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SUNSCREEN USE AND MALIGNANT MELANOMA

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In a new population-based, matched, case-control study from southern Sweden of 571 patients with a first diagnosis of cutaneous malignant melanoma, between 1995 and 1997, and 913 healthy controls aged 16 to 80 years, the association between sunscreen use and malignant melanoma was evaluated. The median sun protection factor (SPF) used by both cases and controls was 6, range 2 to 25. Sunscreen users reported greater sun exposure than non-users. Persons who used sunscreens did not have a decreased risk of malignant melanoma. Instead, a significantly elevated odds ratio (OR) for developing malignant melanoma after regular sunscreen use was found, adjusted for history of sunburns, hair color, frequency of sunbathing during the summer, and duration of each sunbathing occasion [OR = 1.8, 95% confidence interval (CI) 1.1–2.9]. The OR was higher in subjects who reported that sunscreen use enabled them to spend more time sunbathing (adjusted OR = 8.7, 95% CI 1.0–75.8 for always *vs.* never use). The association appeared to hold for subjects who did not suffer from sunburns while using sunscreens, for subjects who used SPF of 10 or lower, and among men. The pattern of a significantly increased melanoma risk was seen only for lesions of the trunk. Our results are probably related mainly to earlier sunscreens of low SPF. They substantiate the hypothesis that sunscreen use, by permitting more time sunbathing, is associated with melanoma occurrence. *Int. J. Cancer* 87:145–150, 2000.
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The only established exogenous causal factor for cutaneous malignant melanoma is exposure to sunlight (IARC, 1992). Particularly sunburn, a special marker of acute intense sun exposure, has shown a consistent association with melanoma development. Sunscreens are unquestionably able to delay sunburns (Gasparro *et al.,* 1998). It has therefore been tempting to extrapolate the protective effects of sunscreens to the prevention of melanoma as well. Consequently, public-health campaigns in several countries have encouraged the public to protect themselves against solar radiation with sunscreens.

In the experimental situation, use of sunscreens has been found to delay the onset of photocarcinogenesis (Kligman *et al.,* 1980; Wulf *et al.,* 1982) and to inhibit mutation of the *p53* gene in keratinocytes (Ananthaswamy *et al.,* 1997) and the incidence of actinic keratoses in humans (Naylor *et al.,* 1995; Thompson *et al.,* 1993). However, concerning melanoma, several epidemiological studies, including our own, have found an increased risk of melanoma associated with use of sunscreens (Autier *et al.,* 1995; Beitner *et al.,* 1990; Elwood and Gallagher, 1999; Graham *et al.,* 1985; Herzfeld *et al.,* 1993; Klepp and Magnus, 1979; Westerdahl *et al.,* 1995).

We have conducted a new population-based, matched, case-control study of cutaneous malignant melanoma in the South Swedish Health Care region, to address the issue further.

MATERIAL AND METHODS

Our study identified 709 persons, aged 16 to 80 years, in the South Swedish Health Care Region with a first histopathological diagnosis of cutaneous invasive malignant melanoma between 1 January 1995 and 30 June 1997, according to the population-based Regional Tumour Registry (Table I). The permission of the physician responsible for the treatment of each patient was sought. In 2 cases, the physician did not respond, and in an additional 33 cases, the patient was considered ineligible by the treating physician (18 were ineligible for psychological reasons, 4 had another serious disease, 3 were dead, 3 refused to participate, 2 had metastases, 1 was misdiagnosed, 1 had not been fully informed, and 1 had moved). Thus, the case group comprised 674 eligible persons (Table I).

For each of these cases, 2 healthy controls, matched by sex, age (within a year), and parish, were selected by random sampling from the National Population Registry of residents of the South Swedish Health Care Region (Table I).

All eligible cases (n = 674) were mailed a comprehensive questionnaire including different epidemiological variables (medical history, medications, family history, constitutional factors, educational level, UV radiation exposure, smoking and alcohol habits) within 2 months following diagnosis. During the same time, all selected controls (n = 1,348) were mailed an identical questionnaire. Non-responders were contacted twice.

A total of 584 cases (86%) and 1,028 controls (76%) answered the questionnaire. Thirteen cases with no matched control and 115 controls with no matched case were excluded. Thus, the subjects consisted of 571 cases (84% of 674 eligible cases) and 913 controls (68% of 1,348 healthy controls selected) (Table I).

The following information was collected with regard to sunscreen use: ever exposure, exposure the first time in the sun each year, regular exposure, sun protection factor (SPF) among regular users, parts of the body exposed to sunscreens, age at first use, age at last use, sunburns despite sunscreen use, and reason for applying sunscreens. Questions were also asked regarding UV radiation, including sunbathing habits, vacations spent in sunny places (places visited for sunbathing and for skiing), number of painful (severe) sunburns (age at the time), exposure to sunbeds, outdoor employment, and duration of each residential period in the Mediterranean or a similarly located country during the 10-year period before the interview. For cases and controls, the following questions regarding sunbathing were asked: Do you sunbathe during the summer (April–September)? If yes, how many times each summer? How long do you usually spend in the sun each time you sunbathe?

Information on constitutional factors, such as skin phototype, hair color, eye color, nevi, and freckles, was collected by the questionnaire. Number of raised nevi was based on the following question: How many raised nevi (raised pigmented lesion larger than 3 mm) do you have on both your arms?

No re-examination of the histopathological slides was undertaken. However, all pathology reports were reviewed to ascertain that each case had a histopathologically confirmed diagnosis of invasive malignant melanoma. According to the pathology reports, the diagnoses were superficial spreading melanoma in 309 cases (54%), nodular melanoma in 76 cases (13%), lentigo maligna melanoma in 57 cases (10%), acral lentiginous melanoma in 3

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TABLE I – SAMPLE SIZE FLOW FOR CASES AND CONTROLS IN A MATCHED CASE-CONTROL STUDY OF MALIGNANT MELANOMA IN THE SOUTH SWEDISH HEALTH CARE REGION BETWEEN 1995 AND 1997

	Cases n (%)	**Controls** n (%)
Identified for inclusion	709[1]	—
Ineligible	35[2]	—
Eligible	674 (100)	1348[3] (100)
Completed questionnaire	584 (87)	1028 (76)
Refused to participate	90 (13)	320 (24)
Cases with no matched control	13 (2)	—
Controls with no matched case	—	115 (8)
Subjects actually studied	571 (84)	913 (68)
Subjects who answered the question on sunscreen use	558 (83)	891 (66)
Ever used sunscreens	413	616
Never used sunscreens	145	275

[1]All persons with primary cutaneous malignant melanoma, between 1 January 1995 and 30 June 1997, according to the population-based Regional Tumour Registry.–[2]Considered ineligible by the treating physician (33 cases) or the physician did not respond (2 cases). –[3]Healthy controls, matched by sex, age and parish, selected by random sampling from the National Registry of residents of the South Swedish Health Care Region.

cases (0.5%), and unclassified invasive malignant melanoma in 113 cases (20%). Thirteen cases (2%) were incorrectly reported as invasive malignant melanoma since they had a diagnosis of *in situ* melanoma.

Analyses were performed on histopathologically confirmed primary cutaneous malignant melanomas including 13 patients with *in situ* melanoma. Odds ratios (ORs) were computed, based on matched pairs, using both univariate and multivariate methods. In the multivariate analyses, conditional logistic regression was used. Multivariate models included adjustments for potential confounding variables, carefully excluding possible intermediate steps in the putative causal path between exposure and disease. Analyses were adjusted for hair color and number of sunburns, which were important risk factors identified in this case-control study as well as in our previous studies (Westerdahl *et al.,* 1994, 1995, 2000). In addition, frequency of sunbathing during the summer and the duration of the practice of sunbathing were included in the model. No adjustments for number of raised nevi were performed since sunscreen use appears to be associated with the development of nevi (Autier et al., 1998) and, therefore, this may not be a true confounder. Inclusion of other constitutional factors, other sun-exposure variables, and/or socio-economic factors into the multivariate models did not contribute significantly to the chosen model. $P < 0.05$ was considered statistically significant, and 95% confidence intervals (CIs) were used. The statistical program Stata was utilized (Stata Corporation, College Station, TX). Occasional missing values for some variables caused slight variations in the numbers of cases and controls used for each analysis. Cases and controls were not contacted to complement missing values. However, for almost all variables, fewer than 5% were missing.

The Ethical Committee of the Medical Faculty of Lund University approved the study. Informed consent was sought from treating physicians, patients, and healthy controls.

RESULTS

Four hundred and thirteen (74%) of 558 cases (data missing for 13 cases) and 616 (69%) of 891 controls (data missing for 22 controls) had ever used sunscreens (Table 1).

Table II displays the characteristics of controls who used sunscreens, separating the exposure as never, sometimes, always acutely (*i.e.,* always the first time in the sun each year and thereafter sometimes), and always. Use of sunscreens was more common among younger persons and among females. Furthermore, sunscreen users reported more raised nevi, more sunburns, and greater sun exposure.

Only 35% of cases and 31% of controls reported that regular (*i.e.,* always) sunscreen use started after 1980.

Among cases who had ever used sunscreens, 56% applied the sunscreen all over the body. The remaining 44% exposed 1 or more of the following body parts: face and neck, arms and hands, and legs and feet. The same figures for sunscreen application were seen among controls. However, in the group reporting regular sunscreen use, a higher proportion applied sunscreen all over the body, among cases 78% and among controls 87%.

Seventy-three percent of cases and 75% of controls who regularly used sunscreen applied an SPF of 10 or lower. The median SPF for both cases and controls was 6, range 2 to 25. Compared with individuals who applied an SPF of 10 or lower, those who used an SPF higher than 10 reported shorter duration of each sunbathing occasion.

The OR for developing malignant melanoma after ever having used sunscreens was 1.3 (95% CI 0.9–1.9), adjusted for history of sunburns, hair color, frequency of sunbathing during the summer (April–September), and duration of each sunbathing occasion.

As shown in Table III, individuals reporting regular use had a significantly increased OR for developing malignant melanoma (adjusted OR = 1.8, 95% CI 1.1–2.9) compared with those never using sunscreens. Interestingly, a significant risk for melanoma was found among regular sunscreen users who usually applied an SPF of 10 or less but not among those who normally applied an SPF greater than 10.

In analyses examining how sunscreens may influence known melanoma risk factors, it was found that sunscreen use increased melanoma risk linked to these variables (Table IV).

Reasons for applying sunscreen are presented in Table V. A majority of individuals either used sunscreens because of previous bad sun experience or to prevent adverse effects to the skin. However, the main reason among regular users was SPF-dependent. For instance, the reason for the majority of regular users to apply sunscreens with SPF of 11 or more was previous bad sun experience. Subgroup analyses on sunscreen use and risk of melanoma by reason for applying sunscreen showed a significant association between sunscreen use and melanoma only for individuals who reported that use enabled more time sunbathing (adjusted OR = 8.7, 95% CI 1.0–75.8 for always *vs.* never using sunscreens). No beneficial effect of regular (*i.e.,* always) sunscreen use was seen either in those who used sunscreens to prevent adverse effect of the sun to the skin (adjusted OR = 1.5, 95% CI 0.6–3.7) or in those who used it because of previous bad sun experience (adjusted OR = 1.0, 95% CI 0.5–2.2). Individuals who reported that they applied sunscreens so that they could spend more time sunbathing reported longer duration of each sunbathing occasion compared with individuals who used sunscreens for all other reasons (Table VI).

Fifty-two percent of cases and 51% of controls had suffered from sunburns despite use of sunscreens. A significant association between sunscreen use and melanoma development was demonstrated only among those who had not experienced sunburns, while using sunscreens (adjusted OR = 1.9, 95% CI 1.0–3.7) (Table VII). Interestingly, these 2 groups differed neither in sunbathing frequency nor in duration of each sunbathing occasion. Sunburn experience while using sunscreen (among regular sunscreen users) was independent of SPF.

ORs (adjusted for history of sunburns, hair color, frequency of sunbathing during the summer, and duration of each sunbathing occasion) for developing melanoma after regular sunscreen use were almost the same among individuals who applied the sunscreen all over the body and those who applied it on 1 or more specific body site(s) (adjusted OR = 2.0, 95% CI 1.1–3.7 and adjusted OR = 2.4, 95% CI 0.5–11.6, respectively).

TABLE II – USE OF SUNSCREENS AMONG CONTROLS IN A MATCHED CASE-CONTROL STUDY OF MALIGNANT MELANOMA IN THE SOUTH SWEDISH HEALTH CARE REGION BETWEEN 1995 AND 1997

	Use of sunscreens			
	Never n (%)	Sometimes n (%)	Always initially + sometimes[1] n (%)	Always n (%)
Total (n = 891)	275 (31)	409 (46)	104 (12)	103 (12)
Sex				
Females (n = 448)	94 (21)	215 (48)	68 (15)	71 (16)
Males (n = 443)	181 (41)	194 (44)	36 (8)	32 (7)
Age				
18–50 (n = 292)	44 (15)	168 (58)	48 (16)	32 (11)
51–80 (n = 599)	231 (39)	241 (40)	56 (9)	71 (12)
Hair colour				
Black/dark brown (n = 235)	89 (38)	101 (43)	19 (8)	26 (11)
Light brown (n = 485)	141 (29)	235 (48)	57 (12)	52 (11)
Blond/fair (n = 106)	22 (21)	48 (45)	18 (17)	18 (17)
Red (n = 38)	8 (21)	13 (34)	10 (26)	7 (18)
Skin phototypes				
III–IV (n = 588)	180 (31)	281 (48)	67 (11)	60 (10)
I–II (n = 276)	74 (27)	123 (45)	36 (13)	43 (16)
Number of raised naevi				
None (n = 751)	257 (34)	338 (45)	79 (11)	77 (10)
≥1 (n = 140)	18 (13)	71 (51)	25 (18)	26 (19)
Frequency of sunbathing April–September				
None (n = 98)	71 (72)	19 (19)	3 (3)	5 (5)
1–14 times (n = 292)	85 (29)	150 (51)	27 (9)	30 (10)
≥15 times (n = 476)	107 (22)	230 (48)	73 (15)	66 (14)
Duration of each sunbathing occasion				
<1 hours (n = 491)	185 (38)	213 (43)	41 (8)	52 (11)
1–3 hours (n = 299)	60 (20)	150 (50)	51 (17)	38 (13)
>3 hours (n = 81)	21 (26)	40 (49)	10 (12)	10 (12)
History of severe sunburns				
Never (n = 482)	193 (40)	192 (40)	41 (9)	56 (12)
1–2 time(s) (n = 341)	60 (18)	184 (54)	53 (16)	44 (13)
≥3 times (n = 31)	4 (13)	20 (65)	6 (19)	1 (3)

[1]Always the first time in the sun each year and thereafter sometimes.–*The number and estimated percentages of total number of controls belonging to a given category are presented.

TABLE III – ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR DEVELOPING MALIGNANT MELANOMA IN RELATION TO SUNSCREEN USE

Factor and category	Cases (n)	Controls (n)	OR (95% CI)	ORa[1] (95% CI)
Use of sunscreens				
Never	145	275	1.0[2]	1.0[2]
Sometimes	269	409	1.3 (1.0–1.7)	1.3 (0.9–1.9)
Always initially + sometimes[3]	52	104	1.0 (0.7–1.5)	0.9 (0.6–1.5)
Always	92	103	1.9 (1.3–2.7)	1.8 (1.1–2.9)
SPF[4]				
None	145	275	1.0[2]	1.0[2]
1–10	63	72	2.4 (1.2–4.8)	2.9 (1.2–19.9)
>10	23	24	1.5 (0.5–4.4)	1.5 (0.3–9.2)
Number of years of regular use				
None	145	275	1.0[2]	1.0[2]
1–20	48	40	3.8 (1.5–9.6)	4.3 (0.8–21.9)
>20	44	63	1.3 (0.6–2.7)	1.7 (0.5–5.6)

[1]Adjusted for hair colour, history of sunburns, frequency of sunbathing during the summer and the duration of each sunbathing occasion. –[2]Referent category.–[3]Always the first time in the sun each year and thereafter sometimes.–[4]Reported sun protection factor (SPF) among those who always use sunscreens in the sun. Data missing on 13 subjects (6 cases and 7 controls).

Adjusted ORs among men and women were 2.3 (95% CI 1.0–5.0) and 1.3 (95% CI 0.7–2.6), respectively, for always *vs.* never using sunscreens.

In an analysis of sunscreen use for subsites of melanoma, the pattern of a significantly increased risk for melanoma was seen only for lesions of the trunk (adjusted OR = 2.5, 95% CI 1.2–5.2 for always *vs.* never using sunscreens).

When the 13 cases with *in situ* melanoma were excluded from the analyses, the results were unaltered.

DISCUSSION

In the present study, we explored sunscreen use habits in more detail than previous studies. Our results give a clue to explain the melanoma–sunscreen paradox (*i.e.*, although sunscreens contain active ingredients which appear to protect against melanoma development, sunscreen use appears to increase melanoma risk). Clearly, in this study, persons who used sunscreens did not have decreased risk of malignant melanoma. Instead, our results suggest that sunscreen use, by permitting

TABLE IV – ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR DEVELOPING MALIGNANT MELANOMA IN RELATION TO VARIOUS FACTORS ACCORDING TO SUNSCREEN USE

Factor and category	OR (95% CI) Use of sunscreen		ORa[1] (95% CI) Use of sunscreen	
	Never	Ever	Never	Ever
Hair colour				
Black/dark brown	1.0[2]	1.3 (0.8–2.1)	1.0[2]	1.5 (0.8–2.8)
Light brown	1.3 (0.8–2.1)	1.6 (1.1–2.5)	1.6 (0.8–3.1)	1.9 (1.1–3.5)
Blond/fair	2.3 (1.0–5.0)	2.3 (1.4–3.8)	1.8 (0.6–5.4)	2.8 (1.4–5.4)
Red	1.6 (0.5–4.7)	3.0 (1.6–5.8)	1.6 (0.3–9.1)	2.2 (1.0–4.9)
Skin phototype				
III–IV	1.0[2]	1.3 (0.9–1.8)	1.0[2]	1.5 (1.0–2.3)
I–II	1.4 (0.8–2.2)	1.6 (1.1–2.3)	1.8 (0.9–3.6)	1.8 (1.2–2.9)
Sunburns after age 19 years				
Never	1.0[2]	1.3 (1.0–1.9)	1.0[2]	1.4 (0.9–2.1)
Ever	1.5 (0.9–2.6)	1.5 (1.1–2.2)	1.2 (0.6–2.5)	1.6 (1.0–2.4)
Frequency of sunbathing April–September				
<15 times	1.0[2]	1.3 (1.0–1.9)	1.0[2]	1.3 (0.8–2.2)
≥15 times	0.8 (0.5–1.3)	1.1 (0.8–1.6)	0.9 (0.5–1.8)	1.2 (0.7–2.0)

[1]Adjusted odds ratios obtained from a model that contained all other variables in this table.–[2]Referent category.

TABLE V – REASON FOR APPLYING A SUNSCREEN AND ITS SUN PROTECTION FACTOR (SPF) AMONG CASES AND CONTROLS

Factor and category	Cases n (%)	Controls n (%)
Reason for applying a sunscreen[1]		
Previous bad sun experience (sunburns and/or photosensitivity)	148 (36)	198 (33)
Prevent adverse effects to the skin	137 (34)	222 (37)
To be able to spend more time sunbathing	76 (19)	135 (22)
Various other reasons	48 (12)	50 (8)
Reason for always applying a sunscreen with SPF 1–10[2]		
Previous bad sun experience (sunburns and/or photosensitivity)	24 (38)	23 (32)
Prevent adverse effects to the skin	19 (30)	30 (42)
To be able to spend more time sunbathing	16 (25)	11 (15)
Various other reasons	4 (6)	8 (11)
Reason for always applying a sunscreen with SPF >10[2]		
Previous bad sun experience (sunburns and/or photosensitivity)	14 (61)	15 (62)
Prevent adverse effects to the skin	3 (13)	5 (21)
To be able to spend more time sunbathing	4 (17)	2 (8)
Various other reasons	2 (9)	2 (8)

[1]Data missing on 4 cases and 11 controls.–[2]Reason among those who always use sunscreens in the sun. Data missing on 6 cases and 7 controls.

TABLE VI – REPORTED DURATION OF EACH SUNBATHING OCCASION ACCORDING TO REASON FOR APPLYING A SUNSCREEN AMONG CASES AND CONTROLS

Factor and category	Duration of each sunbathing occasion		
	<1 hour n (%)	1–3 hours n (%)	>3 hours n (%)
		Cases[1]	
Reason for applying a sunscreen			
Previous bad sun experience (sunburns and/or photosensitivity) (n = 147)	77 (52)	61 (42)	9 (6)
Prevent adverse effects to the skin (n = 134)	71 (53)	58 (43)	5 (4)
To be able to spend more time sunbathing (n = 74)	24 (32)	35 (47)	15 (20)
Various reasons (n = 45)	24 (53)	20 (44)	1 (2)
		Controls[2]	
Reason for applying a sunscreen			
Previous bad sun experience (sunburns and/or photosensitivity) (n = 194)	100 (52)	77 (40)	17 (9)
Prevent adverse effects to the skin (n = 220)	120 (55)	83 (38)	17 (8)
To be able to spend more time sunbathing (n = 132)	48 (36)	62 (47)	22 (17)
Various reasons (n = 48)	28 (58)	16 (33)	4 (8)

[1]Data missing on 13 cases.–[2]Data missing on 22 controls.

more time sunbathing, is associated with an increased risk of melanoma development.

Is the relation between sunscreen use and melanoma occurrence observed in this and previous studies (Autier *et al.*, 1995; Beitner *et al.*, 1990; Elwood and Gallagher, 1999; Graham *et al.*, 1985; Herzfeld *et al.*, 1993; Klepp and Magnus, 1979; Westerdahl *et al.*, 1995) true or spurious? We feel confident that bias, regarding data collection and processing, could not explain our results. Firstly, our study was population-based with a good response rate, reducing the likelihood of selection bias. Secondly, specific attention was paid to defining variables in such a way that one could expect high recall with minimal memory bias. Indeed, a similar questionnaire has been found to yield information with good test–retest reliability (Westerdahl *et al.*, 1996). Still, the influence of non-

TABLE VII – ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR DEVELOPING MALIGNANT MELANOMA IN RELATION TO SUNSCREEN USE FOR SUBGROUPS OF SUBJECTS ACCORDING TO SUNBURN EXPERIENCE WHILE USING SUNSCREENS

Factor and category	Cases (n)	Controls (n)	OR (95% CI)	ORa[1] (95% CI)
	Individuals who had suffered from sunburns despite sunscreen use			
Use of sunscreens				
Never	145	275	1.0[2]	1.0[2]
Sometimes	124	184	1.4 (1.0–2.1)	1.3 (0.8–2.2)
Always initially + sometimes[3]	29	60	1.0 (0.5–1.9)	0.8 (0.4–1.7)
Always	55	58	1.6 (1.0–2.7)	1.3 (0.7–2.3)
	Individuals who had not <u>not</u> suffered from sunburns while using sunscreens			
Use of sunscreens				
Never	145	275	1.0[2]	1.0[2]
Sometimes	135	205	1.2 (0.9–1.8)	1.3 (0.8–2.1)
Always initially + sometimes[3]	22	43	1.1 (0.6–2.1)	1.3 (0.6–2.8)
Always	36	44	2.2 (1.2–4.2)	1.9 (1.0–3.7)

[1]Adjusted for hair colour, frequency of sunbathing during the summer and the duration of each sunbathing occasion.–[2]Referent category. –[3]Always the first time in the sun each year and thereafter sometimes.

differential misclassification (*i.e.,* measurement error that is independent of disease status) may have been considerable since, *e.g.,* the exposure variable sunscreen use included many different sunscreen ingredients that have changed over the years. However, non-differential misclassification leads to under-estimation of the true relationship. Thirdly, we used identical procedures of data collection for cases and controls, to minimize recall bias. In addition, information from cases was collected close in time to the diagnosis, to avoid the influence a diagnosis of melanoma may have on recall of sunscreen use. Indeed, the median SPF used by cases and controls as well as the reported frequency of sunburns despite sunscreen use correspond to previous reports (Wulf *et al.,* 1997). Fourthly, our results persisted after careful adjustments for potential confounders, indicating that sunscreen use is not simply a marker of greater exposure to sunlight or of greater sensitivity to sunlight. However, there is always the possibility of an unknown and unidentified factor and/or a factor not measured in the questionnaire that is associated with the use of sunscreens, giving rise to confounding. Our questionnaire, *e.g.,* did not address behavior and clothing during sun exposure. However, the epidemiological literature on melanoma does not provide any indications of such a confounder.

Yet another explanation may be that the association between use of sunscreens and melanoma was a consequence of former behavior/exposure that subsequently fostered sunscreen use, which in turn appears as a risk factor. Our results did not support this hypothesis since, *e.g.,* there was no significant association between sunscreen use and melanoma in a subgroup of individuals who used sunscreens because of previous bad sun experience. This is in accordance with earlier reports (Autier *et al.,* 1995; Westerdahl *et al.,* 1995).

Our present results point to a role of sunscreens in melanoma development. The increased risk of melanoma appeared to be related to how sunscreens actually are used and not to a direct carcinogenic effect of sunscreen components. In this regard, we did not find any evidence that the melanoma–sunscreen association was caused by misuse of sunscreens resulting in sunburns because a significant increase in melanoma risk was demonstrated only among those who had not experienced sunburns while using sunscreens. Instead, our results suggested that sunscreen use influenced melanoma risk by increasing the amount of UV radiation delivered to the skin. For instance, overall, sunscreen users reported greater sun exposure than non-users. Furthermore, the OR for melanoma development was higher in subjects who used sunscreens to spend more time sunbathing. Indeed, these persons reported longer duration of each sunbathing occasion compared with individuals who used sunscreens for all other reasons. Previous case-control studies (Autier *et al.,* 1995; Westerdahl *et al.,* 1995) and a double-blind, randomized study (Autier *et al.,* 1999) support this prolonged sun exposure hypothesis. According to other findings, it is tempting to suggest that sunscreen use might not entirely have affected melanoma risk by increasing the amount of UV radiation delivered to the skin *per se* but by modifying wavelength transmitted to the skin. Firstly, our study deals mainly with the effect of the older sunscreens since most subjects started to use sunscreens long before modern sunscreens with high SPF (*i.e.,* SPF $\geq$15) and/or the capacity of absorbing wavelengths in the UV-A spectrum were introduced on the market. Most common older sunscreens mainly blocked UV-B (Pathak, 1987). Secondly, increased melanoma risk was associated only with regular use of an SPF of 10 or lower. In general, sunscreens with high SPF are more likely to remove some of the UV-A than those with low SPF (Lim and Cooper, 1999). Finally, a significant association between sunscreen use and melanoma was demonstrated only among those who had not experienced sunburns while using sunscreens. Thus, if we assume that the absence of sunburns in these subjects is a marker of adequate UV-B blocking, the melanoma development could then be associated with transmitted UV-A.

In contrast to our previous study (Westerdahl *et al.,* 1995), only lesions of the trunk were significantly associated with sunscreen use. The reason for this difference is unknown. An explanation could be that a body site with normally relatively low sun exposure is more exposed when sunscreens are frequently used. However, this observation is most interesting since sunscreen use seemed to increase melanoma risk in men but not in women. The latter is in accordance with 4 other studies (Autier *et al.,* 1995; Graham *et al.,* 1985; Herzfeld *et al.,* 1993; Klepp and Magnus, 1979) but not with our previous study (Westerdahl *et al.,* 1995).

In 2 other case-control studies, the use of sunscreens did not appear to have a protective role (Holman *et al.,* 1986; Østerlind *et al.,* 1988). Holman *et al.* (1986) observed an elevated risk prior to controlling for host characteristics. Three additional studies have reported that sunscreen may protect against melanoma (Espinosa Arranz *et al.,* 1999; Holly *et al.,* 1995; Rodenas *et al.,* 1996). Holly *et al.* (1995) found sunscreen use and recreational sun exposure to be protective against melanoma in women. The 2 other reports (Espinosa Arranz *et al.,* 1999; Rodenas *et al.,* 1996) were not population-based and showed different results from ours concerning the association between sun exposure and melanoma risk.

Several experimental animal studies have shown that sunscreens delay the onset of photocarcinogenesis (Kligman *et al.,* 1980; Wulf *et al.,* 1982) and inhibit mutation of the *p53* gene in keratinocytes (Ananthaswamy *et al.,* 1997). However, the only experimental study on melanoma and sunscreen use found that sunscreens did not protect against UV radiation–induced enhancement of melanoma growth in mice (Wolf *et al.,* 1994). Their results cannot be interpreted to mean that sunscreens are unable to prevent the initiation of melanoma formation. So far, it has not been possible to study the role of sunscreens in this respect since there exist no

suitable laboratory animal models that mimic melanoma development in humans. Two placebo-controlled, prospective trials have shown that continuous application of sunscreens can reducethe incidence of actinic keratoses (Naylor *et al.,* 1995; Thompson *et al.,* 1993). Unfortunately, these results must be interpreted cautiously since they included persons highly aware of the danger associated with unconsidered sun exposure. Thus, there is some evidence that sunscreen protects against actinic neoplasia as long as one stays in the sun the same amount of time one would have stayed without sunscreen. Our results may not contradict this conclusion if we take into account that normal sunscreen use probably denotes a modified behavior pattern toward sunlight. In addition, data obtained while studying the keratinocytic system may not be directly transposable to the melanocytic system.

When considering our data together with epidemiological data on sunbed use (Autier *et al.,* 1994; Westerdahl *et al.,* 1994, 2000), a greater impact of UV-A on melanoma development is suggested. This is biologically plausible because in humans there is quite good evidence that UV-A is carcinogenic (IARC, 1992). Furthermore, this is in accordance with a new hypothesis for melanoma induction, which proposes that radiation absorbed by the melanin in melanocytes generates products that may activate the carcinogenic process (Moan *et al.,* 1999). This is thought to be true especially for UV-A since it penetrates the skin deeper than UV-B.

In conclusion, sunscreen users did not have decreased risk of malignant melanoma. Specifically, our results suggest that use of sunscreens, by permitting more time sunbathing, is associated with melanoma occurrence. Finally, recommendations should put more emphasis on attitudes toward sunlight, to reduce overall sun exposure.

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