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Epidemiology of atypical melanocytic naevi: an analytical study in a Mediterranean population*

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Atypical naevi are markers for increased risk of malignant melanoma, providing additional information about melanoma risk beyond that given by common melanocytic naevi. Little is known about the epidemiology of atypical naevi (AN), and available data are limited to predominantly fair-skinned populations. By using a case-control study that included 705 subjects with atypical naevi and 1,782 controls, we have analysed the aetiology of AN in a Mediterranean population, paying particular attention to the role of sunburn. After adjusting for age, sex and years of formal education, the presence of atypical naevi was significantly related to frequent sunburn before the age of 20 (odds ratio, OR, = 1.8; 95% CI, 1.3–2.5). Although less evident, this relationship was maintained by also taking into account the sun sensitivity, expressed as phototype, as a confounder (OR = 1.5; 95% CI, 1.0–2.0). Concerning phenotypical features, an increased risk of having atypical naevi was found for all the parameters included in so-called 'fair complexion', *ie* blue eyes, blond or red hair, fair skin, phototype I–II, and a tendency to freckle. The greatest difference between subjects with and without atypical naevi related to the number of common melanocytic naevi: more than 30 common naevi were found in 41.5% of cases, but only in 9% of controls (OR = 8.0; 95% CI, 6.3–10.3). Overall, the six variables entered in the multivariate model that best predicted the risk of atypical naevi, were: young age, male sex, high educational level, presence of a large number of common naevi, phototype I–II, and a history of painful sunburn. In conclusion, the variables predicting the risk of developing atypical naevi in Mediterranean people are identical to those observed in predominantly fair-skinned populations. The aetiologic role of sunlight has been pointed out and shows a statistically significant relationship between frequent sunburn and the development of atypical naevi also after controlling for the subject's phototype.

Keywords: Atypical naevi, epidemiology, melanocytic naevi.

Introduction

Several epidemiological studies have shown that atypical naevi (AN) are markers for increased risk of malignant melanoma (Grob *et al*, 1990; Halpern *et al*, 1991, 1993a; Schneider *et al*, 1992; Newton *et al*, 1993; Garbe *et al*, 1994). The presence of AN (and their number) provides additional information about melanoma risk beyond the information given by the presence of common acquired naevi (MacKie *et al*, 1989; Grob *et al*, 1990). Clinical assessment of AN, with or without pathological confirmation, is

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then a useful predictor of melanoma risk. In epidemiological studies, the following clinical criteria have been commonly adopted to define AN: (1) diameter larger than 5–6 mm; (2) irregular margin; (3) ill-defined borders; (4) variegated colour; and (5) macular component (Halpern *et al*, 1991; Newton *et al*, 1993). Additional criteria less frequently used are background erythema and accentuated skin markings (Holly *et al*, 1987). In some studies, all the parameters 1–4 were required to define a naevus as atypical (Halpern *et al*, 1991; Newton *et al*, 1993), while in other studies at least three of the above mentioned parameters were sufficient (Grob *et al*. 1990). Data from a case–control study carried out by the German Dermatological Society showed that clinical recognition of at least five atypical naevi (naevi showing all parameters 1–4) without histological examination is a key for identifying subjects at high risk for malignant melanoma (Garbe *et al*, 1994).

The prevalence of AN in the general population ranges from 2% to 17% (Holly *et al*, 1987; Cooke *et al*, 1989; Grob *et al*, 1990). In the Italian population, a survey carried out on male recruits (19–20 years of age) showed a prevalence of 21.3% in this particular population sample (Brogelli *et al*, 1991). Data from the control group (sampled from demographic files) of a case–control study recently performed by us in the Florence district showed a mean prevalence of 3% in the general population (20–69 years of age) (Carli *et al*, 1995).

Despite these data, little is known about the aetiology of atypical naevi. Studies carried out in predominantly fair-skinned populations showed that the presence of AN is significantly related to younger age, more years of formal education (Weinstock *et al*, 1991) and male sex (Garbe *et al*, 1994). The association between sunburn before the age of 20 and AN has not been confirmed by all the authors (Weinstock *et al*, 1991; Garbe *et al*, 1994). No data on the aetiology of AN are available in Mediterranean people. We have now investigated the risk factors for AN in a large clinic-based cross-sectional study within such a population.

Patients and methods

The study population consisted of 2,487 consecutive patients with diagnoses other than malignant neoplasm who presented for the first time to the Pigmented Lesion Clinic of the Dermatology Department of the University of Florence (Italy) between 1 May 1990 and 31 May 1992. All patients were visited by trained dermatologists and the presence (and number) of common and atypical naevi was recorded (see below for criteria of skin examination). The study was designed as a cross-sectional study: from the computerized database, we defined as cases those patients having, independent of diagnosis of suspicious pigmented lesion shown as cause of referral, one or more atypical naevi ($n = 705$). All the remaining subjects, *ie* those not having AN, were considered as controls ($n = 1,782$). Patients diagnosed as having malignant melanoma were not considered in this study.

Clinical examination (count of common melanocytic naevi, atypical naevi, assessment of eye, hair and skin colour) and interview concerning years of formal education, sun sensitivity, history of sunburn, and tendency to freckle were performed during a routine examination by the same two trained dermatologists (P.C. and B.G). For the assessment of melanocytic lesions visits were performed together by the two dermatologists. Results used in the study was derived from a consensus between the two investigators (Carli *et al*, 1995).

Diagnostic criteria for pigmented lesions

The clinical characteristics of pigmented lesions were defined before the start of the study. According to Grob *et al* (1990) and Holly *et al* (1987), atypical naevi were defined as naevi showing at least three of the following clinical parameters: diameter 5 mm or greater (mandatory), ill-defined border, irregular margins, irregularly distributed pigmentation, background erythema, and accentuated skin markings. Clinical diagnosis of common melanocytic naevi and differential diagnosis including lentigines, freckle, naevi spili, congenital naevus-like naevi, café au lait spot, blue naevi, seborrhoeic keratoses and pigmented basal cell carcinoma were performed according to Holly *et al* (1987). This study was begun when preliminary results of a previous case–control study on risk factors for malignant melanoma in the Florence District were available, showing a statistically significant relationship between the presence of AN and melanoma risk (Carli *et al*, 1995). Because the purpose of this study was to evaluate the risk factors for developing AN (a marker of melanoma risk in Mediterranean people), to ensure comparability of data in the present study we used the same criteria for the clinical definition of common and atypical naevi which were adopted in the previous study. Additionally, the examiners were the same (Carli *et al*, 1995).

Dermatological examination and interview

All subjects underwent a whole-body examination (excluding the scalp and genital region); common naevi and atypical naevi were counted separately. Interviews were conducted using a questionnaire before clinical examination. Phototype was assessed according to Fitzpatrick (1975). Sunburn history before the age of 20 was based on the question 'Have you ever been sunburned so severely as to cause pain for two or more days or to cause blistering? ' (Elwood *et al*, 1990).

Statistical analysis

Adjusted odds ratios associated with each variable were computed by means of logistic regression analysis taking into account sex, age groups (15, 15–24, 25–34, 35–44, 45–54, 55–64, 65 or more), and years of formal education as confounders. Factors with $P < 0.05$ were entered in a multifactorial stepwise logistic regression analysis, which was performed using the EGRET statistical package (SERC, 1991). The statistical model best predicting the risk for AN was then obtained.

Results

Considering the first age group (< 15 years) as the reference category, the OR of having AN increases for each age group until the decade 35–44. Afterwards, a steadily, statistically significant reduction of AN risk was found (Table 1).

The male sex showed an increased risk (OR 1.5; 95% CL, 1.2–1.8). Concerning the level of education, after adjustment for age and sex, the risk increased steadily for each level of formal education. No difference in the usual site of work (indoor or outdoor) was found between subjects with AN and controls.

Regarding phenotypic variables, all features included in the so-called 'light complexion' occurred more frequently in cases than in controls, with a statistically significant difference (light brown, blond and red hair: OR ranging from 1.5 to 1.7; green, grey, blue eyes: ORs from 1.9 to 2.7; fair skin OR 2.4, 95% CL, 1.8–3.3). Likewise, considering phototype IV (never burns, always tans) as reference category, a statistically significant trend for increasing risk was found from phototype IV to I (OR 2, $P < 0.01$) (trend test 32.3, 1 df, $P < 0.001$). The tendency to freckle showed an OR of 1.3 (95% CL, 1.1–1.6).

A history of frequent sunburn before the age of 20 was associated with a statistically significant increased risk for AN (OR = 1.8, 95% CL, 1.3–2.5). After adjustment for phototype, such risk remained increased, although it showed a slight reduction in magnitude (OR = 1.5; 95% CL, 1.0–2.0). A tendency to sunburn did not occur to a greater extent among subjects with a greater inability to tan (phototype I), but occurred equally in phototypes I–III (ORs = 1.4, 1.6 and 2.1, respectively; difference $P = 0.882$).

The relation between a history of sunburn and AN did not depend on the number of banal naevi affecting all categories of subjects (< 10 CMN, > 10, < 30, > 30) without statistical significance of ORs.

The most obvious difference between subjects with or without atypical naevi concerned the number of common melanocytic naevi; more than 30 common naevi were found in 41.5% of cases but only in 9% of controls (crude OR = 10.60). After adjustment for age, sex and years of formal education, the presence of more than 30 common naevi resulted (considering < 10 common naevi as the reference category) in an 8-fold increased risk for developing AN (95% CL, 6.3–10.3) (trend test = 264.9, 1 df, $P < 0.001$). This relationship between number of CMN and AN risk could be applied equally to phototypes I, II, III and IV.

To test whether the findings of this study were modified when considering a study base with more homogenous life-style, less age variation in AN expression and less phenotype variation, we repeated the analysis of data, excluding subjects over 45 years of age and phototype IV. Results substantially duplicated those shown when the entire study base was considered. No association with AN risk was found for the history of a melanoma case among relatives (61/704 in cases, 127/1,775 in controls; OR 1.37, N.S.).

Finally, six variables had a statistically significant influence on the relative risk of developing AN (stepwise logistic regression analysis) (Table 1): young age, male sex, high educational level, a large number of common naevi, phototype I–II, and history of more than one sunburn before the age of 20. The high number of common naevi was the strongest indicator of an increased risk for the development of AN.

Discussion

In recent years, epidemiological studies have shown that naevi defined as atypical on the basis of their clinical aspects are markers for increased risk of malignant melanoma (Grob *et al*, 1990; Halpern *et al*, 1991; Schneider *et al*, 1992; Newton *et*, 1993).

Table 1. Odds ratios (ORs) and 95% confidence limits (CL) for developing atypical naevi in relation to phenotypic variables and sun exposure

Variable	Cases	Controls	OR† (95% CI)	OR‡ (95% CI)
Age classes				
<15 years	62	197	1	1
15–24	213	336	1.5 (1.0–2.3)	1.5 (0.9–2.2)
25–34	197	317	1.5 (1.0–2.3)	1.5 (0.9–2.3)
35–44	126	283	1.0 (0.7–1.6)	1.3 (0.8–2.0)
45–54	58	259	0.6 (0.4–0.9)	0.9 (0.6–1.5)
55–64	29	195	0.4 (0.2–0.7)	0.7 (0.4–1.1)
65 or more	14	186	0.2 (0.1–0.4)	0.4 (0.2–0.9)
Sex				
Female	402	1114	12	1
Male	303	668	1.5 (1.2–1.8)	1.4 (1.1–1.7)
Educational level (years)				
< 6	58	379	1	1
8	144	373	1.5 (1.0–2.2)	1.4 (0.9–2.0)
13	364	759	1.6 (1.1–2.3)	1.4 (0.9–2.0)
>13	129	226	2.1 (1.4–3.2)	1.6 (1.0–2.4)
Work				
Indoor	683	1720	1	
Outdoor	22	62	0.9 (0.5–1.6)	
Eye colour				
Black	19	73	1	
Brown	428	1204	1.3 (0.8–2.2)	
Green	126	244	1.9 (1.1–3.4)	
Grey	33	53	2.7 (1.4–5.4)	
Blue	99	207	1.9 (1.1–3.4)	
			(trend test 15.9, $P < 0.001$)	
Hair colour				
Black	81	259	1	
Dark brown	318	948	1.0 (0.7–1.3)	
Light brown	202	384	1.5 (1.1–2.1)	
Blond	91	169	1.5 (1.0–2.3)	
Red	13	21	1.7 (0.8–3.6)	
			(trend test 15.1, $P < 0.001$)	
Skin colour				
Olive, slight and intense	87	327	1.0	
Intermediate	348	951	1.6 (1.2–2.1)	
Fair	270	502	2.4 (1.8–3.3)	
			(test trend 40.0, $P < 0.001$)	
Tendency to freckle				
No	431	1212	1	
Yes	271	567	1.3 (1.1–1.6)	
Phototype				
I	28	48	1.0	1
II	280	488	1.0 (0.6–1.6)	1.2 (0.7–2.1)
III	312	922	0.5 (0.3–0.9)	0.8 (0.4–1.4)
IV	57	210	0.5 (0.3–0.8)	0.8 (0.4–1.5)
			(trend test 32.3, $P < 0.001$)	
History of sunburn				
One or none	623	1665	1	1
Two or more	82	116	1.8 (1.3–2.5)	1.4 (1.0–2.1)
			1.5 *	
Number of common naevi				
< 10	233	1365	1	1
10–30	179	255	3.4 (2.7–4.4)	3.2 (2.5- 4.1)
>30	293	162	8.0 (6.3–10.3)	7.8 (6.0–10.1)

†OR = adjusted for sex, age and years of formal education.

*Adjusted also for phototype.

‡ = Multivariate model including age, sex, educational level, number of common naevi, phototype, history of sunburn: All the factors are mutually adjusted.

Because of the poor relationship between clinical and histological atypia (Grob *et al*, 1988; Piepkorn *et al*, 1989; Klein and Barr, 1990), it is important to stress that clinically atypical melanocytic naevi did not necessarily show histological atypia. In a previous clinico-pathological double-blind study we observed that only 31% of naevi defined as clinically atypical on the basis of the same criteria as adopted in the present study showed architectural disorder plus cytological atypia, while 13% of them were common naevi; the remainder (56%) showed architectural disorder without cytological atypia (Carli *et al*, 1994). Indeed, for the purpose of secondary prevention of melanoma it is important to note that the clinical definition of atypical naevi is a sufficient tool (together with other known markers of risk, such as a large number of banal naevi, fair complexion, a history of sunburn, and the tendency to freckle) for identifying subjects at risk of malignant melanoma (Carli *et al*, 1995).

In this study, an attempt to investigate the aetiology of AN has been made by means of a large analytical study. The definition of study base, the diagnostic criteria for naevi and the statistical methods used are similar to those adopted in studies recently carried out in the white American and German populations (Weinstock *et al*, 1991; Garbe *et al*, 1994). This allows comparison between results obtained in phenotypically different people (fair skinned and Mediterranean).

From our data, young age, male sex, high educational level and those phenotypical features identifying the so-called 'light complexion' resulted in statistically significant risk factors for AN. When the parameter 'young age' is entered in the final model predicting AN risk, then after adjustment for all significant variables and considering < 15 years of age the reference category, the probability of having AN steadily increases until the third decade of life, with a progressive decrease afterwards. These data are in agreement with those observed in fair-skinned populations (Weinstock *et al*, 1991; Garbe *et al*, 1994). Two possible explanations should be given for the decrease of naevi counts with age: disappearance of naevi over time and cohort effect. Recently published data from a survey on the natural history of naevi showed that, in older age groups, there was a tendency for a greater proportion of atypical naevi to be less atypical compared with those in younger age groups. A stable rate of naevus disappearance in all age groups was also observed. However, because of the insufficient magnitude of these phenomena, a significant cohort effect (higher naevus counts in successive births cohorts) must be advocated to explain the decrease in mole count with age (Halpern *et al*, 1993b).

Concerning the association between AN and 'light' phenotype, the relative risks associated with blue eyes, blond and red hair colour, fair skin and a tendency to freckle were no longer significant after simultaneous adjustment for sunburn and number of common naevi, but phototype retained statistical significance (likelihood ratio test = 13.3, 3 df, $P = 0.004$). Indeed, the major indicator of AN risk was found to be the high common naevus count: the probability of subjects with more than 30 common naevi having AN is 8-fold greater than in subjects with < 10 common naevi (best predicting logistic regression model).

Different hypotheses for the strong association between AN and high common naevi counts are: (1) both covariates are different phenotypical aspects of a common genetic trait; and (2) both of them derive from the exposure to the same environmental aetiologic agent, *ie* frequent sunburn. Concerning this latter feature, a relationship between intermittent sun exposure and melanocytic naevi has been observed by different authors (Kopf *et al*, 1985; Weinstock *et al*, 1991; Richard *et al*, 1993; Garbe *et al*, 1994). In our data, the association between frequent sunburn before the age of 20 and the risk of developing AN was statistically significant after adjusting for phototype. This finding means that the history of more than one painful sunburn before the age of 20 is a risk factor for developing AN independently of phototype of the subjects, and it applies equally to phototypes I, II and III. Moreover, when adjusted for number of common naevi, the relationship between sunburn and AN has not been obscured; this should mean that the aetiologic role of sunburn in the development of atypical naevi is different from that played by sunburn towards the development of high common naevi counts. Our results are consistent with those obtained in the particular field of nonfamilial melanoma patients, in which a relationship between childhood sun exposure (including blistering sunburn) and the occurrence of dysplastic naevus syndrome has been found (Titus-Ernstoff *et al*, 1991). Further studies are needed to determine if early intermittent sun exposure increases melanoma risk by initiating atypical naevi, or whether a more complex aetiologic relationship exists among the variables, *ie* sun exposure, high common naevi count, atypical naevi and melanoma development.

In conclusion, as previously reported for predominantly fair-skinned populations, the occurrence of

atypical naevi in a Mediterranean population is significantly related to young age, male sex, high educational level, and fair complexion. Moreover, the risk of developing AN is related to a history of painful sunburn. This finding should add weight to educational efforts aimed at preventing sunburn. A link between AN and a large number of common naevi has been pointed out. As both these variables are risk factors for malignant melanoma, more attention should be paid to elucidating the aetiologic relationship among environmental exposure (sunburn), common and atypical melanocytic naevi and malignant melanoma.

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