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Characterization of nonacral melanoma patients without typical risk factors

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Abstract

A divergent pathway model to cutaneous melanoma is commonly accepted: sun sensitivity/chronic sun exposure and melanocytic instability. Although this dual model explains the development of most melanomas, clinical experience suggests other possible routes. The aim of this study was to explore the characteristics of patients who do not fit with these two pathways. We selected 818 patients with nonacral cutaneous melanoma and defined three groups: nevus-prone individuals, sun-sensitive individuals, and non-nevus-prone and non-sun-sensitive individuals. This group included patients without identifiable melanoma risk factors and comprised 52 patients (5.5% of the overall nonacral melanoma population). These patients were more frequently women, were more likely to present melanoma at a very young age (13.5% before 25 years), to have less frequent personal history of melanoma and remnants of pre-existing nevi, and to present tumors on the trunk and legs. We have identified a group of patients with fewer risk factors for melanoma that needs further studies to increase our understanding of melanoma development.

Keywords

melanoma; nevus; phenotype; route; sun exposure

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Conflicts of interest

There are no conflicts of interest.

Introduction

The incidence of cutaneous melanoma (CM) has increased over the last decades in white populations [1–9]. Ultraviolet exposure is widely accepted as the major environmental cause of CM, but the relationship between risk and sunlight is complex [1–20]. Apparent paradoxes are that indoor workers have a higher risk of CM than outdoor workers, and that some tumors arise in sun-protected skin [2,4,6,9,10,19]. The risk of CM is modulated by environmental conditions and phenotype characteristics [1,3–10,12,14,17,19–21]. The main risk factors for CM are exposure to ultraviolet radiation [1–20], a history of sunburn [1,3,6,7,9,12,14,16,20,22], multiple common and atypical nevi [2,3,5–9,11–13,15,16,19,20,23–25], skin type [1,3,6–9,12,14,16,19,22], hair and eye color [1–4,7–9,12,14–16,19,22], indicators of actinic damage [1,3,12,16,19], and a family history of CM [3,8,12,14,22,23]. In addition, specific genetic alterations support the existence of distinct molecular pathways involved in the development of CM [2,5,6,9,12,13,17,21,26,27]. *BRAF* and *N-RAS* mutations are more common in CM localized in intermittently sun-exposed skin than in chronically sun-damaged skin [2,5,9,11–15,19,21,26]. The abnormal expression of the tumor suppressor gene *p53* is associated with sun sensitivity and chronic exposure to the sun, in contrast with *p53*-negative tumors, mainly related to melanocytic instability [2,9,10,12,17].

These epidemiological and genetic data suggest the existence of different patterns in the development of CM [2,3,5,6,9,12,17,19,22]. One potential route is linked to chronic sunlight stimulation of skin that is particularly sensitive to sun exposure and is associated with photo-damage and relatively few nevi. The second route operates in nevus-prone individuals, is related to melanocytic instability, and requires intermittent exposure to ultraviolet radiation [1–3,5–7,9,12,14,17,19,21]. Melanoma localized in the palms, soles, and mucosal membranes shows an increased rate of chromosomal aberrations [2,5,6,14,26,27] and genetic alterations in *KIT* [26]. Higher frequencies of personal and family histories of noncutaneous neoplasias have been described in acral melanomas [14], suggesting another specific path for acral melanoma [2,5,6,14,17,26,27].

Although the development of most CMs relates to sun sensitivity and melanocytic proliferation, clinical experience suggests that a proportion of nonacral CM develops following a different pathogenic pattern. The aim of this study was to examine a large database of melanoma incident cases from Valencia, Spain, and classify them by the most common known risk factors for melanoma. The ultimate objective was to explore the clinical and epidemiological characteristics of those individuals whose melanoma are unlikely to be related to typical risk factors.

Materials and methods

The present study utilized data from the database of the Dermatology Department of the Instituto Valenciano de Oncología, Valencia, Spain. A detailed description of this database can be found in previous reports [6,14,22]. Briefly, this database includes incident and prevalent melanoma cases definitively treated at our institution. Clinical and pathologic data from these patients have been prospectively collected since January 2000. The study

included incident cases registered from January 2000 to April 2009. Patients with acral and mucosal melanomas and patients with melanoma metastases from an unidentified primary tumor were excluded from the analysis. Also, lentigo maligna melanomas, which are well known to have a clear relationship with chronic sun exposure, were not included in the study population.

Three mutually exclusive groups were initially defined according to the pattern of CM development (Table 1):

1. Group 1: nevus-prone individuals, which included patients with more than 20 common nevi (only those >2 mm in diameter and counted by a dermatologist on the entire naked body).
2. Group 2: sun-sensitive (SS) individuals, comprising red-haired patients, patients with fair skin, and patients with skin phototypes I or II.

To compare clear groups, patients who simultaneously fulfilled the criteria of the two previous groups were excluded from the analyses.

1. Group 3: non-nevus-prone and non-sun-sensitive individuals. The aim of the study was to characterize this group of melanoma patients, which included individuals with less than 20 nevi, brown or black hair and dark eye color, and skin type higher than II. To refine this group, we included only patients who, in addition to these features, did not have any of the following characteristics: a past personal history of severe sunburns, a personal history of nonmelanoma skin cancer, presence of actinic keratoses, presence of solar lentigines, and a family history of melanoma.

The following variables were considered in the comparative analyses of patterns of CM development:

1. Epidemiologic features: age at diagnosis, sex, occupational sun exposure, and personal history of melanoma and noncutaneous neoplasms.
2. Clinical features: presence of solar lentigines, atypical nevus, and tumor site.
3. Histological data: histological subtype, Breslow's tumor thickness, and remnants of pre-existing nevus. Differences in the distribution of the variables investigated among groups and subgroups of patients were evaluated using the χ^2 -test. *P* values were corrected for multiple comparisons using the Bonferroni test. The data collected were analyzed using the SPSS version 15 (SPSS Inc., Chicago, Illinois, USA).

Results

From a total of 939 registered patients, 192 patients were excluded (84 patients with acral CM, 71 patients with lentigo maligna melanoma, 16 patients with mucosal melanoma, and 21 patients with unknown primary tumors). The study population included 747 eligible patients. After excluding all the patients who did not fulfill the criteria for inclusion in any of the defined groups, the final study population included 393 patients, 193 (49.1%) men and

200 (50.9%) women, with a median age at diagnosis of 54 years (interquartile range, 41–66 years).

Among the risk factor groups, 114 (29.0%), 227 (57.8%), and 52 (13.2%) patients belonged to groups 1, 2, and 3, respectively. The characteristics of the different groups are summarized in Table 2. In this table, the corrected *P* value after Bonferroni's correction (result of multiplying the *P* value by the number of variables tested) is also included to point out possible false-positive results that might be present as a consequence of performing multiple comparisons (the chance of finding a significant association is related to the number of variables tested).

The age of diagnosis differed among the three groups of patients (global $P < 0.001$). Group 3 and, to a lesser extent, group 1 patients developed CM earlier in life than group 2 patients. For example, 92.1% of group 1 patients developed CM before 65 years; this proportion was 66.1 and 75.0% in group 2 and 3 patients. Besides, the proportion of group 3 patients younger than 25 years was the highest (13.5%) among all the groups. Groups 2 and 3 had a preponderance of women, although the differences were not significant.

No significant differences in terms of a personal or a family history of noncutaneous neoplasias were found between the groups.

The CM site differed between groups, although the differences were not significant after correction for multiple comparisons (global $P = 0.198$). Nevertheless, the most interesting finding was the proportion of patients with melanoma located on the lower extremities in group 3 patients (34.6%). An expected high rate of trunk melanomas was found in group 1.

As for the CM histological subtypes, nodular melanomas were rarer in group 2 patients (18.9%) than in group 1 or 3 (28.9 and 25.0%, respectively), but these differences were not significant when corrected for multiple comparisons (global $P = 0.352$). The presence of remnants of pre-existing nevus was more frequently found in group 1 patients, as expected, and the lowest rate was found in group 3 patients. However, these differences were not significant after correcting for multiple comparisons (global $P = 0.279$). Breslow's thickness was similarly distributed across all the groups.

Discussion

Epidemiological data support the existence of at least two patterns of non-acral-CM genesis, the first associated with melanocytic proliferation and intermittent sun exposure and the second related to sun sensitivity and chronic sun exposure [1–3,5–7,9,10,12–19,21,22,25].

Although the majority of CMs follow these patterns of development, clinical experience indicates that a proportion of CMs arise through a different route. On studying our large melanoma database [6,28], we confirmed previously defined patterns of melanoma development, but also identified a group of individuals in whom women and very young people were over-represented, but lacked the major known risk factors for melanoma.

Our results generally support previous epidemiologic observations that recognized two different phenotypes at high risk of nonacral CM: the ‘red-skinned red-heads’ (in our study, group 2 patients) and individuals with a substantial number of melanocytic nevi (group 1 patients) [1–3,6,9,12,19]. As expected, and in agreement with the published literature, group 1 patients had a high propensity for melanocytic proliferation and had only occasional sun exposure. In contrast, the pattern of development in group 2 patients was predominantly related to continuous cumulative exposure to sunlight [1–3,6,9,10,13,15–18]. Group 1 patients showed CM at intermittently sun-exposed sites, such as the trunk [1–3,6,9,10,13,15–17,19]. Conversely, and in agreement with published data, group 2 individuals were older at CM diagnosis, which was frequently on sun-exposed body sites and associated with solar damage [1–3,6,9,10,16,17,19].

The main objective of this study was to characterize group 3 patients. This category included 52 patients and represented 5.5% of our entire melanoma population. In these patients, melanoma was less likely to be related to any of the two suggested divergent pathways: cumulative sun exposure (we excluded patients with either a personal history of outdoor jobs or recognized signs of chronic sun damage such as the presence of actinic keratosis, solar lentigines, or a personal history of nonmelanoma skin cancer) or nevus predisposition.

These patients were predominantly women, developed melanoma more frequently at a very young age (under 25 years), and developed less multiple melanomas, which developed mostly on the trunk and the legs. Altogether, the characteristics of this group suggest an as yet unknown etiological pathway and possible susceptibility genes that affect the risk of melanoma beyond pigmentation or nevi-proneness. Larger studies into this subgroup of individuals are warranted to improve our understanding of CM pathogenesis and prevention strategies. The strengths of our study include the large sample size, the uniform collection of data from incident melanoma cases, the physician-assessed clinical and phenotypic characteristics, and the homogeneity of diagnosis and referral procedures. Several limitations should also be considered, including self-reported personal and family medical history, the nonpopulation-based nature of the study, and the lack of a histopathological review of the signs of solar elastosis adjacent to the CM lesions.

In conclusion, we have identified a ‘novel’ group of melanoma cases with fewer known risk factors for melanoma. In addition to its clinical relevance, an accurate characterization of non-nevus-prone, non-sun-sensitive patients can increase our understanding of CM development and possibly improve prevention strategies.

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Table 1

Categories of patients according to the pattern of melanoma development

Category	Group	Criteria
Nevus prone	Group 1	Patients with more than 20 common melanocytic nevi
Sun sensitive	Group 2	Red-haired patients or Patients with phototype I or II
Non-nevus prone and nonsun sensitive	Group 3	Patients who did not fulfill any previous criteria and Do not have family history of melanoma, personal history of severe sunburns, or nonmelanoma skin cancer or presence of actinic keratoses or solar lentigines

Table 2

Characteristics of patients according to the pattern of melanoma development

Number (%)				
	Group 1 (NP) (n= 114)	Group 2 (SS) (n=227)	Group 3 (NNP–NSS) (n= 52)	P (Pc global)*
Epidemiological features				
Age (years)				
<25	4 (3.5)	4 (1.8)	7 (13.5)	<0.001 (<0.001)
25–45	47 (41.2)	53 (23.3)	20 (38.5)	
46–65	54 (47.4)	93 (41.0)	12 (23.1)	
>65	9 (7.9)	77 (33.9)	13 (25.0)	
Sex				0.028 (0.252)
Male	68 (59.6)	101 (44.5)	24 (46.2)	
Female	46 (40.4)	126 (55.5)	28 (53.8)	
Personal history of multiple melanomas				0.049 (0.441)
No	107 (93.9)	220 (96.9)	52 (100)	
Yes	7 (6.1)	7 (3.1)	0 (0)	
Personal history of noncutaneous cancers				NS
No	102 (89.5)	213 (93.8)	48 (96.0)	
Yes	12 (10.5)	14 (6.2)	2 (4.0)	
Family history of other neoplasias (m.v= 22)				NS
No	64 (57.7)	131 (59.5)	29 (72.5)	
Yes	47 (42.3)	89 (40.5)	11 (27.5)	
Clinical features				0.028 (0.252)
Melanoma site				
Head/neck	13 (11.4)	45 (19.8)	8 (15.4)	
Upper limbs	15 (13.2)	44 (19.4)	7 (13.5)	
Trunk	63 (55.3)	92 (40.5)	19 (36.5)	
Lower limbs	23 (20.2)	46 (20.3)	18 (34.6)	
Histological data				
Histological subtype				0.011 (0.099)
SSM	80 (70.2)	166 (73.1)	35 (67.3)	

	Group 1 (NP) (n= 114)	Group 2 (SS) (n=227)	Group 3 (NNP-NSS)	P (Pc global)*
NM	33 (28.9)	43 (18.9)	13 (25.0)	
Other/nonspecified	1 (0.9)	18 (7.9)	4 (7.7)	
Breslow's thickness (m.v. = 47)				NS
1.00 mm	47 (49.0)	92 (45.5)	20 (41.7)	
1.01–4.00 mm	35 (36.5)	84 (41.6)	21 (43.8)	
>4.00 mm	14 (14.6)	26 (12.9)	7 (14.6)	
Remnants of pre-existing nevi (m.v. = 115)				0.031 (0.279)
No	46 (56.1)	107 (65.6)	27 (81.8)	
Yes	36 (43.9)	56 (34.4)	6 (18.2)	

m.v., missing values; NM, nodular melanoma; NNP–NSS, non-nevus-prone nonsun sensitive; NP, nevus prone; Pc, P value after Bonferroni correction; SS, sun sensitive; SSM, superficial spreading melanoma.