” control group. *Am. J. Epidemiol.* **135**, 459–461 (1992)
58. Autier, P., Dore, J.F.: Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. *Int. J. Cancer* **77**(4), 533–537 (1998)
59. Dobson, A.J., Leeder, S.R.: Mortality from malignant melanoma in Australia: effects due to country of birth. *Int. J. Epidemiol.* **11**(3), 207–211 (1982)
60. Elwood, J.M., Gallagher, R.P., Hill, G.B., Pearson, J.C.: Cutaneous melanoma in relation to intermittent and constant sun exposure—the Western Canada Melanoma Study. *Int. J. Cancer* **35**, 427–433 (1985)
61. Osterlind, A., Tucker, M.A., Stone, B.J., Jensen, O.M.: The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. *Int. J. Cancer* **42**, 319–324 (1988)
62. Nelemans, P.J., Rampen, F.H.J., Ruiter, D.J., Verbeek, A.L.M.: An addition to the controversy on sunlight exposure and melanoma risk: a meta-analytical approach. *J. Clin. Epidemiol.* **48**, 1331–1342 (1995)
63. Gandini, S., Sera, F., Cattaruzza, M.S., Pasquini, P., Picconi, O., Boyle, P., et al.: Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur. J. Cancer* **41**(1), 45–60 (2005)
64. Whiteman, D.C., Stickley, M., Watt, P., Hughes, M.C., Davis, M.B., Green, A.C.: Anatomic site, sun exposure, and risk of cutaneous melanoma. *J. Clin. Oncol.* **24**(19), 3172–3177 (2006)
65. Rivers, J.K.: Is there more than one road to melanoma? *Lancet* **363**(9410), 728–730 (2004)
66. Maldonado, J.L., Fridlyand, J., Patel, H., Jain, A.N., Busam, K., Kageshita, T., et al.: Determinants of BRAF mutations in primary melanomas. *J. Natl. Cancer Inst.* **95**(24), 1878–1890 (2003)

67. Curtin, J.A., Fridlyand, J., Kageshita, T., Patel, H.N., Busam, K.J., Kutzner, H., et al.: Distinct sets of genetic alterations in melanoma. *N. Engl. J. Med.* **353**(20), 2135–2147 (2005)
68. Gallagher, R.: Sunbeds—do they increase risk of melanoma or not? *Eur. J. Cancer* **41**(14), 2038–2039 (2005)
69. Gallagher, R.P., Spinelli, J.J., Lee, T.K.: Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. *Cancer Epidemiol. Biomarkers Prev.* **14**(3), 562–566 (2005)
70. IARC Working Group on Risk of Skin Cancer and Exposure to Artificial Ultraviolet Light: Exposure to Artificial UV Radiation and Skin Cancer. International Agency for Research on Cancer, Lyon (2005)
71. Gandini, S., Sera, F., Cattaruzza, M.S., Pasquini, P., Abeni, D., Boyle, P., et al.: Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur. J. Cancer* **41**(1), 28–44 (2005)
72. Ford, D., Bliss, J.M., Swerdlow, A.J., et al.: Risk of cutaneous melanoma associated with a family history of the disease. *Int. J. Cancer* **62**, 377–381 (1995)
73. Petty, E.M., Gibson, L.H., Fountain, J.W., Bolognia, J.L., Yang-Feng, T.L., Housman, D.E., et al.: Molecular definition of a chromosome 9p21 germ-line deletion in a woman with multiple melanomas and a plexiform neurofibroma: implications for 9p tumor-suppressor gene(s). *Am. J. Hum. Genet.* **53**(1), 96–104 (1993)
74. Cannon-Albright, L.A., Goldgar, D.E., Meyer, L.J., et al.: Assignment of a locus for familial melanoma, MLM, to chromosome 9p13-p22. *Science* **258**, 1148–1152 (1992)
75. Nancarrow, D.J., Mann, G.J., Holland, E.A., et al.: Confirmation of chromosome 9p linkage in familial melanoma. *Am. J. Hum. Genet.* **53**, 936–942 (1993)
76. Gruis, N.A., van der Velden, P.A., Sandkuijl, L.A., et al.: Homozygotes for CDKN2 (p16) germline mutation in Dutch familial melanoma kindreds. *Nat. Genet.* **10**, 351–353 (1995)
77. Harland, M., Meloni, R., Gruis, N., Pinney, E., Brookes, S., Spurr, N.K., et al.: Germline mutations of the CDKN2 gene in UK melanoma families. *Hum. Mol. Genet.* **6**(12), 2061–2067 (1997)
78. Hussussian, C., Struwing, J.P., Goldstein, A.M., et al.: Germline p16 mutations in familial melanoma. *Nat. Genet.* **8**, 15–21 (1994)
79. Peters, G.: Tumor suppression for ARF10: the relative contributions of p16INK4a and p14ARF in melanoma. *J. Natl. Cancer Inst.* **100**(11), 757–759 (2008)
80. Zuo, L., Weger, J., Yang, Q., Goldstein, A.M., Tucker, M.A., Walker, G.J., et al.: Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. *Nat. Genet.* **12**(1), 97–99 (1996)
81. Begg, C.B., Orlov, I., Hummer, A.J., Armstrong, B.K., Krickler, A., Marrett, L.D., et al.: Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J. Natl. Cancer Inst.* **97**(20), 1507–1515 (2005)
82. Goldstein, A.M., Stacey, S.N., Olafsson, J.H., Jonsson, G.F., Helgason, A., Sulem, P., et al.: CDKN2A mutations and melanoma risk in the Icelandic population. *J. Med. Genet.* **45**(5), 284–289 (2008)
83. Bishop, D.T., Demenais, F., Goldstein, A.M., Bergman, W., Bishop, J.N., Paillerets Bressac-de, B., et al.: Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J. Natl. Cancer Inst.* **94**(12), 894–903 (2002)
84. Aitken, J., Welch, J., Duffy, D., Milligan, A., Green, A., Martin, N., et al.: CDKN2A variants in a population-based sample of Queensland families with melanoma. *J. Natl. Cancer Inst.* **91**(5), 446–452 (1999)
85. Ung-Juurlink, C.: American Academy of Dermatology 1999 Awards for Young Investigators in Dermatology. The prevalence of CDKN2A in patients with atypical nevi and malignant melanoma. *J. Am. Acad. Dermatol.* **41**(3), 461–462 (1999)
86. Kraemer, K.H.: Sunlight and skin cancer: another link revealed. *Proc. Natl. Acad. Sci. U S A* **94**(1), 11–14 (1997)
87. Boni, R., Vortmeyer, A.O., Burg, G., Hofbauer, G., Zhuang, Z.: The PTEN tumour suppressor gene and malignant melanoma. *Melanoma Res.* **8**(4), 300–302 (1998)
88. Chhajlani, V., Wikberg, J.E.: Molecular cloning and expression of the human melanocyte stimulating hormone receptor cDNA. *FEBS Lett.* **309**(3), 417–420 (1992)
89. Valverde, P., Healy, E., Jackson, I., Rees, J.L., Thody, A.J.: Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nat. Genet.* **11**, 328–330 (1995)
90. Smith, R., Healy, E., Siddiqui, S., Flanagan, N., Steijlen, P.M., Rosdahl, I., et al.: Melanocortin 1 receptor variants in an Irish population. *J. Invest. Dermatol.* **111**(1), 119–122 (1998)
91. Box, N.F., Wyeth, J.R., O'Gorman, L.E., Martin, N.G., Sturm, R.A.: Characterization of melanocyte stimulating hormone receptor variant alleles in twins with red hair. *Hum. Mol. Genet.* **6**(11), 1891–1897 (1997)
92. Wong, T.H., Rees, J.L.: The relation between melanocortin 1 receptor (MC1R) variation and the generation of phenotypic diversity in the cutaneous response to ultraviolet radiation. *Peptides* **26**(10), 1965–1971 (2005)
93. Stratigos, A.J., Dimisianos, G., Nikolaou, V., Poulou, M., Sypsa, V., Stefanaki, I., et al.: Melanocortin receptor-1 gene polymorphisms and the risk of cutaneous melanoma in a low-risk southern European population. *J. Invest. Dermatol.* **126**(8), 1842–1849 (2006)
94. Raimondi, S., Sera, F., Gandini, S., Iodice, S., Caini, S., Maisonneuve, P., et al.: MC1R variants, melanoma and red hair color phenotype: a meta-analysis. *Int. J. Cancer* **122**(12), 2753–2760 (2008)
95. Dwyer, T., Stankovich, J.M., Blizzard, L., FitzGerald, L.M., Dickinson, J.L., Reilly, A., et al.: Does the addition of information on genotype improve prediction of the risk of melanoma and non-melanoma skin cancer beyond that obtained from skin phenotype? *Am. J. Epidemiol.* **159**(9), 826–833 (2004)
96. Zhang, D., Chen, C., Fu, X., Gu, S., Mao, Y., Xie, Y., et al.: A meta-analysis of DNA repair gene XPC polymorphisms and cancer risk. *J. Hum. Genet.* **53**(1), 18–33 (2008)
97. Blankenburg, S., Konig, I.R., Moessner, R., Laspe, P., Thoms, K.M., Krueger, U., et al.: Assessment of 3 xeroderma pigmentosum group C gene polymorphisms and risk of cutaneous melanoma: a case-control study. *Carcinogenesis* **26**(6), 1085–1090 (2005)
98. Blankenburg, S., Konig, I.R., Moessner, R., Laspe, P., Thoms, K.M., Krueger, U., et al.: No association between three xeroderma pigmentosum group C and one group G gene polymorphisms and risk of cutaneous melanoma. *Eur. J. Hum. Genet.* **13**(2), 253–255 (2005)
99. Millikan, R.C., Hummer, A., Begg, C., Player, J., de Cotret, A.R., Winkel, S., et al.: Polymorphisms in nucleotide excision repair genes and risk of multiple primary melanoma: the Genes Environment and Melanoma Study. *Carcinogenesis* **27**(3), 610–618 (2006)
100. Han, J., Colditz, G.A., Liu, J.S., Hunter, D.J.: Genetic variation in XPD, sun exposure, and risk of skin cancer. *Cancer Epidemiol. Biomarkers Prev.* **14**(6), 1539–1544 (2005)
101. Baccarelli, A., Calista, D., Minghetti, P., Marinelli, B., Albetti, B., Tseng, T., et al.: XPD gene polymorphism and host characteristics in the association with cutaneous malignant melanoma risk. *Br. J. Cancer* **90**(2), 497–502 (2004)
102. Debniak, T., Scott, R.J., Gorski, B., Cybulski, C., van de Wetering, T., Serrano-Fernandez, P., et al.: Common variants of DNA repair genes and malignant melanoma. *Eur. J. Cancer* **44**(1), 110–114 (2008)
103. Li, C., Liu, Z., Wang, L.E., Gershenwald, J.E., Lee, J.E., Prieto, V.G., et al.: Haplotype and genotypes of the VDR gene and cutaneous

- melanoma risk in non-Hispanic whites in Texas: a case-control study. *Int. J. Cancer* **122**(9), 2077–2084 (2008)
104. Houghton, A., Flannery, J., Viola, M.V.: Malignant melanoma in Connecticut and Denmark. *Int. J. Cancer* **25**(1), 95–104 (1980)
 105. Weinstock, M.A., Colditz, G.A., Willett, W.C., Stampfer, M.J., Bronstein, B.R., Mihm, M.C., et al.: Moles and site-specific cutaneous malignant melanoma in women. *J. Natl. Cancer Inst.* **81**, 948–952 (1989)
 106. Kruger, S., Garbe, C., Buttner, P., Stadler, R., Guggenmoos-Holzmann, I., Orfanos, C.E.: Epidemiologic evidence for the role of melanocytic nevi as risk markers and direct precursors of cutaneous malignant melanoma. *J. Am. Acad. Dermatol.* **26**, 920–926 (1992)
 107. Rieger, E., Soyer, H.P., Garbe, C., et al.: Overall and site-specific risk of malignant melanoma associated with nevus counts at different body sites: a multicenter case-control study of the German central malignant-melanoma registry. *Int. J. Cancer* **62**, 393–397 (1995)
 108. Chen, Y.T., Dubrow, R., Holford, T.R., Zheng, T., Barnhill, R.L., Fine, J., et al.: Malignant melanoma risk factors by anatomic site: a case-control study and polychotomous logistic regression analysis. *Int. J. Cancer* **67**(5), 636–643 (1996)
 109. Bataille, V., Sasieni, P., Grulich, A., Swerdlow, A., McCarthy, W., Hersey, P., et al.: Solar keratoses: A risk factor for melanoma but negative association with melanocytic naevi. *Int. J. Cancer* **78**, 8–12 (1998)
 110. Whiteman, D.C., Green, A., Parson, P.G.: p53 Expression and risk factors for cutaneous melanoma: a case-control study. *Int. J. Cancer* **77**, 843–848 (1998)
 111. Urso, C., Giannotti, V., Reali, U.M., Giannotti, B., Bondi, R.: Spatial association of melanocytic naevus and melanoma. *Melanoma Res.* **1**(4), 245–249 (1991)
 112. Marks, R., Dorevitch, A.P., Mason, G.: Do all melanomas come from “moles”? A study of the histological association between melanocytic naevi and melanoma. *Australas. J. Dermatol.* **31**(2), 77–80 (1990)
 113. Kaddu, S., Smolle, J., Zenahlik, P., Hofmann-Wellenhof, R., Kerl, H.: Melanoma with benign melanocytic naevus components: reappraisal of clinicopathological features and prognosis. *Melanoma Res.* **12**(3), 271–278 (2002)
 114. Carli, P., Massi, D., Santucci, M., Biggeri, A., Gianotti, B.: Cutaneous melanoma histologically associated with a nevus and melanoma de novo have a different profile of risk: results from a case-control study. *J. Am. Acad. Dermatol.* **40**, 549–557 (1999)
 115. Carli, P., Massi, D., Santucci, M., Biggeri, A., Giannotti, B.: Cutaneous melanoma histologically associated with a nevus and melanoma de novo have a different profile of risk: results from a case-control study. *J. Am. Acad. Dermatol.* **40**(4), 549–557 (1999)
 116. Skender-Kalnenas, T.M., English, D.R., Heenan, P.J.: Benign melanocytic lesions: risk markers or precursors of cutaneous melanoma? *J. Am. Acad. Dermatol.* **33**, 1000–1007 (1995)
 117. Green, A.: A theory of site distribution of melanomas: Queensland, Australia. *Cancer Causes Control* **3**, 513–516 (1992)
 118. Purdue, M.P., From, L., Armstrong, B.K., Krickler, A., Gallagher, R.P., McLaughlin, J.R., et al.: Etiologic and other factors predicting nevus-associated cutaneous malignant melanoma. *Cancer Epidemiol. Biomarkers Prev.* **14**(8), 2015–2022 (2005)
 119. Winnepenninckx, V., van den Oord, J.J.: p16INK4A expression in malignant melanomas with or without a contiguous naevus remnant: a clue to their divergent pathogenesis? *Melanoma Res.* **14**, 321–322 (2004)
 120. Autier, P., Dore, J.F., Cattaruzza, M.S., Renard, F., Luther, H., Gentiloni-Silverj, F., et al.: Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. *J. Natl. Cancer Inst.* **90**, 1873–1880 (1998)
 121. Gallagher, R.P., McLean, D.I., Yang, C.P., et al.: Suntan, sunburn and pigmentation factors and the frequency of acquired melanocytic nevi in children. *Arch. Dermatol.* **126**, 770–776 (1990)
 122. Wiecker, T.S., Luther, H., Buettner, P., Bauer, J., Garbe, C.: Moderate sun exposure and nevus counts in parents are associated with development of melanocytic nevi in childhood: a risk factor study in 1,812 kindergarten children. *Cancer* **97**(3), 628–638 (2003)
 123. Wachsmuth, R.C., Turner, F., Barrett, J.H., Gaut, R., Randerson-Moor, J.A., Bishop, D.T., et al.: The effect of sun exposure in determining nevus density in UK adolescent twins. *J. Invest. Dermatol.* **124**(1), 56–62 (2005)
 124. Green, A., Soroohan, T., Pope, D., et al.: Moles in Australian and British schoolchildren. *Lancet* **2**, 1497 (1988)
 125. English, D.R., Armstrong, B.K.: Melanocytic nevi in children. I. Anatomic sites and demographic and host factors. *Am. J. Epidemiol.* **139**, 390–401 (1994)
 126. Harrison, S.L., MacLennan, R., Speare, R., Wronski, I.: Sun exposure and melanocytic naevi in young Australian children. *Lancet* **344**, 1529–1532 (1994)
 127. Whiteman, D.C., Brown, R.M., Purdie, D.M., Hughes, M.C.: Melanocytic nevi in very young children: the role of phenotype, sun exposure, and sun protection. *J. Am. Acad. Dermatol.* **52**(1), 40–47 (2005)
 128. Fritsch, L., McHenry, P., Green, A., MacKie, R., Green, L., Siskind, V.: Naevi in schoolchildren in Scotland and Australia. *Br. J. Dermatol.* **130**, 599–603 (1994)
 129. Kelly, J.W., Rivers, J.K., MacLennan, R., Harrison, S., Lewis, A.E., Tate, B.J.: Sunlight: A major factor associated with the development of melanocytic nevi in Australian schoolchildren. *J. Am. Acad. Dermatol.* **30**, 40–48 (1994)
 130. Zhu, G., Duffy, D.L., Eldridge, A., Grace, M., Mayne, C., O’Gorman, L., et al.: A major quantitative-trait locus for mole density is linked to the familial melanoma gene CDKN2A: a maximum-likelihood combined linkage and association analysis in twins and their sibs. *Am. J. Hum. Genet.* **65**(2), 483–492 (1999)
 131. Wachsmuth, R.C., Gaut, R.M., Barrett, J.H., Saunders, C.L., Randerson-Moor, J.A., Eldridge, A., et al.: Heritability and gene-environment interactions for melanocytic nevus density examined in a U.K. adolescent twin study. *J. Invest. Dermatol.* **117**(2), 348–352 (2001)
 132. Whiteman, D.C., Watt, P., Purdie, D.M., Hughes, M.C., Hayward, N.K., Green, A.C.: Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J. Natl. Cancer Inst.* **95**(11), 806–812 (2003)
 133. Bulliard, J.L., De Weck, D., Fisch, T., Bordoni, A., Levi, F.: Detailed site distribution of melanoma and sunlight exposure: aetiological patterns from a Swiss series. *Ann. Oncol.* **18**(4), 789–794 (2007)
 134. Cho, E., Rosner, B.A., Colditz, G.A.: Risk factors for melanoma by body site. *Cancer Epidemiol. Biomarkers Prev.* **14**(5), 1241–1244 (2005)
 135. Naldi, L., Altieri, A., Imberti, G.L., Gallus, S., Bosetti, C., La Vecchia, C.: Sun exposure, phenotypic characteristics, and cutaneous malignant melanoma. An analysis according to different clinico-pathological variants and anatomic locations (Italy). *Cancer Causes Control* **16**(8), 893–899 (2005)
 136. Randi, G., Naldi, L., Gallus, S., Di Landro, A., La Vecchia, C.: Number of nevi at a specific anatomical site and its relation to cutaneous malignant melanoma. *J. Invest. Dermatol.* **126**(9), 2106–2110 (2006)
 137. Thomas, N.E.: BRAF somatic mutations in malignant melanoma and melanocytic naevi. *Melanoma Res.* **16**(2), 97–103 (2006)
 138. Lang, J., MacKie, R.M.: Prevalence of exon 15 BRAF mutations in primary melanoma of the superficial spreading, nodular, acral,

- and lentigo maligna subtypes. *J. Invest. Dermatol.* **125**(3), 575–579 (2005)
139. Thomas, N.E., Edmiston, S.N., Alexander, A., Millikan, R.C., Groben, P.A., Hao, H., et al.: Number of nevi and early-life ambient UV exposure are associated with BRAF-mutant melanoma. *Cancer Epidemiol. Biomarkers Prev.* **16**(5), 991–997 (2007)
140. Liu, W., Kelly, J.W., Trivett, M., Murray, W.K., Dowling, J.P., Wolfe, R., et al.: Distinct clinical and pathological features are associated with the BRAF(T1799A(V600E)) mutation in primary melanoma. *J. Invest. Dermatol.* **127**(4), 900–905 (2007)
141. Poynter, J.N., Elder, J.T., Fullen, D.R., Nair, R.P., Soengas, M.S., Johnson, T.M., et al.: BRAF and NRAS mutations in melanoma and melanocytic nevi. *Melanoma Res.* **16**(4), 267–273 (2006)
142. Edlundh-Rose, E., Egyhazi, S., Omholt, K., Mansson-Brahme, E., Platz, A., Hansson, J., et al.: NRAS and BRAF mutations in melanoma tumours in relation to clinical characteristics: a study based on mutation screening by pyrosequencing. *Melanoma Res.* **16**(6), 471–478 (2006)
143. Bauer, J., Curtin, J.A., Pinkel, D., Bastian, B.C.: Congenital melanocytic nevi frequently harbor NRAS mutations but no BRAF mutations. *J. Invest. Dermatol.* **127**(1), 179–182 (2007)
144. Landi, M.T., Bauer, J., Pfeiffer, R.M., Elder, D.E., Hulley, B., Minghetti, P., et al.: MC1R germline variants confer risk for BRAF-mutant melanoma. *Science* **313**(5786), 521–522 (2006)

Skin Cancer - A World-Wide Perspective

Dummer, R.; Pittelkow, M.R.; Iwatsuki, K.; Green, A.;
Elwan, N.M. (Eds.)

2011, XI, 398 p., Hardcover

ISBN: 978-3-642-05071-8