ORIGINAL ARTICLE

Polygenic Risk Scores Stratify Keratinocyte Cancer Risk among Solid Organ Transplant Recipients with Chronic Immunosuppression in a High Ultraviolet Radiation Environment

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Mathias Seviiri[a,b,c], Matthew H. Law[a,b], Jue Sheng Ong[a], Puya Gharahkhani[a], Dale R. Nyholt[b,c], Peter Hopkins[d], Daniel Chambers[d], Scott Campbell[e], Nicole M. Isbel[e], H. Peter Soyer[f,g], Catherine M. Olsen[h,i], Jonathan J. Ellis[b,c], David C. Whiteman[h], Adele C. Green[j,k] and Stuart MacGregor[a,b]

Solid organ transplant recipients (SOTRs) have elevated risks for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), especially in high UVR environments. We assessed whether polygenic risk scores can improve the prediction of BCC and SCC risks and multiplicity over and above the traditional risk factors in SOTRs in a high UV setting. We built polygenic risk scores for BCC (n = 594,881) and SCC (n = 581,431) using UK Biobank and 23andMe datasets, validated them in the Australian QSkin Sun and Health Study cohort (n > 6,300), and applied them in SOTRs in the skin tumor in allograft recipients cohort from Queensland, Australia, a high UV environment. About half of the SOTRs with a high genetic risk developed BCC (absolute risk = 45.45%, 95% confidence interval = 33.14–58.19%) and SCC (absolute risk = 44.12%, 95% confidence interval = 32.08–56.68%). For both cancers, SOTRs in the top quintile were at >3-fold increased risk relative to those in the bottom quintile. The respective polygenic risk scores improved risk predictions by 2% for BCC (area under the curve = 0.77 vs. 0.75, $P = 0.0691$) and SCC (area under the curve = 0.84 vs. 0.82, $P = 0.0260$), over and above the established risk factors, and 19.03% (for BCC) and 18.10% (for SCC) of the SOTRs were reclassified in a high/medium/low risk scenario. The polygenic risk scores also added predictive accuracy for tumor multiplicity (BCC $R^2 = 0.21$ vs. 0.19, $P = 3.2 \times 10^{-3}$; SCC $R^2 = 0.30$ vs. 0.27, $P = 4.6 \times 10^{-4}$).

Journal of Investigative Dermatology (2021) **141,** 2866–2875; doi:10.1016/j.jid.2021.03.034

INTRODUCTION

Solid organ transplant recipients (OTRs) (SOTRs) have significantly elevated risks for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (Garrett et al., 2017; Menzies et al., 2019; Park et al., 2019). This is primarily attributed to chronic immunosuppression in SOTRs (Agraharkar et al., 2004; Yanik et al., 2017). However, exposure to high levels of UVR is also a key environmental risk factor for BCC/SCC (Didona et al., 2018; Kricker et al., 2017; Wu et al., 2014). Given the importance of lifetime UV exposure, traditional host factors (such as age, sex, skin pigmentation, and red hair) influence KC (keratinocyte) cancer risk (Didona et al., 2018; Serna-Higuita et al., 2019). In addition, GWASs have identified germline host risk factors for KC cancers (Chahal et al., 2016a, 2016b; Liyanage et al., 2019; Sarin et al., 2020). Therefore, prevention of these KC cancers among SOTRs should include screening, risk stratification, and prediction. Ideally, these should employ a comprehensive approach that uses both external and host factors.

To date, KC cancer prevention has relied on the assessment of traditional risk factors, but new approaches harnessing genetic information through polygenic risk scores (PRSs) have shown recently to have good potential for improving risk stratification. We have previously reported

[a]*Statistical Genetics Lab, QIMR Berghofer Medical Research Institute, Brisbane, Australia;* [b]*School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia;* [c]*Centre for Genomics and Personalised Health, Queensland University of Technology, Brisbane, Australia;* [d]*Queensland Lung Transplant Services, The Prince Charles Hospital, Brisbane, Australia;* [e]*Department of Nephrology, The Princess Alexandra Hospital, Brisbane, Australia;* [f]*Dermatology Research Centre, The University of Queensland Diamantina Institute, The University of Queensland, Brisbane, Australia;* [g]*Department of Dermatology, Princess Alexandra Hospital, Brisbane, Australia;* [h]*Cancer Control Group, QIMR Berghofer Medical Research Institute, Brisbane, Australia;* [i]*Faculty of Medicine, The University of Queensland, Brisbane, Australia;* [j]*Population Health Group, QIMR Berghofer Medical Research Institute, Brisbane, Australia; and* [k]*Cancer Research United Kingdom (CRUK) Manchester Institute, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom*

Correspondence: Mathias Seviiri, Statistical Genetics Laboratory, Queensland Institute of Medical Research (QIMR) Berghofer Medical Research Institute, 300 Herson Road, Herston, Queensland 4006, Australia. E-mail: Mathias.Seviiri@qimrberghofer.edu.au

Abbreviations: AR, absolute risk; AUC, area under the curve; BCC, basal cell carcinoma; CI, confidence interval; kb, kilobase; KC, keratinocyte; LD, linkage disequilibrium; NRI, net reclassification improvement; OTR, organ transplant recipient; PRS, polygenic risk score; PC, principal component; QSkin, QSkin Sun and Health Study; SCC, squamous cell carcinoma; SOTR, solid organ transplant recipient; STAR, skin tumors in allograft recipient; UKB, UK Biobank

Received 29 November 2020; revised 22 March 2021; accepted 24 March 2021; accepted manuscript published online 2 June 2021; corrected proof published online 11 July 2021

that in a low UV setting such as in the United Kingdom, (i) PRSs derived from the general population enable effective risk stratification for KC cancers among SOTRs; (ii) transplant recipients with a high genetic risk (PRS) have 3.3-fold and 2.1-fold increased risk per 1 SD increase in BCC or SCC PRSs, respectively; and (iii) the PRS improves BCC predictions over and above the traditional risk factors with a 3% increase in the prediction accuracy (area under the curve [AUC]) (Seviiri et al., 2021). Other studies have also shown that PRSs generated from the nontransplant general population can predict the risk of BCC and SCC among SOTRs in low UV settings (Stapleton et al., 2020, 2019).

However, given that high UV exposure and chronic immunosuppression are strong risk factors for BCC and SCC, it remains to be determined whether the findings mentioned earlier apply to SOTRs with chronic immunosuppression in a high UV setting. Secondly, in high UV settings such as in Australia, where many in the population have pale skin, KC cancer incidence rates and tumor multiplicity are extremely high (Pandeya et al., 2017; Way et al., 2020). It is hence of interest to know whether a PRS can predict not only the risk but also tumor burden (multiplicity).

Therefore, this study aims to assess whether PRSs generated from the general population can improve BCC and SCC risk prediction over and above the traditional risk factors in SOTRs in a high UV index environment and whether it can predict multiplicity of KC cancer.

RESULTS

Performance of the PRSs prediction models in the independent QSkin Sun and Health Study validation cohort

The F2 model with a linkage disequilibrium (LD) radius of 5,000 kilobase (kb) and a fraction of causal SNPs of 0.01 was the best predictive model for BCC risk in the QSkin Sun and Health Study (Qskin) with a Nagelkerke's variance (R^2) of 33.7 % (Figure 1a). For SCC, the best predictive model was F3 with an LD radius of 5,000 kb and a casual fraction of SNPs of 0.001 in QSkin with Nagelkerke's R^2 of 35.5% (Figure 1b).

Baseline characteristics in the skin tumors in allograft recipients cohort

The analysis for BCC and SCC was restricted to 331 and 337 participants, respectively, who had complete data on all important variables. At baseline, participants had an average (SD) duration of immunosuppression of 9.61 (8.50) years, they reported a mean (SD) age of 44.4 (14.2) at the first transplantation, and the majority (217, 65.6%) were male. Further baseline characteristics

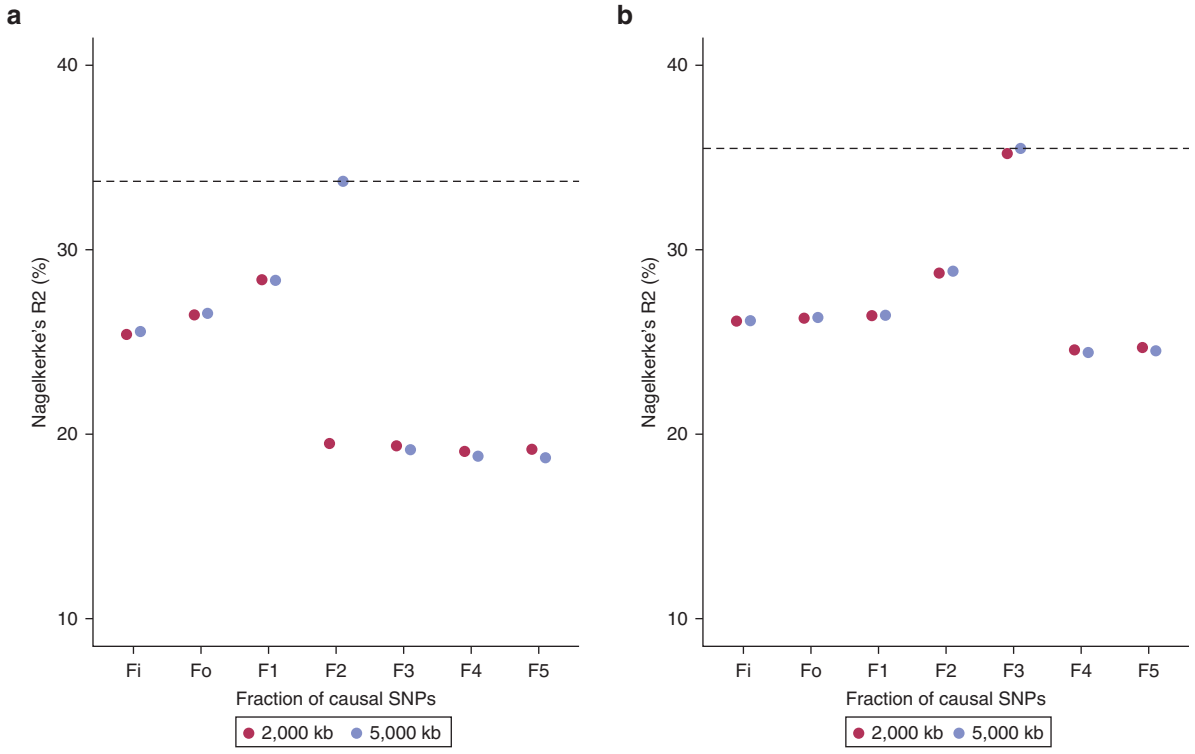

Figure 1. The performance of the BCC and SCC PRS prediction models in the QSkin validation cohort. (**a**) The performance of BCC PRS prediction models in the validation cohort. The x-axis represents the prediction models with different fractions of causal SNPs. Fi represents the infinitesimal model, whereas F0, F1, F2, F3, F4, and F5 represent fractions of causal SNPs of 1, 0.1, 0.01, 0.001, 0.0001, and 0.00002, respectively. The red and cyan colors represent the prediction models at the LD radius of 2,000 kb and 5,000 kb, respectively. The y-axis represents Nagelkerke's variance (R^2) (%) for each of the prediction models. The black dashed line highlights the best predictive model (with the highest Nagelkerke's R^2). (**b**) The performance of SCC PRS prediction models in the validation cohort. The x-axis represents the prediction models with different fractions of causal SNPs. Fi represents the infinitesimal model, whereas F0, F1, F2, F3, F4, and F5 represent fractions of causal SNPs of 1, 0.1, 0.01, 0.001,0.0001, and 0.00002, respectively. The red and cyan colors represent the prediction models at the LD radius of 2,000 kb and 5,000 kb, respectively. The y-axis represents Nagelkerke's R^2 (%) for each of the prediction models. The black dashed line highlights the best predictive model (with the highest Nagelkerke's R^2). BCC, basal cell carcinoma; kb, kilobase; LD, linkage disequilibrium; PRS, polygenic risk score; QSkin, QSkin Sun and Health Study; SCC, squamous cell carcinoma.

are presented in Supplementary Table S1. During the three years of follow up, SOTRs had absolute risks (ARs) of 35.65% (95% confidence interval [CI] = 30.49–41.07%) and 36.80% (95% CI = 31.63–42.19%) for BCC and SCC, respectively.

Association of the PRSs and the risks of BCC and SCC among SOTRs in the skin tumors in allograft recipients cohort

The respective PRSs were associated with the risks of BCC (OR per SD = 1.52, 95% CI = 1.15–2.00, $P = 3.0 \times 10^{-3}$) and SCC (OR per SD = 1.69, 95% CI =1.25–2.28, $P = 7.2 \times 10^{-4}$) after adjusting for the established risk factors and the first 10 principal components (PCs) (Figure 2).

PRSs and risk stratification for BCC and SCC among SOTRs in the skin tumors in allograft recipients cohort

About half of the people with a high genetic risk (in the respective top PRS quintiles) developed BCC (AR = 45.45%, 95% CI = 33.1458.19%) and SCC (AR = 44.12%, 95% CI = 32.08–56.68%) during follow-up (Figure 3a). Despite having a low genetic risk (bottom quintile), SOTRs in the skin tumors in allograft recipients (STARs) cohort had an AR for BCC 2.6 times higher than that in the QSkin validation cohort of 40,438 nontransplant recipients in the same high UV setting after about the same period of follow-up (AR in STAR= 25.37%, 95% CI = 15.53–37.49% vs. AR in QSkin = 9.57%, 95% CI = 9.28–9.86%). Similarly, SOTRs in STAR in the bottom quintile of the PRS had an AR for SCC that was five times higher than that in the QSkin cohort after a similar duration of follow-up (AR in STAR = 20.59%, 95% CI = 11.74–32.12% vs. AR in QSkin = 4.16%, 3.97–4.36% for QSkin) (Figure 3a).

Compared with the SOTRs with a low genetic risk (bottom quintile), SOTRs with a high genetic risk (top quintile) had a 3.5-fold increased risk of developing BCC (OR = 3.66, 95% CI = 1.54–8.72, $P = 3.3 \times 10^{-3}$), whereas those with a moderate genetic risk (the middle 60%) had a 2.0-fold increased risk (OR = 1.95, 95% CI = 0.94–4.04, P = 0.0716), after adjusting for the established risk factors and the first 10 PCs (Figure 3b). Similarly, SOTRs in the top quintile had a 3.2-fold increased risk (OR = 3.21, 95% CI = 1.27–8.17, P = 0.0135) of developing SCC when compared with SOTRs in the bottom quintile (Figure 3b).

BCC and SCC risk prediction modeling with established risk factors and the PRSs in the STAR Cohort

Despite being a high UV index setting with high rates of KC cancers, adding the PRS to the model containing the established risk factors mentioned earlier and the first 10 PCs improved the BCC prediction by 2% (established risk factors + PRS model AUC = 0.77, 95% CI = 0.72–0.82 vs. only established risk factors model AUC = 0.75, 95% CI = 0.70–0.81, P-value for DeLong's test for two correlated receiver operator characteristic curves = 0.0691) (Figure 4a). Of the 331 SOTRs, 19.03% were reclassified within the risk tertiles (high 33.3%, medium 33.3%, low 33.3%) when the PRS was added to the model containing only the traditional risk factors (categorical net reclassification improvement [NRI] = 0.09, 95% CI = −0.01 to 0.18, P = 0.0741 and continuous NRI = 0.29, 95% CI = 0.06–0.51, P = 0.0117) (Table 1). Overall, 9.67% (32 of 331) and 9.37% (31 of 331) of OTRs were reassigned to higher and lower risk categories, respectively.

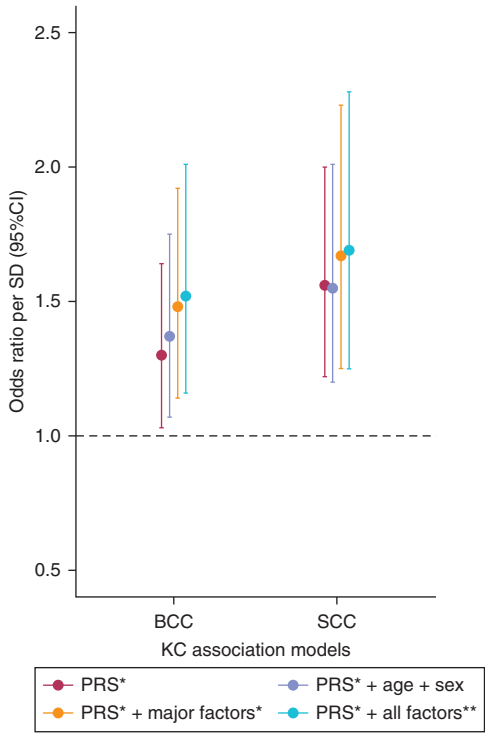

Figure 2. The association of the PRSs and the risks of BCC and SCC among SOTRs in the STAR cohort. PRS* indicates adjusted for 10 PCs. BCC major factors* include age, sex, type of transplantation, immunosuppressive medication, duration of immunosuppression, and skin color. BCC all factors* include major factors + sun exposure, lifetime painful sunburns, skin reaction to the sun, and history of BCC. SCC major factors* include age, sex, type of transplantation, immunosuppressive medication, duration of immunosuppression, and skin color. SCC all factors* include major factors + sun exposure, lifetime painful sunburns, skin reaction to the sun, and history of SCC. Logistic regression was used for analysis adjusting for established skin cancer risk factors + 10 PCs. BCC, basal cell carcinoma; CI, confidence interval; KC, keratinocyte carcinoma; PC, principal component; PRS, polygenic risk score; SCC, squamous cell carcinoma; SOTR, solid organ transplant recipient; STAR, skin tumors in allograft recipient.

Adding the SCC PRS improved the SCC prediction over and above the established skin cancer risk factors by 2% (established risk factors + PRS model AUC = 0.84, 95% CI = 0.80–0.88 vs. only established risk factors model AUC = 0.82, 95% CI = 0.77–0.87, P-value for DeLong's test for two correlated receiver operator characteristic curves = 0.0260) (Figure 4b). When we added the PRS to the base model containing SCC traditional risk factors, 18.10% of the 337 SOTRs were moved to a different risk tertile, including 8.90% and 9.20% moving to a higher and lower risk category, respectively (categorical NRI = 0.13, 95% CI = 0.04–0.22, P = 0.0042 and continuous NRI = 0.36, 95% CI = 0.14–0.57, $P = 1.4 \times 10^{-3}$) (Table 1). We also observed improvement when we considered the top 20% versus the bottom 80% strata for both BCC and SCC (Table 1).

Prediction of the multiplicity (number) of BCC and SCC among SOTRs in the STAR cohort

For BCC, the model with established risk factors (including 10 PCs) had an R^2 of 0.19, whereas adding the PRS increased

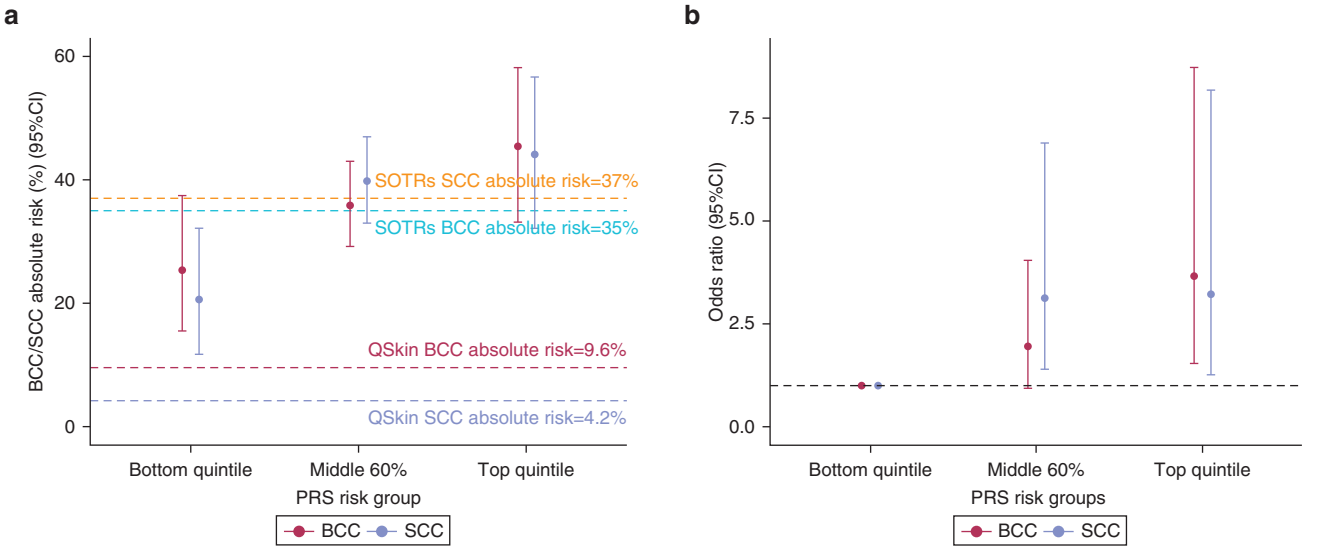

Figure 3. KC risk stratification in SOTRs in the STAR cohort. (**a**) The **a**bsolute risk of BCC and SCC among SOTRs in the STAR cohort. The absolute risks (proportions) and 95% CI for BCC and SCC based on the genetic risk of the PRS: high genetic risk (top quintile), moderate genetic risks (middle 60%), and low genetic risks (bottom quintile) for SOTRs in the STAR cohort; and the respective absolute risks among the general nontransplantee QSkin cohort (n = 40,438). The red color represents BCC, whereas the cyan represents SCC. The x-axis represents the PRS stratum, whereas the y-axis represents the absolute risk BCC or SCC, respectively, after 3 years of follow-up. The purple and green dashed lines represent the absolute risks of BCC (35%) and SCC (37%) among SOTRs in the STAR cohort, respectively. The dashed red and cyan blue lines represent the absolute risks of SCC (4.2%) and BCC (9.6%), respectively, for the nontransplantee QSkin cohort after about 3 years of follow-up. (**b**) OR (95% CI) of BCC and SCC associated with PRS stratum among SOTRs in the STAR cohort, adjusted for established risk factors. The stratification of the risk of BCC and SCC is based on the genetic risk: high (top quintile PRS), moderate (middle 60%), and low (bottom quintile PRS) for SOTRs in the STAR cohort. The red color represents BCC, whereas cyan blue represents SCC. The x-axis represents the PRS strata, whereas the y-axis represents the ORs and 95% CIs. The black dashed line represents the null (1.00) risk for the reference group (bottom PRS quintile). Logistic regression was used for analysis adjusting for established skin cancer risk factors + 10 ancestral PCs. BCC, basal cell carcinoma; CI, confidence interval; KC, keratinocyte carcinoma; PC, principal component; PRS, polygenic risk score; QSkin, QSkin Sun and Health Study; SCC, squamous cell carcinoma; SOTR, solid organ transplant recipient; STAR, skin tumors in allograft recipient.

the R^2 to 0.21. The analysis of variance between the two models indicated that adding the PRS significantly improved the model fit (*P*-value for ANOVA test = 3.2×10^{-3}). Adding the SCC PRS improved the prediction of SCC multiplicity over and above the established risk factors (established risk factors + PRS model $R^2 = 0.30$ vs. established risk factors model $R^2 = 0.27$, *P*-value for ANOVA test = 4.6×10^{-4}).

PRS models for UK Biobank + 23andMe versus UK Biobank only for BCC and SCC

Comparing the PRS derived from the UK Biobank (UKB) + 23andMe versus that derived from only UKB, we found that the AUC was very slightly higher for SCC for the UKB + 23andMe scenario but that the reverse was true for BCC (Supplementary Table S2). However, the results were so similar that we cannot conclude that the larger training dataset (UKB + 23andMe) performed better than the smaller one (UKB only). In general, the larger sample size available from UKB + 23andMe should enable better prediction than that available from one source alone, although in practice, the performance was similar, perhaps owing to the 23andMe phenotype being based on self-report.

DISCUSSION

This study evaluated whether a PRS generated from the general population can be used to stratify the risk of BCC and SCC among SOTRs with chronic immunosuppression in a high UV environment. We found that transplant recipients with a high genetic risk, that is, those in the top quintile, have a high risk of BCC and SCC, with about half of them developing BCC and SCC and having a 3-fold increased risk of BCC and SCC relative to those in the bottom quintile. Despite the strong environmental effect of UVR, the PRS improved both the BCC and SCC risk predictions over and above the established risk factors by 2% and 19.03%, respectively, and 18.10% of the SOTRs had their risk category changed for BCC and SCC. It further showed that the PRS can improve the prediction of BCC and SCC multiplicity over and above the established risk factors.

Our results are consistent with previous findings that SOTRs with a high genetic risk (e.g., those in the top PRS quintile) have a substantially higher risk of developing BCC or SCC than their counterparts with a low genetic risk (e.g., those in the bottom quintile) and that the PRS improves BCC and SCC risk prediction over and above the established clinical and skin cancer risk factors (Seviiri et al., 2021; Stapleton et al., 2019). This study differs from other previous studies in a number of ways. First, we used Ldpred (Vilhjálmsson et al., 2015), a method that considers a large number of genetic markers at the PRS generation stage, in contrast to the LD clump method used in the previous studies (Roberts et al., 2020; Seviiri et al., 2021; Stapleton et al., 2020, 2019). BCC and SCC have strong signals in high LD regions such as HLA, which might lead to an inefficient harnessing of the available information. Our study overcomes

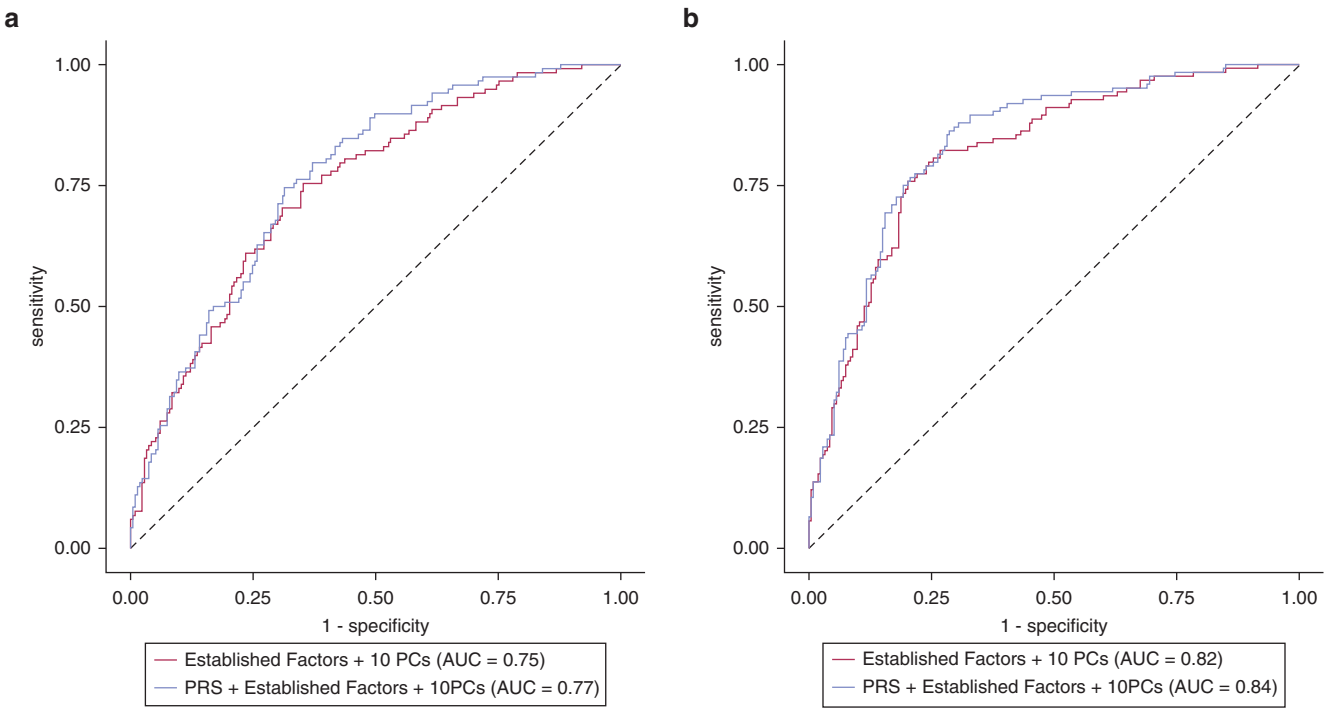

Figure 4. The AUC curve for the prediction of KC risk in the SOTRs in the STAR cohort. (**a**) The receiver operating characteristic curve showing the AUC for BCC prediction models in the STAR cohort; established risk factors + 10 ancestral PCs represented in red, then PRS + established risk factors + 10 ancestral PCs represented in cyan blue for SOTRs in the STAR cohort. The x-axis represents the specificity of 1, whereas the y-axis represents the sensitivity. (**b**) The receiver operating characteristic curve showing the AUC for SCC prediction models in the STAR cohort; established risk factors + 10 ancestral PCs represented in red, then PRS + established risk factors + 10 ancestral PCs represented in cyan blue for SOTRs in the STAR cohort. The x-axis represents the specificity of 1, whereas the y-axis represents the sensitivity. AUC, area under the curve; BCC, basal cell carcinoma; KC, keratinocyte; PC, principal component; SOTR, solid organ transplant recipient; STAR, skin tumors in allograft recipient.

this problem by using the Ldpred method and training the models in an independent cohort using both different LD radius blocks (r^2 = 2,000 kb and r^2 = 5,000 kb) and the fractions of causal variants. Second, it has assessed the performance of a PRS in a high UV environment, where environmental factors greatly increase background BCC or SCC incidence. Previous studies have evaluated the PRS in environments with typically lower UV such as the United Kingdom and United States (Roberts et al., 2020; Seviiri et al., 2021; Stapleton et al., 2020, 2019). About half of the patients in the top quintile developed BCC and SCC within the relatively short 3-year follow-up period. In contrast, as we reported previously, only about 23% of SOTRs in the top quintile in the United Kingdom (a low UV setting) had developed BCC and SCC by late middle age (Seviiri et al., 2021). Third, as opposed to the follow-up of patients immediately after receiving their organ transplant, this study assessed SOTRs with a mean (SD) duration of 9.61 (8.50) years after transplantation and thus with chronic immunosuppression, another key risk factor for KC cancer in SOTRs. Despite the chronic immunosuppression and other established risk factors, the PRSs were able to stratify the risks of both BCC and SCC. Therefore, a PRS can be of clinical importance at any stage of follow-up after transplantation.

Clinical utility

This study has shown that SOTRs with chronic immunosuppression in high UV settings can benefit from the PRS for BCC and SCC risk stratification and prediction (risk and multiplicity). Those at high, medium, and low genetic risk have markedly different ARs, with the risk stratification benefits continuing in the long term (10 years after transplantation). Indeed, the 19.03% (for BCC) and 18.10% (for SCC) of individuals whose risk category changed after adding the PRS may have their treatment options changed. For example, the 9.67% (for BCC) and 8.90% (for SCC) of SOTRs who are reassigned to a higher risk group may consequently have more intense KC cancer preventive interventions than their counterparts in the previously assigned group. The reverse may be applied to the 9.37% (for BCC) and 9.20% (for SCC) who move to a lower risk group.

We show that a PRS that can (in combination with established risk factors) identify SOTRs at a very high AR of developing KC cancer in a high UV environment. These individuals may benefit from enhanced review and screening for KC cancer for purposes of early detection and prevention of KC cancer. In the Australian setting, all SOTRs are at non-negligible KC cancer risk and are frequently placed on waiting lists for specialist dermatology care; further studies are merited to assess how effective a PRS-based approach would be in directing finite resources to those at highest risk. Internationally, in both the high UV setting considered in this study and in a lower UV setting considered previously (Seviiri et al., 2021), a PRS-based approach offers good stratification of risk in SOTRs, and future studies should assess country-specific economic factors underlying when the practical benefits of implementing PRS-based screening may be realized.

Table 1. Cross-Tabulation of the Traditional Risk Factors and Polygenic Risk Score Model Versus Traditional Risk Score Model for Keratinocyte Cancer among Solid Organ Transplant Recipients in the Skin Tumors in Allograft Recipients Cohort

		Traditional Factors[1] + Polygenic Risk Score				
Basal Cell Carcinoma	**Traditional Factors[1]**	**Total, n**	**Low Risk[2], n**	**Moderate Risk[2], n**	**High Risk[2], n**	**Total Reclassified, n (%)**
Model 1	Low risk (tertile 1)	111	99	12	0	12 (10.91)
	Moderate risk (tertile 2)	111	20	71	20	40 (36.03)
	High risk (Tertile 3)	109	0	11	98	11 (10.09)
	Total	331	119	94	118	63 (19.03)
Model 2	Moderate risk (bottom 80%)	265	—	248	17	17 (6.42)
	High risk (top 20%)	66	—	17	49	17 (25.76)
	Total	331	—	265	66	34 (10.27)
Squamous cell carcinoma						
Model 1	Low risk (tertile 1)	113	98	15	0	15 (13.27)
	Moderate risk (tertile 2)	113	19	79	15	34 (30.09)
	High risk (tertile 3)	111	0	12	99	12 (10.81)
	Total	337	117	106	114	61 (18.10)
Model 2	Moderate risk (bottom 80%)	271	—	249	22	22 (8.12)
	High risk (top 20%)	66	—	8	58	8 (12.12)
	Total	337	—	257	80	30 (8.90)

[1]Adjusted for basal cell carcinoma traditional risk factors (age, sex, type of transplantation, immunosuppressive medication, duration of immunosuppression, skin color, sun exposure, lifetime painful sunburns, skin reaction to the sun, and history of basal cell carcinoma). Adjusted for squamous cell carcinoma traditional risk factors (age, sex, type of transplantation, immunosuppressive medication, duration of immunosuppression, skin color, sun exposure, lifetime painful sunburns, skin reaction to the sun, and history of squamous cell carcinoma).
[2]The risk level corresponds to the risk group under the traditional risk factor base model.

PRSs improve the BCC and SCC risk and multiplicity predictions over and above the established risk factors among SOTRs with chronic immunosuppression in a high UV environment. The incorporation of PRSs into the clinical guidelines for KC cancer prevention, including screening, risk stratification, and prediction, may contribute to the reduction of the burden of these cancers among SOTRs with chronic immunosuppression in a high UV setting.

METHODS AND MATERIALS

Discovery cohorts for the PRS derivation: The UKB cohort and 23andMe

We used the UKB and 23andMe cohorts to derive the discovery GWAS summary statistics for BCC and SCC. Detailed descriptions on recruitment, genotyping, quality control, and imputation procedures and processes for the UKB and 23andMe cohorts have been published elsewhere (Bycroft et al., 2018; Chahal et al., 2016b; Sudlow et al., 2015). 23andMe participants provided written informed consent and participated in the research online, under a protocol approved by the external Association for the Accreditation of Human Research Protection Programs–accredited Institutional Review Board, Ethical & Independent Review Services. Participants were included in the analysis on the basis of the consent status as checked at the time data analyses were initiated. For the UKB, the study was approved by the United Kingdom's National North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent. In the UKB, we selected 307,684 nontransplant recipients (20,791 cases and 286,893 controls) for BCC and 294,294 (7,402 cases and 286,892 controls) nontransplant recipients for SCC of European ancestry. Cases were based on International Classification of Diseases 10 or International Classification of Diseases 9 codes, together with histologic International Classification of Diseases for Oncology, 3rd edition codes for BCC and SCC, excluding the respective in-situ BCC and SCC cases. Controls had no history of any cancer. The 23andMe cohort included 287,197 participants (12,945 BCC cases and 274,252 controls) for BCC and 287,137 (6,579 SCC cases and 280,558 controls) for SCC of European ancestry with self-reported data but with >90% sensitivity and >98% specificity for BCC and SCC with a low misclassification rate <10% (Chahal et al., 2016b). The UKB cases were ascertained through linkage of participant data with records at the national cancer registries.

Validation cohort for the PRSs: The QSkin prospective cohort

QSkin is a prospective population-based cohort of adult participants (n ~ 43,000) residing in Queensland, a high UV index setting in Australia (annual average noon clear sky UV index = 10). Participants were aged 40–60 years (mean age = 56 years) and were randomly recruited from the population from 2011 with both clinically validated and self-reported data on skin cancers (Olsen et al., 2012). Details of the phenotype distributions have been published before (Olsen et al., 2012). In 2017, over 17,000 participants were genotyped using the Illumina GSA arrays and imputed to the Haplotype Reference Consortium panel (Loh et al., 2016). The study was approved by the Human Research Ethics Committee of Queensland Institute of Medical Research (QIMR) Berghofer Medical Research Institute, Brisbane, Australia. All participants provided written informed consent. To validate the PRS in a general population sample, we selected 7,304 participants (2,064 cases and 5,240 controls) for BCC and 6,093 participants for SCC (853 cases and

5240 controls) of European ancestry with both genetic and phenotypic data.

Prospective test cohort: the STAR cohort

The STAR study is a cohort of over 600 kidney, liver, and lung OTRs recruited respectively through the Princess Alexandra Hospital (Brisbane, Australia) and Prince Charles Hospital (Brisbane, Australia), the central referral hospitals for OTRs in the state of Queensland. Full details of the cohort and collection of phenotype data have been published previously (Hartman et al., 2018; Iannacone et al., 2015; Plasmeijer et al., 2019). Briefly, baseline recruitment was between 2012 and 2014, with subsequent annual follow-ups until the middle of 2016. At baseline, the key variables recorded were sex; date and type of transplantation (kidney, liver, and lung); duration of immunosuppression (time since transplantation); age at transplantation; skin reaction to the sun (only tans, burns then tans, and always burns); lifetime painful sunburns; sun exposure (during both weekdays and over the weekend); skin color (medium, olive, and fair); red hair color; and type of immunosuppressive medication, including calcineurin inhibitors (cyclosporine, tacrolimus), antimetabolites (azathioprine, mycophenolate), mammalian target of rapamycin inhibitors (sirolimus, everolimus), and corticosteroids (prednisone, used only in addition to other medication). Because all participants had been taking at least one immunosuppressive medication since the time of transplantation, the immunosuppressive medication variable was further reclassified as monotherapy (one immunosuppressive medication), double therapy (two medications), and triple therapy (at least three).

Dermatologists conducted skin examinations for every participant at study baseline and annual follow-up clinics, and all clinically diagnosed BCC/SCC lesions were referred for histologic confirmation. Between annual clinics, patients received quarterly phone calls to ascertain skin cancer treatments, and treating physicians confirmed all histologically diagnosed incident cancers. In addition, regular reviews of pathology laboratories' databases ensured the documentation of all newly diagnosed skin cancers. The study was approved by the human research ethics committees at Queensland Institute of Medical Research (QIMR) Berghofer Medical Research Institute and at Metro South Hospital and Health Service, Brisbane, Australia. All participants provided written informed consent.

Genotyping, quality control, and imputation of genetic data

In 2019, we extracted DNA for 375 adult participants, comprising 252 kidney, 30 liver, and 93 lung OTRs. DNA samples were genotyped using an Illumina GSA chip. We performed standard GWAS quality control procedures on the genotyped data. Individuals were excluded if they failed the sex and heterozygosity check, they were closely related (pihat >0.2), they had high genotype missingness (>3%), or they had divergent ancestry from CEU (European ancestry) (>6 SDs) of the HapMap phase 3 (Figure 5). We further computed the first 10 PCs using selected autosomal SNPs to account for any subtle population stratification effects within the European ancestry group in the subsequent analyses. We also excluded SNPs with a call rate <95%, minor allele frequency <1%, and Hardy–Weinberg equilibrium $P < 1 \times 10^{-6}$. Next, we imputed the genetic data to the Haplotype Reference Consortium reference panel (version r1.1 2016, European population) (Loh et al., 2016) using the Michigan Imputation Server (Das et al., 2016) and Eagle, version 2.4 (Loh et al., 2016) for phasing and Minimac4 for imputation. We retained the SNPs with an imputation score >0.3.

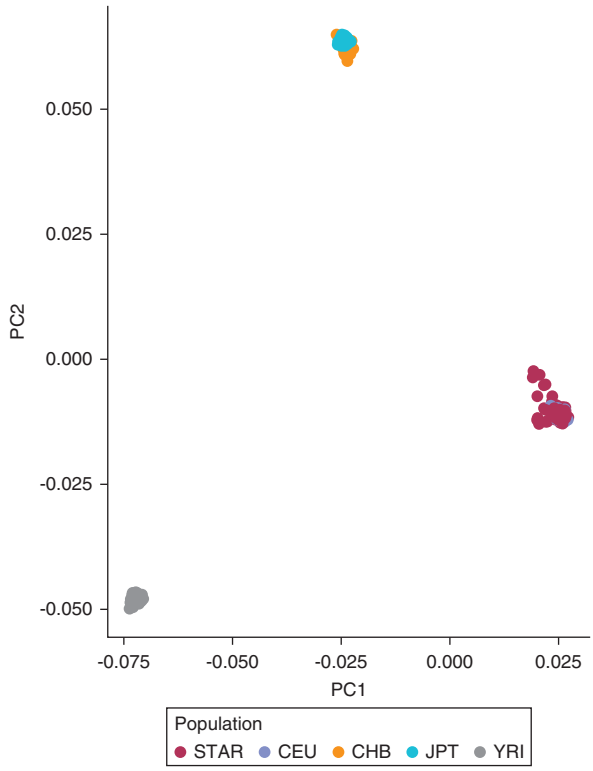

Figure 5. The ancestry diversity plot for the first and second principal ancestral components for STAR and HapMap phase 3 after quality control. The x-axis represents the first ancestral PC1, whereas the y-axis represents the second ancestral PC2. CEU represents the people of European ancestry, clustered around by the participants in the STAR cohort (European ancestry). CHB, JPT, and YRI represent participants of Chinese, Japanese, and African ancestry, respectively, in the Hapmap Phase 3 project. PC, principal component; STAR, skin tumors in allograft recipients.

Statistical analyses

Skin cancer GWAS. We used a training GWAS as conducted in our previous work (Seviiri et al., 2021). Briefly, using UKB data, we performed two case-control GWAS for BCC (20,791 BCC cases and 286,893 controls) and SCC (7,402 cases and 286,892 controls) that excluded SOTRs. The GWAS was conducted using a scalable and accurate implementation of a generalized mixed model (Zhou et al., 2018). Next, we obtained the 23andMe GWAS data for BCC (12,945 cases and 274,252 controls) (Chahal et al., 2016b) and SCC (6,579 cases and 280,558 controls) (Chahal et al., 2016a), and using a fixed-effects inverse variance weighted model, we performed a meta-analysis between the UKB GWAS and 23andMe GWAS for both BCC (total = 33,736 cases and 561,145 controls) and SCC (total = 13,981 cases and 567,450 controls) using METAL (Willer et al., 2010). We restricted the analysis to nonambiguous, autosomal, biallelic SNPs with a minor allele frequency >1%. In the initial GWAS, sex, age, and population stratification using PCs were adjusted for in both the UKB and 23andMe analyses.

Next, we identified the SNPs that were present in both our validation (QSkin) and target (STAR) cohorts. This resulted in 6,559,345 and 6,559,527 SNPs for BCC and SCC discovery GWAS meta-analysis, respectively.

Generation of the PRS models. Our overall approach was to generate multiple PRS models and later select the one that

performed best in an independent validation cohort (QSkin). We generated 14 PRS models (for each trait) in a systematic way using the LDpred method (Vilhjálmsson et al., 2015). LDpred is a Bayesian method that uses all SNPs in the GWAS and weights every SNP by the posterior mean of its conditional effect and LD information from the reference panel. First, using an LD reference panel of 2,000 unrelated individuals of European ancestry from UKB and the GWAS meta-analysis summary statistics (generated as discussed earlier) for BCC and SCC, we generated LDpred-adjusted effect estimates (log ORs) for BCC and SCC separately using different parameters. We first used an LD radius of 2,000 kb with varying fractions of causal SNPs, that is, Fi (infinitesimal model), F0 (1), F1 (0.1), F2 (0.01), F3 (0.001), F4 (0.0001), and F5 (0.00002). Then, we generated similar models using an LD radius of 5,000 kb but maintaining the fractions of causal SNPs mentioned earlier. Therefore, in total, we generated 14 PRS models for BCC and SCC that we applied to our validation data set to select the best predictive model.

Validation of the PRSs in the QSkin cohort. Next, using the LDpred-adjusted effect sizes (log ORs) for the 14 models mentioned earlier as SNP weights and the imputed allelic dosages for the genotypes in QSkin, we generated individual PRSs using PLINK 1.9 (Chang et al., 2015). To select the best predictive model for each trait, we compared the model fit between a model with a BCC or SCC ~ PRS + age + sex +10 PCs and a null model. We selected the best performing model using Nagelkerke's R^2 (Nagelkerke, 1991) computed using the predictABEL R package (Kundu et al., 2011). Model performance for both BCC and SCC in QSkin is presented in Figure 2a and Figure 2b, respectively. This process of selecting the single best model based on the QSkin cohort ensures that we do not induce bias from overfitting when applying our derived PRS to the STAR cohort.

Application of the best predictive PRS model in the STAR cohort. Using the LDpred-adjusted effect estimates for the best predictive models for BCC and SCC, we generated the individual PRSs in the STAR cohort using imputed allelic dosages and PLINK 1.9. PRSs were normalized to express OR per SD increase in the PRS for the associations. We assessed the association between the PRS and the BCC/SCC risk by performing both simple and multiple logistic regression analyses (i.e., model 1, BCC or SCC ~PRS + 10 PCs; model 2, BCC or SCC ~PRS + 10 PCs + age at transplantation + sex; model 3, BCC or SCC ~PRS + major factors; and model 4, BCC or SCC ~PRS + all known factors). In model 3, major factors included age at transplantation, sex, type of transplantation, immunosuppressive medication (monotherapy, double therapy, and triple therapy), duration of immunosuppression, and skin color. All known factors in model 4 included established risk factors: age at transplantation, sex, type of organ transplantation, immunosuppressive medication, history of BCC or SCC, duration of immunosuppression, skin color, sun exposure, lifetime painful sunburns, and skin reaction to the sun. Model 4 was used as the final model.

Next, we divided the PRSs into quintiles. To evaluate whether the PRSs stratify the risk of BCC and SCC in SOTRs, we computed the ORs and 95% CIs for the BCC and SCC risk for participants with high genetic risk (those in the top quintile) and moderate risk (those in the middle 60%) compared with those of individuals in the bottom quintile (adjusting for the established skin cancer risk factors mentioned earlier and 10 PCs). Although the selection of these strata was arbitrary, they have been widely used in similar previous studies (Inouye et al., 2018; Torkamani et al., 2018). Next, we evaluated the ARs for BCC and SCC in the three strata mentioned earlier by computing the proportions of the participants who had developed BCC and SCC within the 3 years of follow-up. We further compared the ARs for BCC and SCC for the SOTRs in the STAR cohort with those in our independent QSkin validation cohort (in the same UV environment) after a similar follow-up period.

Next, we evaluated whether the PRSs improve the BCC and SCC risk predictions over and above the established risk factors by comparing the AUC for the prediction models with and without the PRS, that is, AUC for established risk factors + 10 PCs versus AUC for established risk factors + 10 PCs + PRS. The AUC and 95% CI were computed using the PROC package (Robin et al., 2011) in R (R Foundation for Statistical Computing, Vienna, Austria). In addition, we calculated the NRI when the PRS is added to traditional risk factor models for both BCC and SCC using the predictABEL package (Kundu et al., 2011). We evaluated the NRI in two scenarios: (i) tertiles of risk (high, medium, low) and (ii) two categories (top 20% vs. bottom 80%).

Next, we evaluated whether the PRSs improve the predictions of multiple incident BCCs and/or SCCs per person during the study period over and above the established risk factors by comparing the R^2 explained for linear models with and without the PRS using the ANOVA test using R.

Sensitivity analyses. We further explored whether the results were materially influenced by the 23andMe data by comparing the key findings for the original UKB + 23andMe PRS versus the UKB-only PRS models. First, as described earlier, we used the UKB GWAS for BCC and SCC to develop and validate the UKB-only PRS models (for BCC and SCC). We compared the associations with BCC or SCC, prediction of BCC or SCC risk and multiplicity, AR, and the percentage of people reclassified when we used the original UKB + 23andMe PRS versus the UKB-only PRS models (Supplementary Table S2).

Data availability statement

The underlying data used to develop the polygenic risk scores are available from the UK Biobank with an approved UK Biobank application. The specific UK Biobank data fields (https://biobank.ndph.ox.ac.uk/showcase/search.cgi) used for the analysis of basal cell carcinoma and squamous cell carcinoma were fields 40006 and 40013 for International Classification of Diseases codes and field 40011 for International Classification of Diseases for Oncology 3 codes. For basal cell carcinoma, we analyzed the International Classification of Diseases for Oncology 3 codes 8090, 8091, 8092, 8093, 8094, 8097, and 8098 and codes 8070, 8071, 8072, 8073, 8074, 8075, 8076, and 8078 for squamous cell carcinoma. 23andMe Research Company allows applications to access previously published datasets (https://research.23andme.com/dataset-access/), and we accessed and used specific GWAS summary statistics for basal cell carcinoma (Chahal et al., 2016b) and squamous cell carcinoma (Chahal et al., 2016a). The UK Biobank–only polygenic risk scores for both basal cell carcinoma and squamous cell carcinoma can be accessed at the polygenic risk score catalog (https://www.pgscatalog.org/) on publication. Data for validation and application of the polygenic risk score can be accessed through application to the *Q*Skin Sun and Health Study principal investigator David Whiteman (David.Whiteman@qimrberghofer.edu.au) and the skin tumors in allograft recipients cohort principal investigator Adele Green (Adele.Green@qimrberghofer.edu.au).

ORCIDs
Mathias Seviiri: https://orcid.org/0000-0002-8610-3283
Matthew H. Law: https://orcid.org/0000-0002-4303-8821
Jue Sheng Ong: https://orcid.org/0000-0002-6062-710X
Puya Gharahkhani: https://orcid.org/0000-0002-4203-5952
Dale R. Nyholt: https://orcid.org/0000-0001-7159-3040
Peter Hopkins: https://orcid.org/0000-0003-3261-9345
Daniel Chambers: https://orcid.org/0000-0002-9553-5870
Scott Campbell: https://orcid.org/0000-0003-1338-2151
Nicole M. Isbel: https://orcid.org/0000-0002-9566-7179
H. Peter Soyer: https://orcid.org/0000-0002-4770-561X
Catherine M. Olsen: https://orcid.org/0000-0003-4483-1888
Jonathan J. Ellis: https://orcid.org/0000-0003-0410-5064
David C. Whiteman: https://orcid.org/0000-0003-2563-9559
Adele C. Green: https://orcid.org/0000-0002-2753-4841
Stuart MacGregor: https://orcid.org/0000-0001-6731-8142

CONFLICT OF INTEREST
HPS is a shareholder of MoleMap NZ and E-derm-consult GmbH and undertakes regular teledermatological reporting for both companies. HPS is a medical consultant for Canfield Scientific and Revenio Research Oy and is also a medical advisor for First Derm. DCW is funded by research grants and fellowships from the National Health and Medical Research Council of Australia. DCW has received speaker fees from Pierre Fabre. The remaining authors state no conflict of interest.

ACKNOWLEDGMENTS
The study was supported by a program grant (APP1073898) and a project grant (APP1063061) from the Australian National Health and Medical Research Council. SM and DCW are supported by Research Fellowships from the National Health and Medical Research Council. MS was supported by the Australian Government Research Training Program and the Faculty of Health Scholarship at Queensland University of Technology, Australia. HPS holds a National Health and Medical Research Council Medical Research Future Fund Next Generation Clinical Researchers Program Practitioner Fellowship (APP1137127). This study was conducted using data from UK Biobank (application number 25331), the 23andMe Research Team (United States of America), and QSkin Sun and Health Study (Australia). We thank the research participants and the employees of 23andMe for partly making this work possible. We thank Paul Leo from the Australian Translational Genomics Centre, Institute of Health and Biomedical Innovation, Queensland University of Technology for the genotyping services.

AUTHOR CONTRIBUTIONS
Conceptualization: MS, MHL, SM; Data Curation: MS, MHL, JSO, DCW, CMO, SM, ACG; Formal Analysis: MS; Funding Acquisition: SM, MHL, DCW, ACG; Investigation: MS, MHL, DCW, CMO, JJE, ACG, SM; Methodology: MS, MHL, SM; Project Administration: MS, MHL, SM; Resources: MHL, DCW, CMO, SM; Software: MS; Supervision: SM, MHL, DRN; Visualization: MS; Writing - Original Draft Preparation: MS, SM, MHL, ACG, JSO, PG, DCW, CMO, DRN, PH, DC, SC, NMI, HPS, JJE; Writing - Review and Editing: MS, MHL, JSO, PG, DRN, PH, DC, SC, NMI, HPS, CMO, JJE, DCW, ACG, SM

SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2021.03.034.

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Supplementary Table S1. Baseline Characteristics of the Organ Transplant Recipients in the STAR Cohort Used for BCC analysis

	All Participants, n = 331		Controls, n = 213 (64.4%)		Cases, n = 118 (35.6%)	
Characteristic	**Mean or n**	**SD or %**	**Mean or n**	**SD or %**	**Mean or n**	**SD or %**
Age at first transplantation (yrs)	44.35	14.17	42.03	14.11	48.53	13.35
Sex						
Male	217	65.6	130	61	87	73.7
Female	114	34.4	83	39	31	26.3
Duration of immunosuppression (yrs)	9.61	8.5	9.08	7.93	10.57	9.4
Type of transplantation						
Kidney	221	66.8	134	62.9	87	73.7
Liver	82	24.8	59	27.7	23	19.5
Lung	28	8.5	20	9.4	8	6.8
Immunosuppressive medication						
Monotherapy	15	4.5	11	5.2	4	3.4
Double therapy	53	16	31	14.6	22	18.6
Triple therapy	263	79.5	171	80.3	92	78
Skin color						
Olive/medium	114	34.4	75	35.2	39	33.1
Fair	217	65.6	138	64.8	79	66.9
Sun exposure[1]						
Mild	84	25.4	56	26.3	28	23.7
Moderate	62	18.7	40	18.8	22	18.6
Excessive	185	55.9	117	54.9	68	57.6
Skin reaction to sun exposure						
Only tans	74	22.4	55	25.8	19	16.1
Burns then tans	178	53.8	109	51.2	69	58.5
Always burns	79	23.9	49	23	30	25.4
Lifetime painful sunburns						
Never/once	61	18.4	41	19.2	20	16.9
2–5 times	126	38.1	87	40.8	39	33.1
6–10 times	71	21.5	42	19.7	29	24.6
>10 times	73	22.1	43	20.2	30	25.4
Presence of BCC at baseline						
No	300	90.6	203	95.3	97	82.2
Yes	31	9.4	10	4.7	21	17.8

Abbreviations: BCC, basal cell carcinoma; n, number; STAR, skin tumors in allograft recipients.

[1]Sun exposure: mild, ≤5 hours during weekdays and weekends; moderate, 5+ hours during either the weekdays or weekends; excessive, 5+ hours during both the weekdays and weekends.

Supplementary Table S2. Comparison of Model Performance for the UKB + 23andMe PRS Model Versus the UKB-Only PRS Model

Parameter	UKB + 23andMe PRS Model	UKB-Only PRS Model
Optimal model fit (Nagelkerke's R^2)		
BCC	33.70%	33.47%
SCC	35.50%	28.34%
PRS-KC association (OR per SD [95% CI])[1]		
BCC	1.52 (1.15–2.00), $P = 3.0 \times 10^{-3}$	1.61 (1.22–2.12), $P = 7.7 \times 10^{-4}$
SCC	1.69 (1.25–2.28), $P = 7.2 \times 10^{-4}$	1.45 (1.09–1.93), $P = 0.01073$
Absolute KC risk in top PRS quintile		
BCC	45.45% (33.14–58.19%)	50.00% (37.43–62.57 %)
SCC	44.12% (32.08–56.68%)	50.00% (37.62–62.38%)
Top quintile vs bottom quintile risk (OR [95% CI])[1]		
BCC	3.66 (1.54–8.72), $P = 3.3 \times 10^{-3}$	3.03 (1.03–7.08), $P = 0.01047$
SCC	3.21 (1.27–8.17), $P = 0.0135$	2.19 (0.92–5.22), $P = 0.07571$
KC risk prediction model + PRS (AUC [95%CI])[2]		
BCC	0.77 (0.72–0.82)	0.78 (0.73–0.83)
SCC	0.84 (0.80–0.88)	0.83 (0.78–0.87)
KC multiplicity risk prediction model + PRS (R^2)[2]		
BCC	0.21	0.21
SCC	0.3	0.29
Percentage of people reclassified		
BCC	0.1903	0.2205
SCC	0.181	0.1335

Abbreviations: BCC, basal cell carcinoma; CI, confidential interval; KC, keratinocyte carcinoma; PC, principal component; PRS. polygenic risk score; R^2, variance explained; SCC. squamous cell carcinoma; UKB, UK Biobank.

[1]Adjusted for established factors (age, sex, type of transplantation, immunosuppressive medication, duration of immunosuppression, skin color, sun exposure, lifetime painful sunburns, 10 PCs, skin reaction to the sun, and history of BCC or SCC).

[2]Included established the factors mentioned earlier + PRS.