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Does polygenic risk influence associations between sun exposure and melanoma?: a prospective cohort analysis

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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ABBREVIATIONS

UV – ultraviolet

BCC – basal cell carcinoma

SCC – squamous cell carcinoma

KC – keratinocyte cancer

PRS – polygenic risk score

GWAS – genome-wide association study

MAF - minor allele frequency

HR – hazard ratio

SD – standard deviation

What is already known about this topic?

The relationship between sun exposure and melanoma is complex, and exposure effects are highly modified by host factors and behaviours. The role of genotype on the relationship between UV radiation exposure and melanoma risk is poorly understood.

What does this study add?

We found that country of birth, age at migration, sunburns in childhood/adolescence, and history of keratinocyte cancer/actinic lesions were significantly associated with melanoma risk, while other measures of continuous or more intermittent patterns of sun exposure were not. We found evidence for gene-environment interactions that are consistent with divergent pathways for melanoma development.

SUMMARY

Melanoma develops as the result of complex interactions between sun exposure and genetic factors. Data on these interactions from prospective studies are scant however. We aimed to quantify the association between ambient and personal ultraviolet (UV) exposure and incident melanoma in a large population-based prospective study of men and women residing in a high ambient UV setting, and to examine potential gene-environment interactions. Among participants with genetic data (n=15,373), 420 (2.7%) developed cutaneous melanoma (173 invasive, 247 *in situ*) during a median follow-up time of 4.4 years. Country of birth, age at migration, having greater than 50 sunburns in childhood/adolescence and a history of keratinocyte cancer/actinic lesions were significantly associated with melanoma risk. An interaction with polygenic risk was suggested; among people at low polygenic risk, markers of cumulative sun exposure (as measured by actinic damage) were associated with melanoma. In contrast, among people at high polygenic risk, markers of high-level early life ambient exposure (as measured by place of birth) were associated with melanoma (HR for born in Australia vs. overseas 3.16, 95% CI 1.39-7.22). These findings suggest interactions between genotype and environment that are consistent with divergent pathways for melanoma development.

INTRODUCTION

Ultraviolet (UV) radiation is the only environmental factor that has been consistently implicated as a cause of melanoma, and is estimated to account for between 63 and 90% of melanoma cases.[1,2] The relationship is complex, however, and exposure effects are highly modified by host factors and behaviours. Host factors include germline factors; those that influence pigmentation are particularly relevant. Associations with an intermittent pattern of sun exposure and a history of sunburns have been reported consistently, but not with occupational exposure or a high continuous pattern of sun exposure.[3] However, much of the extant literature on the association derives from case-control studies, which have inherent limitations including selection and recall bias. Of the 57 studies included in the most recent systematic review (published in 2005), five were cohort studies; however, these were all occupational cohort studies, where occupation was used as a proxy for sun exposure measures (i.e. indoor/outdoor work), and all were retrospective in nature.[3] Cohort data published subsequent to the systematic review are limited to four studies in women[4-9] and one in men;[5,9] for one of these, information on sun exposure was only collected for a subset of the cohort,[6] and for others, information on important potential confounders was not collected at baseline.[4,5,9] Significant associations were reported with various definitions of sunburns[4,5,8,9] and 'sunny vacations',[9] but not with measures of cumulative sun exposure[6] or region of residence.[4,5]

Quantifying individual exposure to UV radiation in observational studies is difficult. Measures of sun exposure vary markedly across studies, and generally have low reproducibility.[10,11] Markers of actinic damage, such as actinic keratoses and keratinocyte cancers, can act as proxies of high cumulative UV dose received at the dermo-epidermal junction. The relationship between

personal history of keratinocyte cancer and risk of melanoma has been sparsely studied using prospective data.[12] The role of genotype on the relationship between UV radiation exposure and melanoma risk is also poorly understood. An examination of the potential interaction between genetic factors and UV radiation exposure might elucidate the biological processes that lead to melanoma, and may help identify those people for whom UV exposure is most hazardous, especially as recent analyses have identified population subgroups with no high-risk phenotypic features, but who have high genotypic risk of melanoma.[13]

We aimed to address these issues by examining the association between measures of UV radiation exposure (including measures of actinic damage) and incident melanoma (invasive only; and invasive + *in situ*), including gene-environment interactions, in a large population-based prospective study of men and women residing in a region of high insolation.

METHODS

Study population

The QSkin Sun and Health Study is a prospective cohort study of men and women aged 40-69 years, randomly sampled from the Queensland population (n = 43,794) in 2011. The study design and characteristics of the cohort have been published,[14] and the baseline survey is available online: https://qskin.qimrberghofer.edu.au/page/About/Baseline_survey. The survey included questions about sun exposure and sun protection, demographic items, pigmentary and phenotypic characteristics (including nevus burden at age 21 - whole body, 4 categories), family history of melanoma, past history of skin cancer and general medical history. The repeatability and validity of these items has been reported previously.[15]

We restricted our analyses to participants with genetic data who reported white European ancestry and excluded those with a prior history of invasive or *in situ* melanoma; the final cohort eligible for these analyses included 15,373 participants (Figure S1). A polygenic risk score (PRS) for melanoma was calculated for all 15,373 participants in the analysis sample (see methods below).

The Human Research Ethics Committee at the QIMR Berghofer Medical Research Institute approved the study, and all participants gave their written informed consent to take part.

Outcomes

We examined two separate outcomes: 1) invasive melanomas; and 2) invasive + *in situ* melanomas. Notifications for melanoma are mandatory by law in Queensland, and data on all melanoma diagnoses from baseline up to 31 December 2015 were obtained from the Queensland Cancer Registry, supplemented by pathology reports from major pathology companies servicing Queensland.

Exposure assessment

We considered three groups of UV radiation exposure variables: (1) ambient sun exposure (country of birth: Australia or elsewhere; latitude of birth; region of residence; number of years lived outside Australia); (2) personal exposure to UV radiation (number of sunburns in childhood, adolescence and adulthood; cumulative sun exposure; average number of hours in the sun on weekdays and weekend days; sunbed use [indoor tanning]); and (3) proxies of high

cumulative UV radiation exposure [self-reported history of skin cancers (not melanomas) excised surgically and actinic skin lesions treated destructively].

Participants were asked to report their country of birth, the age they moved permanently to Australia, years of life lived in three regions of Australia (as depicted by a map and labelled 'Northern', 'Central' and 'Southern'), and the region in which they lived the longest as a child/youth (up to age 20 years). The survey asked about the number of times the participant had been sunburned 'so badly that you were sore for at least 2 days, or your skin peeled' as a child, as a teenager/youth, and as an adult (possible responses were 'never', '1-5 times', '6-10 times', '11-20 times', '21-50 times' and '50+ times') and about the number of times they had used sunbeds. Participants were also asked to report the number of hours 'typically spent outdoors and in the sun each day' at ages 10-19, 20-29, 30-39 years and in the past year, separately for weekdays and weekend days (possible responses were 0-1 hours, 1-2 hours, 2-3 hours and 4+ hours). We calculated a measure of cumulative personal exposure as the sum of the number of hours spent outdoors in the sun on week days and week-end days from age 10 through to age at baseline. We used a numerical score for each response category (i.e. 0.5, 1.5, 2.5 and 4.5 hours) and used participant responses 'in the past year' for each year of life after age 40. We categorised the number of hours in the sun in quartiles based on the distribution of the cohort, in total, and separately for weekdays and weekend days. The survey asked about sunscreen and hat use 'when outside in the sun during the past year'. Sunbed use, self-reported history of skin cancer excisions and non-surgical treatments for actinic lesions were highly reproducible (weighted kappas>0.8). Other measures of sun exposure showed moderate-to-good agreement.[15]

Genotyping, imputation and data quality control

A total of 17,786 QSkin participants were successfully genotyped using the Illumina Global Screening array (San Diego, CA, USA) (Figure S1). Genotype data was cleaned using Illumina GenomeStudio/BeadStudio (San Diego, CA, USA) and PLINK (v1.9).[16] We excluded participants with > 5% genotype missingness (n=322), those who were related to another sample at identity by descent $\hat{\pi}$ score > 0.1875 [i.e. closer than a 2nd degree cousin (n=400)], or who were outliers from European reference populations (> 6 SD on PC1 and PC2, n=378) (final n=16,687 as a related pair were also population outliers). After removing 198,387 SNPs with GenTrain score <0.6, Hardy-Weinberg P-value $<1 \times 10^{-6}$, or a minor allele frequency (MAF) <1%, the remaining 496,695 SNPs were imputed to the Haplotype Reference Consortium v1.1 panel[17] using the University of Michigan Imputation Server. We performed genotype phasing with Eagle 2[18] and genotype imputation by minimac version 3.[19] The resulting imputed GWAS data was analysed as dosage data filtered to imputation quality score $\hat{r}^2$ >0.5 and MAF>0.001.

Polygenic risk score

We calculated a PRS for all 15,373 participants who were eligible for these analyses using summary statistics from a melanoma GWAS meta-analysis for 12,874 cases and 23,203 controls;[20] full details are provided in Supplementary Methods. We categorised participants into tertiles based on the distribution of the entire sample (i.e. cases and non-cases). Thus each tertile included approximately the same number of people (T1: n=5112; T2: n=5121; T3: n=5140).

Imputation of missing data

Missing values for sun exposure variables ranged from <1% to 10%; the sunburn variables had the highest amount of missing data (9.7%, 3.4% and 4.7% for sunburns in childhood, adolescence and adulthood, respectively). To avoid losing observations due to missing covariate data during model development, we imputed missing values using PROC MI in SAS v9.4 (SAS Institute, Cary, NC), assuming that data were missing at random. We included all sun exposure variables and the outcome variable [21] in the imputation step; imputation was run over 50 cycles to generate 50 data sets.

Statistical analysis

We used Cox proportional hazards models to estimate the effect of each measure of sun exposure on the risk of first incident melanoma while taking account of the sociodemographic and phenotypic factors as well as sun protection practices. Choice of covariates was guided by direct acyclic graphs. We first examined each factor unadjusted, and then adjusted for age and sex. We then sequentially considered covariates from three groups: (1) those related to pigmentation; (2) family history of melanoma; and (3) sun protection behaviours. For sun exposure variables related to ambient UV levels we considered sun protection behaviours only. For proxies of high cumulative UV exposure we considered pigmentary factors only. Inclusion of covariates in groups 2 and 3, as well as education, did not result in material change to the estimates of effect and thus models with these factors are not presented. For proxies of high cumulative UV exposure we additionally adjusted for education, and both private health insurance and history of "skin checks by a doctor" in the 3 years prior to baseline.

For analyses of the primary outcome (invasive melanoma) we ignored all *in situ* melanomas diagnosed during follow-up. We conducted sensitivity analyses to examine the influence of this approach firstly by censoring the *in situ* melanoma cases, and secondly by treating *in situ* cases occurring during follow-up as a time-varying covariate in the model. For our primary outcome we examined the associations overall, and then by sex and PRS tertiles; interaction was assessed using cross-product terms.

All models were adjusted for death as a competing risk,[22] and statistical significance was inferred at $P < .05$. All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Of 15,373 eligible participants, 8435 (55%) were women and the mean age was 57 years (SD 7.9). During a median (and mean) follow-up time of 4.4 years, 420 (2.7%) participants developed melanoma (173 invasive melanomas, 247 *in situ* melanomas). Of the invasive melanoma cases 47% were female, 60% were of the superficial spreading subtype, and 79% were <1mm (Table S1). On average, cases were older than non-cases at baseline (58.9 years vs. 56.9 years, respectively; p<0.001).

Invasive melanoma

People born in Australia had a higher risk than those born elsewhere, as did those born at latitudes <45º N/S (Table 1). There was no significant association between the region of Australia in which participants lived longest as a child or over the entire lifetime. Compared to

native-born participants, those born overseas who moved to Australia when aged 20 years or older had a significantly lower risk (OR 0.52, 95% CI 0.27-0.98).

A history of greater than 50 sunburns as a child was associated with an over two-fold increased risk; however, the association was not significant after adjusting for hair colour and skin tanning ability (Table 2). Although we found no evidence that melanoma was associated with self-reported cumulative sun exposure, average hours in the sun on weekdays or weekends, or sunbed use, we found significant 2-3 fold elevations in risk with the number of previous keratinocyte cancers and number of treatments for actinic lesions (Table 3). The latter associations were slightly attenuated following adjustment for measures of socio-economic status (highest educational level achieved) and medical system use (private health insurance, self-reported history of physician skin checks).

Sensitivity analyses

Censoring *in situ* melanomas occurring during follow-up made no material difference to the estimates, nor did treating *in situ* melanoma occurring during follow-up a time-varying covariate (data not shown).

Gene/environment interaction

Participants at highest genetic risk for melanoma (PRS tertile 3) had three-fold higher risk of melanoma than those in tertile 1 [HR T3 vs T1 3.02 (95% CI 2.01-4.53); T2 vs T1 1.50 (95% CI 0.96-2.37); Table 4]. We found a significant interaction between genetic risk and country of birth. Being born in Australia was significantly associated with invasive melanoma among

people with a high but not low PRS (P_{int} 0.03; Table 4). In contrast, we found that past history of 6 or more actinic lesions was more strongly associated with invasive melanoma among people at lowest genetic risk (P_{int} 0.03; Table 4). There was no significant difference in the association between sunburns as a youth, sunbed use or past history of skin cancers across PRS groups.

Sex/environment interaction

The associations between sun exposure variables and invasive melanoma did not differ significantly by sex (Table S2). Being born in Australia was associated with melanoma in women but not men, but the difference was not statistically significant.

All melanoma (invasive + *in situ*)

The magnitude of associations for 'all melanoma' (i.e. invasive + *in situ*) was attenuated for most sun exposure variables when compared with 'invasive only' melanomas, except for numbers of actinic lesions, which was similar (Table S3).

DISCUSSION

We have reported risk estimates for melanoma associated with measures of lifetime ambient and personal UV radiation exposure, and markers of cumulative UV damage in a large population-based prospective study of men and women living in a region with high ambient exposure. People who were born in Australia or migrated to Australia at young age, and those who had many sunburns had increased risks of melanoma. Past history of keratinocyte cancer and other actinic lesions were also both strongly associated with melanoma. Other measures of continuous and intermittent patterns of sun exposure were not significantly associated with melanoma in this

study. We examined differences according to sex, finding no significant differences in the associations for men and women, and we considered both *in situ* and invasive melanoma. We also found that some associations with measures of sun exposure varied according to polygenic risk score.

The findings are important given that most of the literature on the association between sun exposure and melanoma derives from case-control studies. These studies are particularly prone to recall bias whereby cases systematically report their past exposure differently from controls on account of awareness of their diagnosis. Such bias is impossible to eradicate through statistical analysis and can only be avoided by using prospective designs. In the current study, all measures of sun exposure and other comprehensive risk factor information were collected at baseline.

Migration studies generally indicate a higher melanoma risk in people who spent their childhood in regions with high ambient UV radiation, and decreasing risk with older age at arrival in such regions.[23-25] Our findings are consistent with those earlier reports, supporting the notion that sun exposure during the 'critical period' of early life is important for future melanoma development. Sunburns in childhood are often reported as posing the greatest risk for melanoma.[3,26] Our data suggest that a high number of sunburns increases the risk of melanoma regardless of when they are received.

We found no association between self-reported cumulative sun exposure and melanoma. The only other prospective study to measure cumulative/continuous sun exposure (other than "sunny vacations" or "wearing a bathing suit"[4,5,8]) is the E3N study,[6] which also reported no association.

This lack of effect with self-reported measures of continuous sun exposure is notable, especially given the strong and significant associations with objective markers of cumulative actinic damage such as numbers of excisions or treatments for skin lesions. Arguably the most likely explanation is non-differential exposure misclassification, which biases estimates towards the null, given the modest repeatability of self-reported measures of personal sun exposure.[15] The limited range of exposure among Queensland residents due to high ambient exposure is an alternative explanation.

The divergent pathway hypothesis for melanoma posits a model whereby individuals with high genetic propensity to develop melanoma may only require modest levels of sun exposure to initiate melanomagenesis, whereas those with low genetic propensity may, in general, require continued high levels of sun exposure to drive tumour development.[27,28] We found some evidence for gene-environment interactions consistent with the divergent pathway hypothesis. In particular, the observation that a history of treatment for actinic lesions (a proxy for high cumulative sun exposure) was more strongly associated with melanoma among people with low than high polygenic risk accords with this hypothesis. Replicating these analyses in prospective datasets from other settings would provide a stronger test of this hypothesis.

Apart from the prospective design and large sample size, strengths of our study include the population-based sampling frame, and complete ascertainment of melanoma events during follow-up. Our analyses of sun exposure stratified by PRS are also novel for a prospective study of melanoma. A weakness was the relatively small number of cases, which resulted in limited power to examine differences in exposure effects on melanoma of different body sites. While

our measures of past sun exposure were self-reported, most showed moderate-to-good agreement (weighted kappa 0.4-0.6) while sunbed use, history of skin cancer excisions and non-surgical treatments for actinic lesions were all highly reproducible (weighted kappas>0.8).[15] We did not confirm the histology of self-reported skin cancers that had been excised prior to baseline (except for melanomas, which were excluded). Histologically confirmed incident keratinocyte cancers are an endpoint of the QSkin study, however, and greater duration of follow-up will enable examination of these relationships according to type of keratinocyte cancer. Lastly, study participants, and those with genotypic data, were more highly educated and were more likely to have had a history of skin cancer than the general population, which may limit generalizability.

In summary, we have reported estimates of the risk of melanoma associated with measures of sun exposure from a large prospective study conducted in a setting of high ambient insolation. We found some evidence of gene-environment interactions that are consistent with divergent pathways to melanoma development. In clinical practice, the advent of genomic medicine will likely have implications for patient care, and clinicians may need to consider genetic risk and its interaction with environmental exposures. In this context, our findings may help to identify and inform persons at high risk of melanoma who stand to benefit most from adopting sun protective behaviours.

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AUTHOR CONTRIBUTIONS

DCW: conceptualization, supervision, funding acquisition, investigation, methodology, writing original draft, reviewing and editing

CO: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, writing original draft, reviewing and editing

ML: data curation, formal analysis, methodology, writing original draft, reviewing and editing

NP: investigation, data curation, formal analysis, methodology, reviewing and editing

AG, RN, SM: funding acquisition, investigation, methodology, reviewing and editing

BT, MI: data curation, reviewing and editing

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Table 1. Measures of ambient sun exposure and risk of first invasive melanoma.

	Participants with invasive melanoma			
	No (n=15,200)	**Yes** (n=173)	**Crude**	**Age & sex adj**
Variables	**n (%)**	**n (%)**	**HR (95%CI)**	**HR (95%CI)**
Born in Australia				
No	2644 (17.4)	22 (12.7)	Reference	Reference
Yes	12,556 (82.6)	151 (87.3)	1.44 (0.92-2.26)	1.50 (0.96-2.34)
Latitude of birth				
≥45º S/N	1782 (11.7)	13 (7.5)	Reference	Reference
<45º S/N	13,418 (88.3)	160 (92.5)	1.63 (0.93-2.87)	1.73 (0.99-3.04)
Region of Australia lived longest up to age 20 years				
Southern region	4538 (33.3)	51 (31.7)	Reference	Reference
Central region	6910 (50.8)	92 (57.1)	1.21 (0.86-1.71)	1.25 (0.89-1.77)
Northern region	2167 (15.9)	18 (11.2)	0.75 (0.44-1.29)	0.78 (0.45-1.34)
Region of Australia lived longest over lifetime				
Southern region	3303 (21.7)	39 (22.5)	Reference	Reference
Central region	9313 (61.3)	116 (67.1)	1.03 (0.71-1.47)	1.04 (0.72-1.49)
Northern region	2584 (17.0)	18 (10.4)	0.58 (0.33-1.01)	0.58 (0.33-1.01)
Age moved to Australia				
Born in Australia	12,565 (82.7)	151 (87.3)	Reference	Reference
1-10 years	699 (4.6)	6 (3.5)	0.71 (0.32-1.61)	0.72 (0.32-1.63)
11-20 years	418 (2.8)	6 (3.5)	1.19 (0.53-2.69)	1.14 (0.50-2.58)
20+ years	1518 (10.0)	10 (5.8)	0.55 (0.29-1.04)	0.52 (0.27-0.98)

Table 2. Measures of personal sun exposure and risk of first invasive melanoma.

	Invasive melanoma				
	No (n=15,200)	**Yes** (n=173)	**Crude**	**Age & sex adj**	**Model 1**[1]
Variables	**n (%)**	**n (%)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Sunburns as a child (less than 10 years)					
Never	3034 (20.0)	30 (17.3)	Reference	Reference	Reference
1-5 times	7029 (46.2)	78 (45.1)	1.02 (0.67-1.57)	1.03 (0.67-1.59)	0.96 (0.62-1.47)
6-10 times	2735 (18.0)	36 (20.8)	1.14 (0.69-1.89)	1.17 (0.70-1.95)	1.03 (0.62-1.72)
11-20 times	1454 (9.6)	12 (6.9)	0.85 (0.44-1.64)	0.89 (0.45-1.73)	0.76 (0.39-1.50)
21-50 times	676 (4.5)	10 (5.8)	1.41 (0.69-2.87)	1.48 (0.72-3.03)	1.28 (0.62-2.65)
>50 times	272 (1.8)	7 (4.1)	2.41 (1.06-5.49)	2.50 (1.10-5.69)	2.14 (0.93-4.92)
Sunburns as a youth (10-20 years old)					
Never	597 (3.9)	4 (2.3)	Reference	Reference	Reference
1-5 times	6593 (43.4)	72 (41.6)	1.53 (0.56-4.20)	1.65 (0.60-4.50)	1.43 (0.52-3.95)
6-10 times	3917 (25.8)	50 (28.9)	1.80 (0.65-4.98)	1.97 (0.72-5.42)	1.67 (0.60-4.63)
11-20 times	2560 (16.8)	26 (15.0)	1.40 (0.49-4.01)	1.55 (0.54-4.41)	1.30 (0.45-3.74)
21-50 times	1136 (7.5)	14 (8.1)	1.75 (0.58-5.31)	1.95 (0.65-5.90)	1.61 (0.53-4.93)
>50 times	397 (2.6)	78 (4.1)	2.49 (0.73-8.52)	2.75 (0.81-9.35)	2.33 (0.68-8.02)
Sunburns as an adult (more than 20 years old)					
Never	2445 (16.1)	26 (15.0)	Reference	Reference	Reference
1-5 times	8174 (53.8)	90 (52.0)	1.06 (0.67-1.67)	1.10 (0.70-1.74)	1.11 (0.71-1.75)
6-10 times	2512 (16.5)	31 (17.9)	1.19 (0.69-2.03)	1.23 (0.72-2.11)	1.24 (0.72-2.12)
11-20 times	1327 (8.7)	14 (8.1)	1.03 (0.53-2.00)	1.05 (0.54-2.05)	1.06 (0.54-2.06)
21-50 times	543 (3.6)	9 (5.2)	1.59 (0.74-3.41)	1.58 (0.73-3.40)	1.63 (0.76-3.51)
>50 times	199 (1.3)	3 (1.7)	1.44 (0.43-4.78)	1.39 (0.42-4.60)	1.51 (0.46-5.02)
Cumulative sun exposure[2]					
Q1	3758 (24.7)	72 (23.7)	Reference	Reference	Reference
Q2	3858 (26.0)	67 (23.1)	0.89 (0.57-1.41)	0.82 (0.52-1.30)	0.85 (0.54-1.33)
Q3	3735 (24.6)	85 (22.5)	0.99 (0.63-1.57)	0.83 (0.52-1.33)	0.87 (0.55-1.39)
Q4	3749 (24.7)	92 (30.6)	1.26 (0.83-1.91)	0.91 (0.58-1.43)	1.01 (0.64-1.58)
Average number of hours in the sun on weekdays[2]					
Q1	3817 (25.1)	45 (26.0)	Reference	Reference	Reference
Q2	3872 (25.5)	42 (24.3)	0.90 (0.58-1.39)	0.88 (0.57-1.37)	0.90 (0.58-1.39)
Q3	3952 (26.0)	40 (23.1)	0.89 (0.57-1.38)	0.82 (0.52-1.28)	0.85 (0.55-1.33)
Q4	3559 (23.4)	46 (26.6)	1.06 (0.69-1.62)	0.87 (0.56-1.35)	0.95 (0.62-1.47)
Average number of hours in the sun on weekend days[2]					
Q1	3889 (25.6)	44 (25.4)	Reference	Reference	Reference
Q2	3991 (26.3)	43 (24.9)	0.97 (0.62-1.52)	0.97 (0.62-1.51)	1.00 (0.64-1.56)
Q3	3907 (25.7)	37 (21.4)	0.86 (0.54-1.36)	0.81 (0.51-1.27)	0.86 (0.55-1.35)
Q4	3413 (22.5)	49 (28.3)	1.25 (0.82-1.91)	1.14 (0.73-1.77)	1.27 (0.81-1.97)
Sunbed use					
Never	13,702 (90.1)	156 (90.2)	Reference	Reference	Reference
Ever	1498 (9.9)	17 (9.8)	1.00 (0.61-1.65)	1.22 (0.74-2.01)	1.31 (0.79-2.18)

[1]Model 1- additionally adjusted for hair colour, tanning ability
[2]Q - Quartile

Table 3. Proxy measures of personal sun exposure and risk of first invasive melanoma.

	Invasive melanoma					
	No (n=15,200)	**Yes** (n=173)	**Crude**	**Age & sex adj**	**Model 1**[1]	**Model 2**[2]
Variables	**n (%)**	**n (%)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Number of skin cancers excised						
None	8854 (58.3)	62 (35.8)	Reference	Reference	Reference	Reference
1	2077 (13.7)	26 (15.0)	1.78 (1.13-2.81)	1.70 (1.08-2.70)	1.63 (1.03-2.59)	1.55 (0.96-2.50)
2-10	3543 (23.3)	65 (37.6)	2.60 (1.84-3.69)	2.39 (1.68-3.40)	2.16 (1.49-3.12)	1.98 (1.33-2.95)
10-20	432 (2.8)	13 (7.5)	4.26 (2.34-7.75)	3.70 (2.03-6.76)	3.17 (1.69-5.93)	2.82 (1.42-5.60)
20+	294 (1.9)	7 (4.1)	3.36 (1.54-7.34)	2.90 (1.33-6.34)	2.39 (1.06-5.38)	2.04 (0.87-4.78)
Number of actinic lesions burnt/frozen off						
None	6088 (40.1)	39 (22.5)	Reference	Reference	Reference	Reference
1-5	4196 (27.6)	43 (24.9)	1.63 (1.05-2.52)	1.55 (1.00-2.40)	1.47 (0.94-2.28)	1.38 (0.87-2.20)
6-10	1556 (10.2)	24 (13.9)	2.44 (1.46-4.07)	2.24 (1.33-3.76)	1.97 (1.16-3.35)	1.82 (1.04-3.16)
11-20	1324 (8.7)	19 (11.0)	2.27 (1.31-3.94)	2.03 (1.16-3.55)	1.77 (1.00-3.12)	1.59 (0.87-2.89)
21-50	1095 (7.2)	21 (12.1)	3.00 (1.76-5.11)	2.65 (1.55-4.53)	2.23 (1.28-3.88)	1.95 (1.09-3.51)
50+	941 (6.2)	27 (15.6)	4.50 (2.75-7.36)	3.85 (2.33-6.36)	3.21 (1.84-5.58)	2.69 (1.41-5.14)

[1]Model 1- additionally adjusted for hair colour, tanning ability

[2]Model 2- additionally adjusted for education, private health insurance, and history of physician skin checks prior to baseline.

Table 4. Measures of UV exposure and risk of first invasive melanoma according to polygenic risk score (n=15,373 participants with genetic data; includes 173 cases).

	T1[1] (n=31 cases)		**T2**[1] (n=47 cases)		**T3**[1] (n=95 cases)		
	Crude	**Age & sex adj**	**Crude**	**Age & sex adj**	**Crude**	**Age & sex adj**	
Variables	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	***P*[2]**
Born in Australia							
No	Reference	Reference	Reference	Reference	Reference	Reference	
Yes	0.76 (0.33-1.77)	0.88 (0.38-2.04)	0.87 (0.42-1.80)	0.86 (0.41-1.78)	3.01 (1.32-6.86)	3.16 (1.39-7.22)	0.03
Sunburns as a youth (10-20 years old)							
Never	Reference	Reference	Reference	Reference	Reference	Reference	
1-5 times	1.27 (0.17-9.55)	1.54 (0.20-11.73)	2.35 (0.32-17.40)	2.40 (0.33-17.40)	1.10 (0.26-4.62)	1.16 (0.28-4.85)	
6+ times	1.37 (0.19-10.12)	1.83 (0.25-13.49)	1.53 (0.20-11.43)	1.51 (0.20-11.16)	1.49 (0.36-6.13)	1.66 (0.41-6.73)	0.37
Sunbed use							
Never	Reference	Reference	Reference	Reference	Reference	Reference	
Ever	1.74 (0.67-4.53)	2.32 (0.92-5.82)	1.30 (0.55-3.07)	1.63 (0.69-3.86)	0.65 (0.28-1.48)	0.77 (0.34-1.74)	0.29
Number of skin cancers excised							
None	Reference	Reference	Reference	Reference	Reference	Reference	
1	1.87 (0.59-5.97)	1.68 (0.52-5.42)	2.83 (1.27-6.30)	2.79 (1.26-6.16)	1.24 (0.65-2.38)	1.16 (0.60-2.22)	
2+	4.40 (2.01-9.60)	3.72 (1.66-8.33)	3.06 (1.59-5.90)	2.79 (1.47-5.29)	2.05 (1.33-3.15)	1.85 (1.19-2.88)	0.28
Number of actinic lesions burnt/frozen off							
None	Reference	Reference	Reference	Reference	Reference	Reference	
1-5	1.30 (0.35-4.84)	1.26 (0.33-4.81)	1.27 (0.59-2.75)	1.24 (0.59-2.62)	1.74 (0.96-3.12)	1.61 (0.89-2.90)	
6+	7.47 (2.83-19.72)	6.74 (2.41-18.81)	1.75 (0.89-3.45)	1.55 (0.79-3.04)	2.28 (1.34-3.87)	1.97 (1.14-3.40)	0.03

[1]T – tertile; [2]P – P-value for interaction