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Cutaneous Melanoma and Sunburns in Childhood in a Southern European Population

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A population-based case-control study of 260 patients (74 males and 186 females, mean age = 56) with cutaneous malignant melanoma and 416 controls (211 males and 205 females, mean age = 55) was conducted in Turin, north-west Italy, to examine the relation between timing of sunburns and sun exposure and melanoma risk within a southern European population, which is still relatively little investigated. Particularly elevated risk was associated with history of sunburns in childhood [odds ratio 5.9; 95% confidence interval (CI) 3.6–9.5], and such risk elevation persisted after allowance for other major melanoma risk covariates. Conversely, risk increase from history of severe sunburns lifelong was lower (odds ratio = 1.7; 95% CI: 1.1–2.4) and was eliminated by allowance for type of skin reaction to sun exposure and history of sunburns in childhood. A significant increase in the risk of cutaneous malignant melanoma was also associated with number of weeks spent on holiday at the beach not only as an adult, but also as a child.
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INTRODUCTION

DESCRIPTIVE EPIDEMIOLOGY studies provide strong support to the evidence that solar radiation is a causative factor in cutaneous malignant melanoma [1, 2]. Largest increases in melanoma incidence and mortality rates have occurred in those white populations who permanently (immigrants) or temporarily (holiday) reside in very sunny areas outside their usual living environment [3]. Also the extraordinary sex/site linked relationship of upward trends (i.e. trunk in males, lower limbs, and more recently, trunk as well in females [4]) strongly points to intermittent ultra violet light exposure as the cause of the epidemic of cutaneous melanoma.

The interpretation of data from case-control studies is less straightforward [5], chiefly on account of difficulties in assessing retrospectively melanoma risk correlates (i.e. exposure and individual sensitivity to solar radiation) in various life periods. Indeed, there is an increasing evidence that the timing of sun exposure is important and that events occurring in the first few decades of life may have a special role in determining the risk of melanoma [1, 4, 6–17]. Most epidemiological data on this issue, however, derives from populations with northern European or British origin.

In order to understand whether sun-related events occurring early in life are of special importance also in white populations with different skin types and lifestyle habits such as southern European populations, we took advantage of a case-control study conducted in Turin, in the north-western part of Italy.

SUBJECTS AND METHODS

Study methods have been described elsewhere [18, 19]. Briefly, all new cases with a histological diagnosis of cutaneous malignant melanoma and resident in the province of Turin (approximately 2.5 million inhabitants) were identified from the information sources of the local Cancer Registry between May 1984 and October 1986. As concerns females, data collection was prolonged by 1 year. A total of 260 cases (186 females and 74 males) were interviewed (age range: 19–92 mean = 56). Participation rate was 85%. The distribution of melanoma cases according to histological subtype was very similar in the two sexes, superficial spreading melanoma subtype accounting for 51% and 52% and lentigo maligna subtype for 9% and 11% in males and females, respectively. Conversely, as concerns the localisation of melanoma, trunk was the most frequent site in males (35% vs. 27% in females) while lower limbs were the predominant one in females (48% vs. 19% in males) [18, 19].

Population controls were chosen randomly from the roster of the National Health Service of Turin and participation rate was 70%. Although controls were not individually matched with cases, their distribution by age and sex was very similar [18, 19]. A total of 416 individuals (211 males and 205 females) agreed to be interviewed (age range: 17–92, mean = 55).

All interviews were carried out by trained interviewers using a standard questionnaire which included information on socio-demographic variables and major potential determinants of risk of melanoma (e.g. hair and eye colour, type of skin reaction to sun exposure (from I to IV [1]), past history of sunburns in childhood and of severe sunburns (i.e. which caused pain for at least 2 days) lifelong, recreational and occupational history, number of weeks spent on various holiday resorts, particularly at the beach, past history of dermatological diseases, etc.) [18].

Odds ratios, together with their 95% approximate confidence interval, and trends in risk were computed with the usual methods for case-control investigations [20]. To account simultaneously for various potential confounders in addition to sex and age in decades, multiple logistic regression with maximum likelihood fitting was used [21].

RESULTS

Table 1 shows the relationship between cutaneous malignant melanoma and history of sunburns. The risk seems to rise with

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Table 1. Odds ratios of melanoma by sunburns in childhood and severe sunburns lifelong. Turin, Italy, 1984–1987

Factor	Category	Melanoma* cases	Controls*	Odds ratio†	(95% confidence interval)
Sunburns in childhood	Never	186	382	1‡	
	Sometimes	48	26	4.4	(2.5–7.5)
	Often	26	6	12.0	(4.6–31.0)
	χ^2_1(trend)			58.7; $P < 0.001$	
	Mild	21	15	3.2	(1.5–1.6)
	Severe	41	16	6.5	(3.4–12.3)
	χ^2_1(trend)			43.8; $P < 0.001$	
Severe sunburns lifelong	Never	180	328	1‡	
	1	50	53	1.7	(1.1–2.6)
	≥2	24	29	1.5	(0.8–2.7)
	χ^2_1(trend)			4.5; $P = 0.04$	

*Some strata do not add up to the total because of missing values.
†Adjusted for sex and age in decades.
‡Reference category.

Table 2. Odds ratios of melanoma according to holidays at the beach. Turin, Italy, 1984–1987

Period	Number of weeks	Holidays at the beach: Melanoma* cases	Controls*	Odds ratio† (95% confidence interval)
Childhood and teenage	0	182	326	1‡
	1–59	42	37	2.8(1.6–4.6)
	≥60	35	51	1.7(1.0–2.9)
	χ^2_1(trend)			8.6; $P = 0.003$
Adulthood§ only	0	74	148	1‡
	1–59	48	98	1.2(0.7–1.9)
	≥60	58	74	1.5(0.9–2.4)
	χ^2_1(trend)			2.7; $P = 0.10$
Lifelong	0	74	148	1‡
	1–29	25	62	0.9(0.5–1.6)
	30–59	34	50	1.6(0.9–2.8)
	60–89	36	51	1.6(0.9–2.9)
	90–119	28	42	1.5(0.8–2.7)
	≥120	59	55	2.3(1.4–3.8)
	χ^2_1(trend)			12.5; $P = 0.001$

*Some strata do not add up to the total because of missing values.
†Adjusted for sex and age in decades.
‡Reference category.
§Only individuals who did not report any holiday at the beach in childhood are included.

increasing frequency of sunburns in childhood (odds ratio = 4.4, 95% confidence interval: 2.5–7.5, and 12.0, 95% confidence interval: 4.6–31.0, for history of sunburns "sometimes" and "often", respectively) and severity of sunburn episodes (Table 1). A significant trend in risk was also found as concerns melanoma and the number of severe sunburns lifelong. The odds ratio for those who reported one and two or more severe sunburns lifelong were 1.7 [95% confidence interval (CI): 1.1–2.6] and 1.5(95% CI: 0.8–2.7), respectively (Table 1).

In Table 2, odds ratios of melanoma according to number of weeks of holiday at the beach in different periods of life are shown. Analyses of the influence of number of weeks in holiday resorts other than at the beach (high mountain, lake, hill, countryside, etc.) were also performed, but are not shown in detail since holidays at the beach were those reported most frequently and which seemed to affect melanoma risk most consistently. A risk increase emerged (approximately 50% increase in individuals who reported 60 or more weeks at any time), but the trend was statistically significant only for holidays at the beach in childhood and lifelong, but not for those in adulthood only (Table 2). As concerns weeks spent at the beach in childhood (but not in adulthood only or lifelong) a U-shaped influence emerged (i.e. odds ratios seem more elevated in those who reported less than 60 weeks as compared with 60 weeks or more) (Table 2). Only 6 melanoma cases and 11 controls spent any week at the beach in childhood but none thereafter, and hence no meaningful analyses on them have been possible.

Based on data in Table 3, Table 4 shows the relation of melanoma risk and sunburns in childhood and severe sunburns lifelong in different models. As concerns sunburns in childhood, the 5-fold increase of risk persisted substantially unchanged whether or not we controlled for number of weeks spent at the beach in childhood or in any holiday resort (not shown) and for hair colour (Table 4). In the analysis that included type of skin reaction, the relationship of childhood sunburns and cutaneous

Table 3. Distribution of 260 melanoma cases and 416 controls according to sunburns and major risk covariates. Turin, Italy, 1984–1987*

Risk covariate	Timing of sunburns		Low-risk: Cases	Low-risk: Controls	High-risk† Cases	High-risk† Controls
Holidays at the beach in the relevant period	Childhood	Never	142	309	43	71
		Ever	40	16	34	16
	Severe, lifelong	Never	72	177	105	146
		Ever	26	30	48	51
Hair colour	Childhood	Never	138	318	48	64
		Ever	48	28	26	4
	Severe, lifelong	Never	135	272	45	57
		Ever	49	72	26	11
Type of skin reaction	Childhood	Never	81	235	97	122
		Ever	5	10	68	22
	Severe, lifelong	Never	77	217	97	88
		Ever	9	27	65	56

*Some strata do not add up to the total because of missing values.
†"High risk" meant holidays at the beach: ≥1 in childhood, ≥30 lifelong; hair colour: light; type of skin reaction: tendency to burn, always or sometimes (I–III).

Table 4. Odds ratios of melanoma by sunburns and major risk covariates. Turin, Italy, 1984–1987

Risk covariate	Timing of sunburns	Odds ratio (95% confidence interval)* Low-risk	High-risk†	Adjusted‡
None	Childhood	—	—	5.9(3.6–9.5)
	Severe, lifelong	—	—	1.7(1.1–2.4)
Holidays at the beach in the relevant period	Childhood	6.3(3.3–12.2)	4.0(1.9–8.5)	5.1(3.1–8.3)
	Severe, lifelong	2.7(1.4–5.2)	1.3(0.8–2.1)	1.6(1.1–2.3)
Hair colour	Childhood	4.8(2.8–8.4)	10.0(3.1–32.4)	5.5(3.4–9.0)
	Severe, lifelong	1.4(0.9–2.1)	3.3(1.4–7.7)	1.6(1.1–2.4)
Type of skin reaction	Childhood	2.1(0.6–7.2)	4.5(2.5–8.2)	3.8(2.3–6.4)
	Severe, lifelong	1.0(0.4–2.3)	1.0(0.6–1.6)	1.0(0.7–1.5)

*Adjusted for sex and age in decades. Those who never reported sunburns in the relevant period were the reference category.
†"High risk" meant holidays at the beach: ⩾1 in childhood, ⩾30 lifelong, hair colour: light; type of skin reaction: tendency to burn, always or sometimes (I–III).
‡Multiple logistic regression models including terms for the relevant risk covariate in addition to the sex and age.

melanoma was attenuated (odds ratio = 3.8), but remained significant.

Also the inclusion of history of severe sunburns lifelong exerted little effect on the apparent influence of sunburns in childhood (odds ratio = 5.3, 95% CI: 3.3–8.6) (Table 5). By contrast, the risk elevation deriving from severe sunburns lifelong was substantially lower (odds ratio = 1.7; 95% CI: 1.1–2.4) and, although it was left unaltered by inclusion of weeks of holiday at the beach lifelong and hair colour, it was eliminated by allowance for type of skin reaction to sun exposure (Table 4) and history of sunburns in childhood (Table 5). Table 5 demonstrates that, as compared with those individuals who never reported any sunburn episode, no risk difference was seen whether or not they experienced severe sunburns lifelong in addition to sunburns during childhood.

Table 5. Interaction between sunburns in childhood and severe sunburns lifelong on melanoma risk. Turin, Italy, 1984–1987

Sunburns in childhood		Odds ratio (95% confidence interval*) Severe sunburns lifelong: Never	Ever	Adjusted odds ratio† (95% confidence interval)
Never	Cases	143	40	
	Controls	316	64	
	OR	1‡	1.4	1‡
	(95% CI)		(0.9–2.2)	
Ever	Cases	37	35	
	Controls	13	18§	
	OR	8.0	4.9	5.3
	(95% CI)	(3.9–16.5)	(2.6–9.2)	(3.3–8.6)
Adjusted		1‡	1.2 (0.8–1.8)	

*Adjusted for sex and age in decades.
†Adjusted for sunburns in childhood or severe sunburns lifelong in addition to sex and age in decade.
‡Reference category.
§Strata do not add up to the total because of missing values.

Table 6. Odds ratios of melanoma by sunburns, histological subtype and location. Turin, Italy, 1984–1987

Characteristic of melanoma	No. of cases	Odds ratio (95% CI)* Sunburns in childhood	Severe sunburns lifelong
Histological subtype			
Superficial spreading	135	6.7(3.8–11.7)	1.8(1.2–2.9)
Other†	125	4.8(2.7– 8.7)	1.5(0.9–2.4)
Location			
Head	65	7.7(2.9–20.2)	1.2(0.5–2.7)
Trunk and neck	54	5.3(2.8–10.0)	2.3(1.4–4.0)
Upper limbs	38	5.4(2.2–13.1)	1.3(0.6–2.9)
Lower limbs	103	5.4(2.9–10.1)	1.6(0.9–2.7)

*Adjusted for sex and age in decades. Those who never reported sunburns in the relevant period were the reference category.
†It includes 26 nodular, 28 lentigo maligna and 71 other subtypes.

No significant interaction of sunburns in childhood or severe sunburns lifelong with sex, age at melanoma diagnosis and other risk correlates emerged (not shown). It is, however, worth noting that odds ratios from both sunburns in childhood and severe sunburns lifelong tended to be approximately twice more elevated in individuals with light hair, but somewhat lower in those who reported a higher number of weeks at the beach. Conversely, the natural tendency of the skin to burn (skin type I–III) seemed to potentiate the unfavourable effect of sunburns in childhood, but not to make any difference as concerns severe sunburns lifelong (Table 4).

All analyses were replicated in superficial spreading and other subtypes separately and in each anatomical location achieving, however, very similar results (Table 6).

DISCUSSION

The present case-control study, the first which allowed a detailed analysis of the relation between the timing of sunburns and risk of cutaneous malignant melanoma in a southern European population, lends further support to the hypothesis that the most important events, from an aetiological viewpoint, may occur early in life. Interestingly, the increased risks seen in the whole data in association with sunburns were found very similarly in superficial spreading melanomas and other subtypes and in each major anatomical location.

A number of other observations suggest that some factor acting in the first few decades of life affects melanoma risk substantially: the secular increases in melanoma incidence and mortality appear to arise from birth-cohort-dependent effects [1, 4] and the influence of social class on the risk is evident among 25- to 35-year old men as well as among older workers

[6]. Furthermore, outdoor work before entering college seems associated with an increased risk of death from melanoma [7].

Studies on immigrants, chiefly from the British Isles to Australia [14, 22] and New Zealand [6], showed that migration in the first decade of life led to a risk of melanoma similar to that of native-born populations while migration at later ages was associated with a lower risk. Indeed, age at migration was, according to Holman and Armstrong [22], a more powerful predictor of melanoma risk than duration of residence in sunny countries.

Before the present investigation, the issue of sunburns in childhood and risk of cutaneous melanoma had been already assessed in several case-control studies, achieving rather consistent results. Lew *et al.* [8], Mackie and Aitchinson [9] and Elwood *et al.* [11] found that severe or frequent sunburns in childhood conferred an approximately 2–3-fold increased risk and that, like in the present study, control for sun sensitivity variables reduced but did not eliminate the association. In the only previous Italian study, however, no significant association with sunburns at any age was found [23].

In fewer investigations a direct comparison of adult to childhood burns was possible. Green *et al.* [12] reported that the effect of sunburns was similar for burns in each of the first 3 decades of life, but had inadequate data to separately evaluate sunburns after 30 years of age. Osterlind *et al.* [15], in Denmark, and Elwood *et al.* [17], in England, described a particularly strong association of cutaneous melanoma with frequency of painful sunburns in childhood but found little evidence of association with the same sunburns in adulthood or within the 10 or 5 years prior to diagnosis, when those who burned at an early age were removed from analysis. Also a nested case-control study conducted within the Nurses' Health Study cohort showed that sunburns between 15 and 20 years of age were associated with melanoma risk, whereas no association was found for sunburns thereafter [16].

The number of sunburns at specified ages can be interpreted as an indicator of sun damage during that period, which is, in turn, determined by sun exposure, habits and sun sensitivity. As an indirect measure of sun exposure the present analysis included the number of weeks spent in various holiday resorts at different ages. A highly significant trend of risk increase with increasing number of weeks spent at the beach in different periods of life was seen. A similar gradient towards increasing risk of cutaneous melanoma with increasing years of practice of outdoor sports has already been reported [18]. The comparison of the effect of such types of presumably intense sun exposure at different ages is, however, hampered by the close collinearity of age-specific holiday histories. We therefore assessed the effect of holiday at the beach only in those individuals who did not report any of them in childhood, thus finding a similar but somewhat weaker association with risk of cutaneous melanoma. Again, events taking place early in life (in this case a measure of sun exposure) seem to have, in this as well as in previous work [17, 24], a particularly important role in the aetiology of cutaneous melanoma.

As concerns sun sensitivity, it is indicated, in the present study, by hair colour (i.e. the constitutional characteristic most closely linked with melanoma risk [18]), and type of skin reaction. Such features clearly did not account for all the risk increase seen in individuals who reported sunburns in childhood, although they completely explained the apparent adverse effect of severe sunburns lifelong.

Some weaknesses and strengths of the present study are worth discussing. Differences in sunburns between melanoma cases and controls may have been potentiated by recall bias. However, it would then be difficult to explain the trend in risk according to frequency and severity of sunburns in childhood and to assume a strong recall bias regarding childhood sunburns, yet little bias regarding severe sunburns lifelong. Inaccuracies in measurements of indicators of sun exposure and sensitivity are major concerns in this as well as previous questionnaire-based investigations on melanoma. Such non-differential misclassification may well have attenuated related odds ratios and ability of allowance for such variables as potential confounders, particularly since the study did not include any measurement of number of naevi. However, since sunburning is a risk factor for naevi and naevi are suspected to be markers of risk and, possibly, precursors of melanoma [1], dealing with them as confounders might well not have been appropriate.

Amongst the strengths of the present study, the inclusion of population controls, the good participation rate and the relative lack of recall bias (the relationship between melanoma and sunburns and sun exposure had not yet gained in Italy, in the study years, wide public attention) are, however, worth mentioning.

In conclusion the present investigation provides a confirmation that sunburns in childhood are a strong risk factor for cutaneous malignant melanoma and that this applies to the Italian population as well as to other more frequently studied white populations. Biologically, this finding may suggest that melanocytes in children are more sensitive to the sun or that, in the context of the multi-stage model of carcinogenesis, very early exposure to the purported carcinogen (i.e. solar radiation) may increase the changes of completing the remaining stages in subsequent life periods. Such influence on early-stage events would represent an interesting similarity between the effect of ionising and non-ionising radiations [25].

It is, of course, impossible to say whether the association of cutaneous melanoma with sunburns in childhood reflects a direct pathological effect of the early damage thus produced, or is simply an easily remembered indicator of tendency to burn, combined with early overexposure [17]. In any case, the present findings strongly point to the importance of focusing educational intervention on the behaviours of children and adolescents also in southern European countries.

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Oral Contraceptives and Breast Cancer Risk in Denmark

Marianne Ewertz

To evaluate the influence of oral contraceptives (OCs) on breast cancer risk, a population-based case-control study was conducted in Denmark. The study population included women aged less than 40 years (203 cases, diagnosed between 1 March 1983 and 31 August 1984, and 212 controls) and women aged 40–59 years (856 cases, diagnosed between 1 March 1983 and 29 February 1984, and 779 controls). Cases were identified from the nationwide clinical trial of the Danish Breast Co-operative Group and the Danish Cancer Registry. The control groups were age-stratified random samples of the general female population. Data on OC use and breast cancer risk factors were collected by self-administered questionnaires. In both age groups, no significant association was detected between breast cancer risk and duration, age at start, latency or recency of OC use. However, the data provided some limited support that OCs containing 50 μg or more oestrogen may be more harmful than pills with a lower oestrogen dose.
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INTRODUCTION

SINCE THE marketing of oral conceptive (OC) pills in the mid-1960s, concern has been present about the effect on breast cancer risk. While reports from the 1970s were generally reassuring, some studies from the early 1980s showed an increased risk of breast cancer in young women. This lead was pursued in a number of studies. However, the results were inconsistent. Recent reviews [1–3] suggest that a possible adverse effect of OC use is confined to women diagnosed with breast cancer before the age of 40 years and who used OCs at a young age. Women exposed to OCs at older ages do not appear to have an increased risk of breast cancer.

In Denmark, OCs were released for general usage in 1966. Currently, 1 in 5 women aged 15–49 years use OCs [4]. Thus, as elsewhere, even a weak causal link between OCs and breast cancer would have great public health impact. To evaluate the influence of OC use on breast cancer risk, a population-based case-control study was conducted in Denmark. Results pertaining to other parts of this study have appeared elsewhere [5–7].

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