Photochemical & Photobiological Sciences

PERSPECTIVE

Cite this: *Photochem. Photobiol. Sci.*, 2018, **17**, 1853

Received 7th November 2017,
Accepted 7th August 2018

DOI: 10.1039/c7pp00411g

rsc.li/pps

Melanoma – role of the environment and genetics

Anne E. Cust,[a,b] Kriti Mishra[c] and Marianne Berwick *[d]

Melanoma rates have increased in populations that are mainly European. The main etiologic factor is ultraviolet radiation, from the sun as well as artificial tanning devices. Host factors such as skin color, number of nevi, hair and eye color and tanning ability are critical factors in modifying an individual's response to the sun. Genetic factors interact with host factors and environmental factors to increase risk. This review summarizes our current knowledge of environment and genetics on melanoma risk and on gene–environment interaction.

Introduction

Melanoma incidence rates have been increasing at more than 3% annually in mainly European-origin populations, with few exceptions.[1] The majority of the estimated 272 000 new cases of cutaneous melanoma diagnosed worldwide in 2013 were from North America, Europe, Australia and New Zealand.[2,3] The main etiological factor for melanoma is exposure to ultraviolet radiation (UVR),[4] both from the sun as well as artificial tanning devices. However, host factors, such as skin color, number of nevi, hair and eye color, and tanning ability are important factors that modify risk. Genetic factors also have an important role in the development of melanoma. New genes have been discovered from evaluating the genetics of families as well as large numbers of melanoma cases. This review summarises our current knowledge on the role of environment and genetics on melanoma risk, and on gene–environment interaction.

Environmental associations

Ultraviolet radiation – UVR

The entire ultraviolet radiation (UVR) spectrum is classified as carcinogenic to humans.[5,6] Since most of UVB (280–315 nm) is removed by stratospheric ozone, about 95% of the midday solar UVR reaching the Earth's surface is UVA (315–400 nm) and 5% UVB. Because individuals are exposed simultaneously to UVA and UVB when outdoors, it is difficult to distinguish between the effects of UVA and UVB in human studies. Both UVA and UVB are established risk factors for sunburn[7–9] and both UVB and UVA may cause melanoma.[4]

UVA and UVB cause DNA damage, and may lead to inadequate DNA repair with subsequent mutagenesis. UVA and UVB lead to both similar and different DNA damage responses, with some controversy over the precise role of UVA.[10,11] However, Moan *et al.* (1999) used epidemiologic data to show that there is a latitude gradient for the three major skin cancers, basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma, demonstrating that the latitude gradient of UVA for melanoma is similar to that for BCC and SCC, and thus UVA may also play a significant role in inducing melanoma in humans.[12] Wood *et al.* (2006) support this suggestion showing that melanin-sensitized oxidant production is a major cause of melanoma.[13] UVR is a complete carcinogen as it not only causes DNA damage but also modifies the body's immune response to carcinogens.[14]

Epidemiologic studies of UVR and melanoma

Measurements of individual sun exposure vary between studies but are commonly classified as *intermittent* (short, intense sun exposure through activities such as sunbathing, outdoor recreations and holidays in sunny climates), *chronic* (more continuous, primarily occupational exposure) and *total* sun exposure (the sum of intermittent and chronic exposure). Many case-control and cohort studies have investigated the association between individual sun exposure and melanoma risk and the results have been summarized in several meta-analyses which showed general agreement in effect size regardless of when published.[4,15–19] Overall, there is strong evidence that an intermittent pattern of sun exposure increases melanoma risk.[17] Sunburn is a biological response to intermittent sun exposure in poorly adapted skin[20] and in multiple analyses a stronger predictor than intermittent exposure itself.[17]

Total lifetime sun exposure is positively associated with melanoma risk, but the relationship is weaker than that for

[a]*Cancer Epidemiology and Prevention Research, Sydney School of Public Health, The University of Sydney, Australia*
[b]*Melanoma Institute Australia, The University of Sydney, Australia*
[c]*University of New Mexico School of Medicine, Albuquerque, New Mexico, USA*
[d]*Division of Epidemiology, Biostatistics and Preventive Medicine, Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, USA. E-mail: Mberwick@salud.unm.edu*

intermittent sun exposure. Paradoxically, measures of more continuous (mainly occupational) sun exposure show no association or a weak inverse association with melanoma risk.

The summary relative risks (RR) and 95% confidence intervals (95% CI) for highest *versus* lowest category of exposure in meta-analyses of more than 50 studies were RR 2.0 (95% CI 1.7–2.4) for sunburn, RR 1.6 (95% CI 1.3–2.0) for intermittent, RR 1.0 (95% CI 0.9–1.0) for chronic and RR 1.3 (95% CI 1.0–1.8) for total sun exposure.[17] Moreover, significantly higher risk was found for intermittent than chronic exposure among studies that published results for both exposure patterns, RR 1.5 (95% CI 1.2–1.8) and RR 1.1 (95% CI 0.9–1.4), respectively.

Possibly this is due to the lower melanin content, sunburn, and lower DNA repair capacity of intermittently exposed skin compared to habitually exposed skin. Sunburn can lead to cell proliferation in replacing apoptotic cells, and habitually exposed skin may have a somewhat thicker stratum corneum, and thus modest protection from tanning, and some upregulation of DNA repair pathways exemplified by fewer thymine dimers after repeated low exposures.[20–23]

Childhood sun exposure in relation to melanoma is difficult to evaluate but is likely to be the most deleterious time of life for sun exposure and subsequent development of melanoma. Migrant studies show that children who migrate to a sunnier country from a less sunny country before the age of 10 adopt the incidence rates of the new country.[24,25] Berwick *et al.* (2014) found that higher UVB dose in early life (age 10) was associated with poorer survival from melanoma.[26] Kricker *et al.* (2007) showed that children at age 10 in the highest tertile of sunburns were at highest risk for melanoma.[27]

Early work by Vincent McGovern and Fears and colleagues led to the development of the intermittent exposure hypothesis of UVR causation of cutaneous melanoma,[28,29] in which melanomas are mainly produced by intermittent exposure to sunlight and are less common when sun exposure is received more or less continuously.[30] Holman *et al.* also proposed two distinct biological pathways by which cutaneous melanoma might develop, one by way of intermittent sun exposure acting primarily as a promoter of melanoma arising in pigmented nevi and mainly of the superficial spreading type and the other by way of a more continuous pattern of sun exposure leading principally to lentigo maligna melanoma.[30] Whiteman *et al.* also advanced a dual or divergent pathway hypothesis for cutaneous melanoma in which "cutaneous melanomas may arise through two pathways, one associated with melanocyte proliferation [or nevus development] and the other with chronic exposure to sunlight"; both pathways include early initiation by sun exposure, but later proliferation is driven in one pathway by host factors in nevus prone people and in the other pathway by accumulation of sun exposure in non-nevus prone people.[31]

Further evidence for the crucial role of UVR in cutaneous melanoma development along these two biological pathways also comes from somatic mutations in the tumour cells. Primary melanomas are characterized by mutations in BRAF, NRAS and TERT, and about 80% of melanomas carry UVR signature mutations (C–T or CC–TT).[32,33] Most of these are considered "passenger" mutations and not "driver" mutations; however, this high prevalence is clearly indicative of a role for UVR in melanomogenesis as is noted also by presence of somatic mutations in normal skin.[34] BRAF mutations, which are present in about 40% of cutaneous melanomas in people of European origin, are associated with characteristics of the nevus-associated pathway: younger age at diagnosis, occurrence on the trunk, superficial spreading type melanoma and absence of chronic sun damage in the skin.[35] NRAS mutations appear not to be associated with nevus count or tumours that show evidence of neval remnants[36] and were associated with chronic sun damage, or solar elastosis, in the skin. In an analysis of 912 patients with first primary cutaneous melanoma, the population-based international Genes, Environment and Melanoma (GEM) study found that 13% of melanomas had an NRAS exon 2 or 3 mutation, 30% had a BRAF exon 15 mutation (associated with UVR exposure), and 57% were wildtype (neither NRAS nor BRAF mutation).[37] TERT promoter mutations (associated with UVR exposure) are present in about 43% of cutaneous melanomas, occur more frequently at sun-exposed sites than non-exposed sites, and tend to co-occur with BRAF alterations.[38]

Indoor tanning

Exposure to indoor tanning (also referred to as sunbeds or solariums) is common in western countries, especially among adolescents and young adults,[39] and there is convincing evidence that using indoor tanning devices is associated with an increased risk of melanoma and keratinocyte skin cancers.[40] The association between indoor tanning and melanoma risk is stronger for younger people and for people exposed to indoor tanning at a younger age.[41–43] A meta-analysis of 27 studies found that, compared to never-users, melanoma risk increased by 20% (95% CI 8–34%) for indoor tanning on at least one occasion, and the risk was higher (59% increase, 95% CI 36–85%) with first use at <35 years of age.[41] There was also a dose–response relationship with number of indoor tanning sessions per year associated with increasing melanoma risk (estimated as 1.8%, 95% CI 0–3.8% per extra session).[41] The strength of the scientific evidence on the risk of indoor tanning and the fact that the impact on melanoma risk is weighted more heavily towards young people helped lead to banning of commercial indoor tanning in Brazil and Australia,[44] and regulatory changes in other countries.

Additional risk factors

Nevi. The association of sun exposure with melanoma risk may be influenced by other factors such as phenotype. For example, nevus-prone people may require only modest sun exposure to initiate melanoma.[42,45] Although the presence of multiple nevi is the strongest risk factor for melanoma, it is under genetic control[46] and there is an interaction between sun exposure and nevi that has been observed in this and other investigations.[47] A study of Australian children found

that increased sun exposure in childhood was significantly associated with an increased number of nevi.[48] A separate study of more than 11 000 European children found that sunburns and holidays in the south were significantly associated with high nevus counts and the occurrence of atypical nevi.[49] Thus, sun exposure also induces nevus development, which subsequently affects risk of melanoma. While nevus number is an important risk factor for melanoma insofar as those with many nevi are at very high risk,[50,51] many individuals with melanoma do not have high numbers of nevi, but exhibit other types of risk factors, such as a fair complexion, or genetic factors that are only now being discovered.

Host phenotype. Pigmentation characteristics, such as skin color, eye color and hair color, are well-established host risk factors for melanoma. An inverse relationship has been consistently demonstrated between melanoma risk and degree of skin pigmentation.[47,50,52,53] Fair-skinned individuals have a much higher risk for developing melanoma than dark-skinned individuals, such that risk estimates in individuals of non-European descent, who are typically darker-skinned, are up to 10–20 fold less than in individuals of European descent, who are typically lighter-skinned.[54,55]

As with many factors affecting melanoma risk, the relationship with pigmentation characteristics is complicated and still not clearly understood.[56] Further complexities lie in the genetic variants associated with pigmentation.

Genetic associations

About 10% of people with melanoma report having a first- or second-degree relative with the disease,[57] which might be due to relatives sharing genetic risk factors or environmental risk factors, or both. The relative risk of melanoma in individuals with one or more affected first-degree relatives was estimated to be 2.06 (95% CI 1.72–2.45) from a meta-analysis of 22 studies, and they estimated that less than 7% of melanoma cases are attributable to familial risk.[58] Similar estimates of familial risk were obtained from a data linkage study of three million families and 30 000 melanomas in Sweden.[59] The standardized melanoma incidence ratio was 2.4 (95% CI 2.1–2.7) for offspring, 3.0 (2.5–3.5) for siblings; 9.0 (4.3–15.3) for siblings when both a parent and a sibling were affected, and 61.8 (5.8–227.2) for offspring whose parent had multiple melanomas.[59] Based on these estimates, they estimated the population attributable risk was less than 3%, accounting for a small proportion of the public health burden of melanoma in Sweden. Higher familial relative risks have been observed in North America than in Australia.[60]

High penetrance gene mutations. *CDKN2A*, a tumor suppressor gene involved in cell cycle control, tumor suppression and melanocyte senescence, was identified in 1994 as the first high-penetrance melanoma susceptibility gene.[61] Only about 2% of all melanoma cases in the population carry a germline *CDKN2A* mutation, but the probability is much higher when a strong family history of melanoma or multiple primary tumors are present.[62] Carriers of a *CDKN2A* mutation have a substantial lifetime risk of developing cutaneous malignant melanoma. Population-based estimates indicate that around 30–50% of mutation carriers will develop melanoma by age 80 years.[63] Lifetime risk estimates derived from clinic-based sampling of families with multiple cases of melanoma range from 58–90% penetrance by age 80 years.[64]

Mutations in the *CDK4* gene are also associated with very high risk of melanoma, however, are very rare and are only found in a handful of melanoma families worldwide.[65] There is also evidence for rare, high penetrance germline mutations in the BRCA-1 associated protein-1 (*BAP1*) gene,[65,66] Rb1 gene,[67] *POT1* gene involved in telomere maintenance,[68,69] and the telomerase reverse transcriptase (*TERT*) gene promoter.[70]

Low to medium-penetrance gene variants. Melanoma-risk gene variants have been identified in nevus development, sun sensitivity, telomere maintenance and other, poorly-characterized, pathways. The melanocortin-1 receptor (*MC1R*) gene, which encodes the melanocyte-stimulating hormone receptor, was identified as the first low-medium penetrance gene associated with melanoma risk.[71] It is one of the major genes that determine skin and hair color, although there is evidence that it acts *via* pigmentary and non-pigmentary pathways to influence melanoma development.[72,73] There are many common variants of *MC1R*; an international population-based study of 3301 people with melanoma observed 85 different variants, 10 of which occurred at a frequency >1%.[74] The prevalence of *MC1R* variants in populations of European origin is about 70% among the general population.[72,73] The variants D84E, R151C, R160W, D294H, R142H and I155T, are usually referred to as 'red hair color (RHC) phenotype' or 'R' variants (associated with red hair, fair skin, freckling and high sun sensitivity) and predict a greater than 2-fold increased risk of melanoma.[72,75] The other *MC1R* variants (usually referred to as 'r' or 'non-RHC') generally have a relatively weak association with red-hair color phenotype and have a weaker association with melanoma risk.[72,75] The summary odds ratios from a meta-analysis of 20 studies was 2.44 (95% CI 1.72–3.45) for RHC variants and 1.29 (1.10–1.51) for non-RHC variants.[75] Some people carry more than one variant, leading to a larger combined effect.[72] It is estimated that 21% of the familial aggregation of melanoma is explained by *MC1R* variants.[72]

Through whole genome sequencing of melanoma-prone families[76] and through a candidate-gene approach, *MITF*, the microphthalmia-associated transcription factor, has also been identified as a medium-penetrance melanoma susceptibility gene. *MITF* regulates several other genes whose functions in melanocytes range from development, differentiation, survival, cell-cycle regulation and pigment production.[76] The *MITF* E318K variant allele is relatively uncommon in the population (about 1% prevalence) and is associated with a 2–3 fold increased risk of melanoma, and higher for those with multiple primary melanomas or a family history of melanoma.[76] The E318K variant allele is associated with a higher nevus count and non-blue eye color.

International genome-wide association studies (GWAS) have led to the discovery of at least 20 common susceptibility

loci that have been reproducibly associated with cutaneous melanoma.[77] These include common variants in or near pigmentation genes, such as *MC1R*, *TYR*, *ASIP*, *SLC45A2*, *OCA2*, and *PLA2G6*; in loci associated with number of nevi, including *ATM*, *CDKN2A-MTAP*, *PLA2G6*, *CCND1* and *TERT*; and in genes acting through other biologic pathways such as telomere maintenance (*TERT*, *PARP1*, *OBFC1* and *ATM*) and DNA repair (*PARP1*, *ATM*). Variants found in the gene regions *ARNT-SETDB1*, *CASP8*, *RMDN2*, *CDKAL1*, *AGR3*, *RAD23B* and *MX2* are associated with melanoma but the functional mechanisms are uncertain.[77] An association has also been identified with a variant in the *FTO* gene, which appears to have a broader function than its obesity-related effects.[78] Several common gene variants for melanoma also overlap with other skin cancers, particularly pigmentation characteristics.[79] Highly exposed skin, such as that on the face and hands,[34] carries high levels of UVR mutations, so it should be noted that there is a great deal more to understanding melanomagenesis than simply mutational status. Additionally, the heritability of melanoma (*i.e.*, the proportion of variance in melanoma risk attributable genetic variance) has been estimated at 0.19–0.30.[80]

Translational studies. Knowledge of melanoma susceptibility genes can be translated into new possible targets for future therapies, and into more accurate melanoma risk prediction tools to support melanoma prevention and early detection strategies. Studies have demonstrated that common genetic factors improve discrimination, and may contribute as much, or more, to melanoma risk prediction as classical risk factors.[81–83] Continuing advances in genomic technologies have made it possible and feasible for genomic information to be available to the public for making health-related decisions about screening and prevention behaviors. Evaluating interventions that communicate personal genomic risk of melanoma to the public with the aim of motivating prevention or screening behaviors is a novel strategy that is being evaluated in some studies in Australia[84,85] and the US;[86,87] these studies are also considering the ethical, social, psychological, sociodemographic and economic impacts of these genomic-based approaches.

More broadly, precision medicine approaches could play a major role in melanoma prevention and screening and are an area of active research. For example, advances in genomics and risk prediction modelling allow a more personalized risk-stratified screening approach that is potentially more effective and efficient than screening based on age alone.[88–90] By stratifying the population into different risk groups using risk prediction models, screening could be tailored to each risk group, for example, with different start and end ages, screening intervals and modalities.[91] More precise melanoma risk assessment, coupled with personalization of screening regimens based on risk, may also derive maximal benefit of screening for subsets of the population at higher melanoma risk, while resulting in less screening and thus potential harm due to misdiagnosis or, in some countries, financial burden for those at lower risk.

Interactions between genes, phenotype and the environment. There are complex interactions between host characteristics, environmental exposures, and genomic factors in causing melanoma.[92] Among people carrying a *CDKN2A* mutation, carriage of *MC1R* variants was associated with melanoma diagnosis at a younger age and with development of multiple melanomas compared with *CDKN2A* mutation carriers with no *MC1R* variants.[93,94] Some studies have shown that sunburns, high levels of sun exposure and presence of nevi further add to melanoma risk for people with a CDKN2A mutation[64,92] while others have suggested no further increased risk associated with sun exposure.[63,95]

Sun exposure, as noted, is an important risk factor for melanoma. How sun exposure interacts with other genetic factors is important. Orlow *et al.* (2018) found that among those with certain variants of vitamin D receptor (VDR) genotypes low sun exposure increased the risk for dying from melanoma.[96] Kricker *et al.* (2010) found that variants in MC1R modified the effects of sun exposure to increase melanomas on the head and neck (P for interaction = 0.01).[97] Further, early life sun exposure modified the effects of MC1R on the later development of melanoma on the head and neck (P for interaction = 0.01).[97]

DNA repair is important for melanoma.[98] Han *et al.* 2005 reported several interactions of the repair variant XPD 751Gln and lifetime severe sunburns (P for interaction 0.03), cumulative sun exposure in a bathing suit (P for interaction 0.04), and a constitutional susceptibility score (P for interaction 0.02).[99] Other forms of ultraviolet radiation interact with DNA repair variants also. In one study FBRSL1 rs4883557 and ERCC6 rs10745261 interacted with indoor tanning (P for interaction = 0.0006) to increase risk for melanoma.[100]

In other analyses, it has been shown that variation in several genes, such as *MC1R* and *MITF*, is more strongly associated with melanoma in people with darker complexions compared to those with fairer complexions.[72,73,101] For example, risk for melanoma among *MITF* carriers with 'low risk' sun sensitivity and nevus phenotypes was as great or greater than among those with 'high risk' phenotypes with few exceptions.[101] This finding suggests that these genetic variants may assist in predicting risk of melanoma in people without classical risk factors.[101]

Further epidemiological studies are required to evaluate gene–gene and gene–environment interactions to better identify high risk groups and stratify prevention advice according to underlying risk. Additionally, there are many possibilities for interaction analyses that could either inform the biology of melanoma or support previous biological findings.

Conclusion

In summary, there is clear evidence that a fair phenotype (light eyes, light hair and skin that doesn't tan easily) and high levels of sun exposure are important risk factors for melanoma. New genetic studies are beginning to shed light

on important genetic factors that are independent or interact with sun exposure to increase risk for melanoma and also that combine together to increase risk. However, attention to basic measurement issues of UVR exposure and skin sensitivity continue to be necessary to evaluate genetic factors precisely.

Conflicts of interest

The authors have no conflict of interest to declare.

Notes and references

1 D. C. Whiteman, A. C. Green and C. M. Olsen, The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031, *J. Invest. Dermatol.*, 2016, **136**(6), 1161–1171.

2 C. Fitzmaurice, Burden of cancer in the Eastern Mediterranean Region, 2005–2015: findings from the Global Burden of Disease 2015 Study, *Int. J. Public Health*, 2018, **63**, 151–164.

3 J. Ferlay, E. Steliarova-Foucher, J. Lortet-Tieulent, S. Rosso, J. W. Coebergh, H. Comber, *et al.*, Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012, *Eur. J. Cancer*, 2013, **49**(6), 1374–1403.

4 IARC, *Solar and Ultraviolet Radiation*, 2012, vol. 100D, pp. 35–101.

5 1345607. Cancer, IAfRoP, IARC monographs on the evaluation of carcinogenic risks to humans: solar and ultraviolet radiation, *IARC Monogr. Eval. Carcinog. Risks Hum.*, 1992, **55**, 1–316.

6 F. El Ghissassi, R. Baan, K. Straif, Y. Grosse, B. Secretan, V. Bouvard, *et al.*, A review of human carcinogens–part D: radiation, *Lancet Oncol.*, 2009, **10**(8), 751–752.

7 R. W. Gange and C. F. Rosen, UVA effects on mammalian skin and cells, *Photochem. Photobiol.*, 1986, **43**(6), 701–705.

8 F. P. Gasparro, Sunscreens, skin photobiology, and skin cancer: the need for UVA protection and evaluation of efficacy, *Environ. Health Perspect.*, 2000, **108**(Suppl 1), 71–78.

9 A. R. Young, C. S. Potten, O. Nikaido, P. G. Parsons, J. Boenders, J. M. Ramsden, *et al.*, Human melanocytes and keratinocytes exposed to UVB or UVA in vivo show comparable levels of thymine dimers, *J. Invest. Dermatol.*, 1998, **111**(6), 936–940.

10 A. Besaratinia and G. P. Pfeifer, Measuring the formation and repair of UV damage at the DNA sequence level by ligation-mediated PCR, *Methods Mol. Biol.*, 2012, **920**, 189–202.

11 A. Q. Khan, J. B. Travers and M. G. Kemp, Roles of UVA radiation and DNA damage responses in melanoma pathogenesis, *Environ. Mol. Mutagen.*, 2018, **59**, 438–460.

12 J. Moan, A. Dahlback and R. B. Setlow, Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation, *Photochem. Photobiol.*, 1999, **70**(2), 243–247.

13 S. R. Wood, M. Berwick, R. D. Ley, R. B. Walter, R. B. Setlow and G. S. Timmins, UV causation of melanoma in Xiphophorus is dominated by melanin photosensitized oxidant production, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**(11), 4111–4115.

14 S. E. Ullrich and S. N. Byrne, The immunologic revolution: photoimmunology, *J. Invest. Dermatol.*, 2012, **132**(3 Pt 2), 896–905.

15 J. M. Elwood and J. Jopson, Melanoma and sun exposure: an overview of published studies, *Int. J. Cancer*, 1997, **73**(2), 198–203.

16 P. J. Nelemans, F. H. Rampen, D. J. Ruiter and A. L. Verbeek, An addition to the controversy on sunlight exposure and melanoma risk: a meta-analytical approach, *J. Clin. Epidemiol.*, 1995, **48**(11), 1331–1342.

17 S. Gandini, F. Sera, M. S. Cattaruzza, P. Pasquini, O. Picconi, P. Boyle, *et al.*, Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure, *Eur. J. Cancer*, 2005, **41**(1), 45–60.

18 S. Gandini, F. Sera, M. S. Cattaruzza, P. Pasquini, R. Zanetti, C. Masini, *et al.*, Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors, *Eur. J. Cancer*, 2005, **41**(14), 2040–2059.

19 Y. M. Chang, J. H. Barrett, D. T. Bishop, B. K. Armstrong, V. Bataille, W. Bergman, *et al.*, Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5700 cases and 7216 controls, *Int. J. Epidemiol.*, 2009, **38**(3), 814–830.

20 F. R. de Gruijl, UV adaptation: Pigmentation and protection against overexposure, *Exp. Dermatol.*, 2017, **26**(7), 557–562.

21 B. A. Gilchrest, M. S. Eller, A. C. Geller and M. Yaar, The pathogenesis of melanoma induced by ultraviolet radiation, *N. Engl. J. Med.*, 1999, **340**(17), 1341–1348.

22 P. Shih, L. G. Pedersen, P. R. Gibbs and R. Wolfenden, Hydrophobicities of the nucleic acid bases: distribution coefficients from water to cyclohexane, *J. Mol. Biol.*, 1998, **280**(3), 421–430.

23 J. M. Sheehan, N. Cragg, C. A. Chadwick, C. S. Potten and A. R. Young, Repeated ultraviolet exposure affords the same protection against DNA photodamage and erythema in human skin types II and IV but is associated with faster DNA repair in skin type IV, *J. Invest. Dermatol.*, 2002, **118**(5), 825–829.

24 H. Levine, A. Afek, A. Shamiss, E. Derazne, D. Tzur, N. Astman, *et al.*, Country of origin, age at migration and risk of cutaneous melanoma: a migrant cohort study of 1,100,000 Israeli men, *Int. J. Cancer*, 2013, **133**(2), 486–494.

25 M. Khlat, A. Vail, M. Parkin and A. Green, Mortality from melanoma in migrants to Australia: variation by age at

arrival and duration of stay, *Am. J. Epidemiol.*, 1992, **135**(10), 1103–1113.
26 M. Berwick, A. S. Reiner, S. Paine, B. K. Armstrong, A. Kricker, C. Goumas, *et al.*, Sun exposure and melanoma survival: a GEM study, *Cancer Epidemiol., Biomarkers Prev.*, 2014, **23**(10), 2145–2152.
27 A. Kricker, B. K. Armstrong, C. Goumas, M. Litchfield, C. B. Begg, A. J. Hummer, *et al.*, Ambient UV, personal sun exposure and risk of multiple primary melanomas, *Cancer Causes Control*, 2007, **18**(3), 295–304.
28 V. McGovern, Melanoblastoma, *Med. J. Aust.*, 1952, **1**(5), 139–142.
29 T. R. Fears, J. Scotto and M. A. Schneiderman, Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States, *Am. J. Epidemiol.*, 1977, **105**(5), 420–427.
30 C. D. Holman, B. K. Armstrong and P. J. Heenan, A theory of the etiology and pathogenesis of human cutaneous malignant melanoma, *J. Natl. Cancer Inst.*, 1983, **71**(4), 651–656.
31 D. C. Whiteman, P. Watt, D. M. Purdie, M. C. Hughes, N. K. Hayward and A. C. Green, Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma, *J. Natl. Cancer Inst.*, 2003, **95**(11), 806–812.
32 A. H. Shain, I. Yeh, I. Kovalyshyn, A. Sriharan, E. Talevich, A. Gagnon, *et al.*, The Genetic Evolution of Melanoma from Precursor Lesions, *N. Engl. J. Med.*, 2015, **373**(20), 1926–1936.
33 C. G. A. Network, Genomic Classification of Cutaneous Melanoma, *Cell*, 2015, **161**(7), 1681–1696.
34 I. Martincorena, A. Roshan, M. Gerstung, P. Ellis, P. Van Loo, S. McLaren, *et al.*, Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin, *Science*, 2015, **348**(6237), 880–886.
35 S. Y. Kim, S. N. Kim, H. J. Hahn, Y. W. Lee, Y. B. Choe and K. J. Ahn, Metaanalysis of BRAF mutations and clinicopathologic characteristics in primary melanoma, *J. Am. Acad. Dermatol.*, 2015, **72**(6), 1036–1046.
36 E. Hacker, C. M. Olsen, M. Kvaskoff, N. Pandeya, A. Yeo, A. C. Green, *et al.*, Histologic and Phenotypic Factors and MC1R Status Associated with BRAF(V600E), BRAF (V600 K), and NRAS Mutations in a Community-Based Sample of 414 Cutaneous Melanomas, *J. Invest. Dermatol.*, 2016, **136**(4), 829–837.
37 N. E. Thomas, S. N. Edmiston, A. Alexander, P. A. Groben, E. Parrish, A. Kricker, *et al.*, Association Between NRAS and BRAF Mutational Status and Melanoma-Specific Survival Among Patients With Higher-Risk Primary Melanoma, *JAMA Oncol.*, 2015, **1**(3), 359–368.
38 K. G. Griewank, R. Murali, J. A. Puig-Butille, B. Schilling, E. Livingstone, M. Potrony, *et al.*, TERT promoter mutation status as an independent prognostic factor in cutaneous melanoma, *J. Natl. Cancer Inst.*, 2014, **106**(9), DOI: 10.1093/jnci/dju246.
39 M. R. Wehner, M. M. Chren, D. Nameth, A. Choudhry, M. Gaskins, K. T. Nead, *et al.*, International prevalence of indoor tanning: a systematic review and meta-analysis, *JAMA Dermatol.*, 2014, **150**(4), 390–400.
40 S. Colantonio, M. B. Bracken and J. Beecker, The association of indoor tanning and melanoma in adults: systematic review and meta-analysis, *J. Am. Acad. Dermatol.*, 2014, **70**(5), 847–857.
41 M. Boniol, P. Autier, P. Boyle and S. Gandini, Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis, *BMJ*, 2012, **345**, e4757.
42 A. E. Cust, M. A. Jenkins, C. Goumas, B. K. Armstrong, H. Schmid, J. F. Aitken, *et al.*, Early-life sun exposure and risk of melanoma before age 40 years, *Cancer Causes Control*, 2011, **22**(6), 885–897.
43 D. Lazovich, R. Isaksson Vogel, M. A. Weinstock, H. H. Nelson, R. L. Ahmed and M. Berwick, Association Between Indoor Tanning and Melanoma in Younger Men and Women, *JAMA Dermatol.*, 2016, **152**(3), 268–275.
44 C. A. Sinclair, J. K. Makin, A. Tang, I. Brozek and V. Rock, The role of public health advocacy in achieving an outright ban on commercial tanning beds in Australia, *Am. J. Public Health*, 2014, **104**(2), e7–e9.
45 M. Kvaskoff, N. Pandeya, A. C. Green, S. Perry, C. Baxter, M. B. Davis, *et al.*, Solar elastosis and cutaneous melanoma: a site-specific analysis, *Int. J. Cancer*, 2015, **136**(12), 2900–2911.
46 V. Bataille, Genetics of familial and sporadic melanoma, *Clin. Exp. Dermatol.*, 2000, **25**(6), 464–470.
47 J. M. Satagopan, S. A. Oliveria, A. Arora, M. A. Marchetti, I. Orlow, S. W. Dusza, *et al.*, Sunburn, sun exposure, and sun sensitivity in the Study of Nevi in Children, *Ann. Epidemiol.*, 2015, **25**(11), 839–843.
48 S. L. Harrison, R. MacLennan, R. Speare and I. Wronski, Sun exposure and melanocytic naevi in young Australian children, *Lancet*, 1994, **344**(8936), 1529–1532.
49 M. Dulon, M. Weichenthal, M. Blettner, M. Breitbart, M. Hetzer, R. Greinert, *et al.*, Sun exposure and number of nevi in 5- to 6-year-old European children, *J. Clin. Epidemiol.*, 2002, **55**(11), 1075–1081.
50 C. M. Olsen, H. J. Carroll and D. C. Whiteman, Estimating the attributable fraction for cancer: A meta-analysis of nevi and melanoma, *Cancer Prev. Res.*, 2010, **3**(2), 233–245.
51 C. Garbe, P. Buttner, J. Weiss, H. P. Soyer, U. Stocker, S. Kruger, *et al.*, Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society, *J. Invest. Dermatol.*, 1994, **102**(5), 695–699.
52 R. Marks, Epidemiology of melanoma, *Clin. Exp. Dermatol.*, 2000, **25**(6), 459–463.
53 B. K. Armstrong and A. Kricker, The epidemiology of UV induced skin cancer, *J. Photochem. Photobiol., B*, 2001, **63**(1–3), 8–18.

54 M. A. Tucker and A. M. Goldstein, Melanoma etiology: where are we?, *Oncogene*, 2003, **22**(20), 3042–3052.

55 V. Bataille and E. de Vries, Melanoma–Part 1: epidemiology, risk factors, and prevention, *BMJ*, 2008, **337**, a2249.

56 D. Fajuyigbe and A. R. Young, The impact of skin colour on human photobiological responses, *Pigm. Cell Melanoma Res.*, 2016, **29**(6), 607–618.

57 N. K. Hayward, Genetics of melanoma predisposition, *Oncogene*, 2003, **22**(20), 3053–3062.

58 C. M. Olsen, H. J. Carroll and D. C. Whiteman, Familial melanoma: a meta-analysis and estimates of attributable fraction, *Cancer Epidemiol. Biomarkers Prev.*, 2010, **19**(1), 65–73.

59 K. Hemminki, H. Zhang and K. Czene, Familial and attributable risks in cutaneous melanoma: effects of proband and age, *J. Invest. Dermatol.*, 2003, **120**(2), 217–223.

60 C. B. Begg, A. Hummer, U. Mujumdar, B. K. Armstrong, A. Kricker, L. D. Marrett, *et al.*, Familial aggregation of melanoma risks in a large population-based sample of melanoma cases, *Cancer Causes Control*, 2004, **15**(9), 957–965.

61 A. Kamb, D. Shattuck-Eidens, R. Eeles, Q. Liu, N. A. Gruis, W. Ding, *et al.*, Analysis of the p16 gene (CDKN2) as a candidate for the chromosome 9p melanoma susceptibility locus, *Nat. Genet.*, 1994, **8**(1), 23–26.

62 M. Harland, A. E. Cust, C. Badenas, Y. M. Chang, E. A. Holland, P. Aguilera, *et al.*, Prevalence and predictors of germline CDKN2A mutations for melanoma cases from Australia, Spain and the United Kingdom, *Hered. Cancer Clin. Pract.*, 2014, **12**(1), 20.

63 A. E. Cust, M. Harland, E. Makalic, D. Schmidt, J. G. Dowty, J. F. Aitken, *et al.*, Melanoma risk for CDKN2A mutation carriers who are relatives of population-based case carriers in Australia and the UK, *J. Med. Genet.*, 2011, **48**(4), 266–272.

64 D. T. Bishop, F. Demenais, A. M. Goldstein, W. Bergman, J. N. Bishop, B. Bressac-de Paillerets, *et al.*, Geographical variation in the penetrance of CDKN2A mutations for melanoma, *J. Natl. Cancer Inst.*, 2002, **94**(12), 894–903.

65 L. G. Aoude, M. Gartside, P. Johansson, J. M. Palmer, J. Symmons, N. G. Martin, *et al.*, Prevalence of Germline BAP1, CDKN2A, and CDK4 Mutations in an Australian Population-Based Sample of Cutaneous Melanoma Cases, *Twin Res. Hum. Genet.*, 2015, **18**(2), 126–133.

66 M. Cheung, J. Talarchek, K. Schindeler, E. Saraiva, L. S. Penney, M. Ludman, *et al.*, Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma, *Cancer Genet.*, 2013, **206**(5), 206–210.

67 K. G. Griewank, R. A. Scolyer, J. F. Thompson, K. T. Flaherty, D. Schadendorf and R. Murali, Genetic alterations and personalized medicine in melanoma: progress and future prospects, *J. Natl. Cancer Inst.*, 2014, **106**(2), djt435.

68 C. D. Robles-Espinoza, M. Harland, A. J. Ramsay, L. G. Aoude, V. Quesada, Z. Ding, *et al.*, POT1 loss-of-function variants predispose to familial melanoma, *Nat. Genet.*, 2014, **46**(5), 478–481.

69 J. Shi, X. R. Yang, B. Ballew, M. Rotunno, D. Calista, M. C. Fargnoli, *et al.*, Rare missense variants in POT1 predispose to familial cutaneous malignant melanoma, *Nat. Genet.*, 2014, **46**(5), 482–486.

70 S. Horn, A. Figl, P. S. Rachakonda, C. Fischer, A. Sucker, A. Gast, *et al.*, TERT promoter mutations in familial and sporadic melanoma, *Science*, 2013, **339**(6122), 959–961.

71 P. Valverde, E. Healy, S. Sikkink, F. Haldane, A. J. Thody, A. Carothers, *et al.*, The Asp84Glu variant of the melanocortin 1 receptor (MC1R) is associated with melanoma, *Hum. Mol. Genet.*, 1996, **5**(10), 1663–1666.

72 A. E. Cust, C. Goumas, E. A. Holland, C. Agha-Hamilton, J. F. Aitken, B. K. Armstrong, *et al.*, MC1R genotypes and risk of melanoma before age 40 years: a population-based case-control-family study, *Int. J. Cancer*, 2012, **131**(3), E269–E281.

73 P. A. Kanetsky, S. Panossian, D. E. Elder, D. Guerry, M. E. Ming, L. Schuchter, *et al.*, Does MC1R genotype convey information about melanoma risk beyond risk phenotypes?, *Cancer*, 2010, **116**(10), 2416–2428.

74 P. A. Kanetsky, T. R. Rebbeck, A. J. Hummer, S. Panossian, B. K. Armstrong, A. Kricker, *et al.*, Population-based study of natural variation in the melanocortin-1 receptor gene and melanoma, *Cancer Res.*, 2006, **66**(18), 9330–9337.

75 P. F. Williams, C. M. Olsen, N. K. Hayward and D. C. Whiteman, Melanocortin 1 receptor and risk of cutaneous melanoma: a meta-analysis and estimates of population burden, *Int. J. Cancer*, 2011, **129**(7), 1730–1740.

76 S. Yokoyama, S. L. Woods, G. M. Boyle, L. G. Aoude, S. MacGregor, V. Zismann, *et al.*, A novel recurrent mutation in MITF predisposes to familial and sporadic melanoma, *Nature*, 2011, **480**(7375), 99–103.

77 M. H. Law, D. T. Bishop, J. E. Lee, M. Brossard, N. G. Martin, E. K. Moses, *et al.*, Genome-wide meta-analysis identifies five new susceptibility loci for cutaneous malignant melanoma, *Nat. Genet.*, 2015, **47**(9), 987–995.

78 M. M. Iles, M. H. Law, S. N. Stacey, J. Han, S. Fang, R. Pfeiffer, *et al.*, A variant in FTO shows association with melanoma risk not due to BMI, *Nat. Genet.*, 2013, **45**(4), 428–432.

79 A. Visconti, D. L. Duffy, F. Liu, G. Zhu, W. Wu, Y. Chen, *et al.*, Genome-wide association study in 176,678 Europeans reveals genetic loci for tanning response to sun exposure, *Nat. Commun.*, 2018, **9**(1), 1684.

80 Y. Lu, W. E. Ek, D. Whiteman, T. L. Vaughan, A. B. Spurdle, D. F. Easton, *et al.*, Most common 'sporadic' cancers have a significant germline genetic component, *Hum. Mol. Genet.*, 2014, **23**(22), 6112–6118.

81 A. E. Cust, C. Goumas, K. Vuong, J. R. Davies, J. H. Barrett, E. A. Holland, *et al.*, MC1R genotype as a predictor of early-onset melanoma, compared with self-reported and physician-measured traditional risk factors:

an Australian case-control-family study, *BMC Cancer*, 2013, **13**, 406.
82 S. Fang, J. Han, M. Zhang, L. E. Wang, Q. Wei, C. I. Amos, *et al.*, Joint effect of multiple common SNPs predicts melanoma susceptibility, *PLoS One*, 2013, **8**(12), e85642.
83 A. E. Cust, M. Drummond, P. A. Kanetsky, A. M. Goldstein, J. H. Barrett, S. MacGregor, *et al.*, Assessing the incremental contribution of common genomic variants to melanoma risk prediction in two population-based studies, *J. Invest. Dermatol.*, 2018, Epub ahead of print.
84 A. K. Smit, D. Espinoza, A. J. Newson, R. L. Morton, G. Fenton, L. Freeman, *et al.*, A Pilot Randomized Controlled Trial of the Feasibility, Acceptability, and Impact of Giving Information on Personalized Genomic Risk of Melanoma to the Public, *Cancer Epidemiol. Biomarkers Prev.*, 2017, **26**(2), 212–221.
85 A. K. Smit, A. J. Newson, R. L. Morton, M. Kimlin, L. Keogh, M. H. Law, *et al.*, The melanoma genomics managing your risk study: A protocol for a randomized controlled trial evaluating the impact of personal genomic risk information on skin cancer prevention behaviors, *Contemp. Clin. Trials*, 2018, **70**, 106–116.
86 J. L. Hay, M. Berwick, K. Zielaskowski, K. A. White, V. M. Rodriguez, E. Robers, *et al.*, Implementing an Internet-Delivered Skin Cancer Genetic Testing Intervention to Improve Sun Protection Behavior in a Diverse Population: Protocol for a Randomized Controlled Trial, *JMIR Res. Protoc.*, 2017, **6**(4), e52.
87 P. A. Kanetsky and J. L. Hay, Marshaling the Translational Potential of, *Cancer Prev. Res.*, 2018, **11**(3), 121–124.
88 N. Pashayan, Q. Guo and P. D. Pharoah, Personalized screening for cancers: should we consider polygenic profiling?, *Pers. Med.*, 2013, **10**(6), 511–513.
89 P. M. Marcus, N. Pashayan, T. R. Church, V. P. Doria-Rose, M. K. Gould, R. A. Hubbard, *et al.*, Population-Based Precision Cancer Screening: A Symposium on Evidence, Epidemiology, and Next Steps, *Cancer Epidemiol. Biomarkers Prev.*, 2016, **25**(11), 1449–1455.
90 C. G. Watts, A. E. Cust, S. W. Menzies, G. J. Mann and R. L. Morton, Cost-Effectiveness of Skin Surveillance Through a Specialized Clinic for Patients at High Risk of Melanoma, *J. Clin. Oncol.*, 2017, **35**(1), 63–71.
91 T. Dent, J. Jbilou, I. Rafi, N. Segnan, S. Tornberg, S. Chowdhury, *et al.*, Stratified cancer screening: the practicalities of implementation, *Public Health Genomics*, 2013, **16**(3), 94–99.
92 V. Chaudru, A. Chompret, B. Bressac-de Paillerets, A. Spatz, M. F. Avril and F. Demenais, Influence of genes, nevi, and sun sensitivity on melanoma risk in a family sample unselected by family history and in melanoma-prone families, *J. Natl. Cancer Inst.*, 2004, **96**(10), 785–795.
93 M. C. Fargnoli, S. Gandini, K. Peris, P. Maisonneuve and S. Raimondi, MC1R variants increase melanoma risk in families with CDKN2A mutations: a meta-analysis, *Eur. J. Cancer*, 2010, **46**(8), 1413–1420.
94 A. M. Goldstein, M. T. Landi, S. Tsang, M. C. Fraser, D. J. Munroe and M. A. Tucker, Association of MC1R variants and risk of melanoma in melanoma-prone families with CDKN2A mutations, *Cancer Epidemiol. Biomarkers Prev.*, 2005, **14**(9), 2208–2212.
95 C. B. Begg, I. Orlow, A. J. Hummer, B. K. Armstrong, A. Kricker, L. D. Marrett, *et al.*, Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample, *J. Natl. Cancer Inst.*, 2005, **97**(20), 1507–1515.
96 I. Orlow, Y. Shi, P. A. Kanetsky, N. E. Thomas, L. Luo, S. Corrales-Guerrero, *et al.*, The interaction between vitamin D receptor polymorphisms and sun exposure around time of diagnosis influences melanoma survival, *Pigm. Cell Melanoma Res.*, 2018, **31**(2), 287–296.
97 A. Kricker, B. K. Armstrong, C. Goumas, P. Kanetsky, R. P. Gallagher, C. B. Begg, *et al.*, MC1R genotype may modify the effect of sun exposure on melanoma risk in the GEM study, *Cancer Causes Control*, 2010, **21**(12), 2137–2147.
98 J. Reichrath and K. Rass, Ultraviolet damage, DNA repair and vitamin D in nonmelanoma skin cancer and in malignant melanoma: an update, *Adv. Exp. Med. Biol.*, 2014, **810**, 208–233.
99 J. Han, G. A. Colditz, J. S. Liu and D. J. Hunter, Genetic variation in XPD, sun exposure, and risk of skin cancer, *Cancer Epidemiol., Biomarkers Prev.*, 2005, **14**(6), 1539–1544.
100 S. M. Torres, L. Luo, J. Lilyquist, C. A. Stidley, K. Flores, K. A. White, *et al.*, DNA repair variants, indoor tanning, and risk of melanoma, *Pigm. Cell Melanoma Res.*, 2013, **26**(5), 677–684.
101 M. Berwick, J. MacArthur, I. Orlow, P. Kanetsky, C. B. Begg, L. Luo, *et al.*, MITF E318K's effect on melanoma risk independent of, but modified by, other risk factors, *Pigm. Cell Melanoma Res.*, 2014, **27**(3), 485–488.

