Risk Factors for Developing Cutaneous Melanoma and Criteria for Identifying Persons at Risk: 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,* 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

Different pigmentary characteristics as well as different parameters of sun exposure have previously been identified as risk factors for developing cutaneous melanoma. The aim of the present study was to identify significant risk factors, determine the related magnitude of their estimated relative risks, and define criteria for the detection of persons at risk. Five hundred thirteen melanoma patients and 498 controls matched for age and sex underwent a whole-body examination for the number and type of melanocytic lesions and were interviewed on ultraviolet exposure and other potential risk factors. The total number of common melanocytic nevi on all body sites represented the most important risk factor in multiple logistic regression analysis with a relative risk of 7.6 for subjects with more than 100 versus no more than 10 melanocytic nevi. Other significant independent risk factors were the number of atypical melanocytic nevi (relative risk, 6.1 for at least 5 melanocytic nevi versus none), the number of actinic lentigines (relative risk, 3.5 for many versus none), hair color, skin type, and reported melanocytic nevus growth. No single parameter of sun exposure was significantly related to melanoma risk in the multivariate analysis. Groups with an estimated relative risk between 1 and 121.0 were distinguished by considering common and atypical melanocytic nevi as well as actinic lentigines as the decisive criteria. In conclusion, even without any information on the case history, whole-body examination and diagnosis of pigmented lesions was found to be an effective strategy for identifying persons at risk of developing melanoma. Furthermore, clinical recognition of at least 5 atypical melanocytic nevi without histologic examination is a key for identifying subjects at high risk. *Key words: melanoma/risk factors/melanocytic nevi/ atypical melanocytic nevi/actinic lentigines/UV irradiation. J Invest Dermatol 102:695–699, 1994*

D uring the last decades, a sharp increase in the incidence of cutaneous melanomas (CM) has been reported in the white populations of western industrial nations. In West Germany, the CM incidence has doubled every 12–15 years [1]. The fact that advanced CM is still incurable made early detection one of the main goals in the fight to reduce increasing CM mortality. Primary prevention as well as the identification of factors responsible for the marked increase in CM have likewise become a focal point of interest.

Risk factors for the development of CM have been examined in a series of case-control studies during the last ten years. Primarily, pigmentary traits like skin type and hair color and parameters of sun

exposure including sunburns have been detected as risk factors for CM development [2–5]. Additionally, the number and type of melanocytic lesions were identified as major risk factors for the development of CM, particularly common melanocytic nevi (MN) [6–14]. In the few investigations differentiating between common MN, atypical MN, and actinic lentigines, all three kinds of melanocytic lesions proved to be markers of an increased CM risk [13,14]. So far, published studies have differed in their proposals concerning major risk factors for the assessment of melanoma risk.

Until now, only a few studies with rather small study groups have carried out a differentiated and exact documentation of pigmented lesions on all body sites [11,13,14], whereas large epidemiologic studies have counted only MN on the arms [7,10,12]. However, the importance of different melanocytic lesions for an accurate risk assessment can only be adequately determined on the basis of exact definitions for the type of melanocytic lesions and by examinations carried out by experienced clinicians. It was therefore the aim of the present study to perform an exact documentation of all different melanocytic lesions on all body sites in large study groups and, additionally, to record detailed data on possible further risk factors. The case-control study on the risk of CM development presented

here is, to date, the largest published study with dermatologic whole-body examinations.

SUBJECTS AND METHODS

Melanoma Patients The present study prospectively included CM patients who had presented for diagnosis from January 1990 until June 1991 at the nine cooperating university departments of dermatology (the documentation time was shorter at three centers). The histopathologic CM diagnosis was established by the dermatohistopathologists of the cooperating centers. The study included a total of 513 CM patients (98% participation rate), 230 male (44.8%) and 283 female (55.2%), with a mean age of 55.7 years (SD ± 16.0 years). 41.7% of the melanomas were superficially spreading melanomas, 15.6% were nodular melanomas, 11.9% were lentigo maligna melanomas, 6.8% were acrolentiginous melanomas, 4.7% were not classifiable, and 19.3% were not definitely classified. Level I melanomas were found in 9%, level II in 17.9%, level III in 36.2%, level IV in 32.5%, and level V in 4.4% (missing data in 33 cases). 91.4% of the CM patients were inpatients; 8.6% were outpatients.

Control Subjects Four hundred ninety-eight non-melanoma patients of the participating dermatologic departments were included as controls (96% participation rate) to permit an adequate dermatologic whole-body examination. Control subjects were matched by sex and age (± 5 years) within each of the cooperating centers to the CM patients of the same center; no appropriate controls were found for 15 CM patients. Reasons for excluding controls from the study were as follows: 1) presentation for pigmented nevi or 2) skin cancer, 3) phototherapy in case history, 4) foreign descent. The exclusion criteria 3 and 4 were also applied to CM patients. To study an ethnically homogeneous collective, only subjects of German, Austrian, and Swiss descent were included. One hundred eighteen age- and sex-matched individuals were not included in the study for the aforementioned reasons (reasons for exclusion: 1, 21.5%, 2, 39.2%, 3, 32.3%, 4, 7%). 89.3% of the controls were inpatients and 10.7% were outpatients. Most of them presented with allergic disorders and eczematous diseases (32.1%), followed by infectious skin diseases and leg ulcers (30.3%), psoriasis and classical dermatologic diseases (21.9%), benign neoplasias (4.1%), and miscellaneous conditions (11.6%). Among the control subjects were 221 male (44.4%) and 277 female (55.6%) subjects, with a mean age of 54.8 years (SD ± 16.1 years).

Diagnostic Criteria for Pigmented Lesions Pigmented lesions with a diameter of at least 2 mm were classified as common melanocytic nevi if they were either a) macular, brown to dark brown, and sharply bordered (junctional nevi), b) papular, regularly, and sharply bordered as well as light to dark brown (compound nevi), or c) papular to nodular and skin-colored to erythematous (dermal nevi). The clinical diagnosis of atypical melanocytic nevi was established when at least three of the following characteristics were present: 1) diameter ≥ 5 mm, 2) ill-defined borders, 3) irregular margin, 4) varying shades in the lesion, and 5) simultaneous presence of papular and macular components. The lower limit of diameter was also at least 2 mm for atypical MN. Lesions were classified as congenital nevus-like melanocytic nevi when their diameter was greater than 10 mm and when they additionally fulfilled three of the following criteria: 1) hypertrichosis, 2) well-defined borders, 3) regular margin, 4) uniform mostly black color, and 5) papular to papillomatous surface. Diagnosis of actinic lentigines was established in lesions with only a macular surface, light brown or grey brown color, and well-defined borders with sometimes finely irregular margins. Before the start of the study, the diagnostic criteria for the various pigmented lesions were defined in a consensus workshop with all examiners from the different centers and were illustrated in a photo documentation that served as diagnositic guideline (HPS, CG).

Dermatologic Examinations All study subjects underwent a whole-body examination in which dermatologists familiar with the examination criteria recorded the pigmented lesions. Common and atypical MN were counted separately according to 12 body regions (excluding the scalp and the genitoanal region) and documented on a standardized computer form. Congenital nevus like MN were likewise recorded (number and size). In addition, the number of Becker's nevi, nevi spili, café-au lait spots, and halo nevi were registered. The number of actinic lentigines were classified in categories of none, few, and many according to a graphic chart. The presence of actinic keratoses and actinic elastosis was documented. Pigmentation characteristics such as eye color, hair color (at the age of 20), and skin pigmentation on the trunk were likewise recorded.

Interviews Prior to the physical examination, all study subjects were interviewed by the investigators using a standardized questionnaire. Data were recorded with regard to profession, occupational sun exposure, recreational sun exposure, especially the type and duration of sun exposure during the last
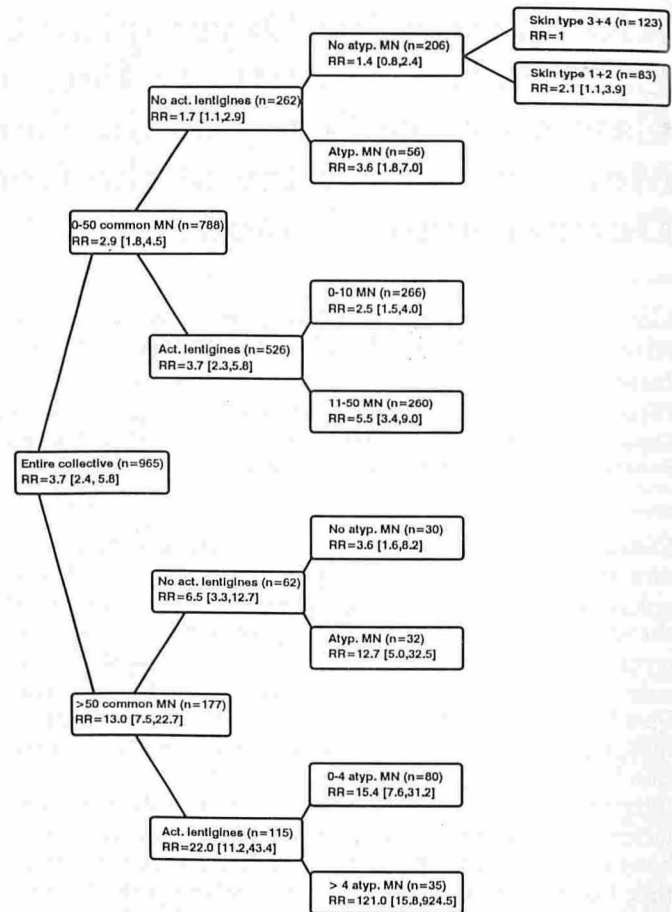

Figure 1. CART analysis of relative risks for developing cutaneous melanoma by combining several risk factors. Estimated relative risks were calculated in comparison to the group with lowest risk; in brackets, 95% confidence intervals.

2 years, the use of sunlamps or sunbeds, the number of painful sunburns throughout life, the number of sunburns in the last 5 years, and before and after completing the age of 20. In addition, the study subjects were asked to state whether new nevi had appeared in the past 5 years or existing ones had increased in size (independently of the development of CM). Study subjects were also asked to specify the presence of freckles in their youth (age 10–20) on the basis of a graphic chart (none, few, a moderate number, many). Finally, the number of blood relatives diagnosed as having melanoma or skin cancer and those with large numbers of MN were recorded.

Statistical Analysis Differences in the frequency of different variables in CM patients and control subjects were initially bivariately tested by the chi-square test. All p values calculated were two sided. Factors with p values less than 0.1 were entered in a multifactorial stepwise logistic regression analysis that was performed using the EGRET statistical package [15]. The following factors were included in the final logistic model: number of common MN, number of atypical MN, frequency of actinic lentigines, hair color, skin type, and the anamnestic statement concerning pigmented nevus growth. Odds ratios and their 95% confidence intervals were determined by the logistic model and interpreted as relative risks for developing CM in this context. Classification of the study collective in risk groups was done by classification and regression tree analysis (CART) [16]. Thereby, the total collective as well as the subgroups were investigated at every step of the analysis to determine which variable yielded the most significant subdivision into a higher and a lower risk group.

RESULTS

Bivariate Analysis Bivariate comparison of the physical examination findings revealed significant differences between CM patients and control subjects for the number of common and atypical MN, the number of actinic lentigines, hair color, eye color, and the

Table I. Multiple Logistic Regression Analysis of Risk Factors and Relative Risks for Developing CM[a]

Risk Factor	Cases (496)	Controls (476)	Relative Risk			
			Unadjusted	[95% CI][b]	Adjusted	[95% CI]
Common melanocytic nevi						
0–10	151	255	1			
11–50	206	183	1.9	[1.4; 2.5]	1.7	[1.3; 2.4]
51–100	72	27	4.5	[2.8; 7.3]	3.7	[2.1; 6.5]
>100	67	11	10.3	[5.3; 20.1]	7.6	[3.5; 16.2]
Atypical melanocytic nevi						
None	313	394	1			
1–4	126	76	2.1	[1.5; 2.9]	1.6	[1.1; 2.3]
≥5	57	6	12.0	[5.1; 28.1]	6.1	[2.3; 16.1]
Actinic lentigines						
None	126	200	1			
Few	282	236	1.9	[1.4; 2.5]	2.1	[1.5; 2.9]
Many	88	40	3.5	[2.3; 5.4]	3.4	[2.1; 5.4]
Hair color						
Black or brown	175	220	1			
Blond	277	243	1.4	[1.1; 1.9]	1.4	[1.0; 1.9]
Red	44	13	4.3	[2.2; 8.2]	3.5	[1.7; 7.2]
Reported growth of MN						
No	334	292	1			
Yes	74	19	3.4	[2.0; 5.8]	2.3	[1.3; 4.1]
Skin type						
3 or 4	259	305	1			
1 or 2	237	171	1.6	[1.3; 2.1]	1.4	[1.0; 1.8]

[a] The logistic model included total number of common MN, total number of atypical MN, actinic lentigines, hair color, skin type, and reported growth of MN.
[b] [95% CI], 95% confidence intervals.

presence of actinic elastosis. The number of common MN on the entire body (mean, CM patients 46.3, control subjects 19.4; median, 21.0 versus 9.0) was found different with the highest statistical significance, followed by the number of atypical MN (mean, 2.0 versus 0.6). Atypical MN were found in 36.6% of CM patients and in 17.1% of controls. There was only little concordance with the prevalence of large melanocytic nevi (≥ 5 mm), which occured in 54.4% of CM patients and 31.3% of controls. No significant differences between CM patients and control subjects were found for other pigmented lesions.

The interviews also revealed significant differences between CM patients and control subjects. The prevalence of freckles in adolescence was higher in CM patients than in control subjects. Also, the light-sensitive skin types 1 or 2 were found more frequently in CM patients than in control subjects. CM patients stated significantly more often that new pigmented nevi had occurred independent of the development of their CM or that pre-existing pigmented nevi had grown in size. For most of the sun-exposure parameters there were no significant differences between CM patients and control subjects. Merely the number of sunburns before the age of 20 was significantly higher in CM patients (p < 0.05). None of the CM patients or controls had more than one blood relative with CM. Fifteen CM patients and five controls reported one blood relative with a diagnosis of CM (p < 0.05).

Multiple Logistic Regression Analysis   From a total of 28 factors included in stepwise logistic regression analysis six had a significant influence (p < 0.05) on the RR of developing CM. The order of their importance using stepwise regression was: the total number of common MN and the number of atypical MN as the most important factors, followed by the number of actinic lentigines, hair color, skin type, and reported pigmented nevus growth (Table I).

The number of common MN was the strongest indicator of an increased risk for the development of CM. Compared to subjects with 0–10 MN over all body areas, those with 50–100 MN already had an increased risk by the factor of 3.7 (after controlling for the five other significant variables), and those with more than 100 nevi by the factor of 7.6. The risk increased steadily with increasing numbers of common MN. A different characteristic was observed for the number of atypical MN. Compared to subjects without

atypical nevi, those with 1–4 atypical MN had a RR increase by the factor of 1.6, but those with five and more nevi had a marked RR increase by the factor of 6.1. No additional risk increase was observed for higher numbers of atypical nevi after controlling for potential confounding.

CART Analysis   Determination of decisive factors for subclassification of different risk groups was done by CART analysis. This type of analysis identifies important combinations of risk factors in the study collective and estimates the associated magnitudes of RR (Fig 1). The number of common MN (≤ 50; > 50) was the parameter that divided the total collective with the highest significance into two subgroups with differing CM risks. The manifestation of actinic lentigines (none; few and many) followed in this analysis as the second most important parameter. The third determining parameter was the presence of atypical MN and an additional subdivision of the number of common MN (0–10; 11–50) in one subgroup. The subclassification was terminated when no additional variable was determined to significantly subdivide the analyzed collectives. An extraordinarily high risk was observed in individuals with at least 5 atypical MN in combination with actinic lentigines and more than 50 common MN (RR = 121). Skin type merely played a role in risk assessment for patients with a negligible number of common MN and no actinic lentigines. A different strategy of CART analysis adjusting for age and sex after the first step was additionally performed (data not given). The same factors became significant in this adjusted CART analysis and the main differences were a lower impact of actinic lentigines as well as the result that exclusively the difference between 0–4 and ≥ 5 atypical MN was significant.

Risk groups for the development of CM were defined on the basis of the CART analysis (Table II). Individuals presenting merely with actinic lentigines or skin type 1 and 2 as risk factors had a low risk of developing CM (factor 2–3). An already moderate risk (factor 3–6) was observed in those with more than 50 common MN, with atypical MN, or with 11–50 MN and the additional occurence of actinic lentigines. A clearly increased risk (factor 10–20) was found in patients with more than 50 common MN and the additional occurence of either atypical MN or actinic lentigines. A markedly increased risk (factor greater than 100) was observed in individuals

Table II. Risk Assessment Scheme for the Combination of Different Risk Factors and Estimated Relative Risks (RR)

Relative Risk of Developing CM	Common MN	Actinic Lentigines	Atypical MN	Skin Type
Low (RR = 2–3)		Yes		
				1–2
Moderate (RR = 3–6)	11–50 >50	Yes	Yes	
Increased (RR = 10–20)	>50 >50	Yes	Yes	
Markedly increased (RR > 100)	>50	Yes	≥5	

with more than 50 MN, at least five atypical MN, and the additional prevalence of actinic lentigines.

DISCUSSION

The present multicenter case-control study included 513 CM patients prospectively recorded by nine university departments of dermatology in Germany, Austria, and Switzerland. Study centers (and their periphery) were selected to obtain a balanced ratio between urban and rural areas. Age and sex distribution, histologic melanoma subtypes, Breslow's thickness, and Clark's level of the present collective were representative for data of 3751 melanoma patients obtained from 41 centers in these countries recorded by the Central Malignant Melanoma Registry during the years 1989–1991 (data not given). Control subjects were selected from the participating centers. To reduce potential bias due to this selection, we excluded patients presenting because of pigmented moles or skin cancer, with a case history of phototherapy and patients of foreign descent. Interestingly, all published studies with whole-body examinations likewise used hospital-based control subjects [11,13,14,17], and inclusion of population-based controls in this type of study remains a future objective.

Number and type of melanocytic lesions over the entire body had the greatest importance for determining the RR of developing CM. Independently of each other, the number of common MN, atypical MN, and actinic lentigines were risk factors that predicted the risk of developing CM with the highest significance of all test parameters. The parameters recorded in the case history were of secondary importance for risk assessment. Hair color at the age of 20, the incidence of freckles in adolescence, and the skin type had the highest significance ($p < 0.001$ in bivariate analysis), followed by reported development of new moles as well as reported mole growth ($p < 0.01$) and finally sunburns before 20 and report of affected blood relatives ($p < 0.05$). Previous case-control studies on the risk of CM development that included both a whole-body examination and an extensive interview also demonstrated the superiority of clinical examination findings for risk assessment over case history data [11,13,14,17].

The CM risk showed an almost linear increase with the number of common acquired MN over the entire body. Common MN were first identified as major risk factors for developing CM by their self-reported frequencies by study subjects [6], later on by MN counts on the arms [7,10,12], and finally by their assessment on all body sites [9,11,13,14]. We could demonstrate in a previous study that the latter method yields the best risk estimations [18]. In the present study, the subclassification into groups with 10, 50, and 100 MN turned out to be the best subdivision for CM risk assessment. The adjusted multivariate analysis revealed that the risk approximately doubles above each of these numbers. Similar observations have been reported by other investigators, although the magnitude of odds ratios (OR) determined in case-control studies varied widely according to the study population and to sample sizes [9,11,13,14].

In the few investigations differentiating between common and atypical MN, the latter have already been identified as an independent risk factor for developing CM [11,13,14,17]. All these studies

defined atypical MN exclusively by their clinical appearance without histologic examination; this study followed the same concept. The presence of even a few atypical MN [1–4] led to a slightly increased CM risk (factor 1.6). A qualitative breakpoint has been observed with 5 or more atypical nevi. In this case, the RR increased by the factor of 6.1 in the adjusted calculation. There was no further increase in the RR of CM development with higher numbers of atypical MN. This finding indicates that preferentially the atypical nevus syndrome with five or more atypical MN may be relevant for CM risk assessment. The magnitude of RR determined here is in good agreement with the factor of seven reported for the presence of sporadic "dysplastic" nevus syndrome in the US population [19]. It is still a matter of debate, if it is possible to give also a histologic definition of this type of MN [20,21], and this problem has to be further elucidated by combined epidemiologic and histologic studies.

The third important factor for CM risk assessment was the presence of actinic lentigines. Even a few actinic lentigines were associated with an increase in the relative CM risk by a factor of 2.1, many actinic lentigines with an increase by a factor of 3.4. A significant increase in the RR with an increasing number of actinic lentigines that is independent of the number of MN was also described in the few previous studies examining this feature [12–14]. In the present study, freckles in childhood and adolescence as well as actinic lentigines at the time of the examination were recorded separately. In the bivariate analysis of this study, a history of freckles in childhood as well as the presence of actinic lentigines at the time of examination were significantly associated with an increased RR for CM. Both parameters were highly significantly related with each other ($p < 0.0001$). In the multiple logistic regression analysis, the history of freckles in childhood was no longer included in the model because the presence of actinic lentigines was found to be the better risk indicator.

Hair color and skin type were identified as additional significant independent risk factors. Several large epidemiologic investigations revealed that the pigmentary traits (skin type, hair color, eye color) are also risk factors for the development of CM [22–25]. In the present study, blond compared to brown or black hair as well as a light-sensitive skin type (type 1 or 2 versus 3 or 4) were associated with an increased RR by the factor of 1.4. Red hair found in 9% of CM cases and 3% of control subjects was associated with a clearly higher risk increase by the factor of 3.5. This magnitude of risk increase for red hair was also observed in a previous case-control study of the German Central Malignant Melanoma Registry [26].

Among all of the parameters determined as indicators for sun exposure, a significant association with CM risk was only found for the number of sunburns before the age of 20 in the bivariate analysis, but this was no longer a significant independent risk factor in the multivariate model. However, the absence of a significant relation between sun exposure parameters, including sunburns before the age of 20, and the risk for developing CM does not exclude the sun as a risk factor. Several studies have proposed a significant correlation between the number of common and atypical MN and sun exposure, particularly sunburns [27–29]. An interpretation of the results of the multivariate analysis can therefore be that the number of MN is more important for CM risk assessment than the reported sunburns before the age of 20. Furthermore, the results of other studies have shown that the number of life-long sunburns competes with the skin type for a significant relation to the CM risk [30]. Still, the skin type itself is no risk factor but becomes one in connection with UV exposure.

The importance of various risk factors for the identification of high-risk individuals was more clearly defined by the CART analysis. In the CART analysis as well, the total number of common MN was the most important parameter, and 50 MN were the best threshold value for determining CM risk patients. The second most important parameter for risk assessment in both subgroups (≤ 50 MN, > 50 MN) was the presence of actinic lentigines, followed by the presence of atypical MN. Already one or even a few atypical MN were important for risk assessment in subjects without

actinic lentigines. An additionally increased risk in subjects with more than 50 common nevi and actinic lentigines, however, was only found when they had five or more atypical MN (RR = 121.0 [15.8, 924.5]). These subjects belong to the group with the sporadic type of the atypical MN syndrome. The large confidence interval in the group with these characteristics is due to the small number of controls (34 CM patients and only one control). This implies that this risk factor constellation is extremely rare in the general population and was only found in 0.2% of controls. We decided not to adjust the CART analysis for age and sex after the first step of subclassification. Particularly actinic lentigines increase in number with increasing age and by adjustment for age their importance for detecting persons at risk may be underestimated.

Risk assessment on the basis of clinically detectable pigmented nevi over the body has the advantage of good reproducibility of test results. Agreement between different clinicians familiar with pigmented lesions was 85–90% in a study on this issue so that MN may be regarded as markers for risk assessment with a highly reliable reproducibility [31].

We conclude that the characteristics obtained through dermatologic whole-body examination are clearly superior to case history data as risk indicators for the development of CM. Recognition of the numbers of common and atypical MN and of the frequency of actinic lentigines and the application of our proposed risk assessment scheme allows the trained physician immediate identification of persons at risk. The magnitudes of RR for the different risk factors determined in the present study may not apply to other geographic areas, and similar studies elsewhere are required. Finally, the present study confirms that clinical recognition of the atypical mole syndrome is a key for identifying persons at high risk of developing CM independently of a specific histological diagnosis.

REFERENCES

1. Garbe C, Thieß S, Nürnberger F, Ehlers G, Albrecht G, Lindlar F, Bertz J: Incidence and mortality of malignant melanoma in Berlin (West) from 1980 to 1986. *Acta Derm Venereol (Stockh)* 71:506–511, 1991
2. MacKie RM, Aitchison T: Severe sunburn and subsequent risk of primary cutaneous malignant melanoma in Scotland. *Br J Cancer* 46:955–960, 1982
3. Holman CDJ, Armstrong BK: Cutaneous malignant melanoma and indicators of total accumulative exposure to the sun: an analysis separating histogenetic types. *J Natl Cancer Inst* 73:75–82, 1984
4. Elwood JM, Gallagher RP, Davison J, Hill GB: Sunburn, suntan and the risk of cutaneous malignant melanoma—the Western Canada Melanoma Study. *Br J Cancer* 51:543–549, 1985
5. Green A, Siskind V, Bain C, Alexander J: Sunburn and malignant melanoma. *Br J Cancer* 51:393–397, 1985
6. Beral V, Evans S, Shaw H, Milton G: Cutaneous factors related to the risk of malignant melanoma. *Br J Dermatol* 109:165–172, 1983
7. Holman CD, 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
8. Swerdlow AJ, English J, MacKie RM, O'Doherty CJ, Hunter JA, Clark J: Benign naevi associated with high risk of melanoma. *Lancet* II:168, 1984
9. 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
10. Green A, MacLennan R, Siskind V: Common acquired naevi and the risk of malignant melanoma. *Int J Cancer* 35:297–300, 1985
11. 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
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. MacKie RM, Freudenberger T, Aitchison TC: Personal risk-factor chart for cutaneous melanoma. *Lancet* II:487–490, 1989
14. Garbe C, Krüger S, Stadler R, Guggenmoos-Holzmann I, Orfanos CE: Markers and relative risk for developing malignant melanoma in a German poplation. *Int J Dermatol* 28:517–523, 1989
15. Breslow NE, Day NE: *Statistical Methods in Cancer Research. I. The Analysis of Case Control Studies,* IARC, Lyon, 1980
16. Breiman L, Friedman JH, Olshen RA, Stone CJ: *Classification and Regression Trees.* Wadsworth International, Belmont, California, 1984
17. Weiß J, Bertz J, Jung EG: Malignant melanoma in southern Germany: different predictive value of risk factors for melanoma subtypes. *Dermatologica* 183:109–113, 1991
18. 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
19. Kraemer KH, Tucker M, Tarone R, Elder DE, Clark WH: Risk of cutaneous melanoma in dysplastic nevus syndrome types A and B. *N Engl J Med* 315:1615–1616, 1986
20. Ackerman AB: What naevus is dysplastic, a syndrome and the commonest precursor of malignant melanoma? A riddle and an answer. *Histopathology* 13:241–256, 1988
21. Piepkorn M, Meyer LJ, Goldgar D, Seuchter SA, Cannon Albright LA, Skolnick MH, Zone JJ: The dysplastic melanocytic nevus: a prevalent lesion that correlates poorly with clinical phenotype. *J Am Acad Dermatol* 20:407–415, 1989
22. Dubin N, Moseson M, Pasternack BS: Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation, and the identification of high-risk populations. *Recent Results Cancer Res* 102:56–75, 1986
23. Gallagher RP, Elwood JM, Hill GB: Risk factors for cutaneous malignant melanoma: the Western Canada Melanoma Study. *Recent Results Cancer Res* 102:38–55, 1986
24. Green A, Bain C, McLennan R, Siskind V: Risk factors for cutaneous melanoma in Queensland. *Recent Results Cancer Res* 102:76–97, 1986
25. Holman CD, 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
26. Weiß J, Garbe C, Bertz J, Biltz H, Burg G, Hennes H, Jung EG, Kreysel HW, Orfanos CE, Petzold D, Schwermann M, Stadler R, Tilgen W, Tronnier H, Völkers M: Risikofaktoren für die Entwicklung maligner Melanome in der Bundesrepublik Deutschland. Ergebnisse einer multizentrischen Fall-Kontroll-Studie. *Hautarzt* 41:309–313, 1990
27. 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
28. Titus Ernstoff L, Ernstoff MS, Duray PH, Barnhill RL, Holubkov R, Kirkwood JM: A relation between childhood sun exposure and dysplatic nevus syndrome among patients with nonfamilial melanoma. *Epidemiology* 2:210–214, 1991
29. 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
30. Beitner H, Norell SE, Ringborg U, Wennersten G, Mattson B: Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Br J Dermatol* 122:43–51, 1990
31. Roush GC, Barnhill RL, Ernstoff MS, Kirkwood JM: Inter-clinician agreement on the recognition of clinical pigmentary characteristics of patients with cutaneous malignant melanoma. Studies of melanocytic nevi, VI. *Br J Cancer* 64:373–376, 1991