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Risk Stratification for Melanoma: Models Derived and Validated in a Purpose-Designed Prospective Cohort

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Abstract

Background: Risk stratification can improve the efficacy and cost-efficiency of screening programs for early detection of cancer. We sought to derive a risk stratification tool for melanoma that was suitable for the general population using only self-reported information.

Methods: We used melanoma risk factor information collected at baseline from QSKIN, a prospective cohort study of Queensland adults age 40 to 69 years at recruitment (n = 41 954). We examined two separate outcomes: 1) invasive melanomas and 2) all melanomas (invasive + in situ) obtained through data linkage to the cancer registry. We used stepwise Cox proportional hazards modeling to derive the risk models in a randomly selected two-thirds sample of the data set and assessed model performance in the remaining one-third validation sample.

Results: After a median follow-up of 3.4 years, 655 (1.6%) participants developed melanoma (257 invasive, 398 in situ). The prediction model for invasive melanoma included seven terms. At baseline, the strongest predictors of invasive melanoma were age, sex, tanning ability, number of moles at age 21 years, and number of skin lesions treated destructively. The model for "all melanomas" (ie, invasive and in situ) included five additional terms. Discrimination in the validation data set was high for both models (C-index = 0.69, 95% confidence interval [CI] = 0.62 to 0.76, and C-index = 0.72, 95% CI = 0.69 to 0.75, respectively), and calibration was acceptable.

Conclusions: Such a tool could be used to target surveillance activities to those at highest predicted risk of developing melanoma over a median duration of 3.4 years.

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Melanoma incidence has increased steadily over the past three decades in most fair-skinned populations (1) and is projected to continue rising in the United States and other nations for several decades (2,3). The two main strategies employed to reduce the burden of melanoma are primary prevention and early detection. Whereas primary prevention seeks to reduce population exposure to sunlight and thereby reduce melanoma incidence, efforts to detect melanomas at an earlier stage (either through organized screening or other case-finding activities) aim to minimize the risk of invasion and metastasis, and thus reduce mortality from melanoma.

The efficacy of population-based screening for melanoma remains unproven (4,5). Instead, the advice in the United States and other countries is to offer screening only to individuals at high risk for melanoma, although no definition of "high risk" has been agreed on (6–10). Targeted screening of those at very high risk for melanoma (ie, family history and/or personal history and/or dysplastic nevus syndrome) has been shown to be both effective (11,12) and cost-efficient (13).

A number of models have been developed to estimate a person's future risk of melanoma, mostly using case–control data, which are prone to recall and other biases (14,15). While several

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models have been developed in prospective cohorts (16–19), only one of those cohorts collected comprehensive information on melanoma risk factors at baseline (17), and it was restricted to women. To date, none of the models developed from prospective data have been made publicly available. Here, we report the development of a tool intended for community use, with which to stratify people based on their predicted risk of melanoma into appropriate early detection activities.

Methods

Study Population

The QSkin Sun and Health Study is a prospective cohort study of men and women age 40 through 69 years at recruitment in 2011 who were sampled randomly from the Queensland population (n = 43 794). A description of the study design and methods has been published previously (20). Participants with a prior history of invasive or in situ melanoma (n = 1811) or who withdrew from the study after baseline (n = 29) were excluded; the eligible cohort included 41 954 participants.

The Human Research Ethics Committee at the QIMR Berghofer Medical Research Institute approved the study, and all participants gave written consent to take part. We adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines for reporting (Supplementary Materials, Tripod checklist, available online) (21).

Data Collection

At baseline, in addition to demographic items and general medical history, we asked participants to estimate their perceived risk of developing melanoma. Comprehensive information relating to known or suspected melanoma risk factors (including ethnicity, pigmentary and phenotypic characteristics, sun exposure, sun protection, use of tanning beds, skin examination practices, family history, and history of skin cancer) was collected via a self-completed survey (available online: https://qskin.qimrberghofer.edu.au/page/About/Baseline_survey).

Melanoma Case Confirmation

Data on all melanoma diagnoses from baseline up to December 31, 2014, were obtained via record linkage to the Queensland Cancer Registry (almost complete ascertainment), supplemented by pathology records when available. We examined two separate outcomes: invasive cutaneous melanomas and all cutaneous melanomas (invasive + in situ).

Candidate Predictor Variables

We selected 28 candidate predictor variables a priori. The demographic characteristics considered were age, sex, education, ethnicity, and private health insurance coverage. Phenotypic factors considered were self-reported eye, hair, and unexposed skin color; skin burning tendency and tanning ability; freckling density and nevus burden at age 21 years. Measures of sun exposure considered were sunburns as a child (<10 years), teenager/youth (10–20 years), and adult (>20 years), cumulative lifetime sun exposure, place of birth (Australia/other), latitude of place of birth ($<\pm45^\circ/\geq\pm45^\circ$), and use of tanning beds. Medical history variables considered were number of skin cancers (not melanomas) excised surgically, number of actinic skin lesions treated destructively, and family history of melanoma. Other factors considered were sunscreen and hat use, smoking status, and alcohol consumption. These items were self-reported at baseline; measures of repeatability and validity have been published (22). Personal history of other cancer (not skin; registry confirmed) was also considered as a candidate predictor.

Imputation of Missing Data

Missing values for most candidate predictor items occurred at a prevalence of less than 1%, but they were higher for the sunburn variables (Table 1; Supplementary Table 1, available online). To avoid potential bias, we imputed missing values for candidate predictors using the fully conditional specification method in PROC MI in SAS v9.4 (SAS Institute, Cary, NC), assuming that data were missing at random. We included all predictor variables and the outcome variable (23) in the imputation step, specifying logistic regression to impute ordinal variables. Imputation was run over five cycles to generate five data sets.

Statistical Analysis

We randomly selected a two-thirds sample of the data set to derive the prediction models (hereafter "derivation sample"; n = 27 975); and assessed model performance in the remaining one-third sample ("validation sample"; n = 13 979).

Risk Model Development

We used Cox proportional hazards modeling to derive the risk model. We tested the proportional hazards assumption for the final model in each imputed data set using the scaled Schoenfeld residuals test.

We first assessed the association between self-perceived risk and first primary melanoma development, and then proceeded to derive predictive models from the pool of 28 candidate variables. To select variables from five imputed development data sets, we used a stepwise selection process consisting of alternating forward selection and backward elimination steps. For each imputation, best subset variables were selected based on a 10% level of statistical significance (two-sided) using the type III test. The final model was run in all five imputed data sets, and we then combined the regression coefficients using a modified version of Rubin's rules suitable for categorical variables (24). We examined the estimates for the final models with and without taking into account competing risk of death (25). We tested two-way interactions between covariates.

In our primary analyses for invasive melanoma, we ignored events during follow-up because our tool estimates future risk; subsequent events cannot be known at the time of risk assessment. To examine the influence of this approach, we conducted a sensitivity analysis in which we censored in situ melanoma cases diagnosed during follow-up. Finally, to examine whether predictive factors differed according to age (<60 years, ≥60 years) and sex, we repeated the process within strata of these variables.

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Table 1. Distribution of selected characteristics of study participants in the QSkin cohort (n = 41 954)

Characteristic	Invasive melanoma cases (n = 257) No. (%)	In situ melanoma cases (n = 398) No. (%)	Noncases (n = 41 299) No. (%)	Total (n = 41 954) No. (%)
Age group, y				
40–49	37 (14.4)	71 (18.4)	11248 (27.2)	11356 (27.1)
50–50	93 (36.2)	137 (34.4)	15732 (38.1)	11962 (38.1)
60+	127 (49.4)	190 (47.7)	14319 (34.7)	14636 (34.9)
Sex				
Female	111 (43.2)	161 (40.5)	22693 (55.0)	22965 (54.7)
Male	146 (56.8)	237 (59.6)	18606 (45.1)	18989 (45.3)
Ethnicity				
Nonwhite	3 (1.2)	7 (1.8)	2666 (6.5)	2676 (6.4)
White	253 (98.4)	389 (97.7)	38213 (92.5)	38855 (92.6)
Missing	1 (0.4)	2 (0.5)	420 (1.0)	423 (1.0)
Private health insurance				
No	69 (26.9)	96 (24.1)	13850 (33.5)	14015 (33.4)
Yes	187 (72.8)	301 (75.6)	27245 (65.9)	27733 (66.1)
Missing	1 (0.4)	1 (0.3)	204 (0.5)	206 (0.5)
Tanning ability				
Tan deeply	26 (10.1)	74 (18.6)	9714 (23.5)	9814 (23.4)
Tan moderately	122 (47.5)	191 (48.0)	20230 (49.0)	20543 (49.0)
Tan a little	70 (27.2)	97 (24.4)	8463 (20.5)	8630 (20.6)
Not tan	36 (14.0)	34 (8.5)	2557 (6.2)	2627 (6.3)
Missing	3 (1.2)	2 (0.5)	335 (0.8)	340 (0.8)
Moles at age 21 y				
None	48 (18.7)	94 (23.6)	11638 (28.2)	11780 (28.1)
A few	128 (49.8)	186 (46.7)	21452 (51.9)	21766 (51.9)
Some	59 (23.0)	83 (20.9)	5896 (14.3)	6038 (14.4)
Many	17 (6.6)	28 (7.0)	1189 (2.9)	1234 (2.9)
Missing	5 (2.0)	7 (1.8)	1124 (2.7)	1136 (2.7)
Hair color				
Black	10 (3.9)	38 (9.6)	4195 (10.2)	4243 (10.1)
Dark brown	74 (28.8)	113 (28.4)	13805 (33.4)	13992 (33.4)
Light brown	109 (42.4)	149 (37.4)	15119 (36.6)	15377 (36.7)
Blond	29 (11.3)	54 (13.6)	5705 (13.8)	5788 (13.8)
Red/auburn	34 (13.2)	39 (9.8)	2228 (5.4)	2301 (5.5)
Missing	1 (0.4)	5 (1.3)	247 (0.6)	253 (0.6)
No. of previous skin cancers removed surgically				
0	97 (37.7)	144 (36.2)	25839 (62.6)	26080 (62.2)
1	37 (14.4)	67 (16.8)	5497 (13.3)	5601 (13.4)
2–10	91 (35.4)	141 (35.4)	8115 (19.7)	8347 (19.9)
11–20	19 (7.4)	23 (5.8)	931 (2.3)	973 (2.3)
20+	11 (4.3)	19 (4.8)	608 (1.5)	638 (1.5)
Missing	2 (0.8)	4 (1.0)	309 (0.8)	315 (0.8)
No. of previous skin lesions destroyed				
0	55 (21.4)	102 (25.6)	19381 (46.9)	19538 (46.6)
1–5	65 (25.3)	93 (23.4)	10796 (26.1)	10954 (26.1)
6–10	35 (13.6)	62 (15.6)	3741 (9.1)	3838 (9.2)
11–20	33 (12.8)	52 (13.1)	2996 (7.3)	3081 (7.3)
21–49	35 (13.6)	35 (8.8)	2285 (5.5)	2355 (5.6)
50+	33 (12.8)	51 (12.8)	1867 (4.5)	1951 (4.7)
Missing	1 (0.4)	3 (0.8)	233 (0.6)	237 (0.6)
Sunscreen use (past year)				
Never	30 (11.7)	63 (15.8)	8728 (21.1)	8821 (21.0)
Less than 50% of the time	121 (47.1)	172 (43.2)	17393 (42.1)	17686 (42.2)
More than 50% of the time	79 (30.7)	129 (32.4)	11207 (27.1)	11415 (27.2)
All the time	27 (10.5)	33 (8.3)	3722 (9.0)	3782 (9.0)
Missing	0	1 (0.3)	249 (0.6)	250 (0.6)
Skin checks by a doctor (past 3 y)				
None	38 (14.8)	45 (11.3)	11604 (28.1)	11687 (27.9)
Once	62 (24.1)	104 (26.1)	12183 (29.5)	12349 (29.4)
2–5 times	119 (46.3)	187 (47.0)	14053 (34.0)	14359 (34.2)

(continued)

Table 1. (continued)

Characteristic	Invasive melanoma cases (n = 257) No. (%)	In situ melanoma cases (n = 398) No. (%)	Noncases (n = 41 299) No. (%)	Total (n = 41 954) No. (%)
More than 5 times	36 (14.0)	59 (14.8)	2477 (6.0)	2572 (6.1)
Missing	2 (0.8)	3 (0.8)	982 (2.4)	987 (2.4)
Family history of melanoma				
No	151 (58.8)	231 (58.0)	25859 (62.6)	26241 (62.6)
Yes	77 (30.0)	120 (30.2)	9131 (22.1)	9328 (22.2)
Missing	29 (11.3)	47 (11.8)	6309 (15.3)	6385 (15.2)

Model Validation

We assessed the model performance using tests for discrimination and calibration. We evaluated discrimination using the C-index and its 95% confidence interval (CI) (26). Rubin's rules were applied to pool the C-index from the five imputed data sets. A C-index of 0.5 indicates discrimination no better than chance, and a C-index of 1.0 indicates perfect discrimination.

To assess calibration, we calculated a linear predictor score for each individual in the development and validation samples based on our model coefficients, and then defined five risk groups based on the quintiles of score among cases, as described by Royston (27). We estimated cumulative hazard at observed time points for each risk group in both the development and validation samples (27) and then plotted the expected vs observed cumulative hazard curves for each risk group (28).

To assess the tool's utility to guide targeted screening (ie, risk stratification), we calculated the "number needed to screen" for different scenarios in which melanoma screening was restricted to groups of individuals defined by their predicted risk score. We calculated the Youden index (29) for each decile of predicted risk to identify the "optimal" cutoff point at which both sensitivity and specificity were maximized. (29). Finally, we conducted decision curve analyses to evaluate the clinical utility of the model across a range of risk thresholds for screening (30,31).

Results

Patient Characteristics

Of 41 954 eligible participants, 54.7% were women, and the mean age was 56 years. Most participants reported white European ancestry (92.6%), and most were born in Australia (80.2%). The mean follow-up time was 3.5 years (median = 3.4 years, interquartile range = 3.3–3.8 years). Distributions of factors that were statistically significant in the final models ($P < .05$) are presented in Table 1 by outcome status; the distribution of statistically nonsignificant candidate predictor items by outcome status is presented in Supplementary Table 1 (available online). During follow up, 655 (1.6%) participants developed melanoma (257 invasive melanomas, 398 in situ melanomas). Of the invasive cases, 75.9% were less than 1 mm and 60.7% were of the superficial spreading subtype (Supplementary Table 2, available online). Key variables were distributed similarly in development and validation samples (Supplementary Table 3, available online).

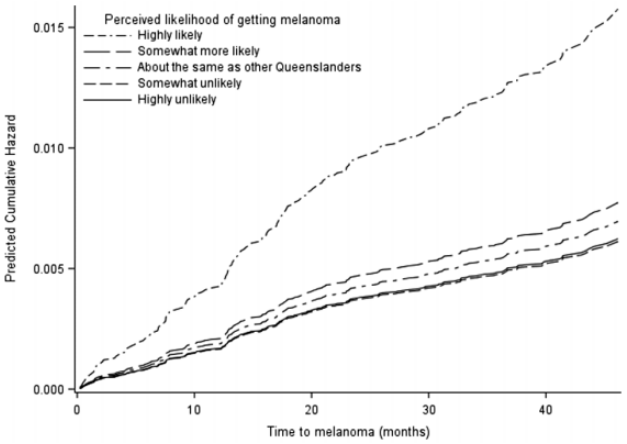

Figure 1. Cumulative hazard of developing invasive melanoma according to self-perceived risk.

Self-perceived Risk

We first examined whether self-perceived risk of developing melanoma alone was predictive of invasive melanoma during follow-up. The group perceiving themselves to be "highly likely" to develop melanoma had statistically significantly higher risks than the other four risk groups (hazard ratio = 2.53, 95% confidence interval [CI] = 1.23 to 5.19, for "highly likely" vs "highly unlikely," $P = .01$) (Figure 1). Self-perceived risk discriminated cases from noncases only slightly better than chance, however (C-index = 0.54, 95% CI = 0.48 to 0.61).

Prediction of Invasive Melanomas

Seven statistically significant predictors were retained in the final model (viz. age, sex, hair color, tanning ability, number of moles at age 21 years, number of skin lesions treated destructively, and sunscreen use) (Table 2). The strongest predictors for invasive melanoma were age, sex, tanning ability, number of moles at age 21 years, and number of skin lesions treated destructively (Table 2). There were no statistically significant interactions between any covariates in the final model.

In the sensitivity analysis, we censored participants diagnosed with in situ melanoma during follow-up: the final model included the same seven terms as the risk model derived from our primary analysis.

Table 2. Specification and performance of the model to predict risk of invasive melanoma: Derivation sample (n = 27 975)

Risk factor	HR (95% CI)	P*
Age group, y		
≤45	1.00 (ref)	
46–50	0.60 (0.28 to 1.32)	
51–55	0.76 (0.38 to 1.53)	
56–60	1.84 (1.01 to 3.36)	
61–65	1.55 (0.83 to 2.91)	
>65	2.34 (1.27 to 4.31)	<.001
Sex		
Female	1.00 (ref)	
Male	2.13 (1.56 to 2.92)	<.001
Tanning ability		
Deeply tan	1.00 (ref)	
Moderately tan	2.39 (1.32 to 4.30)	
Lightly tan	3.50 (1.89 to 6.48)	
Not tan	4.79 (2.37 to 9.69)	<.001
Moles at age 21 y		
None	1.00 (ref)	
A few	1.87 (1.24 to 2.81)	
Some	3.29 (2.07 to 5.23)	
Many	4.42 (2.14 to 9.10)	<.001
Hair color		
Black	1.00 (ref)	
Brown/blond	2.54 (1.12 to 5.78)	
Red/auburn	4.46 (1.79 to 11.14)	.003
No. of previous skin lesions destroyed		
0	1.00 (ref)	
1–5	1.51 (0.96 to 2.39)	
6–20	2.26 (1.44 to 3.53)	
21+	2.51 (1.56 to 4.05)	<.001
Sunscreen use when outside in the sun (past year)		
Never	1.00 (ref)	
Ever	2.01 (1.24 to 3.27)	.005
C-index† pooled (95% CI)		
Derivation	0.79 (0.72 to 0.85)	
Validation	0.69 (0.62 to 0.76)	

*Type 3 P value (two-sided) from development data set (first imputation). CI = confidence interval; HR = hazard ratio.
†Pooled C-index for five imputed data sets.

Table 3. Specification and performance of the model to predict risk of any melanoma (invasive or in situ): Derivation sample (n = 27 975)

Risk factor	HR (95% CI)	P*
Age group, y		
≤45	1.00 (ref)	
46–50	0.80 (0.50 to 1.26)	
51–55	0.86 (0.56 to 1.31)	
56–60	1.48 (1.00 to 2.18)	
61–65	1.56 (1.04 to 2.32)	
>65	1.93 (1.30 to 2.87)	<.001
Sex		
Female	1.00 (ref)	
Male	1.86 (1.53 to 2.28)	<.001
Ethnicity		
Nonwhite	1.00 (ref)	
White	2.49 (1.10 to 5.62)	.03
Private health insurance		
No	1.00 (ref)	
Yes	1.24 (0.99 to 1.54)	.05
Tanning ability		
Deeply tan	1.00 (ref)	
Moderately tan	1.46 (1.09 to 1.96)	
Lightly tan	1.69 (1.22 to 2.34)	
Not tan	1.56 (1.02 to 2.40)	.02
Moles at age 21 y		
None	1.00 (ref)	
A few	1.27 (1.00 to 1.62)	
Some	2.09 (1.57 to 2.78)	
Many	3.58 (2.34 to 5.48)	<.001
Hair color		
Black	1.00 (ref)	
Brown/blond	1.13 (0.78 to 1.62)	
Red/auburn	2.02 (1.27 to 3.19)	.001
No. of previous skin lesions destroyed		
0	1.00 (ref)	
1–5	1.24 (0.92 to 1.66)	
6–20	1.68 (1.23 to 2.30)	
21+	1.60 (1.12 to 2.30)	.006
Family history of melanoma		
No	1.00 (ref)	
Yes	1.24 (1.00 to 1.53)	.03
Sunscreen use when outside in the sun (past year)		
Never	1.00 (ref)	
Ever	1.51 (1.13 to 2.02)	.006
Past history of excisions for skin cancer		
0	1.00 (ref)	
1	1.30 (0.97 to 1.75)	
2+	1.42 (1.10 to 1.84)	.04
Skin checks by a doctor (past 3 y)		
None	1.00 (ref)	
Once	1.46 (1.05 to 2.04)	
2 or more times	1.71 (1.24 to 2.36)	.006
C-index†, pooled (95% CI)		
Derivation	0.74 (0.71 to 0.78)	
Validation	0.72 (0.69 to 0.75)	

*Type 3 P value (two-sided) from development data set (first imputation). CI = confidence interval; HR = hazard ratio.
†Pooled C-index for five imputed data sets.

Prediction of All Melanomas (Invasive + In Situ)

The final model for predicting the risk for all melanomas (ie, invasive + in situ) retained the seven terms identified for invasive melanomas, with five new terms: history of skin checks by a doctor (past three years), number of excisions for skin cancers, private health insurance, ethnicity, and family history of melanoma (Table 3). The strongest predictors were age, sex, moles at age 21 years, and hair color (Table 3).

The prediction models for both outcomes met the proportional hazards assumption. Final models that incorporated death as a competing risk resulted in negligible change to the estimates (data not shown). Several variables were close to the level of statistical significance required for retention in the models, including history of cancer, and for the invasive melanoma model only, history of physician skin checks and self-perceived melanoma risk. Including these factors in the final models did not change the pooled C-statistic or model fit. Thus we have presented the most parsimonious models that retained only statistically significant variables.

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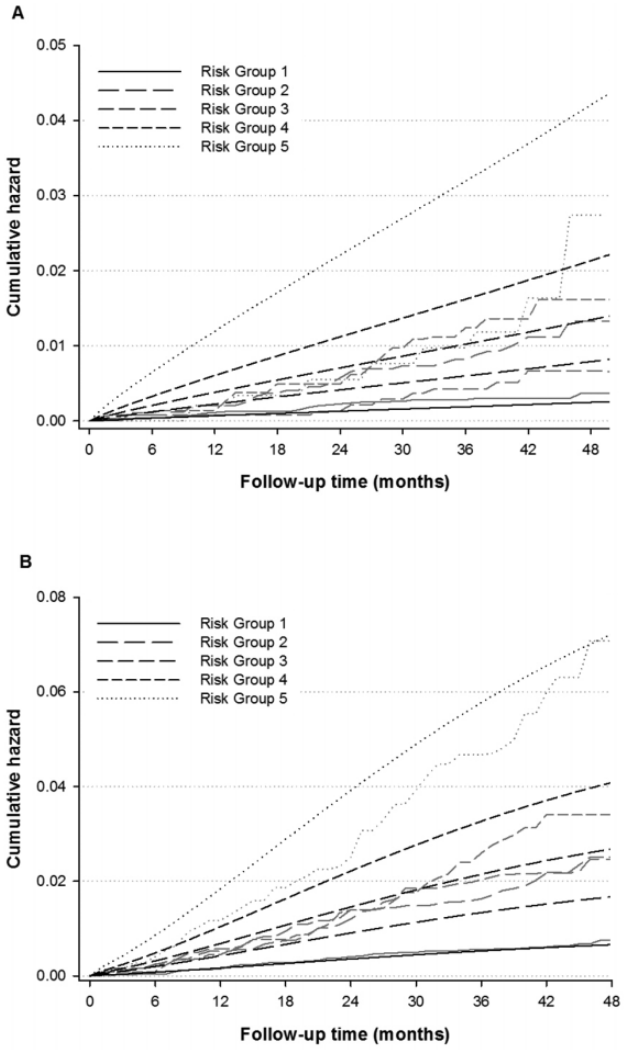

Figure 2. Calibration of the stratification tool across the five risk strata in the validation sample: predicted and observed cumulative hazards of: **(A)** invasive melanoma (n = 80 melanoma cases) and **(B)** all melanoma (n = 210 melanoma cases). **Black lines** represent the predicted cumulative hazard curves, and **gray lines** represent the observed cumulative hazard curves.

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Discrimination and Calibration

Model discrimination in both the derivation and validation samples was high. The mean C-index across the five imputed data sets for the invasive melanoma model was 0.79 (95% CI = 0.72 to 0.85) in the development sample and 0.69 (95% CI = 0.62 to 0.76) in the validation sample (Table 2). The C-index was slightly lower for the "all melanoma" model in the development data set (pooled C-index = 0.74, 95% CI = 0.71 to 0.78) but higher in the validation sample (pooled C-index = 0.72, 95% CI = 0.69 to 0.75) than for the invasive risk model (Table 3). When we plotted observed and predicted cumulative hazards of invasive melanoma for each of five risk strata of cohort participants in the validation sample, we observed reasonable calibration for the three lowest-risk groups, but the model overestimated risk of melanoma for the two highest-risk groups (Figure 2A). We observed better calibration for the model predicting risks of all melanomas (invasive and in situ) (Figure 2B).

Stratified Analyses

We conducted stratified analyses to determine whether predictive factors differed according to age and sex and found some variation in the terms retained in the models. The data became very sparse in some subgroups, however, with low numbers of melanoma cases in the validation sample (Supplementary Tables 4–7, available online).

Optimizing Melanoma Screening

We assessed the sensitivity and specificity of the tool within deciles of predicted risk (Table 4). The Youden index was optimized ($J = 0.35$) in the seventh decile, with a sensitivity of 74.2% and specificity of 60.7%. If this level of predicted risk was the threshold for eligibility to enter a melanoma screening program, then of 34 people meeting or exceeding this threshold, one would develop melanoma (invasive or in situ) over a median duration of 3.4 years. However, a strategy based on that threshold would fail to detect 25.8% of future cases. If the entry criteria for melanoma screening were relaxed so that it was open to all those with predicted risks in the sixth decile or higher, we estimate that 82.1% of melanoma cases would be detected, and the number needed to screen would be 39.

Using decision curve analysis, we found that the net benefit of the risk prediction model was superior to "screen all" or "screen none" approaches when the threshold probability fell between 0.3% and 8.9% (Figure 3). This range of values includes the probability at which the Youden index was maximized (1.37%).

Discussion

Risk stratification tools can improve the efficacy and cost-effectiveness of early detection by identifying those individuals who are likely to benefit from screening (32). We used data from a large cohort to develop a tool to predict risk of developing melanoma over a median duration of 3.4 years. We confirm that self-perceived risk of melanoma correlates poorly with actual risk and is not useful for guiding early detection practices (33). We found that information on seven items yielded a risk prediction index for invasive melanoma with high discrimination (C-index = 0.79, 95% CI = 0.72 to 0.85) and reasonable calibration. The strongest predictors were age, sex, tanning ability, and number of moles at age 21 years, and number of skin lesions treated destructively. Hair color and sunscreen use also independently predicted risk.

There is debate as to whether in situ melanomas should be considered intended end points for early detection. Some argue that in situ lesions are legitimate targets for a screening program as they represent premalignant melanomas. Others argue that most are indolent and that their numbers are increasing due to overdiagnosis (34), a phenomenon that could possibly extend to thin invasive melanomas also. Our study had too few melanomas with thickness greater than 1 mm (47 in total, 30 in the development sample) to derive separate models for thick vs thin melanomas, although such an analysis would clearly be of interest. We contend that these arguments represent the extremes of opinion, and neither wholly represents the reality that some in situ melanomas have malignant potential, whereas others do not (35). We therefore developed models accommodating both points of view by separately examining the predictors of invasive and "all melanomas." Information on

Table 4. Performance of melanoma screening within deciles of predicted risk score (all melanoma)

Predicted risk score decile	Observed absolute risk at 1 y†, %	Observed absolute risk at 2 y†, %	Observed absolute risk at 3 y†, %	Sensitivity, %	Specificity, %	Youden index, J	Cumulative No. needed to screen*
10th	1.34	2.83	4.16	31.5	90.4	0.22	20
9th	0.65	1.61	2.43	49.5	80.5	0.30	26
8th	0.65	1.35	1.93	63.5	70.7	0.34	30
7th	0.36	0.82	1.35	74.2	60.7	0.35	34
6th	0.22	0.84	1.11	82.1	50.7	0.33	39
5th	0.19	0.51	0.73	87.6	40.8	0.28	44
4th	0.21	0.38	0.62	91.9	30.6	0.23	49
3th	0.24	0.43	0.72	96.9	20.6	0.18	53
2th	0.02	0.12	0.21	98.6	10.4	0.09	58
1st	0.07	0.19	0.21	100.0	0.0	0.00	64

*Numbers needed to screen will depend on the prevailing incidence of melanoma in the population to which the tool is applied. Numbers cited here were derived from the QSkin cohort (age 40–69 years; crude melanoma incidence 172 × 10-5 person-years). In populations with lower melanoma incidence, the numbers needed to screen will be higher.

†Observed absolute risk of melanoma calculated using the Kaplan-Meier method for groups classified according to the predicted risk score deciles.

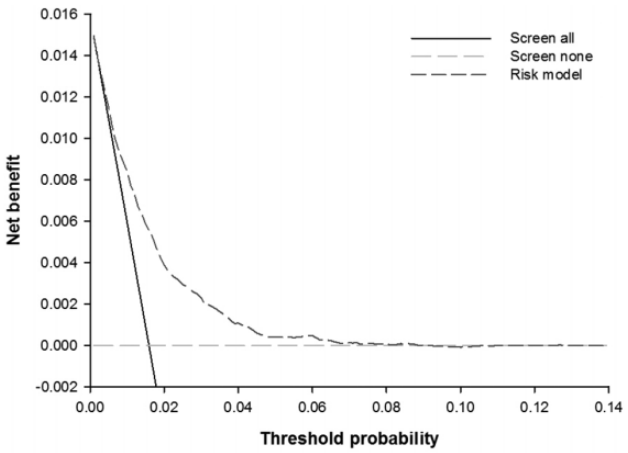

Figure 3. Decision curve analysis of the effect of the prediction model for all melanoma (invasive or in situ). Net benefit is plotted against the continuous range of threshold probabilities, which refer to the absolute risk of melanoma in the next 3.4 years, at which screening would be offered. **Fixed lines** demonstrate the net benefit of "screening all" and "screening none."

12 items predicted risk of "all melanomas" with high discrimination (C-index = 0.74). Seven of the 12 items were also identified as statistically significant predictors of invasive melanomas, and the additional five items included three host characteristics (ethnicity, family history of melanoma, number of excisions for skin cancers) and two items related to higher levels of medical surveillance (private health insurance status and history of physician skin checks).

Only two prediction models for melanoma have been developed in prospective cohort studies. The first model was developed in the Nurses' Health Study (NHS I and II)/Health Professionals Follow-up Study (HPFS) (16); the second was developed in the Melanoma Inquiry of Southern Sweden (MISS) study (17), a population-based cohort of women. The NHS/HPFS prediction model for invasive melanoma considered 13 factors for men and 19 for women; in situ melanomas were not considered. The final model included six items (age, sex, hair color, number of moles, history of severe/painful sunburn, and family history of melanoma). For the NHS, information on some factors was collected in a retrospective survey conducted 16 years after recruitment (36). The discrimination of our risk model for invasive melanoma was higher than the NHS/HPFS risk model (C-index = 0.62). The MISS model predicted risk of all melanomas (invasive and in situ) and included three items (family history of melanoma, number of nevi, and hair color). No C-index or calibration was reported, nor was it internally validated. Other models have been developed using data from case–control studies (37–43) (reviewed by Usher-Smith et al. [14] and Vuong et al. [15]), some of which have been externally validated (44,45). These models, however, are not able to incorporate baseline incidence of melanoma in the populations in which they were derived, and they are also prone to biases inherent in the case–control design. We have previously validated six melanoma risk prediction tools in a population-based sample from Queensland (45), including the model by Cho et al. (16), four derived from case–control data (38–40,44), and one that used registry data and published risk estimates from meta-analysis (46). Although the ability of the models to discriminate between cases and controls was generally high, the calibration was poor.

Our risk stratification model for invasive melanoma thus has advantages over previous models. Strengths include the population-based sampling frame, prospective design, comprehensive capture of salient risk factors and health behaviors at baseline (including factors not assessed in previous studies), prior validation of the baseline questionnaire, complete ascertainment of melanoma events during follow-up (including in situ melanomas), and the analytical approach, which included splitting the cohort into derivation and validation samples.

Population screening for melanoma has been implemented in Germany (48), but it is not advocated by authorities in other jurisdictions. Rather, the advice is for doctors to identify high-risk patients and offer them targeted surveillance (6–10). The tool developed here could be used to identify such patients, although practical implementation would require decisions to be made about an acceptable threshold for action. For example, we have shown that a risk score sufficient to correctly identify 82.1% of melanoma patients would require screening 39 people to detect one case. Setting the threshold for screening to a higher risk score would result in lower sensitivity. Optimizing the threshold for action will depend on the resources available and the tolerance for unscreened cases in the population.

As opposed to causal modeling, which aims to determine whether a factor has a direct effect on an outcome, prediction

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modeling aims to derive a model to best explain the occurrence of an outcome. Thus, the factors retained in prediction models should not be interpreted as being causal.

Limitations of our analyses include reliance upon self-reported factors and relatively short duration of follow-up resulting in a modest number of incident invasive melanoma cases. We sought to validate our risk stratification model using external data sets; however, no other studies have captured information on all of the factors that were statistically significant predictors in our models, including some factors that were highly predictive (eg, prior treatment for actinic skin lesions).

In summary, we have developed a risk stratification tool for melanoma using information that can be captured easily by self-report, and it is thus suitable for use in the general population. Such a tool could be used to guide targeted screening in line with recommendations (6–10). In future research, we plan to implement the stratification tool in clinical settings and assess its effectiveness.

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