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At What Age Do Sunburn Episodes Play a Crucial Role for the Development of Malignant Melanoma

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The age relationship between sunburns and malignant melanoma was investigated in a population-based, matched, case–control study from the South Swedish Health Care Region (the highest risk area for melanoma in Sweden). Between 1988 and 1990, a total of 400 patients with a first diagnosis of malignant melanoma and 640 healthy controls aged 15–75 years answered a comprehensive questionnaire including questions regarding ultraviolet radiation exposure. In addition, a literature review was performed. The average number of episodes of sunburn per year was significantly associated with malignant melanoma (relative risk, RR = 1.9 for ≥ three episodes per year versus never). Outdoor employment during the summer was associated with a decreased risk for the development of malignant melanoma (RR = 0.8). Data from case–control studies and migration studies concerning age relationship between sunburns and melanoma are inconsistent. From our own data, we did not find a higher risk of melanoma developed in individuals who had experienced severe sunburns in childhood. Instead, a significantly increased risk was associated with sunburns after age 19 years, RR = 2.2 for a history of more than five times versus never. Even if the hypothesis is biologically plausible, that episodes of sunburn early in life are associated with a higher risk of melanoma, so far epidemiological evidence is scarce. There is a need for better prospective epidemiological studies addressing this issue.

Key words: melanoma, sunburn, ultraviolet radiation, age, review
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INTRODUCTION

SOLAR RADIATION is believed to cause cutaneous malignant melanoma [1]. However, the association between sunlight and malignant melanoma is complex. Several studies have established a history of sunburns as an important risk factor for the development of malignant melanoma [2–5]. This relationship is particularly interesting since it is an obvious target for prevention. Sunburns experienced in childhood have been suggested to be of more importance than episodes in later life [4, 6, 7]. However, support for this hypothesis from actual epidemiological studies is scarce, and, when reviewing the literature in relation to a recently completed population-based, matched, case–control study in southern Sweden, we found further objectives for again discussing the subject.

MATERIAL AND METHODS

The study identified 509 patients (females: 53.4%, males: 46.6%), aged 15–75 years, in the South Swedish Health Care Region (around the 56th latitude, the highest incidence region of malignant melanoma in Sweden [8]) with a first histopathological diagnosis of malignant melanoma between 1 July 1988 and 30 June 1990, according to the population based Regional Tumour Registry. There are approximately 1.5 million residents in this region. The population is ethnically homogenous. The background level of ultraviolet (UV) radiation is low. Because of the Swedish system of double reporting to the Cancer Registry, the risk of under-registration is small, less than 3% [9]. Information from the Tumour Registry on the presentation site of the tumour was used.

The permission of the physician responsible for the treatment of the patient was sought. In 22 cases, the physicians did not respond, and we did not contact the patients. Of the remaining patients (487), 33 were considered ineligible by the treating physician (21 for psychological reasons, 4 had not been fully informed about their diagnosis, 4 had metastases, 2 had died, 1 had migrated and 1 did not wish to participate).

The remaining 454 patients (211 males and 243 females) were mailed a comprehensive questionnaire including different epidemiological variables (constitutional factors, family history, education level, medical history, medicaments, UV radiation exposure, smoking habits, alcohol and oral contraceptives or other hormonal treatment) within 2 months following diagnosis. 403 patients (88.8%, males 92.9%, females 85.2%) responsed to the questionnaire. 3 of these were found to have no matched control and were thus excluded.

During the same period of time, 913 healthy controls (427 males and 486 females), randomly selected from the National Population Registry of residents of the South Swedish Health Care Region, were mailed the same questionnaire. 707 controls (77.4%) responded. Two controls were matched to each patient by sex, age (within a year) and parish. 67 of these were found to have no matched case and were thus excluded.

The following information was collected with regard to UV radiation: sunbathing habits; vacations spent in sunny places (places visited for sunbathing and places visited for skiing); painful (severe) sunburns (number and age); episodes of blistering sunburn (sunblisters); formation of ulcer due to excessive

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sun exposure (sun ulcer); exposure to sunbeds/sunlamps; outdoor employment; duration of each residential period in a Mediterranean or similar located country during the 10-year period before interview. For cases and controls, the questions regarding sunburns were, "When you sunbathe do you get sunburned? If yes, how many times per year?". The number of episodes per year was categorised into three levels: never, one to two episodes and ≥ three episodes. The history of "severe" sunburns was based on the questions: "Have you ever been sunburned causing severe erythema and pain for a few days? If yes, how many times?", asked in regard to childhood (< age 15 years), adolescence (age 15–19 years) and adulthood (> age 19 years). The number of episodes of sunburns at age under 15 years, 15–19 years and over 19 years, respectively was categorised into three levels: never, one to five times and more than five times.

Estimates of the relative risk (RR) were computed, based on matched pairs, using both univariate and multivariate methods. In the multivariate analyses, conditional logistic regression was used. A P-value of less than 0.05 was considered significant and 95% confidence intervals (CI) were used. For correlations, Spearman's rank correlation coefficient was used (r_S). The statistical program STATA was utilised (Computing Resource Center, 1640 Fifth Street, Santa Monica, California, U.S.A.). Occasional missing values for some variables caused a slight variation in the number of cases and controls used for each analysis.

The study was approved by the Ethical Committee of the Medical Faculty of Lund University. An informed consent was sought from the treating physician, the patient and the healthy control.

RESULTS

Analyses were performed on 400 cases (females, 51.2%; males, 48.8%) with a first histopathological diagnosis of malignant melanoma, according to the Tumour Registry, and 640 matched healthy controls (females, 51.1%; males, 48.9%) who answered a comprehensive questionnaire. In Table 1 the distributions of constitutional factors are given.

No significantly elevated risk for melanoma development was found for persons who had lived in a Mediterranean or similar geographically located country during the 10-year period before interview, crude RR = 1.5 (95% CI 0.8–2.7). Neither did duration (in months) of each residential period show an association with melanoma. No data on residential periods during other specific time periods in life was recorded.

Table 1. *Constitutional characteristics for cases and controls in a matched case-control study of malignant melanoma in southern Sweden between* 1988 *and* 1990

Factor	Category	Cases (%)	Controls (%)
Number of raised naevi	None	332 (83)	576 (90)
	1–3	59 (15)	60 (9)
	>3	9 (2)	4 (1)
Freckling	No	229 (58)	431 (67)
	Yes	168 (42)	209 (33)
Hair colour	Dark brown/black	70 (18)	107 (17)
	Light brown	158 (40)	240 (38)
	Blond/fair	32 (8)	29 (5)
	Red	18 (5)	15 (2)
	Other	120 (30)	240 (38)
Eye colour	Brown	48 (12)	66 (10)
	Blue	215 (54)	307 (49)
	Grey/green	33 (8)	52 (8)
	Other	99 (25)	207 (33)

Outdoor employment during the summer was associated with a decreased risk for the development of malignant melanoma, crude RR = 0.8 (95% CI 0.6–1.0). Adjustments for constitutional factors, history of sunburns, family history of malignant melanoma and use of sunscreens gave the same estimated risk.

Sunbathing habits were also evaluated. The frequency of sunbathing or the duration of the practice of sunbathing was not related to melanoma risk (data not shown).

Vacations spent in sunny places abroad for sunbathing may, compared with normal every day sun exposure in Sweden, mean acute intense sun exposure. When adjusting for constitutional factors (raised naevi, hair colour) and history of sunburns, sunbathing vacations abroad did not show a significant association with malignant melanoma, RR = 1.2 (95% CI 0.8–1.8) for one or more vacations per year versus none. The same was true for vacational skiing.

Episodes of sunblisters or formation of ulcer due to excessive sun exposure were not significantly related to melanoma risk, crude RR = 1.2 (95% CI 0.9–1.6) and 1.2 (95% CI 0.8–1.9), respectively. However, there was a significant association between malignant melanoma and the average number of episodes of sunburn per year, crude RR = 1.5 (95% CI 1.2–2.2) for 1–2 episodes per year and crude RR = 1.9 (95% CI 1.0–3.4) for ≥3 episodes per year. Adjustments for constitutional factors, family history of malignant melanoma and the use of sunscreens gave the same estimated risks.

A significant association between the development of malignant melanoma and the history of severe sunburns after age 19 was seen, RR = 2.2 (95% CI 1.1–4.1) for a history of more than five times (Table 2). A dose–response relationship was evident. After adjustments for raised naevi, red hair colour and blond/fair hair colour, no significant relationship was found with multiple painful sunburns up to age 19 years.

After the exclusion of individuals who have been severely sunburned before age 15 the association between malignant melanoma and sunburns after age 19 was stronger, RR = 6.8 (95% CI 1.6–29) for a history of more than five sunburn episodes (Table 3).

Table 4 shows a model excluding cases and controls who had sunburned more than five times after age 19. Due to collinearity problems, it was not possible to also exclude those who had sunburned one to five times after age 19. As can be seen, sunburns during childhood was still not a significant risk factor for the development of malignant melanoma.

Analyses adjusted for other host factors (e.g. freckles), family history of malignant melanoma and/or use of sunscreens gave essentially the same estimated risks (data not shown).

It was not possible to perform analyses restricted to cases and controls who had only sunburned during either childhood, adolescence or adulthood, since the number of these individuals were too small.

Most of those who suffered painful sunburns in childhood also sunburned in later life. Table 5 shows the correlation between history of sunburns in childhood and in adulthood, r_S = 0.38 for cases and r_S = 0.52 for controls, respectively. Sunburns in childhood and in adolescence as well as sunburns in adolescence and adulthood were also highly correlated (data not shown).

Table 2. Relative risk of malignant melanoma in a matched case–control study of malignant melanoma in southern Sweden between 1988 *and* 1990, *according to painful sunburn in different age groups*

Factor	Category	Cases	Controls	RR† (95% CI)	RR (95% CI)	Test for trend (*P*-value)
Number of sunburns before age 15 years	Never	143	259	1.0‡	1.0‡	
	1–5 times	149	224	1.4 (1.0–1.9)	1.0 (0.6–1.5)	
	>5 times	47	65	1.6 (1.0–2.6)	1.0 (0.5–2.1)	>0.05
Number of sunburns from age 15–19 years	Never	108	209	1.0‡	1.0‡	
	1–5 times	213	312	1.4 (1.0–1.9)	1.3 (0.8–2.0)	
	> 5 times	46	65	1.6 (1.0–2.5)	0.9 (0.4–2.1)	>0.05
Number of sunrburns after age 19 years	Never	123	254	1.0‡	1.0‡	
	1–5 times	205	296	1.5 (1.1–2.1)	1.6 (1.1–2.4)	
	>5 times	48	58	1.9 (1.2–3.1)	2.2 (1.1–4.1)	0.004

*Crude relative risk. †Adjusted for raised naevi, red hair colour and blond/fair hair colour. ‡Reference category.

Table 3. Relative risk of malignant melanoma in southern Sweden between 1988 *and* 1990, *according to painful sunburn in different age groups, after exclusion of all persons who had sunburned before age* 15 *years*

Factor	Category	Cases	Controls	RR† (95% CI)	RR (95% CI)	Test for trend (*P*-value)
Number of sunburns from age 15–19 years	Never	90	185	1.0‡	1.0‡	
	1–5 times	80	111	1.3 (0.8–2.1)	1.0 (0.6–1.8)	
	>5 times	8	65	1.2 (0.2–6.6)	0.3 (0.04–3.0)	>0.05
Number of sunburns after age 19 years	Never	81	188	1.0‡	1.0‡	
	1–5 times	87	129	1.2 (0.7–2.1)	1.5 (0.8–2.9)	
	> 5 times	18	13	2.8 (1.0–7.8)	6.8 (1.6–29)	>0.001

*Crude relative risk. †Adjusted for raised naevi, red hair colour and blond/fair hair colour. ‡Reference category.

Table 4. Relative risk of malignant melanoma in southern Sweden between 1988 *and* 1990, *according to painful sunburn in different age groups, excluding individuals who had sunburned more than five times after age* 19 *years*

Factor	Category	Cases	Controls	RR† (95% CI)	RR (95% CI)	Test for trend (*P*-value)
Number of sunburns before age 15 years	Never	130	251	1.0‡	1.0‡	
	1–5 times	143	210	1.6 (1.1–2.3)	1.2 (0.8–1.9)	
	>5 times	23	34	1.8 (0.9–3.5)	1.1 (0.5–2.7)	>0.05
Number of sunburns from age 15–19 years	Never	101	204	1.0‡	1.0‡	
	1–5 times	202	259	1.6 (1.1–2.2)	1.6 (1.0–2.4)	
	> 5 times	18	31	1.5 (0.8–3.0)	1.0 (0.4–2.7)	>0.05

*Crude relative risk. †Adjusted for raised naevi, red hair colour and blond/fair hair colour. ‡Reference category.

REVIEW OF LITERATURE

In general, the age relationship between development of malignant melanoma and sunburn episodes has been investigated by two methods. First, retrospectively, by case–control studies comparing the history of sunburns in different ages (Table 6). Secondly, indirectly by migration studies comparing domicile close and away from the equator during different time periods in an individuals life (Table 7).

Some interesting case-control studies support the idea of a "critical period" for the relationship between sunburn episodes and malignant melanoma. Lew and associates found that painful and blistering sunburns during either childhood or adolescence were associated with increased risk [6]. In a recent Italian study, elevated risk was associated with history of sunburns in childhood, while the risk increase from history of lifetime severe sunburns was not significant when adjusting for type of skin reaction to sun exposure and history of sunburns in childhood [7]. Østerlind and colleagues have pointed out that the critical period is before age 15 [4]. In the Danish study, a relationship was also seen between melanoma and the number of sunburns in early adulthood or in the 10 years prior to diagnosis [4]. However, this association was not significant after the exclusion of those who were sunburned before age 15. Weinstock and collagues found a significantly increased risk with sunburns

Table 5. Correlation between history of sunburns in childhood and in adulthood in a matched case–control study of malignant melanoma in southern Sweden before 1988 *and* 1990

		After age 19 years			
	Number of sunburns*	Never (*n*)	1–5 times (*n*)	>5 times (*n*)	Total (*n*)
Cases before age 15 years	Never	69	61	13	143
	1–5 times	35	103	6	144
	>5 times	7	15	24	46
	Total	111	179	43	333
Controls before age 15 years	Never (*n*)	170	79	8	257
	1–5 times (*n*)	60	139	14	213
	>5 times (*n*)	6	28	31	65
	Total (*n*)	236	246	53	535

Cases $r_S = 0.38$, *controls* $r_S = 0.52$.

between age 15 and 20 [15]. In 1978, Paffenberger and associates reported an elevated risk of malignant melanoma among the alumni of Harvard University and University of Pennsylvania who had had outdoor employment before college [10].

Alternatively, studies in Australia [13] and Italy [14] have failed to show an age relationship between sunburns and melanoma. Furthermore, in the Western Canada Melanoma Study [11], episodes of severe sunburns in childhood, and in a study from Nottingham, U.K. [12], a history of sunburns at all ages were not found to be significant risk factors, but in both studies a tendency to burn easily and tan poorly throughout life was a significant risk factor. In a more recent English study, neither an association seen with a history of sunburn at ages 8–12 years nor an association seen with tendency to sunburn easily throughout life were significant, when adjusting for other factors [16].

Many studies have not specifically differentiated between exposure in childhood, adolescence and adulthood. A significant association between multiple sunburns and melanoma with an evident dose–response relationship was demonstrated by Green and associates in 1985 [3]. Virtually all burns reported occurred before age 40 years, and it was stated that the effect was similar for burns in each of the first three decades. MacKie and colleagues found that severe sunburn in the 5-year period prior to diagnosis was a risk factor for melanoma development [2]. No lifetime data concerning sunburns were available in this study. In a later study by MacKie and associates, a history of severe sunburn at any time in life was shown to be a strong risk factor [5]. Furthermore, in a subsequent analysis, they found that the age at which severe sunburn occurred was not significant.

Another way of elucidating the importance of different environmental factors is by performing migration studies. Studies from Australia [21], Israel [17, 18] and New Zealand [22] have all consistently shown a higher rate of malignant melanoma in European immigrants to these sunnier climates than in people of the same age and ethnic background living in Europe. In addition, the risks have been demonstrated to be lower among migrants from less sunny places compared with the native-born of these sunny climates. However, in the data from New Zealand, European immigrants from other places than than the British Isles had mortality rates generally similar to their countries of origin [22].

In Israel, the incidence of melanoma among those European born increased with increasing duration of residence in Israel [17, 18]. Green and associates also showed, in relation to age on arrival, a possible relative elevated risk among migrants who had lived in Australia for 40 years or more [23].

In a recent, large migration study, risk of melanoma was related both to duration of stay in Australia and age at arrival [24].

A few studies have gone further and have suggested a critical age for immigration. Holman and colleagues showed that people arriving before age 10 had a risk of the development of superficial spreading melanoma (SSM), similar to that of native-born Australians [21]. The authors found a specific effect of age at arrival independent of duration of stay. Cooke and associates demonstrated that, among British immigrants in New Zealand, the critical age was somewhat higher—before age 30 years [22]. In accordance with these results, Weinstock and colleagues found a positive association between a more equatorial latitude of residence between age 15 and 20 years, and melanoma, but not with latitude of residence at age >30 years [15]. In an American case-control study, a significantly greater percentage of melanoma patients, aged 18–31 years during World War II, served in the tropics than did controls [20].

However, in contrast, age-adjusted incidence rates were found to be higher in Caucasians born outside Hawaii than Caucasians born in Hawaii, particularly among females [19].

DISCUSSION

This paper is based both on results from a population-based, matched, case–control study conducted in southern Sweden between 1988 and 1990 and a review of the current evidence studying the age relationship between sunburns and malignant melanoma.

Our results are in accordance with several previous papers, demonstrating an association between malignant melanoma and a history of sunburns [2–5]. In contrast to some studies, we found no association between vacations spent in sunny places and malignant melanoma [4, 25–27]. However, in three of these studies, no adjustments for history of sunburns and sunbathing were made [25–27], and in the remaining one, the relative risk decreased when adjustments for these possible confounders were carried out [4]. Unfortunately, in the present study we have no information on the total number of journeys abroad, when they took place and names of the places visited.

Table 6. Studies retrospectively comparing history of sunburns in different ages

Study	Location	Number cases/ controls	Age periods investigated	"Critical" age	Risk factor	RR (95% CI)	Adjustments
Paffenberger *et al.* 1978 [10]	U.S.A.	45/180	–	Before college	Outdoor employment	3.9, $P = 0.01$	
Mackie *et al.* 1982 [2]	Scotland	113/113	Past 5 years	Past 5 years	Severe sunburn	2.8 (1.1–7.4)	Social class, skin types, sun exposure
Lew *et al.* 1983 [6]	U.S.A.	111/107	Child, adolescence, adult	Childhood Adolescence	Painful sunburns Blistering sunburns	2.8 (1.3–6.3) 2.05 (1.18–3.56)	No adjustments for host factors
Elwood *et al.* 1984 [11]	W. Canada	595/595	Child, any time	All ages	"Burn only"	1.7 (1.0–2.6)	Sun reaction, host factors,* ethnic origin, sunburn
Green *et al.* 1985 [3]	Queensland, Australia	183/183	Any time	Up to age 30	≥6 severe sunburns	2.4 (1.0–6.1)	Naevi, exact age
Elwood *et al.* 1986 [12]	Nottingham, U.K.	83/83	Any time	All ages	"Burn and tan"	2.8 (1.0–7.8)	Sun reaction, host factors,* sunburn
Holman *et al.* 1986 [13]	W. Australia	507/507	< Age 10, age 15–24, last 10 years	Last 10 years	≥5 severe sunburns	1.55 (0.81–2.96)	Acute, chronic skin reaction, origin, age at arrival, hair colour
Cristofolini *et al.* 1987 [14]	N. Italy	103/205	Child, adolescence adult	Adult	Sunburn, frequent	1.21 (0.71–2.07)	No adjustments for host factors
Osterlind *et al.* 1988 [4]	Denmark	474/926	< Age 15, age 15–24, last 10 years	<15 years	≥5 severe sunburns	2.7 (1.6–4.8)	Sex, host factors*
MacKie *et al.* 1989 [5]	Scotland	280/280	Any time in life	At any time	≥3 severe sunburns 1–2 severe sunburns	7.6 (1.8–32) Males 1.5 (1.0–2.4) Females	Skin type, host factors,* ultra-violet use, tropical recidence
Weinstock *et al.* 1989 [15]	U.S.A.	130/300	Age 15–20, after age 30	Age 15–20	≥5 blistering sunburns	2.2 (1.2–3.8)	No adjustments for host factors
Elwood *et al.* 1990 [16]	Midlands, U.K.	195/195	Age 8–12, age 18–22, last 5 years, last 18–22 years	Age 8–12	Sunburn, ever	2.4 (0.8–7.3)	Tendency to sunburn, host factors,* social class
Zanetti *et al.* 1992 [7]	N. Italy	260/416	Childhood, lifelong	Childhood	Sunburns, ever	3.8 (2.3–6.4)	Sex, age, type of skin reaction

*Other host factors than skin reaction to sunlight.

Table 7. Migration studies

Study	Location	Material	Result
Movshovitz *et al.* 1973 [17]	Israel	All cases of MM 1961–1967 (368)	High incidence in native-born of European origin. Intermediate in the veteran foreign-born Europeans Lower in more recent European born
Anaise *et al.* 1978 [18]	Israel	All cases of MM 1960–1972 (966)	Increasing risk for European born of the same age and ethnic background as the number of years spent in Israel increased
Hinds *et al.* 1980 [19]	Hawaii, U.S.A.	All cases of MM 1960–1977 (333)	Higher age-adjusted rates among Caucasian immigrants than for Hawaii-born Whites (particularly among females)
Brown *et al.* 1984 [20]	New York, U.S.A.	89 cases/65 controls aged 18–31 during World War II	A significantly greater per cent of the melanoma patients served in the tropics than did the controls
Holman *et al.* 1984 [21]	Western Australia	Case-control study, 507 cases/507 controls	Arrival before age 10 was associated with highest risk of SSM (risk similar to native born Australians)
Cooke *et al.* 1985 [22]	New Zealand	All non-Maoris melanoma deaths 1972–1980 (922)	European immigrants had mortality rates similar to their countries of origin. However, in immigrants from the British Isles migration before age 30 was associated with a similar risk to that of the New Zealand-borns
Green *et al.* 1986 [23]	Queensland, Australia	Case–control study, 183 cases/183 controls	Possible increased risk among migrants who had lived in Australia for 40 years or more
Weinstock *et al.* 1989 [15]	U.S.A.	Case–control study, 130 cases/300 controls	A more equatorial latitude of residence between age 15 and 20 was positively associated with melanoma
Khlat *et al.* 1992 [24]	Australia	All melanoma deaths (9709) 1964–1985, using deaths of other cancers (439,090) as controls	Risk of melanoma was related both to duration of stay in Australia and age at arrival. Their relative importance could not be measured

Furthermore, our data indicated, as suggested by others, that continuous long-term occupational sun exposure is not a risk factor, but is instead perhaps even protective [4, 25].

We found no evidence of a relationship between melanoma and sunburns in childhood. Instead, sunburns after age 19 was a significant risk factor for melanoma development, with an evident dose-response relationship. Since the questions on sunburn history were asked with regard to three age-periods consisting of 0–14 years, 15–19 years and after 19 years, we do not know if the oldest age cutoff at 19+ years may even be too young. Data from case-control studies concerning the age relationship between sunburns and melanoma are inconsistent (Table 6). Of 13 studies retrospectively comparing history of sunburns in different ages, only four major studies support the idea of a critical period in early life [4, 6, 7, 15]. Of these four studies, only two were population based [4, 7]. In the Danish study, adjusted elevated risks were found both for young and old ages, but when excluding those with a history of sunburns in childhood, the association with older ages became non-significant [4]. However, since most of those who burned in childhood continued to burn in later life, we think that models excluding cases and controls who had burned in particular time periods are inappropriate (see also Tables 3 and 4). Thus, it cannot be inferred from that analysis that sunburns in childhood are more important than sunburns at older ages. In the present study, we found a similar correlation between sunburns in childhood and sunburns in later life. Interestingly, sunbathing was also found to be significantly associated with melanoma development in the same Danish study, but they found no different in relative risk between sunbathing in childhood and sunbathing in the 10-year period prior to diagnosis [4]. A more recent Italian study also indicated childhood to be the critical period [7]. In this study, questions were asked regarding lifetime sunburns and in childhood, but not regarding sunburns at other specific time periods in life. Furthermore, sunburns in childhood were compared with the lifetime sunburns, which included sunburns in childhood. Lew and associates not only reported an increased risk with sunburns in childhood but also in adolescence [6]. Unfortunately, they did not control for confounding by constitutional risk factors. Furthermore, as stated above, their study as well as the study by Weinstock and colleagues [15] were not population based. Weinstock and colleagues found, among women from a

Nurses' Health cohort, that teenage years (15–20 years) were the critical period. No data on sunburns prior to 15 years of age were collected.

One important methodological issue when performing a multivariate analysis is the issue of which variables to control for. In the presented analyses on sunburn history, we made adjustments for constitutional factors (hair colour and raised naevi). Since we did not record any other information concerning skin reaction to sunlight other than episodes of sunburns, sunblisters and formation of ulcera due to excessive sun exposure, the analyses were not adjusted for skin sensitivity to sunlight. In some investigations, skin sensitivity to sunlight has been found to be an important pigmentary risk factor for melanoma development [11, 28, 29]. However, other studies have failed to find any significant association when adjustments for other potential confounders have been performed [2, 5, 16]. Furthermore, Østerlind and associates showed, in a Danish study (a population ethnically similar to ours), that the major constitutional risk factors were the number of raised naevi on the arm, degree of freckling and light hair colour [30]. Adjusted relative risks associated with skin reaction to sunlight were non-significant. Moreover, it may also be argued that the analyses should not be adjusted for skin sensitivity to sunlight since it is a major correlate and cause of sunburns and would thus reduce estimated relative risks. Similarly, sunburns are correlated with and may cause naevi. Therefore, we also performed analyses adjusted for only naevi and only hair colour (data not shown), which, however, gave the same estimated risks. Sunburn indicates that a high dose of ultraviolet radiation has been delivered and, if the association with malignant melanoma reflects a direct pathological effect of the damage to the skin, variables like skin sensitivity to sunlight or sun exposure history cannot confound the relationship. Two of the four studies supporting a critical period in early life have presented results where control for skin sensitivity was performed [7, 15]. In both cases, the association between sunburn and melanoma was attenuated.

All migration studies in Table 7 have studied individuals migrating to a high incidence area and no study has, to our knowledge, investigated the opposite [17–24]. A higher risk has also been shown in relation to longer duration of stay [17, 18, 22–24]. Holman and associates have gone further and proposed a specific effect of age at arrival independent of duration of stay [21]. However, this was true only concerning the risk of SSM, and was based on the abscence of residual variation by duration of stay after fitting age at arrival. For nodular melanoma (NM), it was impossible to separate the effects of age at arrival and duration of residence since these factors were strongly correlated. Although the pattern of change suggested that childhood migration may be more important than duration of stay, Khlat and colleagues could not determine which was the most important factor determining risk for malignant melanoma since these two factors again were inextricably linked and could not be examined simultaneously [24]. However, in contrast to these findings, Caucasians born outside Hawaii were found to have higher age-adjusted incidence rates than Caucasians born in Hawaii [19].

Probably the most difficult problem in determining the effect of sunburns in different periods in life is the problem of how to design a study which is able to accurately assess this question. The present knowledge is based on retrospective studies relying on self-reported sun-exposure habits. Does an individual really remember what happened, for instance, in childhood? Alternatively, is it possible that painful events in childhood, like severe sunburns, are simply more easily remembered than in later life? It has also been suggested that melanoma patients tend to over-report past sun-exposure habits in an attempt to explain to themselves why they had the diagnosis of malignant melanoma. Furthermore, unfortunately, case-control studies are not always population based and quite often different study bases for cases and controls are used. Another problem is that different studies come from different geographic centres with maybe other constitutional as well as environmental confounders.

A way to (retrospectively) separate the effect of sunburns in different periods in life is to, in a model only, include individuals who were either sunburned in childhood, adolescence or adulthood. However, this is difficult since we found it uncommon to have this exposition pattern (most people had a history of sunburns in at least two time periods), and furthermore these individuals are therefore unlikely to be representative.

In an attempt to address these and other problems, it would be most interesting to perform a prospective cohort study, following a person for a lifetime. This may be the only way to get a true answer. However, an obvious disadvantage with a cohort study is that it takes a very long time before results are evaluable. Furthermore, since migration studies in a way have a higher validity, studies should be carried out looking at fair-skinned individuals migrating from a high incidence area to a low incidence area.

It seems reasonable that the skin of the unprotected child is more susceptible to the UV radiation than the skin of an adult. However, so far the epidemiological evidence in the literature is scarce, and there is a need for more well-designed epidemiological studies including long-term propsective ones. We find no reason to change recommendations for children regarding sun exposure, but recommendations should include sun exposure throughout life and not only be focused on events early in life.

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Immunohistochemical Localisation of Hydroxysteroid Sulphotransferase in Human Breast Carcinoma Tissue: a Preliminary Study

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Understanding the function and regulation of the metabolism of steroid hormones by breast tumours will be instrumental to the development of novel treatments for this widespread disease. We have examined the expression of hydroxysteroid sulphotransferase, an enzyme which inactivates many steroids, in particular androgens, in normal breast tissue and in six ductal-type mammary carcinomas using immunohistochemistry. The enzyme is not expressed in the epithelial cells which line the normal breast duct, but is present in significant amounts in neoplastic cells, suggesting that the gene encoding this protein is activated at some stage of the neoplastic transformation. The implications of this finding for the role of steroid metabolism in breast cancer are discussed.

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INTRODUCTION

EFFECTIVE TREATMENT of hormone-dependent breast carcinomas in their early stages is dependent on the response to hormonal manipulation, and the hormonal micro-environment within breast tumour cells is an important factor in determining this response [1]. Exposure of breast carcinoma cells to free oestrogens has a significant effect on tumour growth rate, and such exposure may be limited by the conjugation (and resultant inactivation) through sulphation of both oestrogens and their androgenic precursors by the sulphotransferase enzyme system.