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Development and external validation study of a melanoma risk prediction model based on self-assessed risk factors

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Abstract

Importance

Identifying individuals at high risk of melanoma can optimize primary and secondary prevention strategies.

Objective

To develop and externally validate a risk prediction model for incident first-primary cutaneous melanoma using self-assessed risk factors.

Design

We used unconditional logistic regression to develop a multivariable risk prediction model. Relative risk estimates from the model were combined with Australian melanoma incidence and competing mortality rates using the Gail method to obtain absolute risk estimates.

Setting

Population-based setting.

Participants

A risk prediction model was developed using the Australian Melanoma Family Study (628cases and 414 controls) and externally validated using four independent population-based studies: the Western Australia Melanoma Study (511 case-control pairs), Leeds Melanoma Case-Control Study (960 cases and 513 controls), Epigene-QSkin Study (44,544, of which 766 with melanoma), and Swedish Women's Lifestyle and Health Cohort Study (49,188 women, of which 273 with melanoma).

Main Outcomes and Measures

We validated model performance internally and externally by assessing discrimination using the area under the receiver operating curve (AUC). Additionally, using the Swedish Women's Lifestyle and Health Cohort Study, we assessed model calibration and clinical usefulness.

Results

The risk prediction model included hair colour, nevus density, first-degree family history of melanoma, previous non-melanoma skin cancer and lifetime sunbed use. On internal validation the AUC was 0.70 (95% CI 0.67-0.73). On external validation the AUC was 0.66 (95% CI 0.63-0.69) in the Western Australia Melanoma Study, 0.67 (95% CI 0.65-0.70) in the Leeds Melanoma Case-Control Study, 0.64 (95% CI 0.62-0.66) in the Epigene-QSkin Study, and 0.63 (95% CI 0.60-0.67) in the Swedish Women's Lifestyle and Health Cohort Study. Model calibration showed close agreement between predicted and observed numbers of incident melanomas across all deciles of predicted risk. In the external validation setting, there was higher net benefit when using the risk prediction model to classify individuals as high risk compared with classifying all individuals as high risk.

Conclusion and Relevance

The melanoma risk prediction model performs well, and may be useful in prevention interventions reliant on a risk assessment using self-assessed risk factors.

Background

Melanoma incidence has been increasing in predominantly fair-skinned populations, with Australia having the world's highest rates.[1] Primary prevention measures, based on sun protection, are a priority for reducing the melanoma burden.[2] Risk prediction models have been proposed as a more accurate and informative way of communicating risk,[3] and may lead to better preventive behaviours among those at high risk. Additionally, risk stratification may assist in planning intervention trials and targeting population prevention interventions.[4]

Most published melanoma risk prediction models have limited reporting of methods and results, and few have been externally validated.[5,6] External validation evaluates model performance using independent data, and is important before routine clinical use.[7] We aimed to develop a model for incident first-primary cutaneous melanoma based on self-assessed risk factors from the Australian Melanoma Family Study[8], and to externally validate the model in the Western Australian Melanoma Study,[9] the Leeds Melanoma Case-Control Study,[10,11] the Epigene-QSkin Study,[12,13] and the Swedish Women's Lifestyle and Health Cohort Study.[14,15]

Methods

Participants

The Australian Melanoma Family Study is a population-based, case-control-family study with 628 incident first-primary cutaneous melanoma cases, 231 controls and 183 spouse or friend controls from Brisbane, Sydney and Melbourne, Australia.[8] Cases were identified from state cancer registries and diagnosed between July 2000 and December 2002 at ages 18-39 years; participation was 54%. Controls were identified from the electoral roll (registration to vote is compulsory in Australia) and were frequency-matched to cases by city, age and sex; participation was 23%. Additionally cases were asked to nominate a spouse or friend as a

potential control participant; with 80% participation. Data were collected using self-administered and interviewer-administered questionnaires.

The Western Australia Melanoma Study is a population-based study with 511 case-control pairs.[9] Cases were identified from clinicians and pathology registers, and diagnosed between January 1980 and November 1981 at ages 10-80 years; participation was 76%. Controls were selected from the electoral roll and were frequency-matched to cases by electoral subdivision, age and sex; participation was 69%. Nurses collected data by administering a questionnaire and recording the number of raised nevi on the arm.

The Leeds Melanoma Case-Control Study is a population-based case-control study with 960 melanoma cases and 513 controls from Yorkshire, United Kingdom.[10,11] Cases were identified from clinicians, pathology registers and cancer registries, and diagnosed between September 2000 and December 2005 at ages 18-76 years; participation was 67%. Controls were selected from the cases' general practice (usually the practice nearest to their home residence) and were frequency-matched to cases by age and sex; participation was 55%. Data were collected using self-administered and telephone-administered questionnaires.

The Epigene-QSkin Study comprised harmonized variables for 766 melanoma cases from the Epigene case-case study[12] and 43,778participants without melanoma from the QSkin Cohort Study.[13] Cases were identified from pathology registers from the Brisbane region, Australia; and diagnosed between April 2007 and September 2010 at ages 18-79 years; participation was 52%. QSkin Cohort Study participants were randomly identified from the electoral roll, at ages 40-69 years and living in Queensland, Australia, between November 2010 and November 2011. Data were collected using self-administered questionnaires.

The Swedish *Women's* Lifestyle and Health Cohort Study is a prospective study with 49,188 women.[14,15] Participants were randomly identified from the Central Population Register at Statistics Sweden, at ages 30-50 years and living in the Uppsala Health Care Region in 1991 or 1992. Linkage of the cohort study to the national cancer registry to 31st December 2011 identified 273 women with incident first-primary melanoma. Data were collected using self-administered questionnaires. The Norwegian twin cohort to the Swedish Women's Lifestyle and Health Cohort Study was not included in the validation analyses because information on family history of melanoma was not collected.[15]

Model Development

We used unconditional logistic regression to derive a multivariable risk prediction model using the Australian Melanoma Family Study. The following self-assessed melanoma risk factors were used as candidate predictors: age, sex, city of recruitment, country of birth, ethnicity, skin colour, eye colour, natural hair colour at age 18 years, skin response to sunlight, nevus density (based on 4-level pictogram; eFigure1), freckle density (based on 6-level pictogram), personal history of non-melanoma skin cancer, first-degree family history of melanoma, blistering sunburn frequency (childhood and lifetime), sunbed use and sunscreen use.[16-20] We adjusted for age, sex and city of recruitment by keeping these variables in each step. Variables with p-values >0.05 were removed using backward selection. Continuous variables were analysed as a linear function, as p-values for non-linearity were >0.05, and then categorised in the final model. Effect modification was tested by adding terms for the interaction between each variable and each other variable included in the final model, one interaction term at a time. We used multiple imputation by chained equations with 10 imputed datasets to impute missing values.[21]

Age (a) from 0 to 85 were divided into 5 year age-groups j (j=1,2,…,16,17; $[0,\tau_1)$, $[\tau_1,\tau_2),\ldots,[\tau_{16},\tau_{17})$). Lifetime (to 85 years of age) and 20-year absolute risks (P) for an individual aged a with relative risk r , was estimated using the Gail method[22] by (i) calculating the attributable fraction (AF) from the distribution of relative risk among the cases[23], (ii) multiplying the Australian age-specific melanoma incidence rates (h_1*) by (1-AF) to give h_1, and (iii) using h_2, the mortality rates from causes other than melanoma between 2007 to 2009 (eTable1) as shown in the following formula.

$$P(a, \tau, r) = \sum_j \{h_{1j}r_j/(h_{1j}r_j+h_{2j})\}\{S_1(\tau_{j-1})/S_1(a)\}\{S_2(\tau_{j-1})/S_2(a)\}[1-\exp\{-5(h_{1j}r_j+h_{2j})\}];$$

where in the summation, the smallest j value satisfies $\tau_{j-1}=$ a, the largest j value satisfies $\tau_j=a+\tau$ and the value of τ is the time interval over which we calculate the absolute risk, for example to calculate 20-year absolute risk τ=20. S_1, the probability of remaining melanoma free up to age τ. τ_j, was estimated by $S_1(\tau_j)=S_1(\tau_{j-1})\exp(-5h_{1j}r_j)$, where $S_1(0)=1$. S_2, the probability of surviving competing risk up to age τ_j, was estimated by $S_2(\tau_j)=S_2(\tau_{j-1})\exp(-5h_2)$, where $S_2(0)=1$.

Model performance and validation

We evaluated model performance in the development dataset (internal validation) and externally using four independent validation datasets by assessing discrimination (the ability to distinguish between those with and without melanoma) using the area under the receiver operating characteristic curve (AUC), with values ranging from 0.5 (no better than chance) to 1 (perfect discrimination).[24] Additionally, we assessed calibration and clinical usefulness in the Swedish Women's Lifestyle and Health Cohort Study [15,25] over 20 years of follow up, by

examining the calibration plot, calibration slope, calibration-in-the-large, net benefit and decision curve (obtained from plotting the net benefit at different absolute risk thresholds). The calibration plot depicts the observed and predicted numbers of incident melanomas by deciles of predicted risk.[26] The calibration-in-the-large (intercept) and calibration slope (slope) is obtained from plotting the log odds of predictions as the predictor, with an intercept of 0 and slope of 1 indicating perfect calibration.[26] Net benefit was calculated by weighing the true-positive against the false-positive classifications at different absolute risk thresholds, the relative weight of the true-positive to false-positive classifications is determined by the absolute risk threshold, with higher net benefit indicating greater clinical usefulness.[27] We used bootstrapping procedures with 1000 repetitions to estimate 95% confidence intervals.

Variables in the validation datasets were harmonized to those in the risk prediction model. The number of raised nevi on the arms (in the Western Australia Melanoma Study) and large asymmetric nevi on lower limbs (in the Swedish Women's Lifestyle and Health Cohort Study) were matched to the approximate nevus counts shown on the Australian Melanoma Family Study pictograms (eFigure1). Data on sunbed use were not collected in the Epigene Study, thus we assumed that none of its participants used sunbeds. Lifetime (to 85 years of age) and 20-year absolute risks were estimated using the Gail method.[22] We excluded validation study participants who had missing values for any of the predictor variables.[28] The total participants included in the analyses and missing rates are shown in eTable2.

Studies were approved by the Human Research Ethic Committees at the University of Sydney, UK Multi-Centre (MREC), Patient Advisory Group (PIAG), QIMR Berghofer Medical Research Institute, and Swedish Data Inspection Board. Data were analysed using

Stata version 12 (for model development) and SAS version 9.3 (for model validation) with two-sided p-values. Statistical significance was inferred at $p<0.05$, except for interaction terms where we used a more stringent $p<0.01$ to allow for multiple testing .[29] We report methods and results in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement.[30]

Results

The final melanoma risk prediction model included hair colour, nevus density, first-degree family history of melanoma, previous non-melanoma skin cancer and sunbed use, with red hair colour and nevus density the strongest predictors of risk (Table 1). Sunbed use was associated with melanoma when analysed as a linear function (p-value= 0.043); but the p-value was 0.20 when categorised. There were no significant interactions between pairs of variables in the final model.

Relative risk estimates for the model predictors were generally similar in the development and validation datasets (Table 1). However, the relative risks for red hair colour in the Western Australian Melanoma Study, and personal history of non-melanoma skin cancer in the Leeds Melanoma Case-Control Study and Epigene-QSkin Study were lower than in the development model. Distributions of the predictor variables in the development and validation datasets are shown in eTable 2.

On internal validation the AUC was 0.70 (95% CI 0.67-0.73) in the development dataset. On external validation the AUC was 0.66 (95% CI 0.63-0.69) in the Western Australia Melanoma Study, 0.67 (95% CI 0.65-0.70) in the Leeds Melanoma Case-Control Study, 0.64 (95% CI 0.62-0.66) in the Epigene-QSkin Study, and 0.63 (95% CI 0.60-0.67) in the Swedish

Women's Lifestyle and Health Cohort Study. The calibration plot showed close agreement between predicted and observed numbers of incident melanomas across all deciles of predicted risk over 20 years of follow-up (Figure 1). In the lowest decile of predicted risk, for example, the model predicted an average of 11.89 melanomas and 11 melanomas were observed. Calibration-in-the-large was -0.20 (95% CI -0.21- -0.19), and calibration slope was 0.79 (95% CI 0.64- 0.95), indicating that the model might give an over-estimate of risk.

Figure 2 compares the decision curves from classifying individuals as high risk using the risk prediction model, classifying all individuals as high risk, and classifying all individuals as low risk (horizontal line at 0) over 20 years of follow up. Classifying individuals as high risk using the model had higher net benefit compared with classifying all individuals as high risk across all 20-year absolute risk thresholds. Classifying individuals as high risk using the model also had higher net benefit compared with classifying all individuals as low risk for 20-year absolute risk thresholds of 1% or less. However for 20-year absolute risk thresholds above 1%, classifying all individuals as low risk had higher net benefit than classifying individuals as high risk using the model. To demonstrate, if the absolute risk threshold for classifying individuals as high risk and warranting prevention intervention is 1% and 100,000 individuals are followed over 20 years, classifying individuals as high risk using the risk prediction model would identify 161 individuals expected to be diagnosed with melanoma (true-positive) and 15,265 individuals without melanoma (false-positive) as high risk. This has a positive net benefit of 0.00007 [calculated as: (true-positive classifications-(% risk threshold/(100-% risk threshold) × false-positive classifications))/ total number of participants= (161–(1/99 · 15,265))/100,000], as the benefit of true-positives outweighs the harms of false-positives at this absolute risk threshold. In comparison, classifying all individuals as high risk would identify 548 individuals expected to be diagnosed with

melanoma (true-positive) and 99,452 individuals without melanoma (false-positive) as high risk. This has a negative net benefit of -0.00456 [calculated as: (548- (1/99 · 99,452))/100,000], as the benefit of true-positives is outweighed by the harms of false-positives at this absolute risk threshold. Classifying all individuals as low risk has a net benefit of zero since there are no true-positives (no benefits) and no false-positives (no harms).

In matched case-control studies, the distribution of risk factors among controls is more similar to the cases than to the general population.[31] We conducted sensitivity analyses to reweight the age and sex distribution of the Western Australia Melanoma and Leeds Melanoma Case-Control studies' controls to the Western Australian and Leeds population respectively. This reweighting procedure did not change the AUC in the Western Australia Study and reduced the AUC to 0.60 (95%0.57-0.62) in the Leeds Melanoma Case-Control Study. This may be due to the small number of controls (and hence large weights) among the youngest age strata in the Leeds Melanoma Case-Control Study (eMethods1, eTable3, eTable4, eTable5). Melanoma incidence rates in Sweden have been increasing but are lower than Australian rates.[1] Sensitivity analyses to recalibrate the risk prediction model using Swedish melanoma incidence and mortality rates from 2009-2011 to estimate the 20-year absolute risk showed little change in model calibration (eMethods2, eTable6, eFigure2). However when we used the lower Swedish melanoma incidence rates from 1991-2011 to estimate the 20-year absolute risk, calibration was poorer (eTable7, eFigure3).

Discussion

This melanoma risk prediction model was developed for use in clinical and population interventions reliant on use of self-assessed risk factors. The model included hair colour, nevus density, first-degree family history of melanoma, previous non-melanoma skin cancer and lifetime sunbed use. The model showed good discrimination on internal validation (AUC= 0.70, 95% CI 0.67 - 0.73), with lower discrimination on external validation (AUCs ranging from 0.63 to 0.67 across the four validation datasets). The model was very well calibrated and had higher net benefit compared with classifying all individuals as high risk across all 20-year absolute risk thresholds.

For discrimination, the model compared well to risk prediction models for melanoma and other cancers. Systematic reviews of melanoma risk prediction models have shown AUCs ranging from 0.62 to 0.86 on internal validation.[5,32] In one of the few models with external validation, Fortes and colleagues reported an AUC of 0.79.[33] Discriminative performance tends to be higher when based on clinically measured nevi,[34] such as in the Fortes and colleagues model ;[33] probably because self-reports tend to underestimate nevus counts in comparison with clinical assessment.[35] AUCs of risk prediction models for other cancers ranged from 0.53 to 0.66 for breast cancer,[36] 0.62 to 0.75 for colorectal cancer,[37,38] 0.67 to 0.73 for lung cancer[39] and 0.52 to 0.93 for prostate cancer,[40] with poorer discrimination on external validation.[41]

A strength of our study was the use of calibration and newer model performance measures: net benefit and decision curve analyses using an independent cohort study. Previous melanoma risk prediction models that reported calibration used the Hosmer-Lemeshow test, which is sensitive to sample size[42] and has low power to detect overfitting of predictor effects.[24] Presenting the calibration plot, calibration-in-the large and calibration slope, as we

have done, is the preferred method.[7,26] To our knowledge, no other melanoma prediction model evaluated model performance using net benefit and decision curve analyses.[5,32,43] A few prediction models for other cancers have found, as we did, that using the model to classify individuals at high risk using reasonably low absolute risk thresholds had higher net benefit compared with classifying all individuals as high risk.[44-46]

Based on net benefit analyses, our model is most useful at classifying individuals as high risk and warranting risk-based interventions if the 20-year absolute risk threshold is 1% or less. In the Australian Melanoma Family Study,[8] our development dataset, 58% of participants had a model-estimated 20-year absolute risk of 1% or less. Examples of Australian Melanoma Family Study participants with a model-estimated 20-year absolute risk of 1% include: 1) a man aged 38 years with light brown hair, some nevi, no first-degree melanoma family history of melanoma, no personal history of non-melanoma skin cancer and 1 to 10 episodes of prior sunbed use; and 2) a woman aged 32 with light brown hair, many nevi, no first-degree melanoma family history, no personal history of non-melanoma skin cancer and no sunbed use. For 20-year absolute risk thresholds set at 1% or less, using the model to classify individuals as high risk for risk-based interventions would be better than either assuming everyone is high risk (intervening) and assuming everyone is low risk (not intervening). However, for 20-year absolute risk thresholds set above 1%, the model would be no better than assuming everyone is low risk (not intervening).

The choice of a risk threshold for intervention will likely vary depending on the efficacy and potential harms associated with the intervention and subsequent management for individuals classified as high risk. If the intervention and subsequent management has high efficacy and low potential harms, then the risk threshold for intervention will be low. In contrast, if the

intervention and subsequent management has low efficacy and high potential harms, then the risk threshold for intervention will be high.

Direct comparison with previous melanoma risk prediction models and validation studies is difficult due to differences in the study designs, predictor variable definitions, data handling and reporting. It is a potential limitation that our model was developed using a dataset in which all melanoma cases were less than 40 years old (i.e. early-onset) at diagnosis. Although there is some evidence that the strength of melanoma risk factors may vary with age,[19] our model performed well on external validation in older populations. Due to few cohort studies having melanoma risk factor data available for external validation, we were only able to evaluate model calibration and net benefit in women in the Swedish Women's Lifestyle and Health Cohort Study over 20 years of follow up. Predictor variables in the validation datasets were harmonised as closely as possible to those in the development model but sunbed use was not collected on all datasets. In assuming no sunbed use in the Epigene Study, and sunlamps to infer sunbed use in the Western Australia Melanoma Study, the discriminative performance of our model is probably an underestimate. Other potential limitations of our study include participation bias and inaccuracy of self-reported risk factors. The discriminative performance of our model would probably have been higher if based on clinically measured nevi,[45] but clinical measurement is more expensive, more time-consuming and less accessible than self-assessment.

This risk prediction model developed using self-assessed risk factors demonstrated good discrimination and calibration, and performed satisfactorily on external validation. It could be used to inform individuals of their risk of developing melanoma, and to stratify them into risk

categories using 20-year absolute risk thresholds of 1% or less for targeted primary and secondary prevention interventions. Feasibility, impact on care and cost-effectiveness should be prospectively evaluated before routinely using a model such as ours in clinical practice.

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Author Contributions

Drs Vuong and McGeechan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Vuong, Armstrong, Cust and McGeechan. Acquisition, analysis, and interpretation of data: Vuong, Armstrong, Cust and McGeechan. Drafting of the manuscript: Vuong, Armstrong, Cust and McGeechan. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Vuong, McGeechan, Davis and Olsen. Obtained funding: Vuong, Cust, Mann and Weiderpass. Study supervision: Armstrong, Cust and McGeechan.

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The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript, or decision to submit the manuscript for publication.

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Figure Legends

Figure 1. Observed and predicted numbers of incident melanomas by deciles of predicted risk over 20 years of follow up using Australian rates from 2007-2009. This graph compares the observed (blue line) and predicted numbers (red line) of incident melanomas by deciles of predicted risk over 20 years of follow up.

Figure 2. Decision curves obtained from plotting the net benefit at different 20-year absolute risk thresholds. This graph compares the decision curves from classifying individuals as high risk using the risk prediction model (blue line), classifying all individuals as high risk (red line), and classifying all individuals as low risk (horizontal line at 0) over 20 years of follow up. Net benefit at different 20-year absolute risk thresholds is calculated as (true-positive classifications – (% risk threshold/ (100 - % risk threshold) × false-positive classifications))/total number of participants.

Table 1. Relative risk[a] estimates for risk factors in the melanoma risk prediction model in the development and independent validation studies

	Melanoma risk prediction model[b]		Western Australian Melanoma Study[c]	Leeds Melanoma Case-Control Study	Epigene-QSkin Study[d]	Swedish Women's Lifestyle and Health Cohort[e]
Variable	Relative risk (95% CI)	P-value	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)
Hair colour						
Black	1.00		1.00	1.00	1.00	1.00
Light brown	1.24 (0.90-1.69)		1.37 (1.02-1.85)	1.6 (1.19-2.14)	1.13 (0.94-1.35)	2.13 (1.46-3.11)
Blonde	2.48 (1.65-3.75)		1.63 (1.09-2.44)	2.49 (1.70-3.65)	1.85 (1.51-2.27)	2.65 (1.79-3.93)
Red	4.29 (2.41-7.65)	<0.00001	1.77 (0.93-3.39)	4.35 (2.64-7.15)	3.49 (2.75-4.43)	3.78 (2.08-6.86)
Nevus density (self-reported)						
None	1.00		1.00	1.00	1.00	1.00
Few	1.37 (0.73-2.58)		1.72 (1.29-2.28)	1.78 (1.23-2.57)	1.2 (0.99-1.46)	1.96 (1.47-2.61)
Some	3.39 (1.80-6.38)		3.37 (2.01-5.67)	3.67 (2.45-5.51)	2.39 (1.92-2.98)	2.75 (1.56-4.87)
Many	5.24 (2.64-10.40)	<0.00001	7.77 (3.53-17.12)	4.62 (2.75-7.77)	5.35 (4.07-7.03)	4.39 (1.78-10.82)
First-degree melanoma family history						
No	1.00		1.00	1.00	1.00	1.00
Yes	1.91 (1.07-3.41)	0.03	2.22 (1.30-3.80)	2.43 (1.18-5.03)	1.61 (1.36-1.89)	2.13 (0.79-5.78)
Personal history of non-melanoma skin cancer						
No	1.00		1.00	1.00	1.00	n/a
Yes	3.18 (1.59-6.33)	0.001	3.37 (2.01-5.65)	1.35 (0.59-3.09)	0.88 (0.76-1.02)	n/a

Table continued

	Melanoma risk prediction model[b]		Western Australian Melanoma Study[c]	Leeds Melanoma Case-Control Study	Epigene-QSkin Study[d]	Swedish Women's Lifestyle and Health Cohort[e]
Variable	Relative risk (95% CI)	P-value	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)
Number of sunbed sessions						
None	1.00		1.00	1.00	n/a	1.00
1 to 10	0.95 (0.62-1.47)		0.91 (0.57-1.46)	0.96 (0.69-1.32)	n/a	
>10	1.59 (0.94-2.69)	0.20		0.88 (0.65-1.18)	n/a	1.58 (1.17-2.14)

[a]Odds ratios were used to estimate the relative risk.

[b] In the melanoma risk prediction model, the model intercept is 0.90 (95% CI -0.59-2.38) and attributable fraction is 0.75 (95% CI 0.73-0.77).

[c] In the Western Australian Melanoma Study, the number of raised nevi on the arms were matched to the approximate nevus counts shown on the Australian Melanoma Family Study nevus density pictograms and sunlamp use was used to infer sunbed use. For sunbed variable, all participants were assigned to none or 1-10 categories.

[d] In the Epigene Study, sunbed use was not collected, thus for this analysis, we assumed that none of its participants used sunbeds.

[e] In the Swedish Women's Lifestyle and Health Cohort Study, the number of large asymmetric nevi on lower limbs were matched to the approximate nevus counts shown on the Australian Melanoma Family Study nevus density pictograms. For sunbed variable, all participants were assigned to none or >10 categories.