Associated Factors in the Prevalence of More Than 50 Common Melanocytic Nevi, Atypical Melanocytic Nevi, and Actinic Lentigines: Multicenter Case-Control Study of the Central Malignant Melanoma Registry of the German Dermatological Society

Claus Garbe, Petra Büttner,* Jürgen Weiß,† Hans Peter Soyer,‡ Ulrich Stocker,§ Sabine Krüger, Marianne Roser,¶ Jörg Weckbecker,** Renato Panizzon,†† Friedrich Bahmer,‡‡ Wolfgang Tilgen,§§ Irene Guggenmoos-Holzmann,* and Constantin E. Orfanos

Department of Dermatology and *Institute of Statistics, University Medical Center Steglitz, The Free University of Berlin; University Departments of Dermatology in †Mannheim, Germany; ‡Graz, Austria; §Lübeck; ¶Hamburg; **Bonn, Germany; ††Zürich, Switzerland; ‡‡Homburg, and §§Heidelberg, Germany

Several case-control studies identified common and atypical melanocytic nevi as major risk indicators for the development of cutaneous melanoma. The present investigation was planned to detect factors associated with the prevalence of these melanoma risk markers. Whole-body examination findings and interview data of 513 melanoma patients and 498 age- and sex-matched control subjects were analyzed. Existence of more than 50 common melanocytic nevi and the presence of atypical melanocytic nevi were significantly related to age and gender, with significantly elevated relative risk for their prevalence before the age of 60 and in males. Additionally, sunburns before the age of 20 were significantly associated with both more than 50 common melanocytic nevi (relative risk = 1.7) and the presence of atypical melanocytic nevi (relative risk = 1.5). Actinic lentigines were found more frequently with increasing age, and the presence of actinic lentigines was significantly related to a tendency of freckling in adolescence (relative risk = 2.0) and to two or more sunburns after the age of 20 (relative risk = 1.6). In conclusion, sunburns before the age of 20 contribute to the development of multiple melanocytic nevi and atypical melanocytic nevi. In adulthood, this type of sun exposure is associated with the development of actinic lentigines. The relative risk of developing cutaneous melanoma increases in association with the development of these benign melanocytic lesions. *Key words: melanocytic nevi/atypical melanocytic nevi/actinic lentigines/freckles/sunburn/melanoma. J Invest Dermatol 102:700–705, 1994*

Common melanocytic nevi (MN) were identified as a major risk indicator for the development of cutaneous melanoma (CM) in a number of case-control studies [1–6]. The relative risk (RR) of CM development increased almost steadily with an increasing number of MN over the entire body [6–10]. The number of atypical MN was found to be an additional significant independent risk factor [7–11]. Furthermore, the number of actinic lentigines is another significant risk factor for the development of CM, whose importance is independent of the number of MN [8,9,12,13].

These benign melanocytic lesions have to be regarded as both markers for an elevated CM risk and possible precursors in a considerable percentage of CM cases. According to recent investigations, about 22–32.5% of all CMs were tumors with histologically detectable associated MN remnants [14–17] and about 7–9% of all CMs occurred in continuity with a dysplastic MN [16,18].

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Reprint requests to: Dr. C. Garbe, Department of Dermatology, University Medical Center Steglitz, Hindenburgdamm 30, W-1000 Berlin 45, Germany.

Abbreviations: CART, classification and regression tree; CM, cutaneous melanoma; MN, melanocytic nevi; RR, relative risk(s).

So far, in case-control studies on risk factors for the development of CM, exogeneous factors like ultraviolet (UV) radiation and host factors like the prevalence of melanocytic lesions were simultaneously evaluated in the same multivariate statistical model [4,5,7–9,12]. The problem here is that both exogeneous factors and host factors compete for a significant status in the multivariate analysis, and that a superiority of the host factors may be due to their better assessibility (physical examination) in comparison to the exogeneous factors (case history data). For example, the influence of UV radiation on the development of MN [19] and thus on an increased risk of CM development could be obscured in that the numbers of MN are more accessible as a CM risk indicator than is case history data on UV exposure.

It was therefore the aim of the present study to find possible factors that are related to the prevalence of CM risk-associated melanocytic lesions. The most important risk indicators for subjects with an increased CM risk in the preceding evaluation of this study were greater than 50 MN on the entire body, one or more atypical MN, and the presence of actinic lentigines. This is the first case-control study on CM risk in which factors significantly associated with each of the aforementioned melanocytic lesions were determined utilizing both multivariate regression and classification and regression tree analysis to identify relevant combinations of associated factors.

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Table I. Criteria for Diagnosis of Common Melanocytic Nevi, Atypical Melanocytic Nevi, Congenital Nevus-like Melanocytic Nevi, and Actinic Lentigines

	Common Melanocytic Nevi (diameter plus at least three criteria)	Atypical Melanocytic Nevi (at least three criteria)	Congenital Nevus-Like Melanocytic Nevi (diameter plus at least three criteria)	Actinic Lentigines (all five criteria)
Diameter	≥2 mm (obligatory)	≥5 mm	≥10 mm (obligatory)	<1 to >10 mm
Border	Well defined	Ill defined	Well defined	Well defined
Margin	Regular	Irregular	Regular	Even or finely irregular
Color	Uniformly light to dark brown or skin colored	Varying within the lesion, different brown shades, partially on erythematous ground	Uniform, dark brown to black	Light brown to grey brown
Surface	Macular or papular	Papular and macular components	Papular or papillomatous, hypertrichosis	Completely macular

SUBJECTS AND METHODS

Study Subjects The present study, designed as a case-control study, included newly diagnosed CM patients and age (± 5 years) and sex-matched control subjects without CM. The CM patients presented between January 1990 and June 1991 and at the nine cooperating centers for first diagnosis. A total of 513 CM patients (44.8% men, 55.2% women) were included in the study. Histopathologic CM diagnosis was carried out by dermatohistopathologists from the participating centers. Four hundred ninety-eight patients from the participating dermatologic clinics were chosen as controls.

Diagnostic Criteria for Pigmented Lesions The clinical characteristics of pigmented lesions were defined before the start of the study by all participants in a consensus workshop according to the criteria of previous investigations [7,9,20] and illustrated by photodocumentation serving as a diagnostic guideline for the examiners (HPS, CG). The diagnostic criteria are given in Table I. The differentiation of seborrhic keratoses and other pigmented lesions like Becker's nevi, nevi spili, cafe-au-lait spots, and halo nevi was done on the basis of their typical morphology.

Dermatologic Examinations and Interviews All subjects underwent a whole-body examination and exact documentation of all pigmented lesions. Common and atypical MN were counted separately according to 12 body regions excluding the scalp and genitoanal region. The number of actinic lentigines was classified as none, few, or many according to a graphic chart. Interviews were conducted using a standardized questionnaire prior to physical examination. The data recorded included the type and duration of occupational and recreational sun exposure as well as sunburns, differentiating between those before and after the age of 20 and during the last 5 years. Additionally, patients were asked to record the presence and density of facial freckles in adolescence (ages 10–20) using a graphic chart.

Statistical Analysis Differences in the frequencies of variables between subjects with more than 50 MN, atypical MN, and actinic lentigines, and those without these pigmented lesions were initially checked bivariately by the χ^2 test. All p values calculated were two-sided. Factors with $p < 0.1$ were entered in a multifactorial stepwise logistic regression analysis, which was performed using the EGRET statistical package [21]. Odds ratios and their 95% confidence intervals were calculated and interpreted in this context as relative risk for the development of pigmented lesions. Furthermore, the importance of associated factors was assessed by classification and regression tree (CART) analysis [22].

RESULTS

Prevalence of More Than 50 Melanocytic Nevi Age was the most important factor associated with the total number of MN. Whereas the proportion of subjects with 50 or more common MN over the entire body was still 29% in those under 40, it was less than 7% in those over 60; this corresponded to an elevated RR for the presence of more than 50 common MN by a factor of 5 in subjects under 40, as compared to those over 60. The second important associated factor was gender. Twenty-two percent of the men, compared to only 14% of the women, had a prevalence of more than 50 MN. Additionally, the data on sunburns were significantly associated with the presence of more than 50 MN. Two or more sunburns before the age of 20 increased the RR by a factor 1.7. An increased risk for the prevalence of more than 50 MN was also observed in patients with one or more painful sunburns lifelong. Interestingly, the CM risk was higher for only one in contrast to two or more painful sunburns (Table II). When analyzing the risk

Table II. Associated Factors in the Prevalence of More Than 50 Common Melanocytic Nevi (MN) Over the Entire Body: Results of Multiple Logistic Regression Analysis (815 Subjects with Complete Data)

	Common Melanocytic Nevi		Relative Risk	
Associated Factors	≤50 MN (n = 670)	>50 MN (n = 145)	Unadjusted [95% CI][a]	Adjusted[b] [95% CI][a]
Age (years)				
<40	119	48	1	1
40–59	242	75	0.77 [0.50,1.2] NS[c]	0.73 [0.47,1.1] NS[c]
≥60	309	22	0.18 [0.10,0.3]	0.18 [0.10,0.3]
Gender				
Women	385	63	1	1
Men	285	82	1.8 [1.2,2.5]	1.9 [1.3,2.8]
Sunburns before the age of 20				
<2	397	66	1	1
≥2	273	79	1.7 [1.2,2.5]	1.7 [1.1,2.6]
Lifelong painful sunburns				
None	251	33	1	1
1	136	45	2.5 [1.5,4.1]	2.2 [1.3,3.8]
≥2	283	67	1.8 [1.2,2.8]	1.0 [0.6,1.7] NS[c]

[a] [95% CI] = 95% confidence interval.
[b] The logistic model included age, gender, sunburns before the age of 20, and lifelong painful sunburns.
[c] NS, not significant.

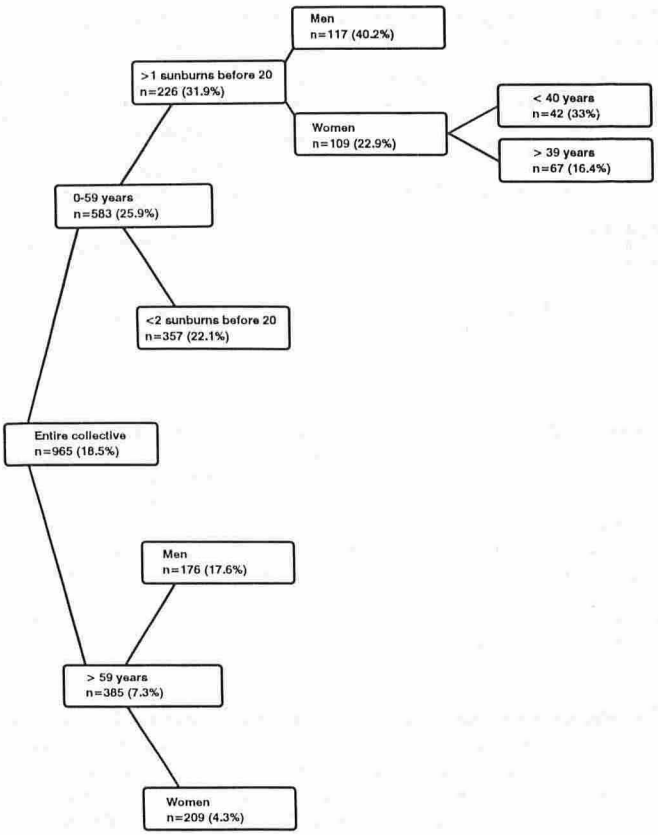

Figure 1. CART analysis of risk factors for the prevalence of more than 50 common melanocytic nevi. In *brackets,* the percentage of subjects with this feature in each subgroup.

for the presence of more than 10 melanocytic nevi with restriction to the control group, similar results were obtained and age and sunburns before the age of 20 were identified as independent risk factors (age ≥ 60 versus < 60: RR = 0.3 [0.2,0.5]; ≥2 sunburns before the age of 20: RR = 2.1 [1.2,3.6]).

CART analysis confirmed that the most significant factor associated with the prevalence of more than 50 common MN over the entire body was young age. In subjects under 60, two or more sunburns before the age of 20 were the most significant risk factor. Those over 60 differed in their risk of presenting with more than 50 MN only by sex. In the present study population, the CART analysis revealed that the presence of more than 50 MN was most frequently found in men before the age of 60 with two or more sunburns before 20 (40.2%) and least often in women age 60 or older (4.3%) (Fig 1).

Prevalence of Atypical Melanocytic Nevi In the logistic regression analysis, age and gender were the most significant risk factors. In the present study population, atypical MN occurred less frequently in older patients (age 60 years or older) or in women (20.4%) than in men (33.7%). Another significant associated factor was again the occurrence of two or more sunburns before the age of 20. In the adjusted analysis, this was associated with an increase in the RR for developing atyical MN by the factor of 1.5 (Table III). When analyzing the risk for the presence of atypical nevi with restriction to the control group, the same factors were identified as independent risk indicators (age ≥ 60 versus < 60, RR = 0.5 [0.3,0.9]; gender men versus women, RR = 1.7 [1.0,2.8]; ≥ two sunburns before the age of 20, RR = 1.6 [1.0,2.7]). Likewise, when analyzing the risk for developing five or more atypical melanocytic nevi for the entire collective the same risk factors revealed to be independent in multivariate regression analysis.

In the CART analysis, age and gender were again associated with the highest significance for the occurrence of atypical MN. After the age of 60, they occurred markedly less frequently and significantly more often in men than in women. In male patients under 60 years of age, two or more sunburns before the age of 20 were significantly associated with the occurrence of atypical MN; there was a 49% prevalance in this group. On the other hand, they were found most rarely in female patients over 60 (14.4%) (Fig 2).

Prevalence of Actinic Lentigines The occurrence of actinic lentigines was highly significantly associated with age in our study population. In subjects older than 60, the RR for the occurrence of actinic lentigines increased by the factor of 12 compared to those under 40 years old. Other significant associated factors were freckles in adolescence and two or more sunburns after the age of 20. The presence of many freckles in adolescence increased the RR for developing actinic lentigines in adulthood by a factor of 2.5; patients who reported having had two or more sunburns after the age of 20 had an RR increased by a factor of 1.6 (Table IV). When analyzing the risk for the presence of actinic lentigines with restriction to the control group similar results were obtained and age, gender, freckles in adolescence, and sunburns after the age of 20 were identified as significant risk factors (age ≥ 60 versus < 40, RR = 18.0 [9.3,34.9]; gender, men versus women, RR = 0.6 [0.4,0.9]; freckles in adolescence, many versus none, RR = 2.9 [1.3,6.9]; ≥ 2 sunburns after the age of 20, RR = 1.6 [1.0,2.5]).

In the CART analysis, age was also the most significant associated

Table III. Associated Factors in the Prevalence of Atypical Melanocytic Nevi Over the Entire Body: Results of Multiple Logistic Regression Analysis (825 Subjects with Complete Data)

	Atypical Melanocytic Nevi		Relative Risk	
Associated Factors	Absent (n = 607)	Present (n = 218)	Unadjusted [95% CI][a]	Adjusted[b] [95% CI][a]
Age (years)				
<40	108	60	1	1
40–59	223	97	0.78 [0.53,1.2] NS[c]	0.72 [0.48,1.1] NS[c]
≥60	276	61	0.40 [0.26,0.61]	0.39 [0.25,0.6]
Gender				
Women	359	92	1	1
Men	248	126	2.0 [1.5,2.7]	2.0 [1.4,2.7]
Sunburns before the age of 20				
<2	366	100	1	1
≥2	241	118	1.8 [1.3,2.5]	1.5 [1.1,2.1]

[a] [95% CI] = 95% confidence interval.
[b] The logistic model included age, gender, and sunburns before the age of 20.
[c] NS, not significant.

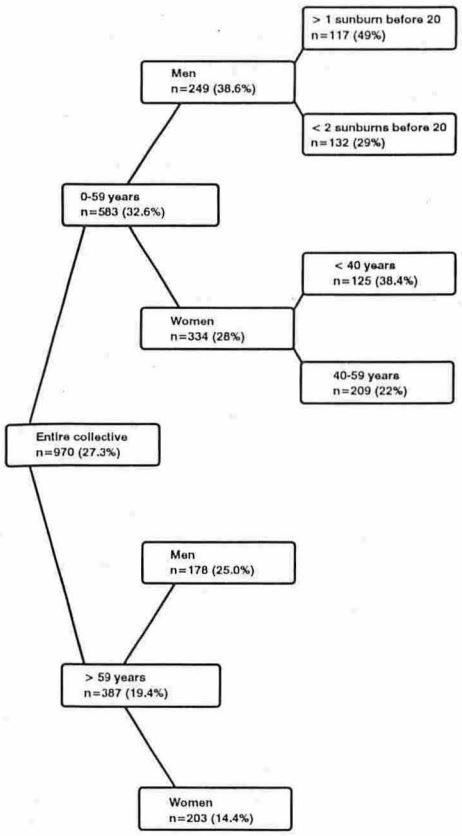

Figure 2. CART analysis of risk factors for the prevalence of atypical melanocytic nevi. In *brackets,* the percentage of subjects with this feature in each subgroup.

factor. In the present study group, actinic lentigines were documented in 75% of the subjects over 40, in contrast to only 33.5% of those younger than 40. In those over 60, freckles in adolescence were the most significant associated factor. In the 40–50-year-old age group, the occurrence of five or more lifelong painful sunburns was significantly associated with the development of actinic lentigines. In subjects younger than 40, two or more sunburns after the age of 20 was a significant associated factor. Altogether, the prevalence of actinic lentigines varied between 26% in subjects younger than 40 with less than two sunburns after the age of 20 and 93% in those older than 60 with freckles in adolescence (Fig 3).

Prevalence of Melanocytic Lesions and Their Relation to Skin Type, Hair Color, and Freckles in Adolescence The bivariate analysis of the relation between skin type, hair color, and freckling tendency on the one hand, and the prevalence of risk-associated pigmented lesions on the other revealed no significant relation between skin type and common MN or actinic lentigines. There was an increased odds ratio for the presence of five or more atypical MN in individuals with skin type 1 or 2 (Table V). Hair color was not significantly related to the number of common MN in bivariate analysis, but a significant association with the number of atypical MN ($p < 0.05$) and the frequency of actinic lentigines ($p < 0.001$) was detected. However, hair color was no longer a significant factor in the multivariate analysis in terms of any of the pigmented lesions analyzed. A highly significant association was found between freckles in adolescence and actinic lentigines in adulthood ($p < 0.0001$). This relation was also significant in the multivariate analysis (see above). Less significant in bivariate analysis was the association between freckles in adolescence and the number of atypical MN ($p < 0.05$) in adulthood (Table V). This was no longer significant in the multivariate analysis.

DISCUSSION

In the present study, the prevalence of common and atypical MN and actinic lentigines has been carefully documented in 513 CM patients and 498 control subjects matched for age and sex. The prevalence of the different pigmented lesions found here is not representative for the general population. The study subjects evaluated here were documented in a case-control study design to determine RR for developing CM and 50% of the entire collective were CM patients. On an average, markedly larger numbers of all three types of pigmented lesions were found in CM patients than in control subjects. In the present investigation, the attempt was made to identify possible exogeneous factors associated with the prevalence of common and atypical MN as well as actinic lentigines.

A major goal of the present study was the investigation of the role of sun exposure in the development of CM as well as of CM-associated melanocytic lesions. Retrospective assessment of sun exposure may be subject to recall bias [23,24]. Recall bias of sun exposure may be particularly increased in older study subjects. Interestingly, childhood blistering sunburns proved to correlate nicely with the minimal erythema dose of UV-B also in adults [24]. Sunburns are

Table IV. Associated Factors in the Prevalence of Actinic Lentigines: Results of Multiple Logistic Regression Analysis (922 Subjects with Complete Data)

	Actinic Lentigines		Relative Risk	
Associated Factors	Absent (n = 313)	Present (n = 609)	Unadjusted [95% CI][a]	Adjusted[b] [95% CI][a]
Age (years)				
<40	125	63	1	1
40–59	128	244	3.8 [2.6,5.5]	4.0 [2.7,5.8]
≥60	60	302	10.0 [6.6,15.1]	12.0 [7.8,18.4]
Freckles in adolescence				
None	194	316	1	1
Few	94	207	1.4 [1.0,1.8]	1.6 [1.2,2.3]
			NS[c]	
Many	25	86	2.1 [1.3,3.4]	2.5 [1.5,4.2]
Sunburns before the age of 20				
<2	181	306	1	1
≥2	132	303	1.4 [1.0,1.8]	1.6 [1.2,2.2]

[a] [95% CI] = 95% confidence interval.
[b] The logistic model included age, gender, freckles in adolescence, sunburns before the age of 20, and lifelong painful sunburns.
[c] NS, not significant.

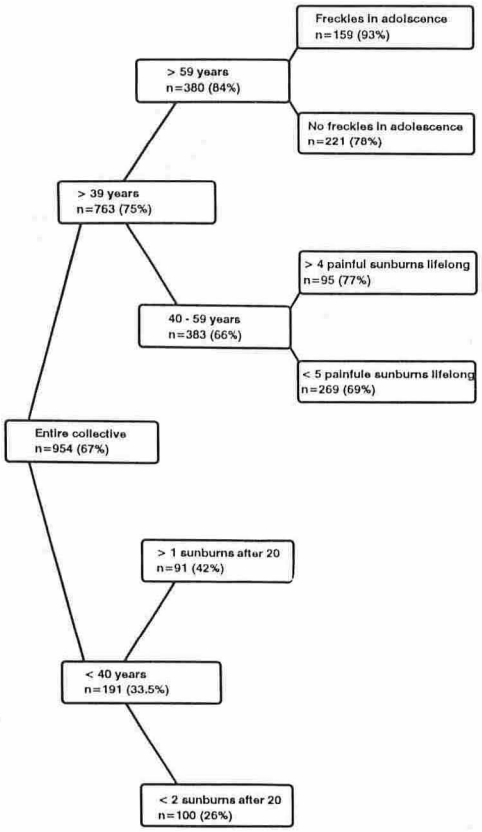

Figure 3. CART analysis of risk factors for the prevalence of actinic lentigines. In *brackets,* the percentage of subjects with this feature in each subgroup.

probably the most reliable parameter in retrospective assessment of sun exposure.

Sunburns at various periods of life indicated the significant association of intense intermittent UV radiation as an exogeneous factor with the presence of large numbers of common MN, the prevalence of atypical MN, as well as the occurrence of actinic lentigines. Sunburns before the age of 20 were significantly related to the number of common MN and the presence of atypical MN in this study. A correlation between sun exposure and the development of common or atypical MN has already been suggested by other investigators [19,25,26].

The number of lifelong painful sunburns was also significantly associated with the number of common MN over the entire body in this study. However, there was an unexpected finding in this context: subjects with only one painful sunburn had not only a markedly increased risk compared to those without sunburns but also to those with two or more sunburns. It is conceivable that this group of patients had experienced one extremely intensive sunburn. This event could, on the one hand, be responsible for the induction of a larger number of MN and, on the other hand, have served as stimulus for subjects to better protect themselves against the sun in the future.

A history of sunburns after the age of 20 was significantly related to the prevalence of actinic lentigines in this investigation. The CART analysis showed that besides sunburns after 20 in the group of those under 40, the prevalence of actinic lentigines in study subjects 40–59 years old was also influenced by the number of lifelong painful sunburns. In those 60 years old or older, freckles in adolescence were related to the prevalence of actinic lentigines. Factors responsible for the development of actinic lentigines have been previously analyzed, particularly within studies on psoralen plus UVA treatment. Besides the skin type, signs of actinic damage were associated with their development [27].

The association between UV exposure, prevalence of MN, and CM development is also suggested by other observations. A considerably higher mean number of MN was reported in geographical areas with strong insolation (California: 97 MN in CM patients and 36 in control subjects [7]) than in Central Europe (Germany: 53 MN in CM patients and 18 in control subjects [9]) or Northern Europe (Scotland: <35 MN in CM patients and <15 in control subjects [6]). Simultaneously with the change in sun exposure habits and the increased CM incidence in the last decades, an increased number of MN over the entire body has also been observed [28]. Interestingly, the anatomic distribution of acquired melanocytic nevi in German CM patients as well as in Canadian white children closely matched that of CM in the respective populations [29,30].

Recently published animal experiments support the view that MN may play an important role in the development of CM. CM growth could be induced in hairless mice by UVA and UVB irradiation after previous induction of dermal melanocytic nevus-like le-

Table V. Relation of Skin Type, Hair Color, and a Freckling Tendency to the Prevalence of Common and Atypical MN and Actinic Lentigines

	Skin type: 1 or 2 versus 3 or 4		Hair color: Red versus Dark or Blond		Freckles: Many versus None or Few	
	RR	[95% CI][a]	RR	[95% CI][a]	RR	[95% CI][a]
Common melanocytic nevi						
0–10	1		1		1	
11–50	1.2	[0.9,1.6]	1.0	[0.5,1.7]	1.1	[0.7,1.7]
51–100	1.6	[1.0,2.4]	1.5	[0.7,3.4]	1.8	[0.97,3.2]
>100	1.0	[0.6,1.6]	0.8	[0.3,2.5]	1.2	[0.6,2.4]
Atypical melanocytic nevi						
0	1		1		1	
1–4	1.1	[0.8,1.5]	1.1	[0.5,2.1]	1.1	[0.7,1.7]
≥5	1.8	[1.1,2.9]	2.8[b]	[1.3,6.0]	2.1	[1.1,3.9]
Actinic lentigines						
None	1		1		1	
Few	1.0	[0.8,1.3]	1.2	[0.6,2.3]	1.3	[0.8,2.2]
Many	1.2	[0.8,1.7]	3.4[c]	[1.6,7.0]	4.4[d]	[2.5,8.6]

[a] [95% CI] = 95% confidence interval.
[b] χ^2 test, $p < 0.05$.
[c] $p < 0.001$.
[d] $p < 0.0001$.

sions using 7,12-dimethylbenz(a)anthracene as an initiator [31]. The only model in which CM could be induced by UV radiation alone is the South American opossum [32].

Age and gender were the major host factors significantly associated with the prevalence of common and atypical MN over the entire body in this study. These factors have also been described by other investigators. Whereas in children the number of MN increased with age [19], it decreased in adults older than 35–40 [33]. All investigators found a markedly greater prevalence of MN in Caucasian males than in females [33–36]. In the present study, there was no significant association between the number of MN and the skin type. Other investigators observed larger numbers of MN in light-skinned, UV-sensitive subjects [34–36] and, additionally, an increased development of atypical MN was described in these subjects [37,38]. On the other hand, a study from Scotland reported a highly significant relation between large numbers of common MN over the entire body and skin types 3 and 4, brown eyes, and brown or black hair color [39]. Associations between skin type and the number of MN may vary in different populations.

In conclusion, intermittent intensive UV radiation with induction of sunburns may be responsible for the development of common and atypical MN as well as actinic lentigines. Intermittent intensive sun exposure with sunburns in childhood and adolescence is related to the induction of common and atypical MN. In adulthood, on the other hand, this is associated with the development of actinic lentigines. Persons with a freckling tendency in adolescence seem to be particularly prone to the development of actinic lentigines. The melanocytic system is apparently only capable of developing MN up to a certain age, whereas later it produces only simple melanocytic hyperplasia with the clinical appearance of actinic lentigines. The presence and number of common and atypical MN and actinic lentigines are the most important risk factors for the development of CM. The present findings confirm that the development of these CM risk-associated pigmented lesions is clearly related to UV exposure. Nevertheless, association is not necessarily causation and the role of genetic factors remains to be investigated in more detail in future studies. The present results may elucidate the complexity of the relationship between UV exposure and CM development.

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REFERENCES

1. Holman CDJ, Armstrong BK: Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. *J Natl Cancer Inst* 72:257–266, 1984
2. Swerdlow AJ, English J, MacKie RM, O'Doherty CJ, Hunter JA, Clark J: Benign naevi associated with high risk of melanoma (letter). *Lancet* II:168, 1984
3. Green A, MacLennan R, Siskind V: Common acquired naevi and the risk of malignant melanoma. *Int J Cancer* 35:297–300, 1985
4. Holman CDJ, Armstrong BK, Heenan PJ, Blackwell JB, Cumming FJ, English DR, Holland S, Kelsall GR, Matz LR, Rouse IL, Singh A, Ten Seldam RE, Watt JD, Xu Z: The causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. *Recent Results Cancer Res* 102:18–37, 1986
5. Green A, Bain C, McLennan R, Siskind V: Risk factors for cutaneous melanoma in Queensland. *Recent Results Cancer Res* 102:76–97, 1986
6. Swerdlow AJ, English J, MacKie RM, O'Doherty CJ, Hunter JA, Clark J, Hole DJ: Benign melanocytic naevi as a risk factor for malignant melanoma. *Br Med J Clin Res Ed* 292:1555–1559, 1986
7. Holly EA, Kelly JW, Shpall SN, Chiu SH: Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol* 17:459–468, 1987
8. MacKie RM, Freudenberger T, Aitchison TC: Personal risk-factor chart for cutaneous melanoma. *Lancet* II:487–490, 1989
9. Garbe C, Krüger S, Stadler R, Guggenmoos-Holzmann I, Orfanos CE: Markers and relative risk for developing malignant melanoma in a German population. *Int J Dermatol* 28:517–523, 1989
10. Grob JJ, Gouvernet J, Aymar D, Mostaque A, Romano MH, Collet AM, Noe MC, Diconstanzo MP, Bonerandi JJ: Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. *Cancer* 66:387–395, 1990
11. Halpern AC, Guerry D 4th, Elder DE, Clark WH Jr, Synnestvedt M, Norman S, Ayerle R: Dysplastic nevi as risk markers of sporadic (nonfamilial) melanoma. A case-control study. *Arch Dermatol* 127:995–999, 1991
12. Österlind A, Tucker MA, Hou Jensen K, Stone BJ, Engholm G, Jensen OM: The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. *Int J Cancer* 42:200–206, 1988
13. Kelly JW, Holly EA, Shpall SN, Ahn DK: The distribution of melanocytic naevi in melanoma patients and control subjects. *Australas J Dermatol* 30:1–8, 1989
14. Gruber SB, Barnhill RL, Stenn KS, Roush GC: Nevomelanocytic proliferations in association with cutaneous malignant melanoma: a multivariate analysis. *J Am Acad Dermatol* 21:773–780, 1989
15. Stolz W, Schmoeckel C, Landthaler M, Braun Falco O: Association of early malignant melanoma with nevocytic nevi. *Cancer* 63:550–555, 1989
16. Marks R, Dorevitch AP, Mason G: Do all melanomas come from "moles"? A study of the histological association between melanocytic naevi and melanoma. *Australas J Dermatol* 31:77–80, 1990
17. Stadler R, Garbe C: Navus-assoziierte maligne Melanome-diagnostische Sicherung und Prognose. *Hautarzt* 42:424–429, 1991
18. Hastrup N, Osterlind A, Drzewiecki KT, Hou Jensen K: The presence of dysplastic nevus remnants in malignant melanomas. A population-based study of 551 malignant melanomas. *Am J Dermatopathol* 13:378–385, 1991
19. Gallagher RP, McLean DI, Yang CP, Coldman AJ, Silver HK, Spinelli JJ, Beagrie M: Suntan, sunburn, and pigmentation factors and the frequency of acquired melanocytic nevi in children. Similarities to melanoma: the Vancouver Mole Study. *Arch Dermatol* 126:770–776, 1990
20. National Institute of Health Consensus Development Conference: Precursors to malignant melanoma. *J Am Acad Dermatol* 10:683–688, 1984
21. Breslow NE, Day NE: Statistical methods in cancer research. I. The analysis of case control studies. *IARC*, Lyon, 1980
22. Breiman L, Friedman JH, Olshen RA, Stone CJ: *Classification and regression trees.* Wadsworth International, Belmont, California, 1984
23. Weinstock MA, Colditz GA, Willet WC, Stampfer MJ, Rosner B, Speizer FE: Recall (report) bias and reliability in the retrospective assessment of melanoma risk. *Am J Epidermiol* 133:240–245, 1991
24. Weinstock MA: Assessment of sun sensitivity by questionnaire: validity of items and formulation of a predictive role. *J Clin Epidemiol* 45:547–552, 1992
25. Kopf AW, Lindsay AC, Rogers GS, Friedman RJ, Rigel DS, Levenstein M: Relationship of nevocytic nevi to sun exposure in dysplastic nevus syndrome. *J Am Acad Dermatol* 12:656–662, 1985
26. Titus Ernstoff L, Ernstoff MS, Duray PH, Barnhill RL, Holubkov R, Kirkwood JM: A relation between childhood sun exposure and dysplastic nevus syndrome among patients with nonfamilial melanoma. *Epidemiology* 2:210–214, 1991
27. Rhodes AR, Stern RS, Melski JW: The PUVA lentigo: an analysis of predisposing factors. *J Invest Dermatol* 81:459–463, 1983
28. Cooke KR, Spears GF, Skegg DC: Frequency of moles in a defined population. *J Epidemiol Community Health* 39:48–52, 1985
29. Krüger S, Garbe C, Büttner P, Stadler R, Guggenmoos-Holzmann I, Orfanos CE: Epidemiologic evidence for the role of melanocytic nevi as risk markers and direct precursors of cutaneous malignant melanoma. Results of a case control study in melanoma patients and non-melanoma controls. *J Am Acad Dermatol* 26:920–926, 1992
30. Gallagher RP, McLean DI, Yang CP, Coldman AJ, Silver HK, Spinelli JJ, Beagrie M: Anatomic distribution of acquired melanocytic nevi in white children. A comparison with melanoma: the Vancouver Mole Study. *Arch Dermatol* 126:466–471, 1990
31. Husain Z, Pathak MA, Flotte T, Wick MM: Role of ultraviolet radiation in the induction of melanocytic tumors in hairless mice following 7,12-dimethylbenz(a)anthracene application and ultraviolet irradiation. *Cancer Res* 51:4964–4970, 1991
32. Ley RD, Applegate LA, Padilla RS, Stuart TD: Ultraviolet radiation-induced malignant melanoma in Monodelphis domestica. *Photochem Photobiol* 50:1–5, 1989
33. Armstrong BK, de Klerk NH, Holman CD: Etiology of common acquired melanocytic nevi: constitutional variables, sun exposure, and diet. *J Natl Cancer Inst* 77:329–335, 1986
34. Rampen FH, van der Meeren HL, Boezeman JB: Frequency of moles as a key to melanoma incidence? *J Am Acad Dermatol* 15:1200–1203, 1986
35. Sigg C, Pelloni F: Frequency of acquired melanonevocytic nevi and their relationship to skin complexion in 939 schoolchildren. *Dermatologica* 179:123–128, 1989
36. Green A, Siskind V, Hansen ME, Hanson L, Leech P: Melanocytic nevi in schoolchildren in Queensland. *J Am Acad Dermatol* 20:1054–1060, 1989
37. Kopf AW, Goldman RJ, Rivers JK, Levenstein M, Rigel DS, Friedman RJ, Bart RS: Skin types in dysplastic nevus syndrome. *J Dermatol Surg Oncol* 14:827–831, 1988
38. Weinstock MA, Stryker WS, Stampfer MJ, Lew RA, Willett WC, Sober AJ: Sunlight and dysplastic nevus risk. Results of a clinic-based case-control study. *Cancer* 67:1701–1706, 1991
39. English JS, Swerdlow AJ, Mackie RM, O'Doherty CJ, Hunter JA, Clark J, Hole DJ: Relation between phenotype and banal melanocytic naevi. *Br Med J Clin Res Ed* 294:152–154, 1987