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Ultraviolet Light Exposure, Pigmentary Traits and the Development of Melanocytic Naevi and Cutaneous Melanoma

A Case-control Study of the German Central Malignant Melanoma Registry

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The present study firstly aimed at understanding the relationship between sun exposure, pigmentary traits and the history of sunburns. Secondly, the significance of UV-exposure for cutaneous melanoma and for melanocytic naevi was investigated.

The case-controlled study comprised 513 patients with primary cutaneous melanoma and 498 controls matched by age and gender. Multivariate logistic regression analysis was used to study melanoma risk factors.

The number of common melanocytic naevi was associated with age, gender, the history of sunburns and UV-exposure during holidays (odds-ratio = 1.9; 95% confidence interval = [1.1, 3.4]) for 3 weeks or more. The number of atypical melanocytic naevi was significantly related to age, gender, pigmentary traits, the history of sunburns and UV-exposure during holidays (odds-ratio = 3.5; 95% confidence interval = [1.4, 9.0]) for 2 months or more.

The results of the present study showed that both the history of sunburn and intensive sun exposure during holidays were important for the development of melanocytic naevi and, therefore, indirectly for cutaneous melanoma. In addition, a particular type of pigmentation was found to be related to atypical melanocytic naevi. ***Key words: melanoma risk factors; risk groups; epidemiologic study.***

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The incidence of cutaneous melanoma has been rapidly increasing, and many efforts have been made to identify risk factors associated with the development of this highly malignant tumour (1–7). In a series of studies, the number and the type of melanocytic lesions proved to be major risk markers for the development of cutaneous melanoma. In particular, the number of common melanocytic naevi (CMN) and, if differentiated, the number of atypical melanocytic naevi (AMN) showed to be independent markers of an increased risk for the development of cutaneous melanoma (8–10).

Increasing evidence points to the possible role of sunlight as a cause of cutaneous melanoma (2, 5, 11). However, different case-control studies on risk factors for the development of cutaneous melanoma revealed different results concerning the influence of UV-exposure (6, 7). Moreover, the number of CMN and AMN may depend on the amount of sun exposure received, and, therefore, failure to prove a direct relationship between UV-exposure and the risk of cutaneous melanoma is not surprising (12).

In two previous articles on the data of the present case-control study, we first confirmed CMN and AMN as major risk markers for the development of cutaneous melanoma, and, in a second independent analysis, we investigated the correlation between sunburns and the number of CMN and AMN (12, 13). In particular, the number of painful sunburns throughout life and the number of sunburns before the age of 20 turned out to be of crucial importance for the development of CMN and AMN. However, sunburns probably function as intermediate variables depending on a variety of factors, including the amount of recreational and occupational sun exposure and pigmentary characteristics of the host. Therefore, the relation between pigmentary traits, sun exposure habits and the number of sunburns was additionally investigated and described in this article. In a second step, the analysis was focused on the influence of various kinds of UV-exposure and pigmentary traits on the development of cutaneous melanoma, CMN and AMN. There is, however, some inevitable duplication of previously reported results.

MATERIALS AND METHODS

Study subjects

Between January 1990 and June 1991, 283 females (55.2%) and 230 males (44.8%) with primary cutaneous melanoma were newly diagnosed at one of the nine cooperating departments of dermatology. A total of 498 control patients of the participating departments of dermatology, matched according to age (±5 years) and gender, were chosen as controls. Further details of the methods were previously published (13).

In short, all subjects underwent a whole-body examination and exact documentation of all pigmented lesions. CMN and AMN were counted separately. Patients with primary cutaneous melanoma and controls were interviewed prior to physical examination, using a standardised questionnaire. The data recorded included the amount of occupational and recreational sun exposure at home and during holidays within the last 2 years, as well as the frequency of the use of sunbeds. The variable UV-exposure during holidays used in multivariate analysis is the sum of days spent with beach activities in North and Middle Europe plus days spent with beach activities in Mediterranean countries and the Tropics. The interview included questions about the history of sunburns, distinguishing between sunburns before and after the age of 20, sunburns within the last 5 years and painful sunburns at any time of life.

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Statistical analysis

The correlation between the different variables of sun exposure, pigmentary traits and cutaneous melanoma, the number of CMN and the number of AMN was initially tested bivariately using Pearson's correlation coefficient, the χ^2 test and the Wilcoxon–Mann–Whitney U-test. All p-values calculated are two-sided and the significance level was chosen to be 0.05. The associations between the history of sun exposure, melanocytic naevi, pigmentary traits and cutaneous melanoma were analysed using multivariate logistic regression analysis. Data handling and bivariate analysis were performed using the statistical package SPSS for Windows. The modules 2R and LR of the statistical package BMDP were applied for multivariate analysis (14).

RESULTS

History of sunburns

Age, gender, skin type and freckles in adolescence proved to be significantly associated with both sunburns before the age of 20 and painful sunburns throughout life, 64.1% of males compared to 52.7% of females reported sunburns before the age of 20, resulting in a significantly increased relative risk for sunburns in males (RR = 1.9). Similarly, 68.9% of males compared to 65.2% of females had at some point experienced painful sunburns, and, therefore, males had an increased relative risk for painful sunburns (RR = 1.5). Skin type 1 or 2 compared to 3 or 4 increased the odds ratio by a factor of 2.0 for the presence of sunburns before the age of 20, and by a factor of 3.0 for the presence of painful sunburns at any time of life. The presence of freckles in adolescence showed an additional independent effect on the history of sunburns.

The amount of sun exposure during the last 2 years, classified into recreational UV-exposure at home, UV-exposure during holidays and occupational UV-exposure, showed no significant influence on the presence of painful sunburns. However, 78.5% of patients with occasional or regular use of sunbeds, compared to 64.5% of patients who never used sunbeds, reported painful sunburns, resulting in a significantly increased estimation of relative risk by a factor of 1.9.

Cutaneous melanoma

Melanocytic naevi and actinic lentigines proved to be the most important independent significant risk factors for cutaneous melanoma in the multivariate logistic regression analysis. Additionally, skin type and hair colour proved to be statistically significant in the calculated model. These results of the present study have already been published (13). None of the variables of sun exposure, nor the history of sunburns proved to have an influence when competing with the other variables in the model. However, in the univariate analysis the number of sunburns before the age of 20 ($p < 0.05$) and UV-exposure during holidays at the beach ($p = 0.0634$) showed at least a borderline significance.

Common melanocytic naevi

Multivariate linear regression analysis revealed independent significant effects of age, gender, painful sunburns throughout life, sunburns before the age of 20 and the amount of UV-exposure during holidays within the last 2 years on the number of CMN. Table I gives the analogous results of the multivariate logistic regression analysis, calculated after classifying the number into 50 or less versus more than 50 CMN.

Pigmentary traits like skin type, hair colour, or freckles in adolescence showed no additional significant effect on the prevalence of CMN. The results given in Table I remained the same, even if the influence of sunburns was not taken into account. Without the influence of sunburns, only hair colour showed an additional significant effect (hair colour blond or red: odds ratio = 1.6; 95% confidence interval = [1.0, 2.4]; $p < 0.05$). However, among the different variables of sun exposure studied, the amount of UV-exposure during holidays within the last 2 years proved to have significant influence on the development of CMN. A more detailed analysis showed that 21 to 39 days of sun exposure during holidays at the beach led to a significant increase in the prevalence of more than 50 CMN by a factor of 1.9 (95%-confidence interval = [1.1, 3.4]) (Fig. 1a). Increasing the number of days spent at the beach consistently increased the odds ratio of CMN, but the effects were not significantly different, compared to the period of 21 to 39 days. The days of sun exposure during holidays within the last 2 years were calculated as the sum of days spent with beach activities in north and middle Europe plus days spent with beach activities in Mediterranean countries and the Tropics.

Atypical melanocytic naevi

Multivariate linear regression analysis revealed an independent significant influence of age, gender, hair colour, freckles in adolescence, sunburns before the age of 20, and the amount of UV-exposure during holidays within the last 2 years on the number of AMN. Table II gives the results of the multivariate logistic regression analysis, calculated after classifying the number into less than 5 versus 5 or more AMN.

In contrast to the results for CMN, blond or red hair colour as well as many freckles in adolescence showed both an additional significant influence on the prevalence of 5 or more AMN. The results given in Table II were alike with and without the effect of sunburn, and the same variables with similar estimations were found to build the model. The days of sun exposure during holidays within the last 2 years likewise proved to be the only important variable of sun exposure. Fig. 1b gives the results of the detailed analysis, showing a consistent increase in the odds ratio of AMN with increasing numbers of days spent with beach activities. The influence, however, was found to be significant only for a period of sun exposure of 2 months or more, with a calculated relative risk of 3.5 (95%-confidence interval = [1.5, 8.8]).

DISCUSSION

The aetiologic role of sun exposure in the development of cutaneous melanoma is still subject of controversial discussion. The relationship between the amount of sun exposure and the potential risk of developing cutaneous melanoma has been doubted because of the following clinical and epidemiological features: cutaneous melanoma predominantly arises during the middle decades of life, and its distribution does not correspond to the body regions with the highest cumulative sun exposure (5). Thus, in contrast to epithelial skin cancer, where a broad consensus exists about the aetiologic role of sun exposure, no clear relation between lifelong cumulative UV-dose and elevated risk of cutaneous melanoma can be established. Furthermore, a number of case-control studies have failed to

Table I. *Influence of sun exposure and pigmentary traits on the prevalence of more than 50 common melanocytic naevi#*

Associated factors	Common melanocytic naevi ≤50 ($n=576$)	>50 ($n=128$)	Odds-ratio [95%CI⁺]	p-value
UV-exposure during holidays⁺⁺	/	/	1.01 [1.01, 1.02]	$p<0.001$
Recreational UV-exposure⁺⁺ at home	/	/	/	$p=0.12$
Occupational UV-exposure⁺⁺	/	/	/	$p=0.67$
Use of sunbeds				
Never	494	97		
Occasional	61	28	/	$p=0.77$
Regular	21	3	/	$p=0.06$
Painful sunburns				
None	208	26	1	
Some	368	102	2.6 [1.4, 4.6]	$p<0.01$
Sunburns before the age of 20				
<2	253	40	1	
≥2	323	88	1.6 [1.0, 2.6]	$p<0.05$
Skin type				
3 or 4	352	70		
1 or 2	224	58	/	$p=0.26$
Hair colour				
Black or brown	240	46		
Blond or red	336	82	/	$p=0.05$
Freckles in adolescence				
None	317	72		
Few, moderate or many	259	56	/	$p=0.26$
Age⁺⁺	/	/	0.96 [0.95, 0.97]	$p<0.0001$
Gender				
Female	340	56	1	
Male	236	72	2.2 [1.4, 3.4]	$p<0.001$

⁺ CI=confidence interval. ⁺⁺ Age, recreational UV-exposure at home, UV-exposure during holidays, and occupational UV-exposure are considered as continuous variables. Therefore, their estimated relative risks cannot be directly compared.
Results of multivariate logistic regression calculated with the data of 704 subjects with complete information.

detect an elevated risk of cutaneous melanoma after sunburns or increased sun exposure (6, 15).

On the other hand, the association between sun exposure and the number of melanocytic naevi was demonstrated in a series of publications (9, 16). Especially, sun exposure before the age of 20 seemed to be crucial for the development of melanocytic naevi. The relation between sun exposure in adolescence and development of melanocytic naevi was likewise proven for Canadian and Australian pupils and was also found in the present study (12, 17, 18). However, as the total number of melanocytic naevi is regarded as the most important risk factor for the development of cutaneous melanoma, it can be assumed that sun exposure may be involved in the development of cutaneous melanoma by the induction of melanocytic naevi. The present study confirms this assumption.

Epidemiological considerations propose the number and kind of sunburns as the most reliable indicators of sun exposure. The history of sunburns is perhaps most easily recalled, compared to other variables of sun exposure. Consequently, studies regarding sunburns showed more consistent results than investigations which included only the amount of recreational or occupational sun exposure (15). One surprising result of the present study was that none of the investigated variables of sun exposure was significantly associated with the number of painful sunburns throughout life. Thus, sunburns did not seem to be directly related to the cumulative amount of sun exposure experienced. On the other hand, sunburns were strongly correlated with pigmentary characteristics in the present analysis. The light-sensitive skin type is per definition characterised by a tendency to sunburn. Thus, a highly significant relationship between light-sensitive skin type and the number of sunburns was found, as expected. The results of the present analysis have shown that sunburns as well as variables of UV-exposure can be simultaneously regarded within one multivariate model, concerning the development of melanocytic naevi, without the expected difficulties of confounding the data.

The estimated relative risk of the prevalence of more than 50 CMN and of five or more AMN increased with the number of days of sun exposure during beach holidays for both

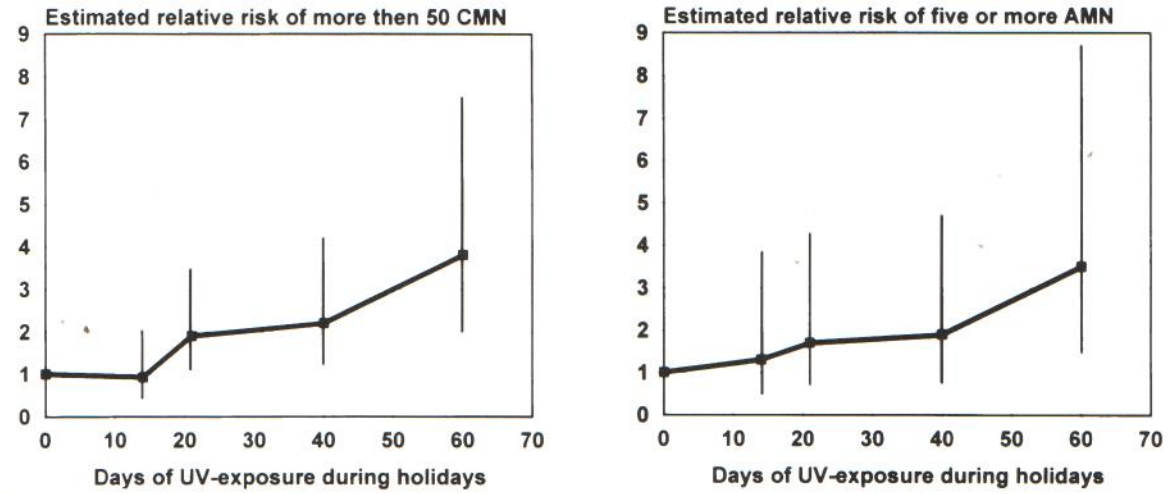

Fig. 1. Estimated relative risks with 95%-confidence intervals of a prevalence of more than 50 common melanocytic naevi (*a*) and of five or more atypical melanocytic naevi (*b*) in relation to the days of UV-exposure during holidays in the last 2 years. Relative risks given were compared to a period of 0 to 13 days of UV-exposure. The estimations are adjusted for the effects of age, gender, painful sunburns and sunburns before the age of 20 for common melanocytic naevi, and for age, gender, sunburns before the age of 20, hair colour, and freckles in adolescence for atypical melanocytic naevi, respectively.

Table II. *Influence of sun exposure and pigmentary traits on the prevalence of less than five, five or more than five atypical melanocytic naevi#*

Associated factors	Atypical melanocytic naevi		Odds-ratio	*p*-value
	<5 ($n=663$)	≥ 5 ($n=48$)	[95% CI^{+}]	
UV-exposure during holidays^{++}	/	/	1.01 [1.00, 1.02]	$p<0.01$
Recreational UV-exposure^{++} at home	/	/	/	$p=0.32$
Occupational UV-exposure^{++}	/	/	/	$p=0.82$
Use of sunbeds				
Never	560	37		
Occasional	40	10	/	$p=0.73$
Regular	23	1	/	$p=0.31$
Sunburns before the age of 20				
None	287	8	1	
Some	376	40	2.6 [1.1, 5.8]	$p<0.05$
Skin type				
3 or 4	403	22		
1 or 2	260	26	/	$p=0.44$
Hair colour				
Black or brown	278	11	1	
Blond or red	385	37	2.6 [1.3, 5.5]	$p<0.01$
Freckles in adolescence				
None, few or moderate	642	42	1	
Many	21	6	4.1 [1.4, 11.9]	$p<0.01$
Age^{++}	/	/	0.97 [0.95, 0.99]	$p<0.01$
Gender				
Female	383	16	1	
Male	280	32	3.3 [1.7, 6.3]	$p<0.001$

$^{+}$ CI = confidence interval. $^{++}$ Age, recreational UV-exposure at home, UV-exposure during holidays, and occupational UV-exposure are considered as continuous variables. Therefore, their estimated relative risks cannot be directly compared.
Results of multivariate logistic regression calculated with the data of 711 subjects with complete information.

northern and southern countries. Interestingly, the effects of recreational sun exposure at home or during sporting activities, as well as occupational UV-exposure, were not statistically significant. Without doubt, the intensity of the sun is higher in southern countries and during beach activities in north or middle Europe, compared to an average day in Germany. Moreover, the duration of sun exposure and the body regions exposed to the sun during holidays spent at the beach are usually considerably different from habits at home. Thus, the results of the present study support the idea that intensive UV-exposure may especially harm untanned skin (19).

In contrast to the results for CMN, the pigmentary characteristics hair colour and facial freckles in adolescence proved to have independently significant effects on the prevalence of five or more AMN. This result stresses the potential importance of genetic factors involved in the development of AMN. The occurrence of many AMN is probably related to a particular type of pigmentation, characterised by blond or red hair colour and a freckling tendency. The pigment type of phæomelanin is assumed to predominantly occur in this type of pigmentation (20).

In conclusion, the results of the present study showed that pigmentary traits as well as sun exposure are involved in the aetiology of melanocytic naevi and, therefore, likewise but indirectly of cutaneous melanoma. The history of sunburns and the duration of highly intensive UV-exposure, as experienced during vacations, both played an important role for the development of CMN and AMN. On the other hand, a particular type of pigmentation was found to be correlated with the occurrence of AMN. However, the aetiology of melanocytic naevi and cutaneous melanoma remains complex, and further studies concerning detailed questions about the various relationships will be needed for its enlightenment.

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