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Occupational sun exposure and risk of melanoma according to anatomical site

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Abstract

Although sunburn and intermittent sun exposures are associated with increased melanoma risk, most studies have found null or inverse associations between occupational (more continuous pattern) sun exposure and melanoma risk. The association of melanoma with occupational sun exposure may differ according to anatomical site, with some studies finding a positive association with melanoma on the head and neck. We examined the association between occupational sun exposure (self-reported weekday sun exposure) and melanoma risk according to anatomical site, using data from two multi-centre population-based case-control studies: the Australian Melanoma Family Study (588 cases, 472 controls) and the Genes, Environment and Melanoma study (GEM; 1079 cases, 2181 controls). Unconditional logistic regression was used to estimate odds ratios (OR) and their 95% confidence intervals, adjusting for potential confounders. Occupational sun exposure was not positively associated with melanoma risk overall or at different body sites in both studies. The GEM study found inverse associations between occupational sun exposure and melanoma on the head and neck (OR for highest vs. lowest quartile: 0.56, 95% CI 0.36-0.86, P_{trend} 0.02), and between the proportion of total sun exposure occurring on weekdays and melanoma on the upper limbs (OR for highest vs. lowest quartile: 0.66, 95% CI 0.42-1.02, P_{trend} 0.03). Our results suggest that occupational sun exposure does not increase risk of melanoma, even of melanomas situated on the head and neck. This finding appeared not to be due to negative confounding of occupational sun exposure by weekend sun.

Keywords

Melanoma; risk factors; sunlight; case-control studies

Introduction

The association between sun exposure and the risk of melanoma appears complex. Previous studies have shown that while sunburn and intermittent sun exposure are associated with

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increased risk of melanoma, there is no, or an inverse, association between occupational (more continuous pattern) sun exposure and melanoma risk.[1-4] Melanomas are thought to arise from several causal pathways, with relationship to sun exposure differing by anatomical site of the melanoma, and the pattern and age-period of sun exposure.[5, 6] In particular, there is some evidence that melanoma on the head and neck is more related to continuous sun exposure whereas melanoma on the trunk and limbs is more related to intermittent sun exposure.[2, 3, 5, 7, 8] Clarifying these associations is important for framing and targeting sun protection messages.

We examined the association between occupational sun exposure and melanoma risk according to anatomical site using two large, multi-centre population-based case-control studies: the Australian Melanoma Family Study (AMFS) and the international Genes, Environment and Melanoma (GEM) study.

Methods

Study samples

Detailed descriptions of study designs, populations, recruitment and data collection have been given elsewhere.[9, 10] In brief, the AMFS included 629 population-based cases, 240 population-based controls and 295 spouse or friend controls from three Australian cities: Brisbane, Sydney and Melbourne.[9] Cases were 18-39 years old, identified from population-based state cancer registries and diagnosed between 1st July 2000 and 31st December 2002 with incident, histopathologically-confirmed, first-primary invasive cutaneous melanoma. Participation was 54% of those eligible and 76% of those contactable. Population controls were 18-39 years old at the time of approach and had no history of invasive or in situ melanoma. They were selected from the electoral roll (registration to vote is compulsory for Australian citizens aged 18 years and over) and frequency-matched to cases by city, age and sex. Participation was 23% of those apparently eligible and 42% of those contactable. Cases were asked to nominate a spouse, partner, or friend as a potential control participant; they were eligible if they were at least 18 years of age and had no history of invasive or in situ melanoma. A potential control was nominated by 59% of cases, and participation was 80% of those nominated.

The GEM study, using a novel study design, included 1207 population-based cases with second or subsequent primary melanoma and 2469 population-based controls with first primary melanoma from nine geographical regions: New South Wales and Tasmania (Australia), British Columbia and Ontario (Canada), Turin (Italy), and California, New Jersey, North Carolina and Michigan (USA). When analysed as a case-control study, this study design finds, in theory, similar aetiological relationships to conventional case-control studies.[10, 11] This theory is supported by comparison of GEM study results with those of other studies[10, 12-14] GEM participants were identified from eight population-based state cancer registries and one hospital centre (Michigan). Cases were diagnosed between 1st January 2000 and 31st August 2003 with second or subsequent primary invasive cutaneous melanoma, except in British Columbia, California, New Jersey and Tasmania where there was additional case ascertainment in 1998 and 1999. Participation was 52% of those eligible. Controls were diagnosed between 1st January and 31st December 2000, except in Turin where control ascertainment was between 1st June 2000 and 31st May 2001. Participation was 54% of those eligible. In the GEM study, 96 controls developed a second primary melanoma over the course of the study and were included as both cases and controls, in keeping with epidemiological principles[15] and previous GEM study analyses.[4, 10, 12, 13]

Ethical approval was obtained in each coordinating centre in each study, and informed written consent from each study participant.

Data collection and measures of occupational sun exposure

AMFS data were collected from 2001 to 2005 and GEM data were collected from 2000 to 2003. In both studies, the participants completed a self-administered and a telephone-administered questionnaire, which collected information on demographics, family history of cancer, phenotype and sun exposure. The AMFS questionnaire was partly based on the GEM questionnaire.

Participants were asked to recall their sun exposure hours in each decade year of life from age 10 onwards (and at age 15 in the AMFS); these included questions on the frequency of sun exposure during weekdays and weekends, frequency of sunburn and blistering, and childhood sun exposure. Additionally, participants were asked about the frequency of sun exposure to the tumour site; AMFS controls were randomly allocated a reference site. Occupational sun exposure was inferred from self-reported sun exposure during weekdays from age 18. Total occupational sun exposure was estimated as the weighted sum of hours of exposure in each decade year of life: for this calculation self-reported sun exposure at age 20 was used to estimate exposure for ages 18-24 and so on for each decade up to 85-94 years of age. We calculated a second measure of occupational sun exposure as the proportion of total sun exposure occurring on weekdays (total weekday sun exposure divided by total sun exposure).

Statistical analysis

Analyses were performed using unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusting for age, sex, site of recruitment, education, self-reported melanoma history in first-degree relatives, skin colour and usual skin response to sun exposure. For AMFS, population controls and spouse or friend controls were combined into one control group for analysis; we have previously shown no statistically significant differences between the sun exposure risk estimates for the separate control groups.[16, 17] We excluded from the analysis participants who were missing data on sun exposure at age 20, any of the covariates, and melanoma patients with unspecified tumour sites. Sun exposure variables were categorised into quarters based on the distribution of controls for AMFS and on the distribution of both cases and controls for GEM, in keeping with previous analyses of these studies.[4, 13, 16] Trend tests were estimated on integer scores (1–4) applied to the quartiles and entered as continuous terms in the regression models. Analyses of occupational sun exposure and melanoma risk may be confounded by weekend sun exposure, because people who have low sun exposure at work (the referent group) might have higher weekend sun exposure and thus higher melanoma risk.[2] To address this possibility, we dichotomised total weekday sun exposure and total weekend sun exposure using a median cut-point, and analysed these variables together using a joint ‘low weekday, low weekend’ sun exposure category as the referent group. We also fitted interaction terms between occupational sun exposure and site, and between weekday and weekend sun exposure as dichotomous and continuous variables. The data were analysed using SAS version 9.2 and statistical significance was inferred at two-sided $p<0.05$.

Results

In AMFS, we observed no association between occupational sun exposure and melanoma risk overall, and little or no evidence that the association varied by anatomical site (Table 1). In GEM, inverse associations were observed for total weekday sun exposure and melanoma on the head and neck (OR for highest vs. lowest quartile: 0.56, 95% CI 0.36-0.86, P_{trend}

0.02), and for the proportion of total sun exposure occurring on weekdays and melanoma on the upper limbs (OR for highest vs. lowest quartile: 0.66, 95% CI 0.42-1.02, P_{trend} 0.03). Further analyses that incorporated weekend sun exposure, with a joint 'low weekday, low weekend' sun exposure category as the referent group, showed little or no association between 'high weekday, high weekend' sun exposure and melanoma risk overall or when stratified by anatomical site (Table 2). Melanoma risk tended to be higher in both studies for people who had intermittent patterns of exposure – 'high weekday, low weekend' and 'low weekday, high weekend' exposure – particularly on the limbs. The odds ratios for these two intermittent categories considered individually were not consistently different from those for the combined category in Table 2 (results not shown). Several low p-values for the interaction between weekday and weekend sun exposure for both GEM and AMFS support the contention that intermittent pattern sun exposure is the pattern most predictive of increased melanoma risk in these data (Table 2).

Stratification of weekday sun exposure by childhood sun exposure did not alter the findings (results not shown). The results were little different when we used sun exposure to the specific melanoma site (estimated using a weighting factor based on the reported amount of time that the site was exposed) as the exposure measure or when we stratified anatomical sites into usually and occasionally sun exposed sites (results not shown).

Discussion

We observed no consistent association between occupational sun exposure and melanoma risk overall and little evidence that this association varied by anatomical site. We also found no evidence that lack of a positive association between occupational sun exposure and melanoma was due to confounding by weekend sun exposure. We observed no increase or decrease in melanoma risk in those with high levels of both weekday and weekend sun exposure (i.e. high continuous pattern of sun exposure) overall or for melanoma of the head and neck. There was, however, evidence that those who had intermittent patterns of exposure ('high weekday, low weekend' and 'low weekday, high weekend' categories) had increased risk of melanoma.

Our results are consistent with some previous studies of occupational sun exposure: two meta-analyses have found an inverse association between continuous sun exposure and melanoma overall[1, 2] and no differences by anatomical site (RR for trunk: 0.91, 95% CI 0.73-1.13 and RR for non-trunk: 0.76, 95% CI 0.58-0.99).[2] Some studies, however, have observed a positive association between occupational sun exposure and melanoma of the head and neck. A pooled analysis of 15 case-control studies estimated a 70% higher risk of head and neck melanoma (OR 1.7, 95% CI 1.0-3.0) for those in the highest vs. lowest category of average weekday sun exposure, at low latitudes.[3] At all latitudes the OR was 1.2 (95% CI 0.9–1.6) for head and neck melanoma.[3] Similarly, a case-control study by Newton-Bishop and colleagues observed a positive association between occupational sun exposure (average weekday exposure) and melanoma of the head and neck using case-control comparisons (OR for highest vs. lowest tertile: 1.67, 95% CI 0.95-2.94) and case-case comparisons (OR for head and neck vs. trunk, highest vs. lowest tertile: 1.70, 95% CI 0.94-3.06 in cooler months and 1.50, 95% CI 0.89-2.52 in warmer months).[8] Other case-case comparison studies reported similar positive associations with melanomas on the head and neck. [5, 18]

When the analysis of melanoma cases is stratified by anatomical site, as done here, the smaller number of cases for each site can lead to a bias towards a null result. In Caini's meta-analysis,[2] a statistically significant difference was observed when anatomical sites were broadly stratified into usually and occasionally sun exposed sites (P =0.01) but not

observed when sites were stratified more specifically into head, trunk, upper limbs and lower limbs (P =0.16). In the AMFS and GEM studies, as in several others,[3, 8] occupational sun exposure was inferred from self-reported sun exposure during weekdays. Other studies have evaluated occupational sun exposure differently, and these differences may have contributed to significant heterogeneity in the meta-analyses[1, 2] and pooled analysis.[3] Studies showing an association between occupational sun exposure and increased melanoma risk on the head and neck were mainly from case-case comparison studies.[5, 8, 18]

There may be other explanations for the observed null or inverse associations of occupational sun exposure with melanoma. Melanin has a role in absorbing ultraviolet radiation, is an antioxidant and scavenges free radicals.[19] More continuous sun exposure increases melanin production and epidermal thickness, and thus may confer protection against melanoma through photoadaptation.[1, 2, 8] Another possible explanation may be differences in sun protection behaviour between people with high and low occupational sun exposure. Preventive interventions have been shown to be effective in encouraging people with high occupational sun exposure to adapt their behaviour and use more sun protection.[20] The association between occupational sun exposure and melanoma risk may be attenuated by greater sun protection among people with high occupational sun exposure.

Our studies benefit from large sample sizes, population-based designs and multi-centre approaches using well validated sun exposure questionnaires. [4, 21-23] To our knowledge, there are no other studies that addressed the possibility of negative confounding of occupational sun exposure by weekend sun exposure as a possible explanation for the apparent lack of an association of occupational sun exposure with melanoma. Potential limitations include the possibility of participation bias because of low participation rates, which were different in the case, population control and friend or spouse control groups in AMFS. Sun exposure measures were self-reported based on retrospective questionnaires and probably, therefore, have considerable measurement error; but previous studies suggest that responses to questions on past sun exposure are reasonably reliable[4, 21-2324] In our studies occupational sun exposure was inferred from sun exposure during weekdays, which may not reflect individual work schedules.[25] Confounding by skin type could also be present, as fair skinned individuals self-select occupations with less sun exposure.[3] Whilst we adjusted for potential confounders including skin colour and skin response to sun exposure, there could be residual confounding by phenotype.

In conclusion, occupational or more continuous pattern sun exposure appears not to increase risk of melanoma overall or on the head and neck. This finding appears not to be due to negative confounding of occupational sun exposure by weekend sun exposure. It stands in contrast to the known high-risk for melanoma with intermittent pattern sun exposure.

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Novelty and impact of paper

A more continuous pattern of sun exposure, which is characteristic of occupational exposure, appears not to increase risk of melanoma overall or on the head and neck in two large multi-centre population-based case-control studies. Moreover, we found no evidence that occupational sun exposure was negatively confounded by weekend sun exposure.

Table 1

Odds ratios for melanoma in relation to weekday sun exposure, stratified by anatomical site

AMFS	All sites				Head and neck				Trunk				Upper limbs				Lower limbs			
	Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]	
Total weekday sun exposure (hours)																				
Q1: <1751	172	118	1.00		23	118	1.00		55	118	1.00		43	118	1.00		51	118	1. 00	
Q2: 1751-4650	174	118	1.09	0.77-1.55	26	118	1.23	0.63-2.38	65	118	1.44	0. 89-2.32	31	118	0.75	0.43-1.32	52	118	1. 05	0. 64-1.72
Q3: 4651-8460	116	118	0.94	0.64-1.37	16	118	1.05	0.49-2.26	35	118	1.01	0. 58-1.75	26	118	0.83	0.46-1.50	39	118	0. 92	0. 54-1.59
Q4: >8460	126	118	1.22	0.82-1.81	14	118	1.15	0.48-2.72	49	118	1.69	0. 96-2.97	27	118	1.07	0.56-2.03	36	118	1. 17	0. 65-2.10
Ptrend			0.51				0.84				0.19				0.92				0. 77	
Pinteraction by site																			0. 85	
Proportion of total sun exposure occuring on weekdays																				
Q1: <0.27	151	117	1.00		20	117	1.00		43	117	1.00		36	117	1.00		52	117	1. 00	
Q2: 0.27-0.43	147	118	0.95	0.66-1.37	18	118	0.91	0.44-1.89	53	118	1.30	0. 78-2.17	32	118	0.92	0.52-1.63	44	118	0. 83	0. 50-1.39
Q3: 0.44-0.57	135	117	0.89	0.62-1.29	20	117	1.02	0.50-2.09	43	117	1.03	0. 60-1.74	31	117	0.91	0.51-1.61	41	117	0. 77	0. 46-1.29
Q4: >0.57	154	117	1.08	0.75-1.56	21	117	1.26	0.62-2.59	64	117	1.51	0. 91-2.49	28	117	0.86	0.48-1.55	41	117	0. 89	0. 52-1.50
Ptrend			0.78				0.49				0.20				0.61				0. 55	
Pinteraction by site																			0. 42	

GEM	All sites				Head and neck				Trunk				Upper limbs				Lower limbs			
	Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]	
Total weekday sun exposure (hours)																				
Q1: <4741	226	592	1.00		52	592	1.00		84	592	1.00		46	592	1.00		44	592	1. 00	
Q2: 4741-11310	218	584	0.81	0.64-1.04	49	584	0.66	0.42-1.03	90	584	0.90	0. 64-1.27	37	584	0.61	0.38-0.99	42	584	0. 88	0. 55-1.41
Q3: 11311-23610	314	515	1.00	0.78-1.27	74	515	0.72	0.47-1.10	123	515	1.00	0. 71-1.41	51	515	0.76	0.48-1.21	66	515	1. 43	0. 91-2.25
Q4: >23610	321	490	0.78	0.61-1.01	87	490	0.56	0.36-0.86	143	490	0.84	0. 59-1.20	50	490	0.59	0.36-0.97	41	490	0. 91	0. 54-1.54
Ptrend			0.19				0.02				0.44				0.09				0. 74	
Pinteraction by site																			0. 34	
Proportion of total sun exposure occuring on weekdays																				

AMFS	All sites				Head and neck				Trunk				Upper limbs				Lower limbs			
	Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]	
Q1: <0.31	305	497	1.00		81	497	1.00		113	497	1.00		61	497	1.00		50	497	1. 00	
Q2: 0.31-0.50	277	548	0.83	0.66-1.04	65	548	0.69	0.47-1.01	114	548	0.93	0. 68-1.27	45	548	0.62	0.41-0.96	53	548	1. 05	0. 68-1.61
Q3: 0.51-0.64	222	590	0.69	0.54-0.87	43	590	0.48	0.32-0.74	100	590	0.78	0. 56-1.08	37	590	0.52	0.33-0.82	42	590	0. 85	0. 54-1.33
Q4: >0.64	274	540	0.88	0.70-1.10	73	540	0.84	0.57-1.23	113	540	0.86	0. 63-1.19	41	540	0.66	0.42-1.02	47	540	1. 14	0. 73-1.78
Ptrend			0.12				0.18				0.24				0.03				0. 83	
Pinteraction by site																			0. 44	

[a] Adjusted for age, sex, site of recruitment, education, melanoma history in first-degree relative, skin colour and usual skin response to sun exposure.

Table 2

Odds ratios for melanoma in relation to the joint effects of weekday and weekend sun exposure, stratified by anatomical site

AMFS	**All sites**				**Head and neck**				**Trunk**				**Upper limbs**				**Lower limbs**			
Sun exposure (median cut-point)	**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]	
Low (low weekday, low weekend)	241	155	1.00		39	155	1.00		88	155	1.00		47	155	1. 00		67	155	1.00	
Intermittent (low weekday, high weekend; or high weekday, low weekend)	220	162	1.23	0.89-1.71	25	162	0.96	0. 50- 1.83	72	162	1.09	0.70-1.70	53	162	1. 43	0.85-2.41	70	162	1.32	0.82-2.11
High (high weekday, high weekend)	127	155	0.99	0.67-1.46	15	155	0.76	0.33- 176	44	155	0.97	0.56-1.69	27	155	1.14	0.58-2.25	41	155	1.08	0.61-1.94
P for interaction (median cut-point)[b]			0.12				0.77				0.61				0. 19				0.23	
P for interaction (continuous variables)[b]			0.01				0.21				0.06				0. 81				0.0017	

GEM	**All sites**				**Head and neck**				**Trunk**				**Upper limbs**				**Lower limbs**			
Sun exposure (median cut-point)	Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]		Cases	Controls	OR and 95% CI [a]	
Low (low weekday, low weekend)	214	862	1.00		33	862	1.00		92	862	1.00		37	862	1. 00		52	862	1.00	
Intermittent (llow weekday,	416	689	1.20	0.95-1.52	111	689	1.37	0.86-2.17	152	689	0.98	0.71-1.36	73	689	1.52	0.95-2.45	80	689	1.41	0.92-2.15

AMFS	All sites				Head and neck				Trunk				Upper limbs				Lower limbs			
Sun exposure (median cut-point)	**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]		**Cases**	**Controls**	**OR and 95% CI** [a]	
high weekend; or high weekday, low weekend)																				
High (high weekday, high weekend)	449	630	1.04	0.81-1.35	118	630	0.90	0.55-1.48	196	630	1.00	0.70-1.43	74	630	1.24	0.74-2.09	61	630	1.07	0.65-1.77
P for interaction (median cut-point)[b]			0.06				0.02				0.87				0.09				0.08	
P for interaction (continuous variables)[b]			0.20				0.37				0.47				0.006				0.05	

[a] Adjusted for age, sex, site of recruitment, education, melanoma history in first-degree relative, skin colour and usual skin response to sun exposure.

[b] P value for interaction between weekday and weekend sun exposure. In addition, the p-value for the interaction between joint sun exposure and anatomical site was 0.85 for AMFS and 0.50 for GEM using median cut-points and 0.02 for AMFS and 0.22 for GEM using continuous variables.