Predicting melanoma risk: theory, practice and future challenges

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Practice points

- Key risk factors for melanoma include age, place of residence, skin color, skin type, nevus burden, freckling tendency, past history of keratinocyte cancer and family history.
- Incorporating risk factor information into a single index to predict the likelihood of the occurrence of a melanoma in the near future has been attempted in multiple research settings; however, the indices appear to vary across populations.
- No risk prediction tools have yet been validated sufficiently to warrant widespread adoption.
- Practitioners are advised to take a clear history, documenting the salient factors noted above, and to examine the patient with particular reference to pigmentation phenotype, nevus density and freckling tendency.

SUMMARY The incidence of melanoma continues to rise in most fair-skinned populations. Strategies to curb the toll from melanoma include targeting the patients who are at highest risk with the aim of either preventing the onset of cancer or intervening early in order to improve survival. The challenge has been to synthesize the available information on risk factors into prediction tools with clinical utility, such that 'high-risk' patients can be identified with accuracy. While a number of risk prediction tools for melanoma have been developed, few have undergone rigorous evaluation of their performance in order to assess calibration or discrimination, and even fewer have been validated in independent populations. Future research should assess the validity of existing tools and seek to integrate the increasing volumes of data being generated by genomic studies.

The incidence of cutaneous melanoma continues to rise in most fair-skinned populations around the world. In Australia, melanoma is the fourth most commonly occurring invasive cancer, with an age-standardized incidence of 50 per 100,000 per year [1]. More than 75,000 Americans are diagnosed with invasive melanomas each year, at an incidence rate of 21 per 100,000 per year [2]. In both populations, rates have been rising in recent decades. Significant increases in melanoma incidence have also been reported in the UK, Canada, New Zealand and many European nations [3,4]. While melanoma mortality has also been rising in most countries, the rates of increase have been much less rapid than those observed for incidence.

In order to curb the toll from this cancer, two complementary strategies have been employed, with mixed success. Primary prevention campaigns aim to reduce the occurrence of new cases of melanoma by reducing population exposure to sunlight. Secondary prevention campaigns seek to reduce morbidity and mortality from melanoma through early detection or screening, based on the fact that survival is correlated inversely with melanoma thickness. Whereas

KEYWORDS

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primary prevention campaigns have typically been directed at entire communities or populations without regard to the actual risks of disease among individuals, most authorities recommend that melanoma surveillance be restricted to patients who are at ‘high risk’ of disease (Table 1). The challenge for practitioners is how to define a patient’s actual risk of melanoma, since none of the guidelines in effect around the world offer a validated algorithm through which melanoma risk might be estimated. Instead, practitioners are presented with diverse lists of factors that confer increased relative risks of melanoma and are then advised to identify high-risk patients and counsel them appropriately.

What is risk prediction & why is it important?

Risk prediction may be defined as the process of estimating the probability that a person will experience a given health event (in this instance, melanoma) during a specific time interval, based on their profile of risk factors. The rationale most often cited for developing

risk prediction tools for cancers and other chronic diseases – namely, the identification of high-risk groups for targeted prevention and surveillance – is widely accepted [5,6].

It has been only relatively recently that algorithms have been developed to synthesize these complex data into tools with practical utility for estimating disease risk. Much of the theory underpinning risk prediction has come from studies of cardiovascular disease. More recently, algorithms for predicting risks of common cancers have been developed [6], including for cancers of the breast [7], colorectum [8], prostate [9,10] and lung [11]. As will be discussed below, these prediction tools have been reasonably successful at identifying groups within the population that are at higher or lower risk of developing cancer, but have typically demonstrated quite limited ability to discriminate between patients with and without cancer at the individual level.

How are risk prediction tools generated?

There are three phases of research required before a risk prediction tool can be considered

Table 1. Guidelines from national agencies advocating the identification of patients who are at high risk for melanoma.		
Agency	Recommendation	Ref.
Cancer Council Australia, Cancer Society of New Zealand, Australasian College of Dermatologists	Recommend that general practitioners develop surveillance programs for patients who are at high risk Recommend that general practitioners assess patients who are concerned and develop appropriate management programs depending on their level of risk	[41]
US Preventive Services Taskforce	Clinicians should be aware that fair-skinned men and women older than 65 years of age, patients with atypical moles and those with more than 50 moles constitute known groups who are at substantially increased risk for melanoma. Other risk factors for skin cancer include family history and a considerable history of sun exposure and sunburns. Benefits from screening are uncertain, even in high-risk patients	[42]
UK Melanoma Study Group British Association of Dermatology	Patients who are at moderately increased risk of melanoma should be advised of this and taught how to self-examine. This includes patients with an atypical mole phenotype, those with a previous melanoma and organ transplant recipients (level Ia, grade B): <ul style="list-style-type: none">• Patients with giant congenital pigmented nevi are at increased risk of melanoma and require long-term follow-up (level IIIa, grade B)• Individuals with a family history of three or more cases of melanoma or of pancreatic cancer should be referred to a clinical geneticist or specialized dermatology services for counseling. Those with two cases in the family may also benefit, especially if one of the cases had multiple primary melanomas or an atypical mole phenotype (level IIa, grade B)	[43]
Australian Cancer Network	Clinical assessment of future risk of melanoma should take into account: <ul style="list-style-type: none">• The person’s age and sex• History of previous melanoma or nonmelanoma skin cancer• Number of nevi (common and atypical)• Family history of melanoma• Skin and hair pigmentation• Response to sun exposure• Evidence of actinic skin damage	[44]

for clinical use: development, validation and impact assessment [12].

• Development

Risk prediction tools are generally developed using data from epidemiologic studies comparing the characteristics of people with and without the disease in question. The aim is to generate the best mathematical formula for estimating a person's future risk of disease by incorporating information about their exposure to known risk factors. Importantly, the formula weights the information regarding each separate factor according to its influence in contributing to the overall risk of melanoma. Thus, factors that are found to be highly influential in conferring risk are weighted more heavily than factors of lesser influence. The weightings are derived using regression techniques that seek to 'explain' the patterns of variation between those with disease and those without. There is no limit to the numbers of predictive factors that can be included in the model, although in practice, tools with fewer items tend to be easier to use and have greater uptake than tools with more items. Moreover, there is the risk of 'overfitting' models when including many predictor terms; this means that the model is highly dependent upon the dataset from which it is derived. Overfitted models tend to perform poorly when tested in independent datasets, underscoring the desire to reduce any prediction model to the minimum number of terms to ensure good performance.

While data from prospective (cohort) studies are preferred for methodological reasons, most risk-prediction tools for cancer, and particularly for melanoma, have been developed using data from case-control studies [13–15]. In developing a tool, the basic steps are to identify those factors that are significantly associated with melanoma and then to measure the magnitude of their association. Consideration must be given to the types of predictive factors to be assessed. For the tool to have utility, the factors should be clearly defined, standardized, simple to measure and highly reproducible [5]. While such criteria are laudable, they present considerable challenges for melanoma prediction tools, where some of the strongest risk factors (e.g., numbers of nevi and numbers of sunburns) are measured with poor precision. A notable difference from etiologic research is

that, in building predictive models, there is no imperative to establish causality for the factors under consideration; on the contrary, many predictive factors will not be direct causes, but will nevertheless prove to be highly reliable, easy-to-measure predictors of melanoma [5].

Once the list of potentially predictive factors has been assembled, analysts then undertake an iterative process of fitting models until a final model is derived that provides the best performance. A full description of the statistical methods employed to achieve this outcome is beyond the scope of this article; interested readers are referred to other sources [12]. Of the model-building techniques available, there is broad consensus that a backwards-elimination procedure (whereby potential factors are progressively eliminated from a fully specified model through a process of statistically driven trial and error) is most likely to yield the best-performing model.

After a model has been derived from a dataset, the next step is to assess its performance. Two key measures of performance are calibration (i.e., how well do the melanoma risks as predicted by the model accord with the observed occurrence of melanoma in the population?) and discrimination (i.e., what is the likelihood that, given two individuals, one with melanoma and one without, the model will assign a higher score to the person with melanoma?). Calibration is typically assessed by separating the study participants (i.e., those with melanoma and those without melanoma) into ten categories based on their predicted probabilities of melanoma, and then plotting the proportion of participants in each category who are actually cases. A risk-prediction tool with near-perfect calibration will plot a line at a 45° angle (i.e., slope = 1), such that the group with the lowest predicted probability will contain no patients with melanoma and the group with the highest predicted probability will consist almost exclusively of patients with melanoma, with all intermediate categories scaled accordingly. Discrimination is reported using the area under the receiving operating characteristic curve (also known as the C statistic), which can take a value of between 0 and 1; values between 0.6 and 0.8 are typical for risk-prediction tools in chronic disease [6].

• Validation

Before a melanoma risk-prediction tool can be considered for clinical practice, its performance

should be assessed in other datasets [16]. This means using the fully specified predictive model derived from the original (test) dataset in order to predict the melanoma risk for patients in a different setting. Validation is necessary because the process of iteratively fitting and refitting models to find the best-performing algorithm tends to arrive at overly optimistic predictive tools. It is not until model performance has been assessed in an independent dataset that its utility can be measured objectively. Various approaches are taken in order to achieve this goal, depending upon the availability of data. Ideally, investigators should test their prediction tool in a sample of patients that is entirely independent from the derivation sample. This is seldom achieved in practice, since it requires a corresponding set of data measuring exactly the same factors in a second sample. Instead, internal validation is often undertaken, whereby the original dataset is split (e.g., 2:1) into two subsamples, with the larger subsample being used to derive the prediction model and the smaller subsample being used for validation. ‘Temporal validation’ is another approach in which patients diagnosed before an arbitrary date form the derivation set and those diagnosed after that date are used for validation. ‘Bootstrapping’ is another method of internal validation that involves creating a large number of new datasets sampled from within the original dataset.

• Impact

The final stage of the development process seeks to assess the influence of the prediction tool in changing clinical practice and/or patient outcomes. Whereas cardiovascular risk prediction tools have been rigorously evaluated for impact [17–19], the literature regarding the evaluation of cancer prediction tools is less mature. As more tools are developed, it is anticipated that their impact will be measured objectively.

Melanoma risk-prediction tools: what is the state of play?

Given the rising incidence of melanoma and its apparent amenability to primary and secondary prevention activities, it is perhaps not surprising that investigators have sought to identify those at the highest risk of disease in the hope that targeted interventions will be successful in reducing the burden of this disease. Since the 1980s,

an avalanche of epidemiologic research has confirmed the roles of the host phenotype and environment (principally exposure to sunlight and artificial ultraviolet radiation) in the development of melanoma. However, corraling these efforts into an easily applicable, valid tool has not been straightforward.

A recent, well-conducted systematic review of the literature identified 19 studies reporting 28 melanoma risk-prediction models [20]. The authors of that review noted marked variation in the methods through which the melanoma risk-prediction models were developed and evaluated, leading to a diversity of items that were measured. Indeed, at least 21 separate factors were reported across the 19 studies, including terms for demographic, phenotypic and clinical characteristics (summarized in Table 2; interested readers are directed to [20] for source material). The total number of factors included in each melanoma-prediction model ranged from two to 12; the median number of predictive factors per model was five and the modal number of factors was four (in seven out of 19 studies). The factor that was most commonly retained in the melanoma-prediction models was the number of melanocytic nevi on the skin (in 14 out of 19 models); other terms in descending order of frequency were age, hair color, skin type, sex, freckling and sunburn history (Table 3). Infrequently utilized predictors included the numbers of atypical nevi, genetic markers, place of birth and measures of exposure to artificial ultraviolet radiation. The absence of information for these putative predictors does not preclude their potential importance, but rather reflects the lack of research into their predictive ability.

Relatively few of the 19 published studies assessed the performance of the tools so derived; of the nine that did [21–28], discrimination (as measured by the C statistic) ranged from 0.62 to 0.86. Such figures are comparable with the performance of prediction tools for other cancers [20], including breast (0.63), colorectal (0.62–0.71), lung (0.63–0.88), prostate (0.52–0.93) and bladder cancers (0.70–0.81).

Only three [13,22,25] of the 19 studies assessed the calibration of their melanoma-prediction tools, and while there was no evidence that the tools were poorly calibrated, the statistical tests for assessing calibration are known to be weak. Thus, it remains an open question as to how well any of these tools perform in

assigning the general population to categories of melanoma risk. Only six studies had performed internal validation [15,21,22,25,26,28], and to date, only one melanoma risk prediction tool has been validated in an external dataset [23]. This tool, derived in an Italian population, was subsequently validated in a separate Brazilian population. Surprisingly, the tool performed with equal discrimination in both populations (area under the curve [AUC]: 0.79), and with similar accuracy in terms of correctly categorizing high-risk patients (89% in Italy vs 80% in Brazil).

In summary, while a relatively large number of studies have developed risk-prediction tools for melanoma, very little is known about the performance of such tools in 'real-life' clinical settings.

Online melanoma risk-prediction tools

In recent years, a number of online risk calculators have been developed (see [Table 4](#)). Several have been developed as web-based versions of the tools described in published studies, including those from the US National Cancer Institute (NCI) [24] and the Victorian Melanoma Service [29]. Others have been developed using established methods for risk prediction and have published their underlying effect estimates online [30], while the provenance of other online tools is unknown [31]. These tools share many common features, including a simple interface for personalized data entry linked to a back-end risk calculator that inserts the patient's responses into the model to generate a measure of risk. The NCI Melanoma Risk Assessment Tool estimates the absolute risk of developing melanoma within the next 5 years, based on US melanoma incidence rates for someone of the same age, sex, race and geographic residence as the patient, together with other characteristics. The majority of online calculators report relative risks, often using qualitative descriptors (e.g., 'above average risk' and 'very much above average risk', among others), which, on the one hand, convey meaning to patients, but are imprecise for the purposes of risk management.

• Limitations of existing tools

In addition to the methodological limitations outlined above (including the rarity of performance testing and internal or external validation), most risk-prediction tools for melanoma

Table 2. Relative frequency of melanoma risk factor assessment in 19 risk-prediction studies.

Factor	Relative frequency
Demographics	
Age	++++
Sex	+++
Phenotype	
Eye color	++
Skin color	++
Hair color	++++
Skin type	++++
Tanning	++
Nevi	+++++
Atypical nevi	++
Freckles	+++
Environmental	
UV – outdoor	++
UV – indoor	+
History of sunburn	+++
Place of birth	+
Place of residence	++
Clinical	
Personal history of melanoma	++
Family history of melanoma	+++
Personal history of nonmelanoma skin cancer	++
Suspicious lesion	++
Actinic skin damage	++
Genetic	
SNPs in candidate genes	++

+: <2 studies; ++: 2–4 studies; +++: 5–7 studies; ++++: 8–10 studies; +++++: >10 studies; SNP: Single-nucleotide polymorphism; UV: Ultraviolet.

are beset by design elements that limit their overall clinical utility. First, with at least one notable exception [23], most tools have been derived for use within a particular population, and the generalizability of models to new populations is open to question. Given the marked variation in melanoma incidence around the world, models that attempt to predict absolute risks of disease are unlikely to be transportable unless they specifically integrate information on the baseline incidence of melanoma in the region in which the patient resides. Other factors that impact on generalizability include the distribution of risk factors in the new population and whether there are other factors that are important for risk in the new population that are not captured by the model. Second, the datasets from which

Table 3. Composition of risk tools in 19 risk-prediction studies.

Study (year)	Age	Sex	Eye color	Skin color	Hair color	Skin type	Tanning	Nevi	Atypical nevi	Freckles	Sunburn
Stefanaki <i>et al.</i> (2013)											
Smith <i>et al.</i> (2012)											
Williams <i>et al.</i> (2011)											
Guther <i>et al.</i> (2011)											
Mar <i>et al.</i> (2011)											
Quereux <i>et al.</i> (2011)											
Fortes <i>et al.</i> (2010)											
Goldberg <i>et al.</i> (2007)											
Fears <i>et al.</i> (2006) [†]											
Cho <i>et al.</i> (2005)											
Whiteman <i>et al.</i> (2005)											
Fargnoli <i>et al.</i> (2004)											
Harbauer <i>et al.</i> (2003)											
Landi <i>et al.</i> (2001)											
Barbini <i>et al.</i> (1998)											
Marrett <i>et al.</i> (1992)											
Garbe <i>et al.</i> (1994)											
MacKie <i>et al.</i> (1989)											
English <i>et al.</i> (1988)											

Black squares indicate that the characteristic was featured in the prediction model published by the respective author.
[†]For the model of Fears *et al.* [24], the lightly shaded cells indicate that the factor was included in sex-specific models only.

the models have been developed have not been large enough to explore the effects of combinations of risk factors on melanoma risk. Hence, most tools to date have simply assumed that the risks associated with each predictive factor are multiplicative, yet this assumption has not been tested explicitly in large datasets and may be incorrect. Third, few melanoma-prediction tools have been derived using prospectively acquired data [25,26,32]; most have been derived from case–control data (either as single studies or meta-analyses) in which information on risk factors was acquired from melanoma patients after their diagnosis. The concern with such studies is that recall of past exposures may be subject to misclassification – both random and nonrandom – with consequences for estimates of risk. This limitation is particularly applicable to measures of past sun exposure and sunburn, which have been demonstrated to have low reproducibility [33,34], but is also applicable to many self-reported phenotypic characteristics that are bedeviled by measurement error. A related issue is that tools have been developed using measures that lack standard definitions or categories, making comparison of tools difficult

across studies. Similarly, all of the models have been derived from predetermined lists of risk factors that vary enormously from study to study. As highlighted in the recent systematic review [20], some factors that are already known to confer substantial risk of melanoma (such as family history, skin type or past history of skin cancer) were not tested for their predictive value in most studies. Obviously, if potentially predictive factors have not been recorded, then they cannot be incorporated into a final model, and so their contribution to risk prediction remains unknown.

Future developments in predicting the risks of melanoma

• Incorporating genetic data

The past decade has seen an explosion of genome-wide association studies directed towards identifying the constitutional genetic variants that affect melanoma risk. With pooled analyses, it is likely that data will be combined to produce ‘genetic risk scores’ so as to estimate melanoma risk, similarly to other chronic diseases [35]. Despite their appeal, early indications are that genetic data will contribute little

Table 3. Composition of risk tools in 19 risk-prediction studies (cont.).

NMSC	Time outdoors	UV lamps	Place of birth	Place of residence	PHx melanoma	FHx melanoma	Genes	Suspicious lesion	Actinic skin damage	Ref.
										[21]
										[45]
										[28]
										[26]
										[29]
										[22]
										[23]
										[32]
										[24]
										[25]
										[46]
										[47]
										[27]
										[48]
										[49]
										[13]
										[50]
										[14]
										[15]

Black squares indicate that the characteristic was featured in the prediction model published by the respective author.

[†]For the model of Fears *et al.* [24], the lightly shaded cells indicate that the factor was included in sex-specific models only.

improvement in performance, if any, to the current prediction models that are based on readily assessable phenotypic and clinical factors. Aside from very low-frequency variants in genes such as *CDKN2A* and *CDK4*, the somatic gene that is most consistently associated with cutaneous melanoma risk is *MC1R*, the melanocortin-1 receptor gene. Variants in this gene are very frequent in European populations and confer increased relative risks for melanoma in the order of 1.5–2.5 [36]. Dwyer *et al.* reported a negligible improvement in the performance of a melanoma-prediction model when *MC1R* genotype data were added to a base model that already included a term for skin pigmentation [37]. A more recent analysis in a Greek population undertook a similar exercise, assessing the additional performance of incorporating genetic information to a base model comprising phenotypic factors alone (i.e., eye color, skin color, sunburn, phototype and tanning) [21]. The AUC of the base model was 0.833. When the genotypes of the three most strongly associated genes were included, the AUC changed marginally to 0.837 (p-value for change in model performance: 0.42). The AUC for a final model including

basic phenotypes plus all eight significant genetic variants was 0.839 (p-value for change in model performance: 0.66). These data highlight the challenge of making use of genomic data for risk prediction, when the risk conferred by each variant is small and the number of potentially informative variants is large.

• Prospective studies

Virtually all melanoma-prediction tools have been derived using risk factor data acquired retrospectively through case–control study designs, raising questions about the validity of exposure measures. A number of large-scale prospective studies are currently in the field that have collected baseline information on melanoma risk factors and are following melanoma as a key end point. These studies, including the QSkin Study [38] in Queensland, Australia, the E3N Cohort [39] in France and The Women’s Lifestyle and Health Cohort [40] from Scandinavia, should be well placed to develop and validate melanoma-prediction tools using prospective data, thereby eliminating the concerns regarding recall bias that have plagued case–control studies.

Table 4. Online melanoma risk-prediction tools.

Organization	Tool	Factors assessed	Output	Ref.
US National Cancer Institute	Melanoma Risk Assessment Tool	Age, sex, place of residence, race, complexion, freckling, nevi >5 mm on the back, nevi <5 mm on the back, blistering sunburn and solar damage	Absolute risk of melanoma in the next 5 years	[51]
Victorian Melanoma Service, Australia	Emily's Melanoma Risk Calculator	Age, sex, place of residence, hair color, freckling, nevi on the arms, atypical nevi on the body, personal history of melanoma, personal history of NMSC and family history of melanoma	Relative risk of melanoma (qualitative)	[52]
Washington University School of Medicine, MO, USA	Your Disease Risk	Age, sex, hair color, eye color, skin type, nevi on the arms, sunburns as a child, immunosuppressive drugs, personal history of any cancer and family history of melanoma	Relative risk of melanoma (qualitative)	[30]
Norwest Skin Cancer Centre, Australia	Skin Cancer Risk Calculator	Age, sex, hair color, freckling, nevi on the arms, sunburns and previous SCC, BCC or melanoma	Relative risk of melanoma (qualitative)	[31]

BCC: Basal cell carcinoma; NMSC: Nonmelanoma skin cancer; SCC: Squamous cell carcinoma.

Conclusion & future perspective

The theoretical framework for developing and validating tools for predicting future risks of disease is now well understood. In the field of melanoma, there has been considerable activity in developing risk-prediction tools. However, the approaches undertaken have been piecemeal. Indeed, it is fair to conclude that the field has been hampered by the considerable variability in the sources and collection of data, the factors considered for inclusion in predictive models, the ways in which risk factors have been categorized for analysis, the choices of analytic models and the extent of performance assessment and validation. To date, there has been no systematic attempt to compare the performance of various models in independent datasets; such an endeavor could make a valuable contribution to our knowledge. Thus, in the absence of rigorous validation, no melanoma-prediction models

can be recommended for routine clinical practice at the present time. In the future, it is anticipated that large-scale prospective studies will offer opportunities for developing and validating prediction tools for melanoma.

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