

# The Influence of Painful Sunburns and Lifetime Sun Exposure on the Risk of Actinic Keratoses, Seborrhic Warts, Melanocytic Nevi, Atypical Nevi, and Skin Cancer

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Painful sunburns are implicated in the pathogenesis of squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Chronic exposure to ultraviolet radiation is known as the most important risk factor for the development of actinic keratoses and squamous cell carcinoma. The purpose of the study was to assess the effect of painful sunburns and lifetime sun exposure on the development of actinic keratoses and seborrhic warts in relation to the development of squamous cell carcinoma and basal cell carcinoma, and on the development of melanocytic nevi and atypical nevi in relation to the development of malignant melanoma. We made use of a cohort of 966 individuals who participated in a case-control study to investigate environmental and genetic risk factors for skin cancer. Exposure measurements for sunlight were collected and actinic keratoses, seborrhic warts, melanocytic nevi, and atypical nevi were counted. Relative risks were estimated using exposure odds ratios from cross-tabulation. Multivariate logistic regression was used to adjust for potential confounders. The recall of painful sunburns before the age of 20 y was associated with an increased risk of squamous cell carcinoma, nodular basal cell carcinoma, and multifocal superficial basal cell carcinoma as well as actinic keratoses. Odds ratios with

95% confidence intervals adjusted for age, sex, and skin type were 1.5 (0.97; 2.3); 1.6 (1.1; 2.2); 2.6 (1.7; 3.8); and 1.9 (1.4; 2.6) for the three types of nonmelanoma skin cancer and actinic keratoses, respectively. Painful sunburns before the age of 20 y were also associated with an increased risk of malignant melanoma and the development of its precursors, melanocytic nevi and atypical nevi. Odds ratios with 95% confidence intervals adjusted for age, sex, and skin type were 1.4 (0.86; 2.1); 1.5 (1.1; 2.0); and 1.4 (0.88; 2.3) for malignant melanoma and the two types of precursors, respectively. Lifetime sun exposure was predominantly associated with an increased risk of squamous cell carcinoma (p-value for trend = 0.03) and actinic keratoses (p-value for trend < 0.0001) and to a lesser degree with the two types of basal cell carcinoma. By contrast, lifetime sun exposure appeared to be associated with a lower risk of malignant melanoma, despite the fact that lifetime sun exposure did not diminish the number of melanocytic nevi or atypical nevi. Neither painful sunburns nor lifetime sun exposure were associated with an increased risk of seborrhic warts. **Key words:** actinic keratoses/atypical nevi/melanocytic nevi/seborrhic warts/skin cancer/ultraviolet light. *J Invest Dermatol* 120:1087–1093, 2003

Ultraviolet light has been identified as the most important environmental risk factor in the development of skin cancer (Preston and Stern, 1992; Kricger *et al*, 1994; Elwood and Jopson, 1997; Armstrong and Kricger, 2001). The three main types of skin cancer that can be distinguished among fair-skinned individuals are squamous cell carcinoma (Alam and Ratner, 2001), basal cell carcinoma (Goldberg, 1996), and malignant melanoma (Gilchrest *et al*, 1999). There are some arguments to subdivide basal cell carcinomas into nodular basal cell carcinomas and superficial multifocal basal cell carcinomas, because these two basal cell

carcinomas show different behaviors and may be different entities (Bastiaens *et al*, 1998).

Painful sunburns are implicated in the pathogenesis of squamous cell carcinoma (Green and Battistutta, 1990), basal cell carcinoma (Kricger *et al*, 1994; 1995; Armstrong and Kricger, 1995), and malignant melanoma (Elwood and Jopson, 1997). Chronic sun exposure is the most important cause of squamous cell carcinoma (Alam and Ratner, 2001), but may be less important for the development of basal cell carcinoma (Kricger *et al*, 1994; Armstrong and Kricger, 1995). By contrast, chronic sun exposure is often found to have a protective effect for the development of malignant melanoma (Elwood and Jopson, 1997).

Actinic keratoses are thought to be precursor lesions of squamous cell carcinomas (Frost and Green, 1994). Actinic keratoses are more frequent in men, in sun-sensitive subjects exposed to chronic sun, and in individuals who have a history of sunburn (Frost and Green, 1994).

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Seborrheic warts are very common skin lesions (Yeatman *et al*, 1997; Gill *et al*, 2000). Except for the sudden eruption of multiple seborrheic warts in association with underlying internal malignancy (known as the sign of Leser-Trelat) no association with malignancy has been reported (Schwartz, 1996). Some authors have suggested that sunlight may play a part in their development in those people who are predisposed to develop them (Yeatman *et al*, 1997).

Excess numbers of melanocytic nevi and clinically atypical nevi are the strongest known risk factors for malignant melanoma (Green and Swerdlow, 1989; Garbe *et al*, 1994; Bouwes Bavinck *et al*, 1996; Rivers, 1996). Sunburns before the age of 20 have been reported to be associated with the development of multiple melanocytic nevi and clinically atypical nevi (Garbe *et al*, 1994).

The purpose of this study was to elucidate further the relationship of painful sunburns and lifetime sun exposure with the development of squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Individuals with nodular basal cell carcinoma and superficial multifocal basal cell carcinoma were studied separately. The influence of painful sunburns and lifetime sun exposure on the development of actinic keratoses and seborrheic warts, the number of melanocytic nevi, and the development of atypical nevi, lesions that are considered potential cutaneous risk markers for the development of skin cancer, was also addressed. We hypothesized that painful sunburns before the age of 20 y would be associated with an increased risk of squamous cell carcinoma, nodular and superficial multifocal basal cell carcinoma, and malignant melanoma, and that lifetime sun exposure would be associated with an increased risk of nonmelanoma skin cancer, but not with an increased risk of malignant melanoma.

## PATIENTS AND METHODS

**Study population** The Leiden Skin Cancer Study was initiated in 1997 as a case-control study of the causes of skin cancer in the Dutch population and has been described earlier (Bastiaens *et al*, 2001; De Hertog *et al*, 2001; Kennedy *et al*, 2001; 2002). The medical ethical committee of the Leiden University Medical Center (LUMC) approved the protocol and all participants gave informed consent.

Cases were men and women, aged between 30 and 80 y, with histologically proven squamous cell carcinoma, basal cell carcinoma, or nonfamilial cutaneous melanoma of the skin (De Hertog *et al*, 2001). Squamous cell carcinoma and basal cell carcinoma cases were newly diagnosed between January 1985 and December 1997 at the Department of Dermatology of the Leiden University Medical Center. Melanoma cases were newly diagnosed between January 1991 and April 1998. Controls in the same age range were recruited at the ophthalmology outpatient clinic of the Leiden University Medical Center (De Hertog *et al*, 2001). This group was chosen because it consisted of patients of the same University Hospital and living in the same region. Furthermore, most eye conditions are not related to painful sunburns or lifetime sun exposure and are not associated with skin cancer. All visitors to the ophthalmology outpatient clinic in the specific age range were asked to provide their names and addresses. Controls were excluded when they had either intraocular melanoma or any skin cancer in their personal history. Both cases and controls were excluded when they were transplant recipients or suffered from rare hereditary skin disorders such as xeroderma pigmentosum or basal cell nevus syndrome (Gorlin's syndrome), or were members of familial atypical mole melanoma families, as these persons are at an increased risk of developing skin cancer. Persons with a dark skin (Fitzpatrick classification V and higher) (Fitzpatrick, 1988), both case subjects and controls, were also excluded, as persons with these skin types rarely develop skin cancers.

All participants who were eligible for the study were sent a letter with an invitation to make an appointment at the dermatology outpatient clinic. Along with the letter a so-called Residence Work Calendar was sent. In this form, every change in residence or working environment had to be marked. All participants were asked to fill in the Residence Work Calendar to facilitate the assessment of lifetime sun exposure. About 70% of the cases and controls who were invited decided to participate in the study.

**Collection of data on risk factors for cutaneous malignancies** The visit at the dermatology outpatient consisted of a standardized interview

and a physical examination (De Hertog *et al*, 2001). A trained interviewer collected data on various potential risk factors for skin cancer such as sun exposure, smoking, and exposure to chemical agents. Interviewers and dermatologists performing the physical examination were blinded for the history of skin cancer.

Information on propensity to burn rather than tan (skin type) and type and duration of sun exposure was collected during the interview using a standardized questionnaire (obtainable from Dr. Bouwes Bavinck). Hours spent outdoors were recorded for working and nonworking days between 9 a.m. and 5 p.m. in the months of May to September. Similarly, during childhood and young adulthood, hours spent outdoors were recorded for school and/or study days and nonschool and/or study days. The whole year was taken into account when people had lived near the equator. Sun exposure during winter holidays to sunny or skiing resorts was also recorded. The Residence Work Calendar was utilized to assist in assessing relevant sun exposures in the past. Data regarding socioeconomic status or family history of skin cancer were not collected.

During physical examination a dermatologist recorded phenotypical characteristics of the participants as well as localization and count of dermatologic lesions of interest (actinic keratoses, seborrheic warts, common melanocytic nevi, and clinically atypical nevi) according to a standard protocol. Clinically atypical nevi were defined as acquired macular or slightly palpable nevi that showed a minimum of any three out of the following five criteria: diameter of 5 mm or larger, asymmetrical shape, ill-defined border, irregular brown pigmentation, and erythema. Nevi showing only one or two criteria were counted as normal nevi, although histologic features of dysplasia sometimes can be found in these nevi. Data on interobserver variability were not collected.

**Statistical analyses** All calculations were performed with the statistical software package JMP version 2 of the SAS Institute, Cary, NC. Comparisons of variable distributions between groups were performed using  $\chi^2$  tests. Relative risks were estimated using exposure odds ratios from cross-tabulation. Multivariate logistic regression was used to adjust for potential confounders. The influence of painful sunburns and lifetime sun exposure on the development of actinic keratoses, seborrheic warts, common melanocytic nevi, and clinically atypical nevi were evaluated for individuals with and without skin cancer combined and also separately for individuals without skin cancer only.

A total of 135 patients had two or more different types of skin cancer. Therefore, the data were analyzed twice. First, all patients with a certain type of skin cancer were analyzed, regardless of the presence of other types of skin cancer; second, only patients with just one type of skin cancer were analyzed. The outcomes of these calculations were not substantially different and therefore only the outcomes regardless of the presence of other types of skin cancer are presented.

## RESULTS

A total of 966 individuals from the Netherlands participated in a case-control study to investigate environmental and genetic risk factors for malignant melanoma and nonmelanoma skin cancer. For this study we used the same data set as in our previous publication (De Hertog *et al*, 2001). The group consisted of 580 patients with skin cancer (161 patients with squamous cell carcinoma, 302 with nodular basal cell carcinoma, 152 with superficial multifocal basal cell carcinoma, 125 with malignant melanoma) and 386 controls. A total of 135 patients had two or more different types of skin cancer (De Hertog *et al*, 2001).

**Baseline characteristics of the population** Characteristics of the study population according to skin cancer status were published earlier (De Hertog *et al*, 2001). Shortly, individuals with nonmelanoma skin cancer were slightly older and individuals with malignant melanoma slightly younger than individuals without any skin cancer and men were over-represented among patients with squamous cell carcinoma and nodular basal cell carcinoma. Skin types I and II were more frequently present among patients with each type of skin cancer (De Hertog *et al*, 2001).

Characteristics of the population according to the presence of actinic keratoses, seborrheic warts, 10 or more nevi, and atypical nevi are presented in **Table I**. In the study group overall, most people were women and had skin types I or II. Among people with actinic keratoses, there were significantly more men and

people with skin types I or II than in the people without actinic keratoses. Among people with seborrheic warts, there were also significantly more men but there were more people with skin types III or IV than in the people without seborrheic warts. The percentage of people with actinic keratoses and seborrheic warts was much higher in the older age groups, whereas people with 10 or more nevi and atypical nevi were much more frequent in the younger age groups. A total of 331 (84.4%) of the 392 people with actinic keratoses had seborrheic warts compared to 360 (62.7%) of the 574 people without actinic keratoses ( $p < 0.00001$ ); 145 (37.0%) of the people with actinic keratoses had 10 or more nevi compared to 338 (58.9%) of the people without actinic keratoses ( $p < 0.00001$ ); and 27 (6.9%) of the people with actinic keratoses had atypical nevi compared to 60 (10.5%) of the 574 people without actinic keratoses ( $p = 0.05$ ). A total of 331 (47.9%) of the 691 people with seborrheic keratoses had actinic keratoses compared to 61 (22.2%) of the 275 people without seborrheic keratoses ( $p < 0.00001$ ); 309 (44.7%) of the people with seborrheic keratoses had 10 or more nevi compared to 174 (63.3%) of the people without seborrheic keratoses ( $p < 0.00001$ ); and 48 (7.0%) of the people with seborrheic keratoses had atypical nevi compared to 39 (14.2%) of the people without seborrheic keratoses ( $p < 0.001$ ). A total of 79 (16.4%) of the 483 people with 10 or more nevi had atypical nevi compared to eight (1.7%) of the 483 people with less than 10 nevi ( $p < 0.00001$ ).

**Distribution of potential precursor lesions among the skin cancer cases and controls** Compared with individuals without any skin cancer, actinic keratoses and seborrheic warts were significantly more often present among individuals with squamous cell carcinoma, nodular basal cell carcinoma, and/or superficial multifocal basal cell carcinoma. The percentages of individuals with actinic keratoses were 73%, 58%, 57%, 28%, and 26% in the 161 cases with squamous cell carcinoma, the 302 cases with nodular basal cell carcinoma, the 152 cases with superficial multifocal basal cell carcinoma, the 125 cases with malignant melanoma, and the 386 individuals without any skin cancer, respectively. Regarding seborrheic warts, these percentages were 86%, 79%, 78%, 50%, and 68%, respectively. Individuals with malignant melanoma had significantly fewer seborrheic warts than individuals without any skin cancer.

Individuals with malignant melanoma had significantly more common melanocytic nevi and atypical nevi. The percentages of individuals with 10 or more nevi were 35%, 47%, 54%, 86%, and 46%, for cases with squamous cell carcinoma, cases with nodular basal cell carcinoma, cases with superficial multifocal basal cell carcinoma, cases with malignant melanoma, and individuals without any skin cancer, respectively. Regarding atypical nevi these percentages were 5%, 7%, 9%, 22%, and 7%, respectively.

**Painful sunburns before the age of 20 y are associated with each type of skin cancer** Painful sunburns before the age of 20 y were associated with each type of skin cancer. The odds ratios, which were adjusted for age, sex, and skin type of the individuals, are presented in **Table II**. The highest odds ratios were obtained before the age of 6 y. The nonadjusted odds ratios were not materially different compared to the adjusted odds ratios. After the age of 20 y, only malignant melanoma was significantly associated with painful sunburns between the age of 20 and 40 y (**Table II**).

**Chronic sun exposure is associated with an increased risk of nonmelanoma skin cancer, but not with an increased risk of malignant melanoma** Lifetime sun exposure was associated with an increased risk of nonmelanoma skin cancer and a decreased risk of malignant melanoma. The nonadjusted odds ratios with 95% confidence intervals to develop squamous cell carcinoma were 3.6 (1.2; 10.4), 5.0 (1.7; 14.7), and 11.8 (4.1; 34.5) for individuals with 20,000–29,999, 30,000–39,999, and 40,000 and more hours of lifetime sun exposure, respectively, compared with individuals with less than 20,000 h of lifetime sun exposure. For nodular basal cell carcinoma the nonadjusted odds ratios were 1.6 (0.90; 3.0), 2.4 (1.3; 4.3), and 3.9 (2.1; 7.1), respectively; for superficial multifocal basal cell carcinoma the nonadjusted odds ratios were 1.3 (0.64; 2.5), 1.6 (0.81; 3.3), and 2.2 (1.1; 4.5), respectively; and for malignant melanoma the nonadjusted odds ratios were 0.31 (0.19; 0.52), 0.13 (0.06; 0.26), and 0.20 (0.10; 0.40), respectively. Adjustment for age, sex, and skin type dramatically changed the odds ratios, which was exclusively caused by adding age to the model (**Table III**). There was still a positive association between increasing lifetime sun exposure and the development of nonmelanoma skin cancer, but statistical significance was not always reached (**Table III**). Similarly, lifetime sun exposure was still protective for the development of malignant melanoma when comparing the two intermediate sun exposure groups with the lowest group, but the protective effect disappeared when comparing the highest sun exposure group with the lowest group (**Table III**).

**Painful sunburns before the age of 20 y are associated with actinic keratoses and nevi, but not with seborrheic warts** Painful sunburns before the age of 20 y were associated with actinic keratoses, 10 or more nevi, and atypical nevi, but not with seborrheic warts. The odds ratios, which were adjusted for age, sex, and skin type of the individuals, are presented in **Table IV**. The nonadjusted odds ratios were not materially different compared to the adjusted odds ratios. Also analyses performed on the subgroup of 386 individuals without any skin cancer showed roughly the same odds ratios. After the age of 20 y, only the development of actinic keratoses was associated

**Table I. Baseline characteristics of the study population with actinic keratoses, seborrheic warts, 10 or more nevi, and atypical nevi<sup>a</sup>**

	All ( $n = 966$ ), $N$ (%)	With actinic keratoses ( $n = 392$ ), $N$ (%)	With seborrheic warts ( $n = 691$ ), $N$ (%)	With 10 or more nevi ( $n = 483$ ), $N$ (%)	With atypical nevi ( $n = 87$ ), $N$ (%)
Gender					
Men	466 (48.2)	254 (64.8)***	353 (51.1)**	234 (48.5) NS	50 (57.5) NS
Women	500 (51.8)	138 (35.2)	338 (48.9)	249 (51.6)	37 (42.5)
Age (y)					
24–49	226 (23.4)	24 (6.1)***	86 (12.5)***	177 (36.7)***	45 (51.7)***
50–59	232 (24.0)	66 (16.8)	160 (23.1)	147 (30.4)	20 (23.0)
60–69	289 (29.9)	156 (39.8)	248 (35.9)	109 (22.6)	20 (23.0)
70–79	219 (22.7)	146 (37.3)	197 (28.5)	50 (10.3)	2 (2.3)
Skin type					
III or IV	433 (44.8)	156 (39.8)**	325 (47.0)*	213 (44.1) NS	38 (43.7) NS
I or II	533 (55.2)	236 (60.2)	366 (53.0)	270 (55.9)	49 (56.3)

<sup>a</sup> \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.0001$ , NS, not significant. The groups are compared with individuals without actinic keratoses, without seborrheic warts, with fewer than 10 nevi, and without atypical nevi, respectively.

**Table II. Association of painful sunburns at different age periods with different types of skin cancer<sup>d</sup>**

	Controls without skin cancer (n = 386), <sup>b</sup> N (%) <sup>c</sup>	Squamous cell carcinoma (n = 161), <sup>b</sup> N (%) <sup>c</sup>	Nodular basal cell carcinoma (n = 302), <sup>b</sup> N (%) <sup>c</sup>	Superficial multifocal basal cell carcinoma (n = 152), <sup>b</sup> N (%) <sup>c</sup>	Malignant melanoma (n = 125), <sup>b</sup> N (%) <sup>c</sup>
Age 0–19 y	142 (36.8)	76 (47.2)	142 (47.0)	91 (60.3)	69 (55.2)
0–5 y	15 (3.9)	11 (7.1)	24 (8.0)	17 (11.4)	23 (18.6)
6–12 y	54 (14.0)	40 (25.2)	71 (23.6)	50 (33.1)	39 (31.5)
13–19 y	111 (28.8)	54 (33.8)	94 (31.1)	62 (40.8)	52 (41.6)
Age 20–39 y	119 (30.8)	55 (34.4)	106 (35.1)	50 (32.9)	59 (47.2)
Age 40–59 y	33 (9.2)	12 (7.6)	35 (11.9)	12 (8.3)	6 (6.8)
Odds ratios with 95% confidence intervals adjusted for age, sex, and skin type					
No sunburns (reference group)		1	1	1	1
One or more sunburns per age group					
Age 0–19 y		1.5 (0.97; 2.3)	1.6 (1.1; 2.2)	2.6 (1.7; 3.8)	1.4 (0.86; 2.1)
0–5 y		2.3 (0.94; 5.8)	2.3 (1.2; 4.7)	3.2 (1.5; 6.7)	3.2 (1.5; 6.7)
6–12 y		1.8 (1.1; 3.0)	1.8 (1.2; 2.7)	2.8 (1.7; 4.4)	1.8 (1.0; 3.0)
13–19 y		1.3 (0.85; 2.1)	1.2 (0.82; 1.7)	1.7 (1.1; 2.6)	1.2 (0.8; 1.9)
Age 20–39 y		1.1 (0.73; 1.7)	1.2 (0.86; 1.7)	1.0 (0.66; 1.5)	1.6 (1.0; 2.5)
Age 40–59 y		0.84 (0.37; 1.8)	1.5 (0.86; 2.4)	0.90 (0.44; 1.8)	0.66 (0.26; 1.7)

<sup>a</sup>Some patients have more than one type of skin cancer.

<sup>b</sup>The numbers of individuals in these categories do not always add up to the total number, because of some missing values and because some individuals were younger than 40 y.

<sup>c</sup>Number of individuals with one or more sunburns at different age periods.

**Table III. Association of lifetime sun exposure with different types of skin cancer<sup>d</sup>**

Lifetime sun exposure (h)	Controls without skin cancer (n = 386), N (%)	Squamous cell carcinoma (n = 161), N (%)	Nodular basal cell carcinoma (n = 302), N (%)	Superficial multifocal basal cell carcinoma (n = 152), N (%)	Malignant melanoma (n = 125), N (%)
8932–19,999	50 (13.0)	4 (2.5)	18 (6.0)	13 (8.5)	49 (39.2)
20,000–29,999	158 (40.9)	45 (27.9)	93 (30.8)	52 (44.2)	48 (38.4)
30,000–39,999	103 (26.7)	41 (25.5)	87 (28.8)	44 (28.9)	13 (10.4)
40,000 and more	75 (19.4)	71 (44.1)	104 (34.4)	43 (28.3)	15 (12.0)
Odds ratios with 95% confidence intervals adjusted for age, sex, and skin type					
8932–19,999		1	1	1	1
20,000–29,999		2.4 (0.77; 7.4)	1.2 (0.61; 2.2)	1.1 (0.54; 2.3)	0.50 (0.28; 0.90)
30,000–39,999		2.1 (0.57; 7.5)	1.5 (0.72; 3.3)	1.9 (0.81; 4.6)	0.47 (0.17; 1.3)
40,000 and more		6.5 (1.7; 25.6)	2.3 (0.96; 5.7)	1.6 (0.56; 4.4)	1.4 (0.40; 4.8)
Test for trend		P (trend) = 0.03	P (trend) = 0.06	P (trend) = 0.07	P (trend) = 0.66

<sup>a</sup>Some patients have more than one type of skin cancer.

with painful sunburns but mainly when the sunburns occurred between the age of 40 and 60 y (Table IV).

**Chronic sun exposure is associated with an increased risk of actinic keratoses, but not with an increased risk of seborrheic warts or nevi** Lifetime sun exposure was associated with an increased risk of actinic keratoses. The nonadjusted odds ratios with 95% confidence intervals to develop actinic keratoses were 3.1 (1.7; 5.6), 5.9 (3.2; 10.8), and 19.0 (10.2; 35.4) for individuals with 20,000–29,999, 30,000–39,999, and 40,000 and more hours of lifetime sun exposure, respectively, compared with individuals with less than 20,000 h of lifetime sun exposure. Adjustment for age, sex, and skin type dramatically lowered the odds ratios, which was again exclusively caused by adding age to the model (Table V).

The nonadjusted calculations also showed an association between lifetime sun exposure and an increased risk of seborrheic warts. The nonadjusted odds ratios with 95% confidence intervals to develop seborrheic warts were 2.8 (1.9; 4.3), 5.3 (3.3; 8.5), and 7.5 (4.6; 12.4) for individuals with 20,000–29,999, 30,000–39,999, and 40,000 and more hours of lifetime sun exposure, respectively, compared with individuals with less than 20,000 h of lifetime sun exposure. This association, however, disappeared completely after adjustment for age, sex, and skin type (Table V).

By contrast, the nonadjusted calculations showed a negative association between lifetime sun exposure and the presence of 10

or more nevi and atypical nevi. The nonadjusted odds ratios with 95% confidence intervals to develop 10 or more nevi were 0.60 (0.39; 0.95), 0.25 (0.16; 0.40), and 0.19 (0.12; 0.31) for individuals with 20,000–29,999, 30,000–39,999, and 40,000 and more hours of lifetime sun exposure, respectively, compared with individuals with less than 20,000 h of lifetime sun exposure, and for atypical nevi the nonadjusted odds ratios were 0.94 (0.52; 1.7), 0.24 (0.11; 0.54), and 0.28 (0.13; 0.61), respectively. Again, however, this association completely disappeared after adjustment for age, sex, and skin type (Table V).

The relative contribution of increasing age and lifetime sun exposure is presented in Table VI. With increasing age the percentage of individuals with actinic keratoses and seborrheic warts is strongly increasing, whereas the percentage of individuals with 10 or more nevi and atypical nevi is strongly decreasing. With increasing lifetime sun exposure only the percentage of individuals with actinic keratoses is increasing (Table VI).

## DISCUSSION

This study confirmed the existing literature that the recall of painful sunburns before the age of 20 y is associated with an increased risk of squamous cell carcinoma, nodular and superficial multifocal basal cell carcinoma, and malignant melanoma. In addition to the existing literature, this study showed that the recall

**Table IV. Association of painful sunburns at different age periods with actinic keratoses, seborrheic warts, 10 or more nevi, and atypical nevi<sup>a</sup>**

	All ( <i>n</i> = 966) <sup>b</sup> , N (%) <sup>c</sup>	With actinic keratoses ( <i>n</i> = 392) <sup>b</sup> , N (%) <sup>c</sup>	With seborrheic warts ( <i>n</i> = 691) <sup>b</sup> , N (%) <sup>c</sup>	With 10 or more nevi ( <i>n</i> = 483) <sup>b</sup> , N (%) <sup>c</sup>	With atypical nevi ( <i>n</i> = 87) <sup>b</sup> , N (%) <sup>c</sup>
Age 0–19 y	426 (44.1)	189 (48.3)	286 (41.5)	248 (51.4)	49 (56.3)
0–5 y	71 (7.4)	35 (9.1)	41 (6.0)	48 (10.0)	10 (11.5)
6–12 y	203 (21.1)	100 (25.6)	142 (20.6)	119 (24.8)	24 (27.6)
13–19 y	310 (32.1)	128 (32.7)	201 (29.1)	185 (38.4)	40 (46.0)
Age 20–39 y	321 (33.3)	130 (33.3)	216 (31.3)	173 (35.9)	34 (39.1)
Age 40–59 y	86 (9.7)	46 (11.9)	61 (9.1)	40 (9.7)	8 (11.0)
Odds ratios with 95% confidence intervals adjusted for age, sex, and skin type					
No sunburns (reference group)		1	1	1	1
One or more sunburns per age group					
Age 0–19 y		1.9 (1.4; 2.6)	0.96 (0.69; 1.3)	1.5 (1.1; 2.0)	1.4 (0.88; 2.3)
0–5 y		3.0 (1.7; 5.4)	0.87 (0.49; 1.5)	1.6 (0.87; 2.9)	1.2 (0.55; 2.5)
6–12 y		2.1 (1.4; 3.1)	1.3 (0.90; 2.0)	1.2 (0.84; 1.8)	1.2 (0.69; 2.0)
13–19 y		1.5 (1.1; 2.1)	0.88 (0.63; 1.2)	1.4 (1.0; 1.9)	1.7 (1.0; 2.7)
Age 20–39 y		1.2 (0.87; 1.7)	0.91 (0.65; 1.3)	1.0 (0.76; 1.4)	1.2 (0.74; 1.9)
Age 40–59 y		2.0 (1.1; 3.3)	0.77 (0.45; 1.3)	1.0 (0.61; 1.6)	1.3 (0.59; 3.0)

<sup>a</sup>The groups are compared with individuals without actinic keratoses, without seborrheic warts, with fewer than 10 nevi, and without atypical nevi, respectively.

<sup>b</sup>The numbers of individuals in these categories do not always add up to the total number, because of some missing values and because some individuals were younger than 40 y.

<sup>c</sup>Number of individuals with one or more sunburns at different age periods.

**Table V. Association of lifetime sun exposure with actinic keratoses, seborrheic warts, 10 or more nevi, and atypical nevi<sup>a</sup>**

	All ( <i>n</i> = 966), N (%)	With actinic keratoses ( <i>n</i> = 392), N (%)	With seborrheic warts ( <i>n</i> = 691), N (%)	With 10 or more nevi ( <i>n</i> = 483), N (%)	With atypical nevi ( <i>n</i> = 87), N (%)
Lifetime sun exposure (h)					
8932–19,999	123 (12.7)	14 (3.6)	52 (7.6)	89 (18.4)	18 (20.7)
20,000–29,999	346 (35.8)	98 (25.0)	233 (33.7)	212 (43.9)	48 (55.2)
30,000–39,999	254 (26.3)	109 (27.8)	202 (29.2)	101 (20.9)	10 (11.5)
40,000 and more	243 (25.2)	171 (43.6)	204 (29.5)	81 (16.8)	11 (12.6)
Odds ratios with 95% confidence intervals adjusted for age, sex and skin type					
8932–19,999		1	1	1	1
20,000–29,999		1.6 (0.79; 3.0)	1.2 (0.69; 1.9)	1.4 (0.78; 2.3)	1.5 (0.8; 2.9)
30,000–39,999		1.8 (0.81; 3.8)	0.95 (0.47; 1.92)	1.2 (0.61; 2.4)	0.58 (0.18; 1.9)
40,000 and more		4.5 (1.9; 10.5)	1.3 (0.54; 3.0)	1.2 (0.55; 2.6)	0.85 (0.20; 3.5)
Test for trend		P (trend) < 0.0001	P (trend) = 0.34	P (trend) = 0.36	P (trend) = 0.21

<sup>a</sup>The groups are compared with individuals without actinic keratoses, without seborrheic warts, with fewer than 10 nevi, and without atypical nevi, respectively.

of painful sunburns before the age of 20 y is associated with an increased risk of actinic keratoses, 10 or more melanocytic nevi, and clinically atypical nevi, but not with an increased risk of seborrheic warts. Painful sunburns after the age of 20 y were only associated with an increased risk of malignant melanoma but not with nonmelanoma skin cancer, despite the fact that an association was observed of painful sunburns between the age of 40 and 60 y and an increased risk of actinic keratoses.

As expected, lifetime sun exposure was associated with an increased risk of squamous cell carcinoma and to a lesser degree with the two types of basal cell carcinoma, but not with an increased risk of malignant melanoma. By contrast, lifetime sun exposure appeared to be protective for the development of malignant melanoma, although, after adjustment for age, sex, and skin type, the protective effect disappeared in those individuals with the highest amount of lifetime sun exposure. Lifetime sun exposure was also associated with an increased risk of actinic keratoses, but lifetime sun exposure was not associated with the development of seborrheic warts or the disappearance of common melanocytic nevi and atypical nevi.

Increasing age was the strongest factor determining the development of actinic keratoses and seborrheic warts. Increasing age was also the strongest factor determining the disappearance of melanocytic nevi and atypical nevi. The steep decrease of the number of melanocytic nevi with age has been reported before in both the immunocompetent population (Garbe *et al*, 1994; Bataille *et al*, 1998) and renal transplant recipients (Bouwens

Bavinck *et al*, 1996). Age was the strongest confounder in the relation between lifetime sun exposure and the outcome of precursor lesions and skin cancer.

Our findings confirm earlier reports that the recall of painful sunburns before the age of 20 y is associated with the development of nonmelanoma skin cancer and malignant melanoma (Green and Battistutta, 1990; Kricker *et al*, 1995; Elwood and Jopson, 1997). Sunburns, particularly in childhood, may be considered to be initiating events in the sequence of developing a malignancy (de Gruijl, 1999), but these sequences may be different for the different types of skin cancer.

Acute and chronic sun exposure may promote both the development of actinic keratoses and the subsequent squamous cell carcinomas (Alam and Ratner, 2001). Ultraviolet radiation generates specific mutations (through pyrimidine dimers) in the p53 tumor-suppressor gene (Brash *et al*, 1991; Alam and Ratner, 2001). Normally, keratinocytes with damaged DNA sequences undergo apoptosis. Keratinocytes with dysfunctional p53, however, cannot undergo apoptosis and instead undergo clonal expansion, which is manifested clinically as the development of actinic keratoses (Alam and Ratner, 2001). Uncontrolled proliferation of abnormal cells finally could lead to squamous cell carcinoma. Seborrheic warts do not appear to play a role in this sequence of events.

Based on earlier studies (Kricker *et al*, 1994; 1995) and on our own findings, the development of nodular and superficial multifocal basal cell carcinoma may also be promoted by acute and

**Table VI. Association of increasing age and lifetime sun exposure with the percentage of individuals with actinic keratoses, seborrheic warts, 10 or more nevi, and atypical nevi**

Age (y)	Lifetime sun exposure (h × 1000)				P (trend)
	8–19, No. (%)	20–29, No. (%)	30–39, No. (%)	40 or more, No. (%)	
<b>Actinic keratoses</b>					
24–49	93 (7.5)	115 (11.3)	13 (15.4)	5 (40.0)	0.04
50–59	18 (16.7)	118 (28.0)	69 (21.7)	27 (55.6)	0.03
60–69	8 (37.5)	77 (42.9)	94 (46.8)	110 (69.1)	0.001
70–79	4 (25.0)	36 (52.8)	78 (61.5)	101 (78.8)	0.0003
P (trend)	0.01	<0.00001	<0.00001	0.003	
<b>Seborrheic warts</b>					
24–49	93 (31.2)	115 (43.5)	13 (38.5)	5 (40.0)	0.18
50–59	18 (72.2)	118 (71.2)	69 (65.2)	27 (66.7)	0.43
60–69	8 (87.5)	77 (87.0)	94 (84.0)	110 (86.4)	0.91
70–79	4 (75.0)	36 (88.9)	78 (93.6)	101 (89.9)	0.72
P (trend)	0.00006	<0.00001	<0.00001	0.0004	
<b>Ten or more nevi</b>					
24–49	93 (77.4)	115 (79.1)	13 (84.6)	5 (60.0)	0.97
50–59	18 (66.7)	118 (68.6)	69 (59.4)	27 (48.1)	0.05
60–69	8 (50.0)	77 (40.3)	94 (36.2)	110 (36.4)	0.45
70–79	4 (25.0)	36 (25.0)	78 (19.2)	101 (25.3)	0.73
P (trend)	0.001	<0.00001	<0.00001	0.01	
<b>Atypical nevi</b>					
24–49	93 (18.3)	115 (22.6)	13 (7.7)	5 (20.0)	0.99
50–59	18 (0)	118 (11.9)	69 (5.8)	27 (7.4)	0.50
60–69	8 (12.5)	77 (9.1)	94 (5.3)	110 (6.4)	0.40
70–79	4 (0)	36 (2.8)	78 (0)	101 (1.0)	0.06
P (trend)	0.53	0.0006	0.13	0.01	

No. refers to the total number of individuals in that category. The percentage refers to individuals with actinic keratoses, seborrheic warts, 10 or more nevi, and atypical nevi within that category, respectively.

chronic sun exposure, although the effect of chronic sun exposure is less pronounced than in the development of squamous cell carcinomas.

Acute and chronic sun exposure may exert different effects in the sequel from common melanocytic nevi, clinically atypical nevi to malignant melanoma (Elwood and Jopson, 1997; Gilchrest *et al*, 1999). Acute painful sunburns may promote the development of common melanocytic nevi, clinically atypical nevi, and thus, or possibly independently, the development of malignant melanoma. Although there are some contradictory findings regarding the association between chronic lifetime sun exposure and malignant melanoma, most studies found that chronic lifetime sun exposure was associated with a protective effect on the development of malignant melanoma. This could be explained by the protective mechanisms, which are associated with heavy chronic sun exposure, such as tanning and skin thickening, but this may not be the total explanation (Elwood and Jopson, 1997; Gilchrest *et al*, 1999). Although it cannot be excluded that sun exposure during adult life promotes the disappearance of nevi, which could be an additional explanation of a decreased risk of malignant melanoma, in our study the disappearance of nevi was completely explained by increasing age of the individuals, and chronic sun exposure had no additional effect.

The inverse association between age and the number of nevi can be simply explained by the disappearance of nevi with age, but could also be explained in a different way: the decline in nevus numbers may also reflect a change in nevus prevalence across birth cohorts (Green and Swerdlow, 1989). For example, 13- to 15-year-old children who were born between 1977 and 1978 had some 5- to 6-fold higher prevalence of nevi than a comparable group of children born two decades earlier (Green *et al*, 1995).

Case-control studies have some clear limitations. One should be alert to several potential sources of bias at every stage of study design, specifically regarding the selection of controls ("selection bias"). Selection bias results when controls (or cases) are included in or excluded from a study because of some characteristics they

exhibit that are related to exposure to a candidate causal factor. In addition, all the inaccuracies that may lead to a wrong estimation of exposure can be responsible for "information bias". Examples of information bias are "recall bias" and "wish bias". Recall bias is when individuals with a disease tend to think about the causes of their disease or to have heard about the possible causes of their disease and are thus more likely to remember their exposure histories differently from controls. By contrast, cases may also tend to deny exposure more than controls, as they wish to show that the disease is not their fault (wish bias). In this study, it is not conceivable that the observed positive and negative associations between sun exposure and skin cancer are merely the result of recall bias and wish bias, as it is not likely that recall bias would have mainly occurred in cases with nonmelanoma skin cancer and wish bias mainly in cases with malignant melanoma. As this study is a hospital-based study, the results can only be generalized to hospital-based populations.

In conclusion, the recall of painful sunburns before the age of 20 y was associated with an increased risk of all three types of nonmelanoma skin cancer as well as actinic keratoses. Painful sunburns before the age of 20 y were also associated with an increased risk of malignant melanoma and the development of its precursors, melanocytic nevi and atypical nevi. Lifetime sun exposure was only associated with an increased risk of squamous cell carcinoma and actinic keratoses and to a lesser degree with basal cell carcinoma. By contrast, lifetime sun exposure was associated with a decreased risk of malignant melanoma, despite the fact that lifetime sun exposure did not diminish the number of melanocytic nevi or atypical nevi. Seborrheic warts did not appear to play a role in the sequence of any of these events.

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## ADDENDUM

Members of the Leiden Skin Cancer Study are, in alphabetical order: Nathalie van Amsterdam, Maarten T. Bastiaens, Wilma Bergman, Marjo J.P. Berkhout, Jan N. Bouwes Bavinck, Ingeborg L.A. Boxman, René Broer, Jan A. Bruijn, Marianne Crijns, Mariet Feltkamp, Nelleke A. Gruis, Sofie A.E. De Hertog, Juliette J. Hoefnagel, Jeanet A.C. ter Huurne, Cornelis Kennedy, Christine J. Kielich, Iris Kuijken, Sjan P.M. Lavrijsen, Linda H.C. Mulder, Marloes Polderman, Marinus C.G. van Praag, Jan ter Schegget, Caesar Sterk, Linda Struijk, Jan P. Vandenbroucke, Bert J. Vermeer, Christianne A.H. Wensveen, Rudi G.J. Westendorp.

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