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Biologic markers of sun exposure and melanoma risk in women: pooled case-control analysis

Catherine M. Olsen[1,†], **Michael S. Zens**[2,†], **Adele C. Green**[1], **Therese A. Stukel**[2,3], **C. D'Arcy J. Holman**[4], **Thomas Mack**[5], **J. Mark Elwood**[6], **Elizabeth A. Holly**[7], **Carlotta Sacerdote**[8], **Richard Gallagher**[6], **Anthony J. Swerdlow**[10], **Bruce K. Armstrong**[11], **Stefano Rosso**[9], **Connie Kirkpatrick**[12], **Roberto Zanetti**[9], **Julia Newton Bishop**[13], **Veronique Bataille**[14,15], **Yu-Mei Chang**[13], **Rona Mackie**[16], **Anne Østerlind**[17], **Marianne Berwick**[18], **Margaret R. Karagas**[2,‡], and **David C. Whiteman**[1,‡]

[1] Cancer and Population Studies group, Queensland Institute of Medical Research, Brisbane, Australia

[2] Section of Biostatistics and Epidemiology, Department of Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA

[3] Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada

[4] School of Population Health, The University of Western Australia, Western Australia, Australia

[5] Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA

[6] Cancer Control Research Program, British Columbia Cancer Agency, Vancouver, British Columbia, Canada

[7] Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

[8] Unit of Cancer Epidemiology, University of Turin, Torino, Italy

[9] Piedmont Cancer Registry, CPO, Centre for Cancer Prevention, Torino, Italy

[10] Institute of Cancer Research, Section of Epidemiology, Sutton, Surrey, UK

[11] Sydney School of Public Health, University of Sydney, Australia

[12] Franciscan Health System, Tacoma, Washington, USA

[13] Section of Epidemiology and Biostatistics, Leeds Institute of Molecular Medicine, Leeds, UK

[14] Twin Research and Genetic Epidemiology Unit, St Thomas' Campus, Kings College London, UK

[15] Dermatology Department, West Herts NHS Trust, Hemel Hempstead General Hospital, Herts, UK

[16] Department of Public Health and Health Policy, University of Glasgow, Glasgow, UK

[17] Kobenhausevej 25, DK 3400 Hillerød, Denmark

[18] Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, USA

[†]Equal first authors
[‡]Equal senior authors

Writing group: Catherine M. Olsen, Michael S. Zens, Therese A. Stukel, Adele C. Green, Margaret R. Karagas, David C. Whiteman

Abstract

A model has been proposed whereby melanomas arise through two distinct pathways dependent upon the relative influence of host susceptibility and sun exposure. Such pathways may explain site-specific patterns of melanoma occurrence. To explore this model, we investigated the relationship between melanoma risk and general markers of acute (recalled sunburns) and chronic (prevalent solar keratoses) sun exposure, stratified by anatomic site and host phenotype. Our working hypothesis was that head and neck melanomas have stronger associations with solar keratoses and weaker associations with sunburn than trunk melanomas. We conducted a collaborative analysis using original data from women subjects of 11 case–control studies of melanoma (2575 cases, 3241 controls). We adjusted for potential confounding effects of sunlamp use and sunbathing. The magnitude of sunburn associations did not differ significantly by melanoma site, nevus count or histologic sub-type of melanoma. Across all sites, relative risk of melanoma increased with an increasing number of reported lifetime 'painful' sunburns, lifetime 'severe' sunburns and 'severe' sunburns in youth ($p_{trend}<0.001$), with pooled odds ratios for the highest category of sunburns vs no sunburns of 3.22 (95%CI 2.04–5.09) for lifetime 'painful' sunburns, 2.10 (95%CI 1.30–3.38) for lifetime 'severe' sunburns, and 2.43 (95%CI 1.61–3.65) for 'severe' sunburns in youth. Solar keratoses strongly increased the risk of head and neck melanoma (pOR 4.91, 95% CI 2.10–11.46), but data were insufficient to assess risk for other sites. Reported sunburn is strongly associated with melanoma on all major body sites.

INTRODUCTION

A model has been proposed whereby melanomas arise through two distinct causal pathways; one indicated by an association with melanocytic nevi and the other with markers of accumulated sun exposure.[1, 2] The model hypothesizes that nevus-prone individuals require sunburn to initiate the development of melanoma, and that subsequent promotion and progression of the developing tumour is driven primarily by other factors. Among this group of people, melanomas are more likely to arise among the numerically large and ontogenetically "unstable" populations of melanocytes on the trunk and high cumulative sun exposure is not required. In contrast, the model hypothesizes that people who are less prone to nevi require ongoing sun exposure to drive melanoma development, beyond that required for initiation. Among these people, the model predicts that melanomas will tend to arise on sun-exposed body sites at older ages and be associated with markers of chronic sun exposure.

In support of this model, we have found that high nevus counts are strongly associated with melanoma of the trunk but less so, if at all, with melanoma of the head and neck.[3] It appears that the relationship between sun exposure and melanoma might also vary by site, with evidence that melanomas of the head and neck are more strongly associated with accumulated sun exposure than are those of the trunk.[4] Similar findings have been reported by others.[5–11] Emerging molecular and genetic evidence provides strong support that melanomas at different body sites evolve through different pathways. Specifically, melanomas arising on the head and neck are more likely to over-express p53 protein, [1, 12] whereas melanomas arising on the trunk are more likely to carry mutations in *BRAF*. [13–16]

In this work we aimed to explore whether melanomas at different body sites have different associations with two specific markers of sun exposure. Our hypothesis for these analyses was that head and neck melanomas would have stronger associations with solar keratoses, as a measure of chronic sun exposure, and that they would have weaker associations with sunburn, as a measure of acute exposure, than do trunk melanomas.

Specifically, solar keratoses are hyperkeratotic, epidermal tumours caused by accumulated sun exposure and are most common in people with fair skin; [10, 17] their presence can therefore be regarded as a marker of accumulated sun exposure modified by host susceptibility to sun-induced skin damage. Sunburns are an indicator of acute, intense exposures to sunlight, modified by pigmentation phenotype.[18] While these patterns of exposure are not mutually exclusive (since people can experience sunburns and also develop solar keratoses), their utility in epidemiologic studies stems from having fair-to-moderate repeatability, [19, 20] and for solar keratoses, objective measurement.

A number of studies have examined the relationship between sunburn history and melanoma risk by anatomic site; however their findings are inconsistent, perhaps due to the heterogeneity in recording and coding data and/or the poor reproducibility of sun exposure measures.[19, 21, 22] Cho and colleagues et al. [9] observed that melanomas at different anatomical sites varied in their relationships with sunburn: a history of severe and painful sunburns was most strongly related to melanoma of the upper limbs. Walter and colleagues reported a higher risk of melanomas on the trunk following recent severe sunburns than was the case for non-truncal melanomas.[23] Other studies,[8, 24] and a pooled analysis of 15 case-control studies[25] have reported no consistent differences across body sites,[8] or did not test the significance of the differences.[24, 25] A recent meta-analysis of nine studies reported higher pooled RRs for melanoma on 'sun-exposed sites' (defined as 'arms', 'head' and sites classified as 'sun exposed' by individual study authors) with sunburns, but the differences across individual sites were not significant.[26] Two studies [2, 10] and a pooled analysis [25] have previously reported that solar keratoses are more common in people with melanoma on chronically sun-exposed sites than those with melanoma on intermittently exposed sites.

Here, we report on new analyses using a large dataset to examine the relationships between markers of acute, intense sun exposure episodes (self-reported sunburns) and accumulated sun exposure (solar keratoses) and melanoma on different body sites. Our analyses extend previous investigations by examining the associations by histologic sub-type and phenotypic measures. The analyses are restricted to women as the pooled dataset was originally established to examine reproductive and sex hormone effects on risk of melanoma in women.[27, 28]

METHODS

A detailed description of the methods used in our collaborative analysis has been published elsewhere.[27, 29] Strict criteria were used to minimize inter-study heterogeneity and ensure comparable study quality. Briefly, we analyzed studies completed as of July 1994 that included newly diagnosed melanomas, collected data on important risk factors for melanoma (i.e., pigmentary traits and sun exposure history) through a personal interview, and included at least 100 women with melanoma and 100 women without. Data were available for all but one study that met these criteria.[30] Descriptive statistics for each of the analysis variables were compared with published results and provided to the original study investigators to ensure their accuracy. Table 1 summarizes the characteristics of the eleven studies that collected relevant exposure data and met our inclusion criteria.[31–42] Nine of these studies were population-based.

Analysis Variables

There was considerable variation in the way sunburns were defined and counted in the individual studies. Self-reported history of severe sunburns in lifetime (ever/never) was reported by eleven studies [31–37, 39–42] and in childhood or adolescence by nine studies.[31, 32, 34–37, 40–42] The childhood or adolescent exposure variable included sunburns reported in the first two decades of life. Severe sunburns were defined as painful and/or peeling and/or

blistering sunburns. Where studies reported 'painful', 'blistering' and 'peeling' separately, we considered these together as 'severe' sunburns, and defined 'severe' burns as the maximum number of sunburns recorded from any of these three exposure categories. Where the number of sunburns was reported categorically, the mid-point of the category was used. Full details on the derivation of the main sunburn exposure variables are provided in Supplementary Table A. A smaller group of studies reported separately on lifetime history (ever/never) of painful sunburns.[31, 36, 37, 40] Some of the studies provided adequate information to categorize the number of sunburns as: lifetime severe sunburns (1–5, 6–25, ≥26); [31, 32, 34–37, 39–42] severe sunburns in childhood (1–5, 6–15, ≥16); [31, 32, 34–37, 40] and lifetime painful sunburns (1–5, 6–25, ≥26).[31, 36, 37, 40] Only two studies [31, 35] reported on the presence of solar keratoses; these were categorized as none, few, 5–10 and >10 in one study (left hand, arm and face),[35] and as 'none', 'mild', 'moderate' and 'severe' in the second study.[31] Two variables were created for the solar keratoses analyses: 1) 'any' versus 'none' and 2) 'none', 'some' (mild) and 'many' (moderate to severe). The latter 3-level variable was used as a continuous variable when testing for significant differences across sub-groups. Nevus burden was collected in all studies, most commonly as a single measure on the upper arm, as previously reported.[3] For the analyses here, the variable was expressed categorically (none, 1–4, 5–10, >10).

Statistical Analysis

We used a two-stage method of analysis to obtain study-specific odds ratios (ORs) and pooled odds ratios (pORs) and 95% confidence intervals (CIs).[29] In the first stage, each study was analyzed according to its original design. For pair-matched studies, we used conditional logistic regression and for frequency matched studies, we used unconditional logistic regression and stratified by age (<35, 35–44, ≥45 years). To evaluate inter-study variability, we examined the study-specific ORs and tested for statistical heterogeneity using a chi-square test. The pooled exposure effect was estimated in a second-stage linear model as the average of the study-specific ORs, weighted by the inverse marginal variances. The marginal variance was the sum of the individual study variance and the variance of the random study effect. In the absence of heterogeneity, the marginal variance was the study-specific variance alone.[29] We used a critical value of t=2.2 for all two-stage analyses, regardless of number of studies in the analysis, to be consistent with the t-statistic that would be used with joint models. We examined the data for potential sources of heterogeneity by stratifying on type of control group, (population versus hospital-based controls) and the style of questionnaire (telephone versus in-person interview).

All studies matched cases and controls by age, either in pairs or by frequency. All models were adjusted for sunlamp use and history of sunbathing. We did not include skin type or other pigmentary characteristics as covariates in the models since these factors are putatively in the causal pathway. Instead, we conducted stratified analyses to assess whether the effects of sunburn varied across specific sub-groups. Our first analyses were based on melanomas of all types and on all body sites combined. We then separately computed odds ratios for each of the primary exposure variables by anatomic site (head & neck, trunk, upper limbs and lower limbs), nevus count (upper two categories vs lower two categories), skin type and histologic subtype. To assess stratum-specific effects (e.g., anatomic site, histologic subtype), we broke the pair-matched sets and analyzed the studies stratified by age (e.g., <35, 35–49, ≥45 years) using unconditional logistic regression. For the histologic subtype analyses we stratified cases into two groups: 1) superficial spreading melanoma (SSM), nodular melanoma (NM), and melanoma not otherwise specified (NOS); 2) lentigo maligna melanoma (LMM). For the skin type stratification, 7 of the 11 studies had grouped women into 3 categories of skin type (burn only, burn then tan, tan only); for the remaining four studies women were grouped into four categories of skin type. We therefore stratified in two

ways: 1. Skin that burns only vs skin that burns then tans/tan only; 2. Skin that burns/burns then tans vs tans only. To examine possible modifying effects by the *MC1R* genotype we created a proxy variable based on self-reports of hair colour. Participants were re-categorized into two groups: 1) red hair and 2) other hair colour. Tests for trend were based on continuous variables. Analyses were conducted using SAS (SAS Institute, Cary, North Carolina, USA).

We tested for heterogeneity in the association between the number of sunburns/solar keratoses and melanoma risk by anatomic site of melanoma and other stratum effects, using a two-stage test of inequality similar to the two-stage models used for other analyses.[29] In the first stage, the relationship between melanoma risk and sunburn was estimated separately for each study and each stratum, where numbers of sunburns/solar keratoses were analyzed as continuous variables; models were adjusted for age, sunlamp use and history of sunbathing as above. This produced a separate slope for each study-stratum combination. In the second stage, analysis of variance was used to construct an F-test for differences in the stratum-specific slopes.

RESULTS

Totals of 2575 cases and 3241 controls from 11 studies [31–37, 39–42] were included in the analyses of ever severe sunburn; 2067 cases and 2694 controls from nine studies [31, 32, 34–37, 40–42] for ever severe sunburn in childhood/adolescence (Table 1). In the combined dataset, cases were slightly older than controls (mean age 48.0 vs 46.6 years respectively). Amongst cases, women with melanomas of the head and neck were considerably older than those who developed melanoma of the trunk (51.8 vs. 45.1 years; $p < 0.0001$). Women with melanoma of the lower or upper limbs were significantly younger than the women with melanoma of the head and neck, and significantly older than women with melanoma of the trunk (47.5 years for lower limb melanoma and 47.3 years for upper limb melanoma; $p<0.001$).

Table 2 presents the pooled odds ratios (pOR) for the association of melanoma with sunburn for all women. The relative risks of cutaneous melanoma increased monotonically with increasing number of severe sunburns ($p_{trend}<0.001$), severe sunburns in youth ($p_{trend}<0.001$) and painful sunburns ($p_{trend}<0.001$). Both severe sunburns and severe sunburns in youth were strongly and statistically significantly associated with an increased risk of melanoma, with significant trends for increasing numbers of sunburns. Six or more painful sunburns also were associated with a significantly increased risk, again with a significant trend ($p<0.001$). The presence of solar keratoses was associated with a pOR of 4.31 (95% CI 2.34–8.04).

The site-specific associations with the various measures of self-reported sunburns were similar. The associations generally appeared strongest for melanomas of the lower limbs (pORs 1.36, 1.92 and 1.33 respectively for ever vs never severe sunburn, ever vs never severe sunburn in youth and ever vs never painful sunburn) (Table 3), however none of the tests for heterogeneity across anatomic sites were statistically significant. A statistically-significant increased risk of melanoma of the head and neck was associated with the presence of solar keratoses (pOR 4.91, 95% CI 2.10–11.46); there were insufficient data to analyze the risk of melanoma at other body sites associated with the presence of solar keratoses.

We conducted further analyses stratified by histologic subtype (LMM only, SSM/NM/NOS), nevus count (high, low) hair colour (red hair, other hair colour) and age (<50, ≥ 50). Associations between sunburns and melanoma risk were observed for women with both high

and low nevus counts, and there was no evidence that the magnitude of the associations differed across these strata (data not presented). No consistent differences were noted for melanomas of different histologic subtypes (Table 4). Increasing numbers of sunburns were not associated with melanoma in women with red hair, whilst strong associations were seen for women without red hair (significant trends were observed for increasing numbers of 'painful', 'severe' and 'severe' sunburns in youth ($p<0.001$; Table 5); tests for heterogeneity across hair colour stratum were significant for 'severe' sunburns ($p=0.002$) and 'severe' sunburn in youth ($p=0.03$) but not 'painful' sunburns ($p=0.41$). Stratifying by age (<50, ≥ 50 years) suggested that the association between sunburns and melanoma was strongest in younger women (<50 years); these differences were statistically significant for both 'painful' sunburns ($p=0.049$) and 'severe' sunburns in youth ($p=0.02$). In women ≥ 50 years a significant trend was observed for 'severe' sunburns only and not 'painful' sunburns or 'severe' sunburns in youth (Table 6). The analyses stratified by skin type were uninformative; no consistent differences were observed for the various measures of self-reported sunburns across different skin-type stratifications (data not shown).

We observed heterogeneity for the 'painful' sunburn variable (ever/never) only for all women and individual strata for some sub-groups. This heterogeneity was due to lower estimates from the Danish study; [40] no heterogeneity was evident when this study was excluded from the analyses.

DISCUSSION

The results of our pooled analyses have confirmed a 2–3 fold higher risk of melanoma at all body sites associated with a high number of self-reported sunburns, but we found no statistically significant evidence that the magnitude of the risks varied by site of melanoma. While not statistically different from other sites, the associations appeared to be strongest for melanoma of the lower limbs. Somewhat higher risks were also noted in younger women, and in women without red hair. We found no evidence that the sunburn-melanoma association was modified by nevus count or differed by histologic sub-type.

The weak associations between sunburns and melanoma among women with red hair are noteworthy, and several explanations are possible. Women with red hair who are sun-sensitive may systematically avoid multiple sunburns, and this may explain the weaker association between sunburns and melanoma this group of women compared to women without red hair. A similar phenomenon has been previously reported whereby men and women self-select for outdoor work based upon their sun-sensitivity and phenotype.[43] We cannot exclude chance as an explanation however, since there were relatively few women with red hair contributing to these analyses.

Our results generally agree with the published literature including the recent meta-analysis of 24 studies that also found no significant heterogeneity in the association between sunburns and melanomas of different body sites.[26] Only three studies included in the current pooled analyses [32, 35, 37] were included in the meta-analyses. Similarly, the pooled analyses by Chang et al.[25] did not report significant differences in the association between sunburns (both in childhood and adulthood) and melanoma of different body sites, although they did not test the significance of the differences. While that previous analysis included data from nine of the studies reported here, it included data from men as well as women, and was designed to address different research questions.

Only two studies included in our pooled analyses collected information on solar keratoses. There were insufficient data to examine the relationship between solar keratoses and melanoma at body sites other than the head and neck, where a strong association was noted.

Reported results on the association between solar keratoses and risk of melanoma are scant, [2, 10, 25] and yet this is arguably the most reliable marker of high cumulative sun exposure. Rigorous investigation into the association between solar keratoses and melanoma should be pursued, along with other markers of high accumulated sun exposure such as photoageing.[44]

Do these findings "falsify" the divergent pathway hypothesis for melanoma? Not necessarily. Sunburns may be an insufficiently specific measure of acute sun exposure alone to test this hypothesis, or it may be that sunburn is a component of both paths to melanoma. Our observation that sunburn was associated with melanomas at all body sites, and that the magnitude of association did not differ between melanomas of the trunk and head, would support the latter. Recent genome-wide association studies have identified a number of common genetic variants associated with pigmentation and nevus development that relate to melanoma risk in Caucasian populations at all latitudes.[45] It is not yet known whether these variants are associated with different site distributions of melanoma or whether they modify the risks associated with nevi or levels of personal sun exposure. Our study did not entail the analysis of genetic data, but these possibilities deserve further exploration.

Strengths of our study include the large number of cases and controls made possible by pooling data from 11 individual case–control studies. The analyses relied on individual data combined into a single dataset following a rigorous data cleaning and harmonization protocol, as distinct from meta-analyses, with an enhanced ability to control for confounding in individual studies.[29] Pooling these data increased our statistical power to examine sunburn exposure in relation to melanoma, and allowed sub-group analyses to examine the effects by age, histologic subtype, nevus density and body-site distribution. Additionally, the individual study data were collected before there was a widespread awareness of the causes of melanoma, and thus recall bias is likely to be considerably less of a concern than in studies conducted more recently.

Several limitations of these analyses must be acknowledged. First, there was substantial heterogeneity in defining and collecting information on sunburns among the studies. Individual studies collected data on sunburn with different degrees of detail on severity, ranging from ever severe sunburn (often in countries with high sunburn prevalence in general) to exact number of peeling and blistering episodes (in countries with low sunburn prevalence). There was variable interpretation and/or reporting of such study terms as 'painful' and 'severe' among studies. In addition, most of the primary study data used in these analyses were obtained during the 1980s. Sunlamps used during that period differed markedly from those in use today, which must be considered when interpreting these results. A second limitation was limited power in our analyses of solar keratoses and our stratified analyses by hair colour and histological subtype (LMMs). Third, reliance on recalled sunburns may have resulted in misclassification since the reproducibility of such data is modest.[19] However, such misclassification is likely to be non-differential by anatomical site of melanoma. Finally, our pooled analyses were restricted to women because the original collaborative pooling project was established to examine factors associated with female sex steroids. It is well established that the anatomical site distribution of melanoma differs for men and women [46] and thus it would be prudent to examine the relationship between UV biomarkers and site-specific melanoma in relation to the divergent pathway hypothesis in men.

In summary, we found sunburn to be positively associated with melanoma at all body sites, but found no statistical support for site-specific differences in sunburn-melanoma associations. There are insufficient data to draw conclusions regarding site-specific differences in risk with solar keratoses, which merits further research. Case-control studies, the mainstay for melanoma research during the past three decades, are limited by their

reliance on recall of past sun exposure. A prospective study that collected salient phenotypic data at baseline and gathered sun exposure information at periodic intervals over time might assist in delineating the sequence of exposures that result in melanoma at different anatomic sites, although such a study would present formidable logistical challenges.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the eleven studies included in the pooled analyses of sunburn and melanoma in women.

Study	Diagnosis Years	Age range	Geographic location	Number of:		Case Sources (Response Rate)	Histology	Control Sources (Response Rate)	Exposure Measurement			
				Cases[e]	Controls[e]				'Painful' sunburns	'Severe' sunburns	'Severe' sunburns in youth	Solar Keratoses
Hospital/clinic-based												
Bataille et al. (1996)	1989–1993	16–75	North East Thames region, UK	255	253	Hospital pathology reporting (61%)	155 SSM[a] 36 NM[b] 16 LMM[c] 48 Other[d]	Hospital outpatients, general practice surgeries (95%)		Yes/No number	Yes/No number	Yes/No number
Elwood et al (1990)	1984–1986	20–79	Midlands, England	139	139	Pathology Laboratories (91%)	127 SSM[a] 12 NM[b]	Hospital inpatients and outpatients (78%)		Yes/No number	Yes/No number	
Swerdlow et al. (1986)	1979–1984	15–84	Scotland	90	109	Dermatology departments; Plastic surgery unit	48 SSM[a] 23 NM[b] 9 LMM[c] 10 Other[d]	Hospital inpatients and outpatients		Yes/No		
Population-based												
Gallagher et al. (1985)	1979–1981	20–79	Western Canada	215	251	Cancer Registries (88%)	159 SSM[a] 40 NM[b] 16 Other[d]	Medical plan subscribers (59%)	Yes/No number	Yes/No number	Yes/No number	
Green et al. (1985)	1979–1980	15–81	Queensland, Australia	114	114	Pathology Laboratories (97%)	79 SSM[a] 9 NM[b] 23 LMM[c] 3 Other[d]	State electoral roll (92%)		Yes/No number	Yes/No number	Yes/No number
Holly et al. (1995)	1981–1986	25–59	San Francisco, California, USA	452	935	Cancer Registry (79%)	355 SSM[a] 61 NM[b] 13 LMM[c] 23 Other[d]	Random digit dial (77%)	Yes/No number	Yes/No number	Yes/No number	
Holman et al. (1984)	1980–1981	10–79	Western Australia	278	278	Pathology Laboratories (90%)	168 SSM[a] 14 NM[b] 37 LMM[c] 59 Other[d]	Electoral roll, student roll (participants <18 years of age) (69%)	Yes/No number	Yes/No number	Yes/No number	
Langholz et al. (2000)	1978–1983	<65	Los Angeles, USA	341	366	Cancer Registry (79%)	251 SSM[a] 56 NM[b] 2 LMM[c]	Neighborhood controls		Yes/No number		

Study	Diagnosis Years	Age range	Geographic location	Number of:		Case Sources (Response Rate)	Histology	Control Sources (Response Rate)	Exposure Measurement			
				Cases[e]	Controls[e]				'Painful' sunburns	'Severe' sunburns	'Severe' sunburns in youth	Solar Keratoses
							32 Other[d]					
Østerlind et al. (1988)	1982–1985	20–79	East Denmark	211	362	Cancer Registry (92%)	143 SSM[a] 41 NM[b] 27 Other[d]	Population Register (82%)	Yes/No number	Yes/No number	Yes/No number	
Smith et al. (1998)	1987–1989	≥ 18	Connecticut, USA	307	231	CT Tumor Registry (76%)	195 SSM[a] 23 NM[b] 42 LMM[c] 23 Other[d]	Random digit dial (70%)		Yes/No number	Yes/No	
Zanetti et al. (1990)	1984–1987	19–92	Turin, Italy	182	203	Cancer Registry (89%)	96 SSM[a] 20 NM[b] 20 LMM[c] 46 Other[d]	National health service register (51%)		Yes/No number	Yes/No	

[a] SSM - superficial spreading melanoma,

[b] NM – nodular melanoma,

[c] LMM - lentigo maligna melanoma

[d] includes unclassified or other melanoma

[e] number of cases and controls with sunburn data

Table 2

Adjusted[a] pooled odds ratios (95% confidence intervals) for melanoma in women in relation to sunburn and solar keratoses

Exposure Measure		All Women[b]		
	Number of Studies	Cases	Controls	p OR (95% CI)
'Painful' sunburn				
Never		325	575	1.00
Ever	4	831	1251	1.39 (0.94–2.06)*
Never				1.00
1–5	4	604	365	1.12 (0.87–1.43)
6–25	4	478	310	1.66 (1.24–2.24)
26+	3	116	122	3.22 (2.04–5.09)
				Trend $p<0.001$
'Severe' sunburn				
Never		626	767	1.00
Ever	11	1949	2474	1.29 (1.09–1.52)
Never				1.00
1–5	10	848	1096	1.14 (0.94–1.38)
6–25	8	522	678	1.70 (1.20–2.40)
26+	5	353	315	2.10 (1.30–3.38)
				Trend $p<0.001$
'Severe' sunburn in youth				
Never		1428	1845	1.00
Ever	9	639	849	1.60 (1.33–1.91)
Never				1.00
1–5	7	332	519	1.34 (1.07–1.67)
6–15	4	155	214	1.85 (1.35–2.52)
16+	3	82	83	2.43 (1.61–3.65)
				Trend $p<0.001$
Solar keratoses				
None		104	153	1.00
Any	2	28	87	4.34 (2.34–8.04)

*Significant heterogeneity, random effects model used (see text).

[a]Adjusted for age, sunlamp use and history of sunbathing

[b]Numbers may not sum to total because of missing data

Table 3

Adjusted[a] pooled odds ratios (95% confidence intervals) for melanoma in women in relation to sunburn, stratified by anatomical site of melanoma

	Head & Neck[b]			Trunk[b]			Lower Limbs[b]			Upper Limbs[b]		
	Cases/controls	**No. of studies**	**p OR (95% CI)**	**Cases/controls**	**No. of studies**	**p OR (95% CI)**	**Cases/controls**	**No. of studies**	**p OR (95% CI)**	**Cases/controls**	**No. of studies**	**p OR (95% CI)**
'Painful' sunburn												
Never	36/575		1.00	84/575		1.00	139/575		1.00	63/575		1.00
Ever	94/1251	4	1.33 (0.80–2.20)	248/1251	4	1.36 (1.00–1.87)	295/1251	4	1.33 (1.00–1.75)	188/1251	4	1.42 (0.66–3.04)*
Never			1.00						1.00			
1–5	39/477	3	1.23 (0.67–2.29)	117/604	4	1.32 (0.93–1.86)	131/604	4	1.11 (0.81–1.52)		4	1.28 (0.84–1.94)
6–25	29/470	3	2.83(0.48–16.56)*	86/470	3	1.28 (0.84–1.96)	106/478	4	1.70 (1.13–2.54)		2	1.99 (1.11–3.55)
26+	100/12	1	-	36/109	2	2.28 (1.25–4.15)	40/116	3	3.50 (1.90–6.46)		1	-
			Trend p<0.001			Trend p=0.001			Trend p<0.001			Trend p<0.001
'Severe' sunburn												
Never	81/555		1.00	157/692		1.00	235/767		1.00	98/679		1.00
Ever	158/1182	8	1.02 (0.73–1.44)	591/2440	10	1.25 (0.97–1.62)	673/2474	11	1.36 (1.07–1.72)	312/2087	9	1.21 (0.88–1.66)
Never			1.00			1.00			1.00			1.00
1–5	91/535	5	0.90 (0.61–1.32)	281/1048	9	1.26 (0.96–1.66)	267/1096	10	1.19 (0.91–1.55)	150/1045	9	1.17 (0.84–1.63)
6–25	24/127	2	1.25 (0.50–3.14)	155/678	8	1.59 (1.02–2.49)	183/677	8	1.86 (1.22–2.84)	99/198	4	1.99 (1.12–3.53)
26+	13/29	2	2.41 (0.95–6.11)	100/302	4	1.57 (0.84–2.93)	106/306	4	1.94 (1.03–3.68)	25/100	1	-
			Trend p<0.001			Trend p<0.001			Trend p<0.001			Trend p<0.001
'Severe' sunburn in youth												
Never	116/942		1.00	375/1470		1.00	493/1632		1.00	177/1257		1.00
Ever	57/761	4	1.33 (0.83–2.13)	190/826	6	1.25 (0.96–1.63)	209/809	8	1.92 (1.48–2. 50)	139/786	5	1.54 (0.98–2.40)
Never			1.00			1.00			1.00			1.00
1–5	25/442	3	1.01 (0.54–1.89)	96/472	4	1.11 (0.80–1.54)	114/486	6	1.73 (1.26–2.38)	58/439	3	1.52 (0.64–3.65)
6+	24/260	2	3.36 (1.53–7.38)	74/274	3	1.60 (1.08–2.40)	64/278	3	2.24 (1.41–3.56)	55/253	1	-
			Trend p<0.001			Trend p<0.001			Trend p<0.001			Trend p<0.001
Solar keratoses												
None	13/100		1.0	23/53			19/100			13/100		
Any	19/28	2	4.91 (2.11–11.46)	25/14	1	-	21/14	1	-	15/14	1	-

* Significant heterogeneity, random effects model used (see text).

[a] Adjusted for age, sunlamp use and history of sunbathing

[b] Numbers may not sum to total because of missing data

Table 4

Adjusted[a] pooled odds ratios (95% confidence intervals) for melanoma in women in relation to sunburn, stratified by histologic subtype of melanoma

	SSM, NM, NOS[b]			LMM[b]		
	Cases/controls	**No. of studies**	**p OR (95% CI)**	**Cases/controls**	**No. of studies**	**p OR (95% CI)**
'Painful' sunburn						
Never	310/575		1.00	10/264		1.00
Ever	782/1251	4	1.36 (0.93–2.00)*	40/949	2	1.86 (0.81–4.27)
Never			1.00			1.00
1–5	340/604	4	1.16 (0.93–1.45)	17/98	1	-
6–25	295/478	4	1.61 (1.22–2.13)	11/432	2	1.19 (0.38–3.70)
26+	117/116	3	2.83 (1.88–4.25)	19/90	0	-
			Trend $p<0.001$			
'Severe' sunburn						
Never	467/698		1.00	48/284		1.00
Ever	1758/2404	10	1.42 (1.18–1.69)	70/592	4	0.69 (0.43–1.17)
Never			1.00			1.00
1–5	729/1048	9	1.27 (1.05–1.54)	50/451	4	0.67 (0.41–1.09)
6–25	494/678	8	1.75 (1.29–2.37)	12/89	1	-
26+	346/315	5	2.08 (1.38–3.13)			
			Trend $p<0.001$			
'Severe' sunburn in youth						
Never	1150/1711		1.00	38/515		1.00
Ever	594/844	8	1.61 (1.35–1.93)	17/650	2	1.76 (0.76–4.12)
Never			1.00			
1–5	311/514	6	1.40 (1.13–1.73)	5/375	1	-
6+	234/299	5	1.95 (1.49–2.55)	5/253	1	-
			Trend $p<0.001$			
Solar keratoses						
None	91/153		1.00	8/100		
Any	69/28	2	4.09 (2.27–7.36)	15/14	1	-

*Significant heterogeneity, random effects model used (see text).

[a] Adjusted for age, sunlamp use and history of sunbathing

[b] Numbers may not sum to total because of missing data

Table 5

Adjusted[a] pooled odds ratios (95% confidence intervals) for melanoma in women in relation to sunburn, stratified by hair colour (red vs. other)

	Red hair[b]			Other hair colour[b]		
	Cases/controls	**No. of studies**	**p OR (95% CI)**	**Cases/controls**	**No. of studies**	**p OR (95% CI)**
'Painful' sunburn						
Never	60/78		1.00	263/497		1.00
Ever	136/122	4	1.28 (0.76–2.14)	693/1125	4	1.44 (0.85–2.46)*
Never			1.00			
1–5	57/57	3	1.20 (0.69–2.12)	296/536	4	1.24 (0.69–2.24)*
6–25	13/9	2	1.99 (0.77–5.20)	267/446	4	1.54 (1.16–2.06)
26+		0	-	105/103	3	2.90 (1.89–4.44)
			Trend p=0.43			Trend p<0.001
'Severe' sunburn						
Never	138/93		1.00	483/668		1.00
Ever	197/158	6	0.85 (0.57–1.26)	1591/2198	11	1.43 (1.19–1.72)
Never			1.00			1.00
1–5	142/108	5	0.84 (0.55–1.30)	670/956	10	1.26 (1.03–1.54)
6–25	34/23	3	1.29 (0.59–2.85)	436/620	9	1.81 (1.30–2.51)
26+		0	-	297/281	5	2.20 (1.41–3.44)
			Trend p=0.95			Trend p<0.001
'Severe' sunburn in youth						
Never	254/204		1.00	1135/1608		1.00
Ever	110/81	6	1.16 (0.73–1.84)	520/766	9	1.57 (1.29–1.90)
Never			1.00			1.00
1–5	55/35	4	1.33 (0.71–2.49)	267/479	7	1.28 (1.02–1.60)
6+	25/22	1	-	205/266	5	1.96 (1.47–2.60)
			Trend p=0.78			Trend p<0.001
Solar keratoses						
None		0		95/144		1.00
Any		0		75/28	2	3.68(1.13–12.00)*

* Significant heterogeneity, random effects model used (see text).

[a] Adjusted for sunlamp use and history of sunbathing

[b] Numbers may not sum to total because of missing data

Table 6

Adjusted[a] pooled odds ratios (95% confidence intervals) for melanoma in women in relation to sunburn, stratified by age at diagnosis of melanoma (<50 years, ≥50 years)

	Women <50 years			Women ≥ 50 years		
	Cases/controls	**No. of studies**	**p OR (95% CI)**	**Cases/controls**	**No. of studies**	**p OR (95% CI)**
'Painful' sunburn						
Never	154/315		1.00	171/260		1.00
Ever	561/861	4	1.58(0.91–2.73)*	270/390	4	1.17 (0.87–1.57)
Never			1.00			1.00
1–5	213/377	4	1.32 (0.97–1.79)	152/227	4	1.06 (0.76–1.47)
6–25	242/371	4	2.01 (1.41–2.86)	67/105	3	1.17 (0.72–1.90)
26+	95/81	2	4.78 (2.73–8.35)	21/27	2	1.55 (0.69–3.48)
			Trend p<0.001			Trend p=0.14
'Severe' sunburn						
Never	237/334		1.00	389/433		1.00
Ever	1179/1608	11	1.28 (0.99–1.65)	770/866	11	1.31 (0.92–1.64)
Never			1.00			1.00
1–5	454/668	10		394/428	10	1.16 (0.90–1.48)
6–25	368/502	8	1.21 (0.92–1.58)	157/178	8	1.24 (0.81–1.90)
26+	252/219	5	2.06 (1.11–3.84)	94/96	4	1.34 (0.70–2.58)
			Trend p<0.001			Trend p<0.001
'Severe' sunburn in youth						
Never	583/900		1.00	582/648		1.00
Ever	469/633	8	1.91 (1.52–2.40)	155/208	6	1.14 (0.83–1.57)
Never			1.00			1.00
1–5	240/384	7	1.68 (1.29–2.19)	84/125	4	1.03 (0.70–1.53)
6+	200/232	5	2.66 (1.90–3.74)	35/66	3	0.86 (0.50–1.48)
			Trend p<0.001			Trend p=0.56
Solar keratoses						
None	45/63		1.00	39/52		1.00
Any	18/2	1	-	66/24	2	3.47 (1.69–7.12)

* Significant heterogeneity, random effects model used (see text).

[a] Adjusted for age, sunlamp use and history of sunbathing

[b] Numbers may not sum to total because of missing data