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Independent evaluation of melanoma polygenic risk scores in UK and Australian prospective cohorts

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Running title: Melanoma polygenic risk scores in UK and Australian prospective cohorts

What's already known about this topic?

- Melanoma risk has a substantial inherited (germline) genetic component.
- Polygenic risk scores (PRS) have the potential to improve risk stratification for melanoma screening, but PRS-based risk prediction requires independent validation in prospective cohorts, especially assessing calibration.
- A recent, large melanoma genome-wide association study has increased the number of genetic variants independently associated with melanoma risk from 45 (in 21 genetic regions) to 68 (in 54 genetic regions).

What does this study add?

- PRS enhanced melanoma risk prediction, with better performance of a PRS based on genetic associations from a larger, more diverse meta-analysis.

- Population-average risks at age 50 years might be reached 10-20 years earlier by individuals with the 20% highest PRS and 10-20 years later by those with 20% lowest PRS.
- Re-calibration of 10-year absolute risks for application to specific populations may be necessary, and will facilitate translation to clinical practice.

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Summary

Background: Previous studies suggest polygenic risk scores (PRS) may improve melanoma risk stratification. However, there has been limited independent validation of PRS-based risk prediction, particularly assessment of calibration (comparing predicted to observed risks).

Objectives: To evaluate PRS-based melanoma risk prediction in prospective UK and Australian cohorts with European ancestry.

Methods: We analysed invasive melanoma incidence in UK Biobank (UKB; n=395,647; 1,651 cases) and a case-cohort nested within the Melbourne Collaborative Cohort Study (MCCS, Australia; n=4,765; 303 cases). Three PRS were evaluated: 68 SNPs at 54 loci from a 2020 meta-analysis (PRS68); 50 SNPs significant in the 2020 meta-analysis excluding UKB (PRS50); 45 SNPs at 21 loci known in 2018 (PRS45). 10-year melanoma risks were calculated from population-level cancer registry data by age group and sex, with and without PRS adjustment.

Results: Predicted absolute melanoma risks based on age and sex alone underestimated melanoma incidence in UKB (ratio expected/observed cases E/O=0.65, 95% confidence interval (95%CI) 0.62-0.68) and MCCS (E/O=0.63, 95%CI 0.56-0.72). For UKB, calibration was improved by PRS-adjustment, e.g. PRS50-adjusted risks E/O=0.91, 95%CI 0.87-0.95. Discriminative ability for PRS68- and PRS50-adjusted absolute risks was higher than for risks based on age and sex alone (ΔAUC 0.07-0.10, $p<0.0001$), and higher than for PRS45-adjusted risks (ΔAUC 0.02-0.04, $p<0.001$).

Conclusions: A PRS derived from a larger, more diverse meta-analysis improves risk prediction compared to an earlier PRS, and might help tailor melanoma prevention and early detection strategies to different risk levels. Re-calibration of absolute risks may be necessary for application to specific populations.

Introduction

Polygenic risk scores (PRS) aggregate the effects of many genetic variants across the genome into a single score aiming to reflect an individual's genetic risk of disease. PRS are increasingly showing potential for risk-stratified cancer prevention, early detection and screening.[1-4] This includes cutaneous melanoma, a relatively lethal form of skin cancer with high and growing global burden (estimated >324,000 new invasive melanoma diagnoses and >57,000 deaths worldwide in 2020, rising to >424,000 new invasive diagnoses and >84,000 deaths in 2040)[5]. While ~75% of melanomas globally have been attributed to excess ultraviolet radiation exposure,[6] multiple other risk factors are known, including number of nevi (e.g. 3.63-fold relative risk for people with 1+ atypical nevi)[7] and genetic predisposition .[8-10] Previous case-control studies have shown that incorporating melanoma PRS in risk prediction models improves discriminatory accuracy compared to models using only traditional risk factors.[12]

The lack of proper evaluation of model calibration using prospective cohorts has hindered the integration of PRS into risk assessment for clinical and public health practice.[13,14] Calibration measures the agreement between the predicted risks from the model and the observed risks in a population. A poorly calibrated model could lead to under- or over-screening of individuals in a risk-stratified screening program, reducing the program's benefits and cost-effectiveness. To date, calibration of PRS-based predicted absolute melanoma risks has not been assessed.[12,15] This is important because absolute risks (e.g. 10-year risk) are commonly used for risk communication in clinical settings and to determine eligibility in national cancer screening programs.[16]

Recently, a larger and more population-diverse melanoma genome-wide association study (GWAS) increased the number of known susceptibility variants to 68 independent associations located in 54 genetic regions (loci),[10] more than doubling the numbers of known risk loci compared with earlier GWAS and PRS (with 45 SNPs at 21 loci included in the PRS in a 2018 study).[12] It is, therefore, also of interest to compare the risk prediction performance of the previously proposed PRS with an analogous PRS based on the new GWAS.

To address these research questions, we evaluated different PRS-based predicted melanoma risks in prospective UK and Australian cohorts, assessing their association with melanoma, calibration, and discriminative ability.

Materials and methods

Study samples

UK Biobank[17] (UKB) is a prospective cohort study of ~500,000 participants recruited in 2006-2010 ("baseline"). Deaths and invasive melanoma diagnoses, the primary outcome, were ascertained using linkage to death and cancer registry records (see Appendix S1). Records were censored for completeness on 31/03/2016 and 31/10/2015 for participants recruited in England/Wales and Scotland, respectively. All participants were genotyped, with further genotype imputation described previously.[17]

The prospective Melbourne Collaborative Cohort Study[18] (MCCS) recruited 41,513 Melbourne residents in 1990-1994. To broaden the range of measured lifestyle exposures,

particularly Mediterranean diet, there was an increased effort to recruit Greek and Italian migrants. A subcohort was defined by randomly selecting 4,710 participants from those who attended the second follow-up wave in 2003-2007 ("baseline" for the current analysis). Records of deaths and invasive melanoma diagnoses were ascertained using linkage to death and cancer registries (see Appendix S1), and were censored for completeness on 30/06/2016. Subcohort members and all MCCS participants who developed invasive melanoma within 10 years of the second follow-up visit and before 30/06/2016 were genotyped, followed by imputation of additional genetic variants (see Appendix S1).

In both studies, we applied extensive quality control to genetic data, excluded non-European participants and those with melanoma diagnosis before baseline (see Appendix S1). We ascertained participants' self-reported sex, ethnicity, ease of tanning (noting that the "ethnic group(s)" question in MCCS has also been interpreted as country of birth), and age at baseline. The first 20 genetic principal components (PCs) were calculated to account for potential population stratification (i.e. confounding of genetic associations by ancestry). For UKB, we also obtained information on skin and hair colour, education, and the postcode-based Townsend deprivation index (derived from national census data on unemployment, car ownership, home ownership, and overcrowding, see Appendix S1).[19]

All participants provided informed consent at recruitment; UKB was approved by the North West Centre for Research Ethics Committee (11/NW/0382) and the MCCS by the Cancer Council Victoria Human Research Ethics Committee.

PRS

We calculated three PRS based on 1) 68 SNPs at 54 loci from a 2020 meta-analysis[10] (PRS68); 2) 50 SNPs at 42 loci significant in the 2020 meta-analysis after exclusion of UKB participants to avoid overfitting and ensure a truly independent validation dataset (PRS50); and 3) 45 SNPs at 21 loci as analysed in a 2018 study[12] (PRS45). Table S1 shows all variants in the three PRS, their odds ratios and allele frequencies. After quality control, the UKB data included all variants for the three PRS, while the MCCS data included 66, 49, and 43 variants for PRS68, PRS50 and PRS45, respectively. We followed a previously described approach[20] to determine genotype-specific relative risks at each variant, then used genotype dosages and a log-additive model to obtain a PRS-specific relative risk for each participant and each PRS (see Appendix S1).

Statistical methods

Population-average and PRS-adjusted predicted absolute melanoma risks

DevCan v6.7.8 was used to calculate sex-and-age-specific absolute 10-year risks of melanoma, with 5-year groupings for age, adjusting for death as competing risk.[21] The calculation was performed using population-wide cancer incidence, and cancer and all-cause mortality data from each of Victoria (Australia), Scotland, and England/Wales (see Appendix S1). For Victoria, we used data for 2009-2013; for Scotland and England/Wales, we performed separate calculations using data for 2001-2005, 2006-2010, and 2011-2015. UKB participants were assigned absolute risks for Scotland if recruited in Glasgow/Edinburgh, and risks for England/Wales otherwise. We rescaled the 10-year absolute risks for each participant to account for different individual follow-up time (see

Appendix S1). PRS-adjusted predicted absolute melanoma risks were obtained by multiplying the corresponding sex-and-age-specific absolute risk by the participants' PRS-specific relative risk (separately for each PRS).

Association between PRS and participant characteristics

Associations between each PRS (log-transformed) and participant characteristics were calculated using multivariable generalised linear regression models (R function "glm") that included age, sex, ethnicity, ease of tanning, and 20 PCs, and univariable models separately for age, sex, ethnicity, and ease of tanning. For UKB, we also evaluated associations of PRS with skin and hair colour, education, and the Townsend deprivation index (using univariable and multivariable models). To account for multiple testing, a Bonferroni multiple-testing correction for 28 tests and the three PRS was applied (significance at $p<0.0006$).

Association between PRS and melanoma incidence

Associations between the PRS (log-transformed) and melanoma incidence were evaluated using Fine-Gray competing risks regression with death as competing risk, adjusting for age, sex, ethnicity, ease of tanning, and 20 PCs. The function "crr" (R package "cmprsk") was used to calculate subhazard ratios (SHR) and 95% confidence intervals (95%CIs). To facilitate comparisons with other studies, we calculated SHRs per 1 standard deviation (sd) of each PRS (for MCCS, sd was based on subcohort participants). Significance was defined at $p<0.017$, applying a Bonferroni multiple-testing correction for the three PRS. We compared the fully-adjusted results to unadjusted and partially-adjusted results, and also tested the association for PRS risk quintiles and deciles (see Appendix S1). For the MCCS, the results were verified using a weighted Cox regression model designed for case-cohort studies (see Appendix S1).

Calibration

Calibration of unadjusted (age-and-sex-specific) and PRS-adjusted predicted absolute risks was evaluated by comparing the expected ("*E*") with the observed ("*O*") numbers of melanoma cases ("*E/O*" ratio) for all participants and separately for males and females, overall and for each risk quintile (see Appendix S1). Robust 95%CIs were used for the MCCS case-cohort design.[22] Calibration of risk quintiles was further evaluated after rescaling of risks to achieve *E/O*=1 overall (separately for males and females). For UKB, calibration by Townsend deprivation index quartiles was also assessed.

Discrimination

The area under the receiver operating characteristic curve (AUC) was calculated for the PRS-based relative risk, as well as the unadjusted (age-and-sex-specific) and PRS-adjusted predicted absolute risks (see Appendix S1). The AUC represents the probability that the predicted risk is higher for a randomly chosen case than a non-case, with 0.5 corresponding to random ranking and 1.0 to perfect discrimination. P-values for AUC comparisons were obtained using the Delong test for correlated curves (function "roc.test", R package "pROC"). We also calculated the classification true and false positive rates, true and false negative rates, sensitivity, specificity, positive and negative likelihood ratios at 5%, 10%, …, 95% risk thresholds.

R^2 on the liability scale

We converted the AUC values for the PRS relative risk, as well as the unadjusted and PRS-adjusted absolute risks, to the explained variation (R^2) on the liability scale[23] (see Appendix S1).

Estimated 10-year absolute risks by PRS quintile and age

To illustrate risk-stratification, the predicted absolute 10-year melanoma risk by PRS50 quintile was estimated based on the association results in UKB and MCCS (see Appendix S1).

Results

After quality checks, we analysed genetic and phenotypic data from 395,647 UKB participants, and separately, 4,765 MCCS participants (Table 1). Of these UKB participants, 1,651 (0.4%) were diagnosed with invasive melanoma during the follow-up period (median 7.2 years, interquartile range 6.5-7.8 years). The MCCS case-cohort included 303 participants diagnosed with melanoma in the 10 years following the baseline for this study. Figure S1 shows the PRS distributions in cases and non-cases.

Associations of melanoma PRS with participant characteristics including traditional melanoma risk factors

In both cohorts, all three PRS were strongly and consistently associated with self-reported ease of tanning (Table S2). We also found multiple associations between the PRS and genetic PCs (Table S2). In UKB, skin and hair colour were also highly associated with all three PRS (Table S3). Self-reported ethnicity was associated with the PRS in univariable analyses, but not in multivariable analyses that adjusted for genetic PCs (Appendix S1, Table S3).

Association of melanoma PRS with melanoma incidence

All three PRS were associated with melanoma incidence (Table 2), with generally stronger associations in UKB than the MCCS (e.g. non-overlapping 95%CIs for PRS68 and PRS45 fully-adjusted SHR estimates). Moreover, in both cohorts, the PRS45 SHR estimates were smaller than, and outside the 95%CIs for PRS50 and PRS68 estimates; fully-adjusted SHRs per 1 sd of PRS45, PRS50, and PRS68 were 1.61, 1.73, and 1.80 in UKB, and 1.25, 1.47 and 1.47 in MCCS, respectively.

In UKB, associations between the PRS and melanoma incidence were robust to inclusion of different covariates, and only minimally (3-4%) attenuated when additionally adjusting for skin and hair colour. In the MCCS, associations between the PRS and melanoma incidence were slightly more attenuated (12-14%) by the inclusion of traditional melanoma risk factors and genetic PCs as covariates, but remained highly statistically significant.

We also considered the association of PRS quintiles and deciles with melanoma incidence (Figure S2, Table S4). The results were consistent with the analysis of the PRS as a continuous score, with stronger associations observed in UKB than in the MCCS (Appendix S1).

Calibration of absolute melanoma risks with and without PRS

We found that absolute 10-year melanoma risks calculated based on population-level cancer registry data have risen sharply in England/Wales over 2001-2015, especially for

males and older age groups, with some increases also observed in Scotland (Figure S3). Nonetheless, we observed an under-prediction of melanoma incidence in UKB when using sex-and-age-specific risks based on 2001-2005, 2006-2010 and 2011-2015 population-level data, with the ratio of expected to observed cases *E/O* of 0.41 [95% CI 0.39-0.43], 0.55 [0.53-0.58] and 0.65 [0.62-0.68], respectively (Table S5). The 2011-2015 period corresponds to the last five years of follow-up of UKB participants, so the absolute 10-year risks based on this period were used for further analysis.

We found that PRS68- and PRS50-adjusted absolute risks still under-predicted melanoma incidence in UKB (*E/O*=0.89 [95%CI 0.85-0.94] and 0.91 [0.87-0.95], respectively; Figure 1a), but less so than the unadjusted risks based on age and sex alone. For PRS45-adjusted absolute risks the *E/O* was 0.73 [95%CI 0.70-0.77]. The under-prediction of risks was similar for males and females (Figures S4, S5), and stronger for participants with higher socioeconomic status as quantified by the Townsend deprivation index (e.g. unadjusted absolute risks: least deprived quartile *E/O*=0.57 [95%CI 0.52-0.62], most deprived quartile *E/O*=0.85 [95%CI 0.76-0.95]; Figure S6).

The calibration results were similar in the MCCS, where the sex- and age-specific absolute melanoma risks based on population-wide cancer registry data for Victoria, Australia, also under-estimated melanoma incidence (*E/O*=0.63 [95%CI 0.56-0.72]; Figure 1b). The PRS68 and PRS50-adjusted absolute risks resulted in similarly under-predicted incidence (both *E/O*=0.66 [95%CI 0.58-0.75]) and the under-prediction was more pronounced for PRS45 (*E/O*=0.54 [95%CI 0.48-0.62]). Across unadjusted and PRS-adjusted risks, the under-prediction was stronger for males than females (Figure S4, S5).

For PRS68 and PRS50, we did not find relative under- or over-prediction by absolute risk quintile when re-calibrating the mean overall absolute risks to *E/O* =1 (Figure 2, Appendix S1).

Discriminative ability of absolute melanoma risks with and without PRS

Figure 3 shows the discriminative ability of the unadjusted (age-and-sex-specific) and PRS-adjusted absolute risks, including sensitivity, specificity, and the AUC. In UKB, PRS-adjustment of absolute risks improved discrimination (AUC difference between PRS-adjusted and unadjusted risks for each of the three PRS: ΔAUC 0.07-0.10, $p<10^{-10}$). In the MCCS, the incremental improvement from PRS-adjustment was smaller (ΔAUC 0.03-0.07, p<0.0001 for PRS68 and PRS50, p=0.07 for PRS45); however, the AUC for the unadjusted absolute risks was higher in the MCCS than UKB, resulting in similar AUCs for the PRS-adjusted absolute risks (0.69 for PRS68 for both cohorts). In both UKB and the MCCS, the PRS68- and PRS50-adjusted absolute risks had higher discriminative ability than the PRS45-adjusted absolute risks (p<0.0001).

At a threshold of the top predicted risk decile, the PRS68- and PRS50-adjusted absolute risks had >90% specificity and >24% sensitivity for predicting melanoma incidence in both UKB and the MCCS (Table S6, Appendix S1). At a threshold of the top predicted risk quartile, the PRS68- and PRS50-adjusted absolute risks had >75% specificity and >46% sensitivity for predicting melanoma incidence in both UKB and the MCCS.

Explained variation on the liability scale

PRS68 explained ~5% variation on the liability scale, with similar estimates for PRS50 (~4.5%) and a slight decrease for PRS45 (2.1-3.7%, see Table S7 and Appendix S1). PRS-adjusted absolute risks explained more variation than the unadjusted risks (e.g. PRS50-adjusted absolute risk: 6.2% (95%CI 5.3-7.2%) in UKB and 7.0% (4.8-9.6%) in the MCCS; unadjusted risk: 1.4% (1.0-2.0%) and 3.0% (1.6-4.9%), respectively).

Estimated 10-year absolute risks by PRS quintile and age

Figure 4 shows the estimated 10-year absolute risks of melanoma by sex, age and top/bottom PRS50 quintile. The population-average 10-year risk of invasive melanoma at age 50 years was estimated to be reached 10-20 years earlier for those in the top PRS50 quintile, and 10-30 years later for those in the bottom PRS50 quintile.

Sensitivity analyses

The results presented above were robust to the factors assessed in multiple sensitivity analyses (see Appendix S1).

Discussion

We evaluated performance of three melanoma PRS using data from large-scale UK and Australian cohorts. We found that PRS-adjustment of age-and-sex-specific absolute risks determined from population data improved discriminative ability of the risk prediction. The PRS68- and PRS50-adjusted sex-and-age-specific absolute risks in our study had AUCs of 0.68-0.69, suggesting moderate discriminative ability. Whether this discriminative accuracy would be sufficient for specific risk-stratified melanoma prevention or early detection approaches will depend on the benefits, harms, and costs of the specific interventions. We have provided data on sensitivity and specificity of the PRS-adjusted absolute risks at different risk thresholds to enable health-economic evaluations of risk-stratified strategies. Our analysis of estimated absolute risks by age and top/bottom PRS50 quintile suggests that risk thresholds corresponding to the population-average risks at age 50 years might be reached 10-20 years earlier by individuals with the 20% highest PRS, and 10-20 years later by individuals with the 20% lowest PRS. The prediction could likely be improved by incorporating information from variants that do not meet genome-wide significance thresholds in association studies.[24] Due to extensive, population-dependent correlations between genetic variants (linkage disequilibrium), optimising the set of variants used in a PRS and the weights allocated to them is an active area of research. The choice of method can be disease-dependent (a reflection of different genetic architectures), so further work is needed to carry out a comprehensive comparison of different methods for melanoma.

Calibration of absolute melanoma risks was not straightforward, with age-and-sex-specific risks derived from population data (without consideration of PRS) under-predicting melanoma risks for participants of both cohorts. Adjustment of age-and-sex-specific risks by PRS reduced the under-prediction, but further work will be required to build well-calibrated risk prediction models. Potential reasons for the under-prediction include that our analyses were restricted to European-ancestry participants only, which could lead to higher melanoma incidence compared to the whole UK and Victorian populations. Increases in melanoma risks determined from population-wide data might also be due to changes in risk exposure and/or different diagnostic practices. Finally, the higher incidence of melanoma in

UKB and MCCS participants than in the general population could reflect some overdiagnosis in more health-seeking participants, as participants from both cohorts are more likely to have greater health literacy than the general population.[25] Melanoma incidence in UKB was higher for participants with higher socioeconomic status, so over-representation of participants with higher socioeconomic status in the cohorts[25] could also contribute to the higher incidence than in the general population.

Comparing the three PRS, we found that PRS68 performed slightly better than PRS50 in UKB, as expected given that UKB data contributed to the meta-analysis from which PRS68 was derived. We did not see a difference in performance between PRS68 and PRS50 in the MCCS. This highlights the importance for independence between PRS construction and validation data.[24] To our knowledge, this is the first evaluation of the risk prediction performance for the PRS68 and PRS50 melanoma risk scores. A previous evaluation[12] of the PRS45 score in UK and Australia case-control studies, and a Southern-European study[26] of a 204-variant score including non-genome-wide-significant variants based on pre-2020 data, found similar or slightly weaker associations of PRS with melanoma incidence. Other studies[27,28] evaluating melanoma PRS used smaller sets of variants (16-24) known prior to 2020. A 55-variant PRS based on the 2020 meta-analysis PRS has also been associated with melanoma risk (hazard ratio 1.46 per sd) in Australians aged 70+ years,[15] but no assessment of calibration was performed.

Considering any melanoma risk models, a recent systematic review identified 46 different models from 40 publications, commonly using nevi (78% of models), but with little consistency regarding other risk factors included.[29] Notably, only five publications assessed AUC using independent validation data. For four risk models, the 95%CIs for the external validation AUC in the original publication or a later study overlapped the AUC estimates of 0.68-0.69 for the PRS50-adjusted absolute risks reported here (see Appendix S1). Only one risk model incorporating clinically-assessed factors had a higher validation AUC (0.73, 95%CI 0.70-0.75, see Appendix S1).[30] Thus, the discrimination of the models based on genomic risk factors, age and sex examined here is similar to externally validated phenotype-based risk models. Incorporating genomic risk information into the best-available phenotype-based risk models might further improve risk prediction in the future.[12]

The PRS68 and PRS50 scores were based on a larger meta-analysis than the older studies underlying PRS45, and performed better than the PRS45, especially in the more ethnically diverse MCCS. The 2020 meta-analysis had improved representation of southern European populations compared to previous large-scale melanoma GWAS, which could improve melanoma risk predictions for countries with more diverse European ancestry such as Australia. Previous research[31,32] demonstrates the importance of increasing diversity of participants in genetic association studies that are used to construct PRS, and failure to do so could lead to widening health disparities when PRS are used in practice.

Our work has several limitations. We only included participants of European ancestry, so results cannot be extrapolated to different populations. In the MCCS data, self-reported ethnicity could also reflect differences in migration status (e.g. those selecting Australian ethnicity were perhaps more likely to be born in Australia and thus have higher underlying

risk due to higher ambient ultraviolet radiation). The results from the MCCS had more uncertainty due to a smaller sample size.

Our work also has multiple strengths. We used data from two large prospective cohorts, ensuring the evaluations of melanoma PRS were valid in different settings. Moreover, we calculated absolute risks that include competing mortality risks, which is important to not over-estimate melanoma risks for older age groups.[33] The results were reported according to best-practice for PRS reporting[34] and details for the PRS have been deposited in the Polygenic Score Catalog[35] to enable re-use. We also conducted thorough sensitivity analyses to verify the robustness of our results.

In conclusion, newer melanoma PRS derived from a larger meta-analysis have better risk prediction performance than earlier PRS, and could be used to tailor melanoma prevention and early detection strategies to different risk levels. Re-calibration of 10-year absolute risks may be necessary when applied to specific populations. Ensuring risk prediction models are well-calibrated and can be applied to diverse populations remain key aspects for future research.

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Contributions

Conception and study design: AEC, RJM, JS. UKB data extraction and QC: MMI, DTB. MCCS data collection, data extraction, genotyping, QC and imputation: RJM, RLM, GGG, XW, TND, MCS. MCCS additional QC: JS, JYL. GWAS meta-analysis without UKB data: MHL. Funding acquisition: GJM, AEC, RJM. PRS analyses: JS, RJM, AEC. Interpretation of results: all authors. Writing - original draft: JS, AEC. Writing - editing: all authors.

Data availability

Bona fide researchers can apply to access the UK Biobank data for health-related research that is in the public interest as described on the UK Biobank website (https://www.ukbiobank.ac.uk/enable-your-research, accessed 26/04/2021). The MCCS data can be made available on request to pedigree@cancervic.org.au.

Supporting Information

Appendix S1: Supplementary Methods and Results
Supplementary Figures S1-6
Supplementary Tables S1-7
PRS Reporting Checklist (based on GRIPS)

Figure Legends

Figure 1. Calibration of PRS-adjusted and unadjusted (based on age and sex only) absolute melanoma risks in UK Biobank and the MCCS, by risk quintile.

(a) Calibration of absolute melanoma risks in UKB based on population-wide data for 2011-2015.

(b) Calibration of absolute melanoma risks in the MCCS based on population-wide data for 2009-2013.

Bars show 95% confidence intervals.

Figure 2. Calibration of absolute melanoma risks after re-scaling to *E/O*=1 in (a) UKB and (b) the MCCS, by risk quintile.

Bars show 95% confidence intervals.

Figure 3. PRS-adjustment improves discriminative ability of absolute melanoma risks in (a) UKB and (b) the MCCS. Shaded areas indicate 95% confidence intervals. Absolute risks were calculated based on population-level cancer registry data, age and sex, with and without PRS adjustment. The straight diagonal line (grey) represents the line of no discrimination. AUC: area under the receiver operating characteristic curve (with 95% confidence intervals). ns: $p>0.05$; ** $p<0.001$; *** $p<0.0001$; **** $p<10^{-10}$.

Figure 4. Estimated 10-year absolute melanoma risks and 95%CIs by top or bottom PRS50 quintile and age based on data from (a) UKB and population-wide data for England/Wales, and (b) the MCCS and population-wide data for Victoria, Australia.

(a) The estimated population-average 10-year risk of invasive melanoma for 50-year old males in England/Wales was 0.28%, which is estimated to be reached 15 years earlier and 15 years later for males in the top and bottom PRS50 quintiles, respectively. Similarly, the estimated population-average 10-year risk of melanoma for 50-year old females in England/Wales was 0.31%, estimated to be reached more than 20 years earlier for those in the top PRS50 quintile, and not before age 80 for those in the bottom quintile. The results were similar for Scotland.

(b) For Victoria, the estimated population-average 10-year risk for 50-year old males was 0.67%, estimated to be reached about 10 years earlier and 10 years later for those in the top and bottom quintiles, respectively. For females, the population-average 10-year risk at age 50 was 0.52%, estimated to be reached 10 years earlier and not before age 80 for those in the top and bottom PRS50 quintiles, respectively.

Tables

Table 1. Characteristics of UK Biobank (UKB) and Melbourne Collaborative Cohort Study (MCCS) participants. *Participants with non-European ancestry were excluded, so participants who self-reported Australian/New Zealand ethnicity in the MCCS descended from European migrants.

	UKB			MCCS			
	Cohort (n=395,647)	**Cases (n=1,651)**		**All participants with follow-up 2 visit (n=20,556)**	**Subcohort (n=4,528)**	**Cases (n=303)**
Incident melanoma cases: n (%)	1,651 (0.4)	1,651 (100.0)	Incident melanoma cases: n (%)	304 (1.5)	66 (1.5)	303 (100.0)
Death before melanoma: n (%)	11,832 (3.0)	0 (0.0)	Death before melanoma: n (%)	2,585 (12.6)	343 (7.6)	0 (0.0)
Sex: Male (%)	183,417 (46.4)	815 (49.4)	Sex: Male (%)	8,047 (39.2)	1,737 (38.4)	178 (58.7)
Age: mean (SD)	56.91 (7.95)	58.95 (7.49)	Age: mean (SD)	63.5 (7.2)	63.4 (7.2)	65.0 (6.9)
Follow-up time: mean (SD)	7.16 (0.79)	7.26 (0.81)	Follow-up time: mean (SD)	9.7 (1.3)	9.7 (1.2)	9.6 (1.5)
Ethnicity: n (%)			Ethnicity: n (%)			
British	378,305 (95.6)	1,588 (96.2)	*Australian/New Zealand**	15387 (74.9)	3,400 (75.1)	277 (91.4)
Irish	11,375 (2.9)	45 (2.7)	*British/Irish*	1459 (7.1)	316 (7.0)	16 (5.3)
White / Any other white background	5,965 (1.5)	18 (1.1)	*Greek/Italian/ Maltese*	3705 (18.0)	812 (17.9)	10 (3.3)
Ease of tanning: n (%)			Ease of tanning: n (%)			
Never tan, only burn	69,500 (17.6)	343 (20.8)	*Burn, rarely tan*	4,940 (24.0)	1,095 (24.2)	85 (28.1)
Mildly or occasionally tanned	83,561 (21.1)	400 (24.3)	*Burn, then tan*	10,111 (49.2)	2,230 (49.2)	163 (53.8)
Moderately tanned	156,426 (39.6)	641 (38.9)	*Tan, rarely burn*	5,505 (26.8)	1,203 (26.6)	55 (18.2)
Very tanned	78,190 (19.8)	244 (14.8)				
Missing	7,609 (2.0)	20 (1.2)				

SD: standard deviation

Table 2. Associations between melanoma PRS and with melanoma incidence, after adjustment for traditional risk factors and genetic principal components (all p-values are significant after Bonferroni multiple-testing correction). Associations per PRS quintile and decile see Table S4 and Figure S2.

		UKB		MCCS	
Covariates	**PRS**	**SHR[1] [95%CI[2]]**	**p-value**	**SHR [95%CI]**	**p-value**
Age, sex	PRS68	1.78 [1.70-1.86]	$<1x10^{-15}$	1.65 [1.49-1.83]	$<1x10^{-15}$
	PRS50	1.72 [1.65-1.80]	$<1x10^{-15}$	1.64 [1.48-1.82]	$<1x10^{-15}$
	PRS45	1.61 [1.54-1.68]	$<1x10^{-15}$	1.42 [1.28-1.58]	$5.7x10^{-11}$
Age, sex, ethnicity	PRS68	1.78 [1.71-1.87]	$<1x10^{-15}$	1.51 [1.35-1.68]	$9.5x10^{-14}$
	PRS50	1.72 [1.65-1.80]	$<1x10^{-15}$	1.50 [1.35-1.67]	$1.5x10^{-13}$
	PRS45	1.61 [1.54-1.68]	$<1x10^{-15}$	1.29 [1.16-1.45]	$7.7x10^{-6}$
Age, sex, ethnicity, ease of tanning, 20 genetic PCs	PRS68	1.80 [1.71-1.88]	$<1x10^{-15}$	1.47 [1.31-1.67]	$3.6x10^{-10}$
	PRS50	1.73 [1.65-1.81]	$<1x10^{-15}$	1.47 [1.30-1.66]	$5.4x10^{-10}$
	PRS45	1.61 [1.53-1.69]	$<1x10^{-15}$	1.25 [1.10-1.42]	$6.2x10^{-4}$
Age, sex, ethnicity, ease of tanning, 20 genetic PCs, education, Townsend deprivation index	PRS68	1.80 [1.71-1.89]	$<1x10^{-15}$	-	-
	PRS50	1.73 [1.65-1.81]	$<1x10^{-15}$	-	-
	PRS45	1.61 [1.54-1.69]	$<1x10^{-15}$	-	-
Age, sex, ethnicity, ease of tanning, 20 genetic PCs, skin colour, hair colour	PRS68	1.74 [1.65-1.83]	$<1x10^{-15}$	-	-
	PRS50	1.67 [1.59-1.76]	$<1x10^{-15}$	-	-
	PRS45	1.55 [1.47-1.63]	$<1x10^{-15}$	-	-
Age, sex, ethnicity, ease of tanning, 20 genetic PCs, education, Townsend deprivation index, skin colour, hair colour	PRS68	1.74 [1.66-1.83]	$<1x10^{-15}$	-	-
	PRS50	1.67 [1.60-1.76]	$<1x10^{-15}$	-	-
	PRS45	1.55 [1.47-1.63]	$<1x10^{-15}$	-	-

[1] SHR: subhazard ratio per 1 standard deviation (sd) of PRS on log-scale, with death as competing risk (for the MCCS, sd was based on subcohort participants)
[2] 95%CI: 95% confidence interval

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