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Relationship between sun exposure and melanoma risk for tumours in different body sites in a large case-control study in a temperate climate

Julia A Newton-Bishop, **Yu-Mei Chang**, **Faye Elliott**, **May Chan**, **Susan Leake**, **Birute Karpavicius**, **Sue Haynes**, **Elaine Fitzgibbon**, **Kairen Kukalizch**, **Juliette Randerson-Moor**, **David E Elder***, **D Timothy Bishop**, and **Jennifer H Barrett**
Section of Epidemiology and Biostatistics, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK

*Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, USA

Abstract

Aim—A melanoma case-control study was conducted to elucidate the complex relationship between sun exposure and risk.

Methods—960 population-ascertained cases, 513 population and 174 sibling controls recruited in England provided detailed sun exposure and phenotype data; a subset provided serum 25-hydroxyvitamin D_3 levels.

Results—Phenotypes associated with a tendency to sunburn and reported sunburn at ≥20 years of age were associated with increased melanoma risk (OR 1.56, 95% CI 1.23-1.99). Holiday sun exposure was not associated with an increased melanoma risk although this may be in part because reported sun exposure overall was much lower in those with a sun-sensitive phenotype, particularly among controls. Head and neck melanoma was associated with less sun exposure on holidays at low latitudes (OR 0.39, 95% CI (0.23-0.68) for > 13 hours /year compared to <3.1). Overall the clearest relationship between reported sun exposure and risk was for average weekend sun exposure in warmer months, which was protective (OR 0.67, 95% CI 0.50-0.89 for highest versus lowest tertile of exposure). Serum vitamin D levels were strongly associated with increased weekend and holiday sun exposure.

Conclusions—Sun-sensitive phenotypes and reported sunburn were associated with an increased risk of melanoma. Although no evidence was seen of a causal relationship between holiday sun exposure and increased risk, this is consistent with the view that intense sun exposure is causal for melanoma in those prone to sunburn. A protective effect of regular weekend sun exposure was seen, particularly for limb tumours, which could be mediated by photoadaption or higher vitamin D levels.

Corresponding author Professor Julia Newton Bishop Professor of Dermatology Section of Epidemiology and Biostatistics, Leeds Institute of Molecular Medicine, St James's Hospital, Beckett Street, Leeds LS9 7TF, UK Tel +44 113 2064573 Fax +44 113 2340183 j.a.newton-bishop@leeds.ac.uk.

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Introduction

Many case-control studies have established phenotypic and behavioural risk factors for melanoma in populations of European origin, summarised in meta-analyses (1-3). A pooled analysis by our group (4) of 15 studies confirmed that recreational sun exposure and sunburn are strong predictors of melanoma at all latitudes, whereas measures of occupational and total sun exposure appear to predict melanoma on usually-exposed body sites only at low latitudes (4). Thus in Europe and much of North America the dominant pattern of sun exposure associated with risk in fair-skinned individuals was shown to be recreational.

The relationship between sun exposure and risk is however thought to be complex: for example some studies have suggested that occupational sun exposure might actually be protective for melanoma (2). Hypotheses developed to explain this apparent anomaly are that continuous sun exposure (not associated with severe sunburn) might be protective for melanoma either by inducing photoadaption (increased melanisation and epidermal thickening)(5) or as a result of the induction of higher levels of vitamin D. Intense sun exposure leads to both DNA damage and immunosuppression (6), which are together thought to mediate carcinogenesis, and photoadaption is thought to reduce the DNA damage (5). There are limited data to support a role for vitamin D in melanoma prevention, although some have hypothesized such a role (7). There was no evidence in a recently published cohort study of a protective effect of reported greater vitamin D intake on melanoma risk (8) for example, but there are genetic data to suggest that inherited variation in the vitamin D receptor (*VDR*) gene is associated with melanoma risk, recently published in meta-analyses (9).

We have carried out a large case-control study using a very detailed sun exposure questionnaire (10) in order to better understand the complexities of the relationship between sun exposure and melanoma risk.

Materials and methods

Studies were approved by the UK Multi-Centre Research Ethics Committee (MREC) and the Patient Information Advisory Group (PIAG). Population-ascertained incident melanoma cases were recruited to a case-control study in a geographically defined area of the UK (Yorkshire and the Northern Region south of the River Tyne) (67% participation rate); 960 cases (aged 18 to 76 years) were diagnosed in the period from September 2000 to December 2005, as described previously (9, 11). Recruitment (and therefore blood sampling) took place wherever possible 3 to 6 months after diagnosis. The 513 population-ascertained controls were identified by the cases' family doctors as not having cancer, and were randomly invited from individuals with the same sex and within the same 5-year age group as a case (55% response rate). In the UK, individuals are generally registered with the family doctor nearest geographically to their residence so that this is held to be a means of identifying suitable controls. Descriptive statistics were obtained from the cancer registry of cases diagnosed in a similar time period to examine the comparability of the sample with the incident case population (Table 1).

Where possible we also sought to recruit sibling controls for cases; we asked cases if they would invite a sibling (usually the nearest in age living within a reasonable distance) to participate in the study. 845 cases had a sibling and 397 were happy to seek their participation, and of these 174 participated. The number of sibling controls was smaller than hoped; many cases wished to keep their diagnoses private within the family and therefore did not want to invite participation from a sibling. In this paper we therefore report risk

estimates determined by comparing cases and population controls primarily, but we have used the sibling control group for secondary comparisons.

Data Collection

An initial postal questionnaire was completed by all participants (including a life-long residence calendar), and comprehensive sun exposure data were subsequently collected by telephone, based upon that residence calendar. Age, sex, natural hair colour at age 18 years, propensity to burn, ability to tan, skin colour of inside upper arm and freckling as a child using Gallagher's freckle chart (12) were self-reported. A measure of deprivation (the Townsend Score) was derived from the subject's current postcode based on 2001 UK Census data (13). We refer to this henceforth as the deprivation score. Higher scores are indicative of residence in more deprived communities. The highest educational level achieved was also recorded as another measure of socioeconomic status. Data on the intake of supplements containing vitamin D were collected from cases (but not from controls) as we were originally primarily concerned to establish the role of vitamin D in survival from melanoma. Participants were examined by research nurses, who recorded eye colour (blue/grey, green/hazel or brown) and freckling scores for face, arms and shoulders.

Serum 25-hydroxyvitamin D_2 and D_3 measurement

A single serum sample taken at recruitment was cryopreserved at −80°C from the majority (846, 88%) of cases, sibling controls (128, 74%) and a subset (193, 38%) of population controls for the measurement of serum vitamin D levels, as previously described (14). Sampling took place during defined time periods: where cases were not sampled this was predominantly because at the beginning of the study serum was not collected. Sampling of population controls was limited due to financial reasons to the controls recruited in years 2004 and 2007. Vitamin D_2 and D_3 levels were summed: this sum is henceforth referred to as "serum vitamin D level".

Statistical methods

Sun exposure measures were derived from the questionnaire data. All aggregated sun exposure variables were summed and weighted by self-reported frequency and duration and averaged by age at diagnosis for cases or age at interview for controls. Aggregated sun exposure variables were classified into thirds based on their distribution in the control population. Data on self-reported significant sunburns (defined as causing pain for two or more days) were dichotomised as ever/never reporting sunburn, both before the age of 20 years and at or after the age of 20 years.

In order to derive a proxy measure for sun-sensitivity, factor analysis was applied to six correlated variables: hair colour, eye colour, self-reported freckling as a child, propensity to burn, ability to tan and skin colour on the inside upper arm. Multivariate imputation was used to impute incomplete data for the factor analysis. The estimated first factor scores were averaged over the five imputation sets; the average was used as a proxy for sun sensitivity. The median score was used as the cut-off point to partition participants into sun-sensitive and non-sun-sensitive phenotypes. Multivariate imputation was carried out using the MICE package in R version 2.9.2 (Vienna, Austria).

Nonparametric Wilcoxon two-sample tests were used to assess the association between binary and continuous measures. Chi-squared tests were used to determine the association between categorical variables, and Spearman's correlation was adopted to examine association between continuous measures. Adjusted means (least squares means) of serum vitamin D levels, corrected for sex, age and month sampled, deprivation score and vitamin D supplementation intakes (cases only), were calculated for different sun exposure groups.

Unconditional logistic regression models adjusted for age, sex and deprivation score were used to examine the effects of sun exposure on melanoma risk, and odds ratios (OR) and 95% confidence intervals (CI) were presented. Unconditional polytomous logistic regression models adjusted for age and sex were used to study different patterns of sun exposure between melanoma cases, using trunk melanoma cases as the baseline group to which those with tumours on other sites were compared. Conditional logistic regression models were employed to examine the effects of sun exposure and serum vitamin D levels on melanoma risk in the subset of 105 cases with matched siblings for both of whom we had serum vitamin D measurements. (In a small proportion more than one sibling was recruited). These analyses were carried out using SAS version 9.1 for PC (Copyright, SAS Institute Inc. Cary, NC, USA).

Results

The recruited patients were broadly representative of the total eligible population of melanoma cases (Table 1), with a similar sex ratio (15). The differences predominantly reflect the study upper age limit of 76 years resulting in proportionately fewer head and neck tumours.

Cases and population controls were of similar age and sex with a small excess of young cases (under 40 years) and older controls. Cases were marginally more deprived than the controls (two sample t-test, p=0.01), as reported previously (9), and achieved slightly lower educational standards (12% of cases graduated from University compared with 16% of controls (X^2 =3.26, 1 df, p=0.07). 52 cases (5%) and 10 controls (2%) reported a family history of melanoma within first-degree relatives (p=0.001).

Table 2 shows the association of phenotypic risk factors with melanoma. As expected, pale eyes and blond/red hair were predictors of risk. Reported facial freckling as a child was significantly associated with risk; OR for many compared with none was 2.53 (95% CI 1.53-4.16). Reported very fair skin of the upper inside arm was significantly associated with increased risk (compared with olive skin) (OR 2.83, 95% CI 1.84-4.36)). Similar results were obtained for other measures such as ability to tan and propensity to burn. Self-reported freckling correlated well with the nurses' assessment (p<0.0001, Table 1s (supplementary data)). Hair, skin colour and sun-sensitivity were highly correlated, being partially genetically co-determined (16). We employed factor analysis to create a sun-sensitivity variable. The factor loadings for hair colour, eye colour, self-reported freckling as a child, propensity to burn, ability to tan and skin colour (0.44, 0.21, 0.38, 0.55, 0.66 and 0.61, respectively) resulted in a unimodal, approximately symmetric distribution (Figure 1s).

Cases were more likely to report significant sunburn than controls (Table 2), irrespective of tumour site (Table 4s). OR for melanoma, associated with at least one sunburn, at or over the age of 20 years was 1.56 (95% CI 1.23-1.99) and under the age of 20 years OR 1.24 (95% CI 0.96-1.59), in analyses corrected for age, deprivation score and sex but not phenotype. None of these estimates were altered much when additionally adjusted for sun exposure (weekend sun exposure in warmer months) (Table 2). Increased number of sunburns at or after age 20 was associated with increasing risk (OR for 1 sunburn versus none 1.01 (95% CI1.00-1.02), for 10 sunburns 1.14 (95% CI 1.03-1.26) and for 20 sunburns 1.30 (95% CI 1.06-1.60) adjusted for age and sex (data not shown)).

Sun exposure and risk

Sun-sensitive controls reported less sun exposure for all measures than did non-sensitive controls (Table 2s), but particularly for average holiday exposure (p=0.002) and average weekend exposure in warmer weather (p=0.007). Within cases, the differences were much

less marked. Table 3s shows that average holiday exposure was positively correlated with average weekend exposure (correlation coefficient $r_s = 0.12$, $p<0.0001$) but not correlated with average weekday exposure ($r_s = 0.02$, $p=0.42$). The pattern of sun exposure which was most correlated with reported sunburn was holiday exposure ($r_s = 0.15$, $p<0.0001$, for sunburn in childhood, $r_s =0.10$, $p=0.0001$, for sunburn after age 20).

The pattern of reported sun exposure showing the clearest association with melanoma risk overall (Table 3) was average weekend exposure in warmer months, where increasing exposure was protective for melanoma (OR 0.72, 95% CI 0.55-0.94) for 4-5 hours and (OR 0.67, 95% CI 0.50-0.89) for more than 5 hours, compared with under 4 hours per day. When the data were analysed for tumours in different body sites, the protective effect of increased weekend sun exposure was strongest for limb tumours and tumours on rare body sites (non-sun exposed sites such as acral, genital) (Table 4s), although the overall differences were not statistically significant. Head /neck melanoma was associated with significantly less sun exposure on holidays at low latitudes, but with higher average levels of weekday exposure in cooler months (ORs 2.05 (95% CI 1.18-3.57) and 1.67 (95% CI 0.95-2.94), for 0.9-1.5 hours and >1.5 hours versus ≤0.9 hours per day respectively). Case-case comparison using polytomous logistic regression showed borderline evidence of a difference in risk from weekday sun exposure in cooler months by body site (p=0.08), the biggest observed difference being between head and neck tumours and those on the trunk (Table 5s). Case-sibling control comparisons are shown in Table 3; because of the small sample size the confidence intervals are very wide, but the risk estimates are consistent with the protective effects seen using population controls, particularly for holiday sun exposure.

Table 4 shows the effect of sun exposure on risk stratified by phenotype. ORs for melanoma associated with at least one sunburn at or over the age of 20 years were 1.66 (95% CI 1.16-2.38) and 1.24 (95% CI 0.88-1.75) for sun-sensitive and non- sun-sensitive phenotypes respectively, corrected for age, sex and deprivation score (Table 4).

Red hair and freckles represent the most extreme sun sensitivity, so the data were also analysed separately for individuals with neither red hair nor freckles, freckles alone and both red hair and freckles (Table 6s). In this analysis, a protective effect of average weekend exposure in warmer months was strongest for those with neither red hair nor freckles (OR 0.56, 95% CI 0.33-0.95) for more than 5 hours exposure compared with less than 4 hours. There was no evidence of benefit for those with red hair (OR 0.85, 95% CI 0.29-2.53). The protective effect of higher average weekend sun exposure in warmer months persisted when the data were adjusted for age, sex, deprivation, sunburn history and hair colour in a multivariable analysis (OR=0.66, 95% CI 0.48-0.90 for upper tertile compared with the lowest (data not shown).

Vitamin D levels and sun exposure

In order to further investigate the protective effect of greater weekend sun exposure in summer months we looked at the correlation between reported sun exposure and serum vitamin D levels in cases and population controls. The reported sun exposures most significantly associated with higher vitamin D levels were average weekend exposure in warmer months and holiday exposures at low latitudes in cases (Table 7s). These effects were seen after adjustment for age, sex, month sampled, reported dietary supplementation with vitamin D (available for cases) and Townsend (deprivation) score (linear trend p=0.0002 for cases).

Vitamin D levels were only measured in a minority of population controls, so the power to conduct a case-control comparison of vitamin D levels is severely limited. In multivariable analysis within the 805 cases and 187 controls for which we had serum vitamin D levels,

weekend sun exposure remained protective for melanoma after adjustment for vitamin D (OR=0.46, 95% CI 0.30-0.72 for upper tertile compared with the lowest); serum vitamin D level was not independently protective (OR=0.89, 95% CI 0.76-1.04 per 20 nmol/L increase), but an independent effect cannot be excluded.

We also compared cases and their matched sibling in conditional logistic regression analysis. Adjusting for age, sex and season of year sampled, serum vitamin D levels showed significant protective effects (p ranged between 0.01 and 0.03 for four seasons). We adjusted finally for hair colour, given that vitamin D levels are lower in our study in fair skinned people, but again significant protective effects for serum vitamin D levels were observed (OR=0.64, 95% CI 0.46-0.87 per 20 nmol/L increase across seasons, data not shown).

Discussion

The lack of a simple cumulative relationship between melanoma risk and sun exposure has caused difficulties in interpreting and conveying the nature of risk to the public. This has further recently been compounded by concerns that low levels of vitamin D, which might result from sun avoidance designed to reduce melanoma risk, could have negative effects on health generally (17, 18).

We therefore carried out a case-control study addressed to better understanding the relationship between sun exposure and risk in a population living at high latitude. The study benefits from a large sample size, and a very detailed validated sun exposure questionnaire, developed and used internationally. We have tested for multiple putative risk factors, so that p-values presented must be interpreted bearing this in mind. The limitations also include those of case-control studies generally, namely the possibility of recruitment and recall of information biases. Comparison with cancer registry data for the geographical area showed that the sample of cases was reasonably representative of the total melanoma population except that the study did not recruit over the age of 75 years, and as there were fewer elderly patients we therefore recruited fewer participants with head and neck tumours. Population controls were less deprived than the cases, which is likely to represent participation bias in controls. We recruited sibling controls as a useful additional comparison group, less subject to bias of ascertainment, although this method of control selection does produce less power due to shared genes and shared exposures. The number of siblings recruited was disappointing and we therefore used the sample as a secondary comparison group, but the results of this study do show the value of using two control groups in that we were able to demonstrate effects of similar magnitude in both groups. In order to further investigate the protective effect of regular weekend sun exposure we sought evidence for a possible role for vitamin D and a limitation of the study is that we had incomplete data collection on use of vitamin D supplements and serum vitamin D measurements from only a sample of the controls. Furthermore we had only one measure of vitamin D, although a recent paper has suggested that in screening cohorts at least that vitamin D levels are relatively stable over time (19). The sample was also taken after diagnosis in cases and the level might therefore have been modified by behaviours after diagnosis.

Phenotypic characteristics associated with increased risk of melanoma were as reported in many case-control studies, and the ORs reported here were very similar to those reported in Gandini's meta-analysis (3). The association of sun-sensitive phenotypes with an increased melanoma risk is entirely consistent with recent findings in genome-wide association studies, in which the most significant genetic associations with melanoma were in genes determining pigmentation phenotypes (20-22). We report data to support the view, however, that the relationship between phenotypes and melanoma risk is complicated, since sun-sensitive individuals reported less sun exposure than those with more sunburn resistant skin.

The study showed a clear relationship between reported sunburn and overall melanoma risk. The pattern of sun exposure most predictive of sunburn was holiday sun exposure, so that these data are supportive of previously reported studies including our pooled data analysis (4) that intermittent sun exposure sufficient to cause burning is the major risk factor for melanoma overall. This case-control study showed no evidence, however, for a relationship between reported intermittent or recreational sun exposure and increased melanoma risk. Indeed there was even a suggestion of a protective effect. A previous large UK case-control study also showed little evidence of an effect of sunny holidays on risk (23). Fair skinned controls reported less sun exposure than darker skinned controls, which is consistent with recently reported data from a healthy twin study (24) in which vitamin D levels were reported to be lower in those with sun-sensitive phenotypes. It is possible that the relationship between risk and sunny holidays was weaker in both these studies because of recall bias. Sun-sensitive people were shown in this study moreover to be both at increased risk and to report less sun exposure than darker skinned individuals and this complexity may make the results of the usual case-control comparisons unclear. It is also possible that as the controls in our study were of slightly higher socioeconomic status than cases they had more access to sunny holiday sun exposure, although we have attempted to adjust for this using a measure of social deprivation.

Risk of melanoma on the head and neck (Table 3) showed some association with higher weekday sun exposure in cooler months, although the pattern was irregular, and with lower sunny holiday exposure, consistent with previous published data to suggest that melanoma in these sites is associated with occupational or chronic sun exposure in individuals postulated to have less access to sunny holidays. We hypothesize that we were able to estimate the risk of melanoma associated with this type of sun exposure in temperate climates better in this case-control study than in our previous pooled data analysis because we had much more detailed data on different patterns of sun exposure, which was the main purpose and strength of this study.

The study shows a statistically significant protective effect of higher weekend sun exposure after adjustment for a measure of deprivation, and this behavior was associated with higher vitamin D levels. These data support the hypothesis that, whilst sunburn is a risk factor for melanoma, regular sun exposure may also be protective for those living at high latitude. There was some weak evidence for this in our previous pooled data analysis, in that at higher latitudes there was a non-significant protective effect of higher total sun exposure (4). In the study reported here much more detailed sun exposure data were collected, and it is therefore possible in the case-control study to look at weekend sun exposure, which was not possible in the previous pooled data analysis. Although there was no statistically significant differences for sibling controls and cases the case-sibling control comparisons showed similar risk estimates and provide supportive evidence for this complex relationship between sun exposure and melanoma risk.

A protective effect of regular weekend sun exposure on melanoma risk might be mediated by photoadaption or as a result of higher consequent vitamin D levels, or the observation in this study may reflect bias due to the recruitment of controls of higher socioeconomic status. We utilized data on serum vitamin D levels to investigate this further. We have shown that greater reported weekend sun exposure was associated with higher vitamin D levels, supporting the hypothesis that a protective effect of weekend sun exposure might be mediated via higher levels of vitamin D. We have previously reported a case-control comparison for serum vitamin D levels (9) in a smaller sample set, in which we saw no significant differences between cases and controls. The adjusted OR per 20 nmol/L increase of serum vitamin D across seasons was 0.94 (95% CI 0.79-1.12) (9). In the current analysis the serum vitamin D levels were not quite independently protective for melanoma

(OR=0.89, 95% CI 0.76-1.04 per 20 nmol/L increase) in a comparison between cases and population controls, but cases had significantly lower vitamin D levels than their sibling controls in the small subset available for this analysis. These data therefore support the hypothesis that a protective effect of weekend sun exposure might be mediated via higher levels of vitamin D synthesis. Since vitamin D levels were measured some months post-diagnosis, it is possible however that this difference may reflect subsequent sun avoidance in cases, although equally cancer patients often start to supplement their diet after diagnosis.

There are few published data to suggest a protective role for vitamin D in melanoma susceptibility: a recent cohort study for example reported no protective effect of supplemental vitamin D intake on melanoma risk although serum levels were not measured (8), and from the paper it would appear that the authors were not able to adjust for sun exposure. We considered whether photoadaption was a more likely explanation of the protective effective of weekend sun exposure. That there was some protective effect of weekend sun exposure for truncal melanoma as well as melanoma on the limbs, (where photoadaption is likely to be less marked), argues against the hypothesis that photoadaption may be the means by which weekend sun exposure might protect. Furthermore in our study we saw a protective effect for melanoma even in non-sun exposed rare sites such as acral lentiginous and genital melanoma. Which might suggest that photoadaption is a less likely explanation. Data moreover suggest that photoadaption does not protect against the sunburn-induced immunosuppression (25) which is thought central to melanoma carcinogenesis. Clearly further studies are needed to understand the means by which moderate sun exposure may be protective for melanoma.

In conclusion, this large study has confirmed that sunburn and sun-susceptible phenotypes are associated with melanoma risk. It has provided important information to support the view that, although sunburn is associated with melanoma, regular weekend sun exposure may be protective for melanoma in populations living at high latitude. The data suggest that this effect may be mediated at least in part by higher vitamin D levels, but photoadaption is an alternative hypothesis.

Data presented here suggest that individuals with sun-sensitive skin types are at increased risk of melanoma, and advice to them should be to avoid sunburn and behaviours associated with sunburn such as sunbathing. The possibility that low vitamin D levels may be a risk factor for melanoma and are certainly harmful to health generally, means that such fair skinned people should consider taking vitamin D supplements (at doses recommended by their local health authorities), if they are sun avoidant. For non-sun-sensitive individuals the data suggest that regular moderate sun exposure may be protective for melanoma and is shown to be associated with higher vitamin D levels. In these individuals therefore, not least because of the beneficial effects of vitamin D to health generally, there is an argument to suggest that regular sun exposure should be supported in countries with relatively low levels of ambient UV radiation, provided that no burning occurs. Sunburn and large cumulative sun exposures should be avoided. Comparison of these data with those from sunnier countries is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

OR	odds ratio
CI	confidence intervals

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Table 1

Age and sex distribution of cases and population controls, and tumor characteristics of cases in the study. We have compared the case characteristics with those for the same geographical region as a whole in the period 2000-2003 (14) on the basis of the stratified sampling scheme employed for recruitment. The end date for the population norms precedes the end date of recruitment into the study but is the latest date of available complete data within the cancer registry.

Risk factor	Controls	Cases	P^	Populationenorms*
Sex				
Male	211 (41.1%)	384 (40.0%)		42.4%
Female	302 (58.9%)	576 (60.0%)	0.67	57.6%
Age in years				
< 40	61 (11.9%)	201 (20.9%)		18.5%
40-50	85 (16.6%)	203 (21.2%)		15.3%
50-60	133 (25.9%)	228 (23.7%)		17.9%
60-70	133 (25.9%)	219 (22.8%)		19.6%
> 70	101 (19.7%)	109 (11.4%)	<0.0001	28.7%
Education				
Primary/secondary school	155 (30.3%)	328 (35.8%)		
Six form/vocational training /university not graduated	165 (31.2%)	286 (32.2%)		
University graduated	80 (15.6%)	112 (12.2%)		
Other	110 (21.5%)	183 (20.0%)	0.16	
Townsend score				
Quartile 1 (most affluent)	123 (24.3%)	168 (17.8%)		
Quartile 2	134 (26.5%)	246 (26.1%)		
Quartile 3	121 (23.9%)	239 (25.3%)		
Quartile 4 (most deprived)	128 (25.3%)	290 (30.8%)	0.01	
Body mass index				
<24.9	244 (48.5%)	375 (39.9%)		
24.9-29.9	184 (36.6%)	370 (39.3%)		
>29.9	75 (14.9%)	196 (20.8%)	0.01	
Self reported family history of melanoma (1st degree relatives)				
No	503 (98.0%)	898 (94.5%)		
Yes	10 (2.0%)	52 (5.5%)	0.001	
Tumor site				
Trunk		334 (34.8%)		26.6%
Limbs		447 (46.6%)		52.3%
Head and neck		123 (12.7%)		18.2%
Others		56 (5.8%)		2.9%
Breslow thickness				
<0.75mm		163 (17.2%)		17.2%
0.75-1mm		220 (23.3%)		29.1%
1-2mm		296 (31.3%)		24.0%

Risk factor	Controls	Cases	p^	Populationе norms*
2-3mm		127 (13.4%)		10.0%
>3mm		140 (14.8%)		20.6%

*Overall population norm was calculated by weighted average of population norm with Breslow <0.75mm (17.2%) and ≥0.75mm (82.8%).

^P-values were based on Chi-squared tests for sex, education and self reported family history of melanoma, and based on two-sample t-tests for age, Townsend score and BMI.

Table 2

Phenotypic characteristics, reported sunburn and melanoma risk

Risk factor	Controls	Cases	OR* (95% CI)	OR^ (95% CI)
Eye color				
Brown	77 (15%)	106 (11%)	1	1
Green/Hazel	196 (39%)	326 (34%)	1.24 (0.87-1.77)	1.24 (0.87-1.78)
Blue/Grey	233 (46%)	514 (54%)	1.71 (1.21-2.41)	1.68 (1.18-2.37)
Natural hair color				
Black/Brown	407 (81%)	623 (67%)	1	1
Blond	68 (13%)	182 (20%)	1.76 (1.29-2.41)	1.80 (1.31-2.47)
Red	29 (6%)	121 (13%)	2.85 (1.85-4.41)	2.97 (1.91-4.64)
Self reported freckles as child				
None	193 (38%)	223 (25%)	1	1
Very few	131 (26%)	271 (30%)	1.58 (1.18-2.12)	1.55 (1.15-2.09)
Few/Some	161 (31%)	321 (36%)	1.51 (1.14-2.01)	1.48 (1.11-1.98)
Many	27 (5%)	82 (9%)	2.53 (1.53-4.16)	2.64 (1.57-4.43)
Reported skin color inside upper arm				
Olive/Brown	60 (12%)	71 (8%)	1	1
Fair	365 (72%)	569 (61%)	1.29 (0.89-1.88)	1.34 (0.92-1.95)
Very fair	79 (16%)	286 (31%)	2.83 (1.84-4.36)	2.95 (1.91-4.58)
Ability to tan				
Go very brown and deeply tanned	77 (15%)	103 (11%)	1	1
Get moderately tanned	259 (52%)	379 (41%)	1.31 (0.90-1.91)	1.19 (0.84-1.68)
Get mildly or occasionally tanned	121 (24%)	331 (36%)	1.88 (1.27-2.80)	2.23 (1.53-3.26)
Get no suntan at all or only freckled	42 (8%)	110 (12%)	2.24 (1.06-4.76)	2.06 (1.28-3.33)
Propensity to burn				
Go brown without any sunburn	62 (12%)	77 (8%)	1	1
Get mildly burnt followed by some tanning	281 (56%)	463 (50%)	1.14 (0.81-1.60)	1.37 (0.94-2.01)
Have a painful sunburn for a few days followed by peeling	145 (29%)	347 (38%)	2.13 (1.47-3.09)	1.96 (1.31-2.94)
Get a severe sunburn with blistering	12 (2%)	34 (4%)	2.14 (1.33-3.42)	2.22 (1.04-4.75)
Sun sensitivity score §				
Quartile 4	182 (35%)	197 (21%)	1	1
Quartile 3	139 (27%)	216 (23%)	1.38 (1.02-1.86)	1.40 (1.03-1.90)
Quartile 2	119 (23%)	249 (26%)	1.85 (1.36-2.51)	1.89 (1.39-2.59)
Quartile 1	73 (14%)	298 (31%)	3.66 (2.62-5.11)	3.62 (2.57-5.10)
Sunburn under age 20				
Never	347 (73%)	561 (65%)	1	1
At least once	130 (27%)	297 (35%)	1.24 (0.96-1.59)	1.24 (0.95-1.60)
Sunburn at or after age 20				
Never	315 (68%)	511 (58%)	1	1
At least once	147 (32%)	365 (42%)	1.56 (1.23-1.99)	1.56 (1.22-2.00)

§ Sun sensitivity score was derived by factor analysis using hair color, eye color, self reported freckle as child, propensity to burn, ability to tan and skin color of inside upper arm with average factor loading being 0.44, 0.21, 0.38, 0.56, 0.66 and 0.61, respectively.

* ORs are corrected for age, sex and Townsend (deprivation) score.

^ ORs are corrected for age, sex, Townsend (deprivation) score and weekend sun exposure at warmer month.

Total numbers of cases and controls may vary due to missing data.

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Table 3

Associations between sun exposure and melanoma risk.

	Case-control analysis				Case-matched sibling analysis		
	Control	Case			Sibling control	Matched case	
	N (%)	N (%)	OR* (95% CI)	OR^ (95% CI)	N (%)	N (%)	OR§ (95% CI)
Daily exposure							
Average (hours/day)							
≤1.9	165 (34%)	333 (37%)	1	1	64 (40%)	49 (33%)	1
1.9-2.5	160 (33%)	272 (31%)	0.80 (0.61-1.06)	0.79 (0.60-1.05)	49 (30%)	61 (42%)	1.68 (0.90-3.11)
>2.5	161 (33%)	285 (32%)	0.88 (0.66-1.17)	0.96 (0.72-1.28)	49 (30%)	37 (25%)	1.11 (0.56-2.20)
Weekday exposure							
Average in warmer month (hours/day)							
≤0.9	167 (34%)	306 (34%)	1	1	56 (355)	52 (36%)	1
0.9-1.5	162 (33%)	303 (34%)	0.98 (0.74-1.29)	0.76 (0.57-1.00)	53 (33%)	46 (32%)	0.85 (0.49-1.48)
>1.5	161 (33%)	281 (32%)	0.95 (0.72-1.26)	1.04 (0.78-1.38)	52 (32%)	47 (32%)	1.01 (0.55-1.84)
Average in cooler month (hours/day)							
≤0.9	167 (34%)	306 (34%)	1	1	50 (31%)	41 (28%)	1
0.9-1.5	162 (33%)	303 (34%)	0.98 (0.74-1.29)	1.00 (0.75-1.32)	53 (33%)	68 (47%)	1.62 (0.88-2.97)
>1.5	161 (33%)	281 (32%)	0.95 (0.72-1.26)	1.04 (0.78-1.40)	59 (36%)	37 (25%)	0.71 (0.37-1.38)
Weekend exposure							
Average in warmer month (hours/day)							
≤4.0	168 (34%)	377 (42%)	1	1	66 (41%)	72 (49%)	1
4.0-5.0	164 (33%)	262 (29%)	**0.72 (0.55-0.94)**	**0.72 (0.55-0.95)**	57 (35%)	34 (23%)	**0.46 (0.24-0.88)**
>5.0	161 (33%)	262 (29%)	**0.67 (0.50-0.89)**	**0.70 (0.52-0.94)**	39 (24%)	41 (28%)	0.99 (0.50-1.94)
Average in cooler month (hours/day)							
≤2.5	167 (34%)	334 (37%)	1	1	62 (38%)	62 (42%)	1
2.5-3.5	163 (33%)	315 (35%)	1.01 (0.77-1.33)	1.05 (0.79-1.39)	55 (34%)	57 (39%)	0.99 (0.56-1.77)
>3.5	163 (33%)	254 (28%)	0.79 (0.58-1.06)	0.85 (0.63-1.16)	46 (28%)	28 (19%)	0.52 (0.25-1.11)
Holiday exposure							
Average (hours/year)							
≤46.2	167 (34%)	345 (38%)	1	1	58 (35%)	60 (40%)	1

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	Case-control analysis				Case-matched sibling analysis		
	Control	Case			Sibling control	Matched case	
	N (%)	N (%)	OR* (95% CI)	OR^ (95% CI)	N (%)	N (%)	OR§ (95% CI)
46.2-71.3	161 (33%)	259 (28%)	**0.75 (0.57-0.98)**	**0.75 (0.56-0.99)**	50 (30%)	38 (25%)	0.68 (0.37-1.24)
>71.3	163 (33%)	312 (34%)	0.87 (0.66-1.15)	0.94 (0.71-1.24)	57 (35%)	53 (35%)	0.84 (0.42-1.67)
From 10am to 2pm (hours/year)							
≤23.3	166 (34%)	363 (40%)	1	1	53 (32%)	59 (39%)	1
23.3-37.9	162 (33%)	272 (30%)	0.78 (0.60-1.03)	0.82 (0.62-1.08)	55 (33%)	35 (23%)	0.59 (0.32-1.08)
>37.9	161 (33%)	277 (30%)	**0.76 (0.58-1.00)**	0.82 (0.62-1.09)	57 (35%)	57 (38%)	0.88 (0.46-1.70)
Holiday exposure below 45°N							
Average (hours/year)							
≤6.4	166 (34%)	320 (35%)	1	1	48 (29%)	56 (37%)	1
6.4-26.5	163 (33%)	287 (31%)	0.84 (0.63-1.11)	0.90 (0.68-1.20)	61 (37%)	37 (25%)	0.55 (0.30-1.00)
>26.5	162 (33%)	309 (34%)	**0.75 (0.56-1.00)**	0.83 (0.62-1.12)	56 (34%)	58 (38%)	0.90 (0.43-1.87)
From 10am to 2pm (hours/year)							
≤3.1	167 (34%)	331 (36%)	1	1	52 (32%)	58 (38%)	1
3.1-13.0	160 (33%)	278 (30%)	0.79 (0.60-1.05)	0.84 (0.63-1.12)	58 (35%)	35 (23%)	0.57 (0.31-1.04)
>13.0	162 (33%)	303 (33%)	**0.73 (0.54-0.97)**	0.82 (0.61-1.10)	55 (33%)	58 (38%)	1.00 (0.49-2.02)

*ORs were corrected for age, sex, Townsend (deprivation) score.

^ORs were corrected for age, sex, Townsend (deprivation) score and sun sensitivity score.

§ORs were corrected for age, sex and Townsend (deprivation) score in conditional logistic regression analysis.

Findings significant at the 5% level are shown in bold.

Total numbers of cases and controls may vary due to missing data.

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Table 4

Relative melanoma risk of different pattern of sun exposure (tertile groups) by sun sensitivity phenotype

	Sun-sensitive phenotype			Non- sun-sensitive phenotype			P for interaction
	Control N (%)	Case N (%)	Adj OR* (95% CI)	Control N (%)	Case N (%)	Adj OR* (95% CI)	
Sunburn before age 20							
Never	119 (66%)	294 (60%)	1	228 (77%)	266 (73%)	1	
At least once	61 (34%)	197 (40%)	1.15 (0.80-1.66)	69 (23%)	100 (27%)	1.07 (0.73-1.52)	0.73
Sunburn at or after age 20							
Never	113 (63%)	261 (52%)	1	202 (71%)	249 (66%)	1	
In least once	65 (37%)	238 (48%)	**1.66 (1.16-2.38)**	82 (29%)	127 (34%)	1.24 (0.88-1.75)	0.25
Daily exposure							
Average (hours/day)							
≤1.9	68 (37%)	196 (39%)	1	97 (32%)	137 (35%)	1	
1.9-2.5	62 (34%)	167 (33%)	0.87 (0.58-1.31)	98 (32%)	105 (27%)	0.73 (0.50-1.08)	
>2.5	52 (29%)	138 (28%)	0.91 (0.59-1.41)	109 (36%)	146 (38%)	0.92 (0.63-1.34)	0.80
Weekday exposure							
Average in warmer month (hours/day)							
≤1.4	67 (36%)	188 (37%)	1	100 (33%)	141 (36%)	1	
1.4-2.2	69 (38%)	163 (32%)	0.80 (0.53-1.20)	92 (30%)	100 (26%)	0.72 (0.49-1.07)	
>2.2	48 (26%)	155 (31%)	1.11 (0.72-1.71)	113 (37%)	147 (38%)	0.92 (0.64-1.33)	0.82
Average in cooler month (hours/day)							
≤0.9	70 (38%)	182 (36%)	1	97 (32%)	124 (32%)	1	
0.9-1.5	67 (36%)	177 (35%)	0.94 (0.64-1.42)	95 (31%)	126 (33%)	1.02 (0.70-1.50)	
>1.5	47 (26%)	143 (28%)	1.11 (0.72-1.72)	114 (37%)	137 (35%)	0.94 (0.64-1.37)	0.70
Weekend exposure							
Average in warmer month (hours/day)							
≤4.0	66 (36%)	229 (45%)	1	102 (33%)	148 (38%)	1	
4.0-5.0	72 (39%)	138 (27%)	**0.53 (0.35-0.80)**	92 (30%)	124 (32%)	0.95 (0.65-1.39)	
>5.0	46 (25%)	141 (28%)	0.79 (0.50-1.25)	115 (37%)	120 (31%)	**0.65 (0.45-0.96)**	**0.02**
Average in cooler month (hours/day)							

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	Sun-sensitive phenotype			Non- sun-sensitive phenotype			P for interaction
	Control N (%)	Case N (%)	Adj OR* (95% CI)	Control N (%)	Case N (%)	Adj OR* (95% CI)	
≤2.5	73 (39%)	203 (40%)	1	94 (31%)	131 (33%)	1	
2.5-3.5	63 (34%)	176 (35%)	1.06 (0.71-1.58)	100 (32%)	139 (35%)	1.02 (0.69-1.49)	
>3.5	49 (26%)	130 (26%)	0.93 (0.60-1.46)	114 (37%)	123 (31%)	0.77 (0.52-1.14)	0.78
Holiday exposure							
Average (hours/year)							
≤46.2	75 (40%)	201 (39%)	1	92 (30%)	143 (36%)	1	
46.2-71.3	63 (34%)	147 (29%)	0.83 (0.55-1.25)	98 (32%)	112 (28%)	0.70 (0.48-1.03)	
>71.3	48 (26%)	167 (32%)	1.19 (0.78-1.83)	115 (38%)	145 (36%)	0.77 (0.53-1.10)	0.30
From 10am to 2pm (hours/year)							
≤23.3	74 (40%)	214 (42%)	1	92 (30%)	148 (37%)	1	
23.3-37.9	65 (35%)	152 (30%)	0.80 (0.53-1.20)	97 (32%)	120 (30%)	0.80 (0.55-1.18)	
>37.9	45 (24%)	147 (29%)	1.10 (0.71-1.70)	116 (38%)	130 (33%)	**0.66 (0.45-0.96)**	0.14
Holiday exposure below 45°N							
Average (hours/year)							
≤6.4	78 (42%)	191 (37%)	1	88 (29%)	128 (32%)	1	
6.4-26.5	61 (33%)	156 (30%)	1.01 (0.68-1.52)	102 (33%)	131 (33%)	0.77 (0.52-1.14)	
>26.5	47 (25%)	168 (33%)	1.12 (0.72-1.73)	115 (38%)	141 (35%)	**0.64 (0.44-0.95)**	0.16
From 10am to 2pm (hours/year)							
≤3.1	76 (41%)	200 (39%)	1	91 (30%)	130 (33%)	1	
3.1-13.0	63 (34%)	152 (30%)	0.88 (0.59-1.32)	97 (32%)	126 (32%)	0.79 (0.53-1.16)	
>13.0	45 (24%)	161 (31%)	1.05 (0.68-1.63)	117 (38%)	142 (36%)	**0.66 (0.45-0.97)**	0.26

^Sun sensitivity phenotype was derived by factor analysis using hair color, eye color, self reported freckle as child, propensity to burn, ability to tan and skin color of inside upper arm with average factor loading being 0.44, 0.21, 0.38, 0.56, 0.66 and 0.61, respectively; top 50% of the first factor score estimates were assigned the sun-sensitive phenotype, bottom 50% of first factor score estimates were assigned non- sun-sensitive phenotype.

*Odds ratios were reported from models including age, sex, Townsend (deprivation) score, sun exposure, sun sensitivity phenotype and interaction between sun exposure and sun sensitivity phenotype.

Findings significant at the 5% level are shown in bold.

Total numbers of cases and controls may vary due to missing data.