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Development and external validation study of a melanoma risk prediction model incorporating clinically-assessed naevi and solar lentigines

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Novelty and Impact: We present a melanoma risk prediction model, which includes clinically-assessed whole-body naevi and solar lentigines, and self-assessed risk factors including pigmentation phenotype, sun exposure, family history and history of non-melanoma skin cancer. This model performs well on discrimination, the model's ability to distinguish between individuals with and without melanoma, and may assist clinicians to stratify patients by melanoma risk for targeted preventive interventions.

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Abstract

Melanoma risk prediction models could be useful for matching preventive interventions to patients risk. We developed a model incorporating clinical-assessed risk factors for incident first-primary cutaneous melanoma using unconditional logistic regression with backward selection on the Australian Melanoma Family Study (461 cases and 329 controls) and externally validated it using the Leeds Melanoma Case-Control Study (960 cases and 513 controls).

Candidate predictors included clinically-assessed whole-body naevi and solar lentigines, and self-assessed risk factors pigmentation phenotype, sun exposure, family history and history of non-melanoma skin cancer. We evaluated the predictive strength and discrimination of the model risk factors using odds per age- and sex-adjusted standard deviation (OPERA) and the area under curve (AUC), and calibration using the Hosmer-Lemeshow (H-L) test.

The final model included the number of naevi ≥2mm in diameter on the whole body, solar lentigines on the upper back (a 6-level scale), hair colour at age 18 years and personal history of non-melanoma skin cancer. Number of naevi was by far the strongest risk factor; the OPERA was 3.51 (95% CI 2.71-4.54) in the Australian study and 2.56 (95% CI 2.23-2.95) in the Leeds study. The AUC was 0.79 (95% CI 0.76-0.83) in the Australian study and 0.73 (95% CI 0.70-0.75) in the Leeds study. The H-L test p-value was 0.30 in the Australian study and <0.001 in the Leeds study.

This model incorporating clinically assessed risk factors had good discrimination, and could be used by clinicians to stratify patients by melanoma risk for the targeting of preventive interventions.

Introduction

Melanoma incidence has been increasing among fair-skinned populations, with the highest incidence rates in Australia, New Zealand, North America and Europe.[1] Risk factors include sun exposure, sunbed use, common and dysplastic naevi, Fitzpatrick skin type I and II, freckle density, skin colour, eye colour, hair colour, family history and a number of susceptibility genes, with sun exposure recognized as the major environmental risk factor.[2-5] Australian primary care prevention guidelines recommend a stratified approach to melanoma prevention, which includes: (1) sun protection for people at average melanoma risk, (2) sun protection and clinical-skin examinations for people at increased melanoma risk; and (3) sun protection, clinical-skin examinations and self-skin examinations for people at high melanoma risk.[6]

Risk prediction models provide a single personalised assessment of an individual's risk based on a combination of melanoma risk factors rather than relying on multiple individual risk factors, and may assist clinicians in matching preventive interventions to risk levels.[7] Many melanoma prediction models use self-assessed risk factors for reasons of feasibility, time and cost.[8] However, individuals tend to underestimate their naevus counts,[9] and clinically-assessed dermatological risk factors may improve model performance.[10] We aimed to develop a model for incident first-primary cutaneous melanoma using both clinically- and self-assessed risk factors from the Australian Melanoma Family Study,[11] and externally validate the model using the Leeds Melanoma Case-Control Study.[12]

Materials and methods

Study participants

Table 1 details the Australian and Leeds population-based case-control studies,[11, 12] which shared measurement protocols.

The Australian Melanoma Family Study is a population-based, case-control-family study.[11] Data were collected using self-administered and telephone-administered questionnaires, and skin examinations were conducted by dermatology trainees on 461 incident first-primary cutaneous melanoma cases and 329 controls from Brisbane, Sydney and Melbourne, Australia. Cases, diagnosed between July 2000 and December 2002 at ages 18-39 years, were identified from state cancer registries. Controls were identified from the electoral roll (registration to vote is compulsory in Australia) or nominated by cases, and were frequency-matched to cases by city, age and sex.

The Leeds Melanoma Case-Control Study is a population-based case-control study.[12] Data were collected using self-administered and telephone administered questionnaires, and skin examinations were conducted by research nurses on 960 incident first-primary cutaneous melanoma cases and 513 controls from Yorkshire, United Kingdom. Cases, diagnosed between September 2000 and December 2005 at ages 18-76 years, were identified from clinicians, pathology registers and cancer registries. Controls were identified from the cases' general practice (usually the practice nearest to their home residence), and were frequency-matched to cases by age and sex.

Model Development

The model was developed with the Australian study data.[11] All relevant candidate predictors were included: demographic factors- age, sex, city of recruitment; clinically-assessed factors- total number of naevi ≥2mm diameter, number of raised naevi ≥2mm in diameter, number of

dysplastic naevi ≥2mm in diameter, and solar lentigines on the upper back (based on a 6-level pictogram); and self-assessed risk factors- freckle density (based on 6-level pictogram), country of birth, ethnicity, skin colour, eye colour, natural hair colour at age 18 years, skin response to sunlight, height, weight, blistering sunburn frequency (childhood, lifetime), sunbed use, sunscreen use, personal history of non-melanoma skin cancer and first-degree family history of melanoma. Previous studies have shown fair to moderate agreement between clinically- and self-assessed skin colour, and good agreement between clinically-and self-assessed eye colour and hair color.[9] We have previously shown that a 'pigmentation phenotype score' derived from self-assessed risk factors comprising childhood freckling, skin colour, eye colour, hair colour, ability to tan and propensity to sunburn, gave the same improvement to discrimination in a melanoma risk prediction model as did a pigmentation phenotype score that incorporated clinically-assessed skin reflectance, eye colour and hair colour (incremental improvement to the AUC was 0.053 for the self-assessed score and 0.047 for the clinically-assessed score).[10] For this reason we selected self-assessed pigmentation phenotype risk factors because it is more efficient and less costly for patients to complete risk factor information in the waiting room than for the clinician to complete during the consultation. However, it was important to include clinically-assessed naevi and solar lentigines in the risk prediction model as these are usually more difficult for patients to assess and our previous study showed that clinical assessment of naevi and solar lentigines gave much higher improvement in the AUC than self-assessed naevi (incremental improvement to the AUC was 0.048 for self-assessed naevi, 0.111 for clinically-assessed naevi and 0.063 for clinically-assessed solar lentigines).[10]

We used unconditional logistic regression with backward selection in which the study design variables age, sex and city of recruitment were kept in each step and other variables with p-

values >0.05 were removed. Effect modification was tested by adding terms for the interaction between pairs of variables in the final model. Multiple imputation by chained equations with 10 imputed datasets was used to impute missing values.[13]

Relative risks and odds per age- and sex-adjusted standard deviation (OPERA)[14] were calculated as a way of comparing the predictive strengths , in terms of differentiating cases from controls, for variables included in the final model. As described elsewhere,[15] remaining lifetime (to 85 years of age) absolute risk was estimated using the Gail method[16] by combining relative risks with Australian melanoma incidence and competing mortality rates (Online Table 1).

Model performance and validation

The model was internally validated with the Australian study and externally validated with the Leeds study data.[11, 12] We assessed discrimination, the model's ability to distinguish between individuals with and without melanoma, using the area under curve (AUC).[17] In age and sex-matched case-control studies, the distributions of risk factors among controls may be more similar to cases than the general population;[18] we therefore reweighted the age and sex distribution of the control participants to the general population (Online Method 1). Bootstrap procedures were used with 1000 repetitions to estimate the 95% confidence intervals.

We assessed overall calibration, the agreement between the model's predicted and observed risk, using the Hosmer-Lemeshow (H-L) test, where the predicted and observed risks of melanoma were compared across deciles of predicted risk using a chi-square test, and a high test p-value indicates good overall calibration.[17] The predicted risk was applied to the logistic

regression model as a fixed term, while the intercept could vary to account for the higher proportion with melanoma in the case-control studies.

The same variables were used in both studies except for solar lentigines, which was not measured in the Leeds study. Instead, we used freckle density as a proxy for solar lentigines in the Leeds analysis, as there was moderate agreement between these variables in the Australian study (Spearman correlation coefficient=0.28, 95% CI 0.21-0.35, $p<0.001$). Leeds study participants with missing values for any of the predictor variables were excluded. Online Table 2 shows the distributions of the predictor variables in the analyses.

Ethical approvals were obtained from the University of Sydney and the relevant UK Multi Centre Ethics Committee (MREC) and Patient Information Advisory Group (PIAG). All participants gave written informed consent. Statistical analyses were conducted using Stata version 12 for model development and SAS version 9.3 for model validation. Two-sided statistical significance was inferred at $p<0.05$, except for interaction terms where $p<0.01$ was used to allow for multiple testing.[19] We report methods and results in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement.[20]

Results

The final model included the total number of naevi ≥2mm, solar lentigines on the upper back, hair colour at age 18 years and personal history of non-melanoma skin cancer. There were no significant interactions between pairs of variables in the final model. Relative risk and OPERA estimates are shown for both studies in Table 2, the number of body naevi ≥2mm in

diameter was by far the strongest predictor in terms of differentiating cases from controls on a population basis.

The AUC was 0.79 (95% CI 0.76-0.83) on internal validation in the Australian study and was 0.73 (95% CI 0.70-0.75) on external validation in the Leeds study. The AUC did not increase when the age and sex distribution was reweighted to the general population (Online Table 3). The H-L test p-value was 0.30 on internal validation and <0.001 on external validation. Figure 1 shows that the poor calibration for the Leeds study was due to the model under-estimating risk at lower risk levels and over-estimating risk at higher levels. In sensitivity analyses, calibration in the Leeds study did not improve when we re-calculated lifetime absolute risks using Leeds incidence and mortality rates, or when using naevus quartile cut-points based on the Leeds rather than Australian dataset (results not shown).

Discussion

This melanoma risk prediction model incorporating clinically-assessed naevi and solar lentigines had good discrimination that was maintained on external validation; and good overall calibration internally but less so externally. Consistent with previous melanoma risk prediction models, we observed higher melanoma risks and greater predictive strength from naevus counts equivalent to 10-20 fold interquartile risk ratios.[8] Solar lentigines mostly arise from prolonged sun exposure, and are a recognised melanoma risk factor,[21] but have not been included in previous models.[8]

This model's discrimination compares well with previous melanoma risk prediction models, which reported AUCs from 0.62 to 0.93, although most of these were not externally validated.[8, 22, 23] There is higher discriminative performance for models using clinically-

assessed than self-assessed dermatologic risk factors such as naevus counts, probably because they are more accurately measured by clinicians.[9] Our previous model using only self-assessed risk factors[15] reported lower AUCs, ranging from 0.63 to 0.70 on external validation, although this can be improved by incorporating data on common genomic variants.[24] The low p-value for the H-L test indicated poor overall calibration on external validation. Although the model was very good at discriminating melanoma risk level across both studies, the personal lifetime absolute risk estimates were less accurate in the Leeds study. However, in the absence of cohort studies with clinically-assessed melanoma risk factors, we were unable to estimate absolute measures of calibration or evaluate net benefit.

Strengths of our study include the multi-centred, population-based design, comprehensive assessment of risk factors and inclusion of clinically-assessed dermatologic risk factors in the model development and external validation. The Australian and Leeds study shared measurement protocols to ensure that risk factors were measured consistently across the studies and that clinical assessments were conducted with the same protocol. We used robust statistical approaches, including multiple imputation to impute missing data and external validation of the model in an independent population.

A limitation was the use of freckle density as a proxy for solar lentigines in the Leeds study. Although there was moderate correlation between freckle density and solar lentigines, solar lentigines were a stronger predictor than freckle density in the Australian study; thus the estimated external validation discriminative performance is probably an underestimate. Other potential limitations of case-control studies include possible selection bias and recall bias.[11]

In summary, this melanoma risk prediction model incorporating clinically-assessed risk factors has good discrimination, with ability to distinguish between individuals with and without melanoma across two populations with different ambient sun exposure. The model may be useful for offering tailored preventive interventions such as sun protection advice and skin screening based on personal risk level, in primary care and other clinical settings where dermatologic risk factors can be assessed. Prospective evaluation of the clinical risk prediction model will be important to estimate absolute calibration, net benefit, cost-effectiveness, and impact on risk behaviours or melanoma outcomes.

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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: All authors. Drafting of the manuscript: Vuong. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Vuong, McGeechan and Davis. Obtained funding: Vuong and Cust. 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.

Financial Disclosure of the Authors

None reported.

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Table 1. Summary of the Australian Melanoma Family Study (development dataset) and Leeds Melanoma Case-Control Study (external validation dataset)

Study	**Study design**	**Geographical location**	**Cases/ Controls**	**Case ascertainment**	**Control ascertainment**	**Diagnosis age**	**Diagnosis years**	**Data collection**
Australian Melanoma Family Study	Population-based case-control-family study	Brisbane, Sydney and Melbourne, Australia	461/329	State cancer registries	Electoral roll[a] and spouses or friends of cases	18-39 years	2000-2002	Skin examinations by dermatology trainees, and self-administered and telephone-administered questionnaires
Leeds Melanoma Case-Control Study	Population-based case-control study	Yorkshire, United Kingdom	960/513	Clinicians, pathology registers and cancer registries	General practice[b]	18-76 years	2000-2005	Skin examinations by research nurses, and self-administered and telephone-administered questionnaires

[a] Population-based controls were identified from the electoral roll and frequency-matched to cases by geographical location, age and sex; and spouse/friend controls were nominated by the cases.
[b] Controls were identified from the cases' general practice patient lists and were frequency-matched to cases by age and sex.

Table 2. Relative risk estimates[a] and odds per adjusted standard deviation (OPERA)[b] for the multivariable melanoma risk prediction model on the Australian Melanoma Family Study (development dataset) and Leeds Melanoma Case-Control Study (external validation dataset)

	Australia Melanoma Family Study		**Leeds Melanoma Case-Control Study[d]**	
Risk factor in the model[c]	**Relative risk[a] (95% CI)**		**Relative risk[a] (95% CI)**	
Total number of whole-body naevi ≥2mm diameter[e,f]				
< 28	1.00		1.00	
28-61	3.10 (1.47 - 6.53)		2.88 (2.15 – 3.86)	
62-143	6.74 (3.32 - 13.67)		6.28 (4.18 - 9.43)	
More than 144	20.03 (9.76 - 41.09)		28.72 (8.79 – 93.81)	
Solar Lentigines on upper back[d,e]				
<20%	1.00		1.00	
20%	1.41 (0.68 - 2.92)		2.71 (1.70- 4.31)	
40%	2.08 (0.97 - 4.46)		2.43 (1.52 – 3.87)	
60%	2.81 (1.25 - 6.29)		2.20 (1.34 – 3.61)	
80%	3.08 (1.40 - 6.76)		2.34 (1.36 – 4.03)	
100%	3.49 (1.29 - 9.41)		0.77 (0.35 -1.67)	
Hair colour at age 18				
Black/ dark brown	1.00		1.00	
Light brown	1.22 (0.80 - 1.85)		1.62 (1.19 – 2.20)	
Blonde	2.29 (1.30 - 4.03)		2.46 (1.64 – 3.68)	
Red	3.29 (1.39 - 7.78)		4.17 (2.45 – 7.09)	
Personal history of non-melanoma skin cancer				
No	1.00			
Yes	9.76 (2.09 – 45.54)		1.31 (0.56 - 3.04)	
Analysed as OPERAs[b]	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**
Total number of body naevi ≥2mm diameter [e,f]	3.51 (2.71-4.54)	<0.001	2.56 (2.23-2.95)	<0.0001
Solar Lentigines on upper back [d,e]	1.50 (1.19-1.89)	0.001	0.95 (0.83-1.08)	0.41
Hair colour at age 18 years	1.37 (1.15-1.63)	0.001	1.44 (1.27-1.64)	<0.0001
Personal history of non-melanoma skin cancer	1.12 (0.93-1.34)	0.236	0.98 (0.87-1.11)	0.81

[a] Odds ratios were used to estimate relative risks, and were adjusted for all other variables in the model as well as age, sex and city of recruitment.

[b] The OPERA scores are calculated for variables included in the prediction model to enable comparison of the predictive strengths, in terms of ability to differentiate cases from controls, of the risk factors across different diseases and populations using the formula OPERA= exp [In (RR)/A]=RR^{s}; where RR is relative risk, and A=1/s adjusted standard deviations.[14] The standard deviations were adjusted for age (in 5 year intervals) and sex using the control data. Given the difference between the upper and lower quartiles of a normal distribution is approximately 2.54 standard deviations, the estimated OPERA risk gradients are equivalent to interquartile risk

ratios of $3.51^{2.54} \sim 24$ (95% CI 13-47) for the total number of body naevi ≥ 2mm diameter, $1.50^{2.54} \sim 2.8$ (95% CI 1.6-5.0) for solar lentigines on the upper back, $1.37^{2.54} \sim 2.2$ (95%CI 1.4 -3.5) for hair colour at age 18 years, and $1.12^{2.54} \sim 1.3$ (95% CI 0.8 – 2.1) for personal non-melanoma skin cancer.

[c] The model intercept was 0.53 (95% CI 0.05 - 5.79) and attributable fraction, as calculated from the distribution of relative risk among the cases,[25] was 0.96 (95% CI 0.95-0.97).

[d] In the Leeds Melanoma Case-Control Study, freckle density categorized by the cut points 20%, 40%, 60%, 80%, 100% was used as a proxy for solar lentigines (Spearman correlation coefficient=0.28, 95% CI 0.21- 0.35, $p<0.0001$).

[e] Assessed from clinical examinations in dermatology clinics.

[f] Based on quartile cut-points in the Australian Melanoma Family Study controls.

Figure Legends

Figure 1. Observed versus predicted risk of incident melanomas across on internal and external validation. This graph compares the observed and predicted risk of incident melanomas on internal validation in the Australian Melanoma Family Study (blue line) and on external validation in the Leeds Melanoma Case-Control Study (orange line), with perfect overall calibration (black line).