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ORIGINAL ARTICLE

Increased Risk of Developing a Second Primary Cutaneous Nevus-Associated Melanoma in Patients Previously Diagnosed with the Disease

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KEYWORDS
Nevus-associated melanoma;
Second melanomas;
Risk factors;
Multiple melanoma

Abstract
Background: Patients diagnosed with primary cutaneous melanoma have a greater lifetime risk of developing further melanomas. Most of these melanomas appear to arise de novo, but a proportion of them develop in pre-existing melanocytic nevi.
Objective: To determine risk factors associated with the development of a second cutaneous melanoma arising on a nevus in patients diagnosed with cutaneous melanoma.
Patients and methods: A series of 981 patients diagnosed with cutaneous melanoma was selected; 47 of them had been diagnosed with a second melanoma. These 47 patients were classified into 2 groups according to whether or not there was histological evidence that the melanoma was associated with a nevus.
Results: Age at diagnosis less than 40 years, tumor location on the trunk, and superficial spreading subtype were independent risk factors for the appearance of a primary melanoma on a nevus. The only factor associated with the appearance of a second nevus-associated melanoma was that the first melanoma was also associated with a nevus (odds ratio, 9.51; 95% confidence interval 1.6-56.56; P=.042).
Conclusions: Nevus-associated melanomas develop mainly in young patients, on the trunk, and are of the superficial spreading subtype. A history of primary cutaneous melanoma arising on a nevus is associated with a 9-fold increase in the risk of developing a second nevus-associated melanoma. These findings highlight the need for careful follow-up of all melanocytic lesions in patients who have had a primary nevus-associated melanoma.

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PALABRAS CLAVE
Melanoma sobre nevo;
Segundos melanomas;
Factores de riesgo;
Melanoma múltiple

Riesgo aumentado del desarrollo de un segundo melanoma cutáneo primario sobre un nevo en pacientes diagnosticados previamente de melanoma cutáneo primario sobre nevo

Resumen

Antecedentes: Los pacientes diagnosticados de un melanoma cutáneo tienen más riesgo que el resto de la población de padecer nuevos melanomas a lo largo de su vida. La mayoría de estos melanomas aparecen «de novo», pero existe un porcentaje de ellos que se desarrolla sobre nevos melanocíticos previos.
Objetivo: Determinar los factores de riesgo asociados al desarrollo de un segundo melanoma cutáneo sobre nevo en pacientes diagnosticados de melanoma cutáneo.
Métodos: Se seleccionaron los datos de 981 pacientes diagnosticados de un primer melanoma cutáneo, 47 de los cuales habían sido diagnosticados de un segundo melanoma. Todos los pacientes fueron clasificados en función de si el melanoma presentó o no asociación histológica a un nevo.
Resultados: La edad inferior a 40 años, la localización en el tronco y el subtipo histológico de extensión superficial fueron los factores de riesgo independientes asociados al desarrollo de un primer melanoma sobre nevo. El único factor asociado al desarrollo de un segundo melanoma sobre nevo fue que el primer melanoma también se hubiera presentado asociado a un nevo (OR: 9,51, 95% de intervalo de confianza: 1,6-56,56; p = 0,042).
Conclusiones: Los melanomas se desarrollan asociados a un nevo principalmente en pacientes jóvenes, en el tronco y del subtipo tipo de extensión superficial. A su vez, el desarrollo de un primer melanoma sobre nevo aumenta el riesgo hasta 9 veces de desarrollar un segundo melanoma sobre un nevo previo. Estos hallazgos subrayan la importancia del seguimiento estrecho de todas las lesiones melánicas en los pacientes que han desarrollado un primer melanoma sobre nevo.

Introduction

Two different pathogenic pathways have been proposed to explain clinical and epidemiological observations in the development of melanoma. In 1998, Whiteman et al[1] suggested that there was a pathway resulting from instability of melanocytes and another pathway resulting from chronic sun exposure. The first pathway is associated with the presence of multiple nevi and freckles and the second is linked to nonmelanoma skin cancer and involves the expression of p53 in the primary tumor.

More recently, it has been reported that melanomas presenting at sites with intermittent exposure to sunlight often have mutations in the *BRAF* and *NRAS* genes, whereas *C-KIT* and *CCDN1* mutations are more common in melanomas that present at sites unexposed to sunlight (eg, mucosal and acral melanomas).[2]

The existence of a pathway involving melanocyte instability—in which an individual is assumed to be susceptible to melanocytic proliferation—is also supported by the observation that patients with multiple nevi, whether melanocytic or dysplastic, are at greater risk of developing melanoma. In addition, up to around 20% of cutaneous melanomas are associated with a nevus.[3,4] Some studies have found that these nevus-associated melanomas, in contrast to melanomas unassociated with nevi, are more common on the trunk and tend to present in younger patients and those with a greater density of nevi.[3,4] Those studies also found that nevus-associated melanomas are usually of the superficial spreading subtype. These observations suggest that the pathway leading to nevus-associated melanoma involves melanocyte instability.

Given that we know that patients who have developed a first cutaneous melanoma are at greater risk of developing a second cutaneous melanoma and that many of these patients have multiple nevi, we hypothesized that when patients develop a second melanoma, this is more likely to occur in association with a nevus in cases where melanocyte instability is present.[5-8]

The primary objective of this study was to investigate the risk factors for presenting a second cutaneous melanoma in association with a nevus. A secondary objective was to identify the risk factors associated with developing a first melanoma in association with a nevus in our sample.

Patients and Methods

In this retrospective, observational study, data from the melanoma database of the Dermatology Department of the Instituto Valenciano de Oncología, Valencia, Spain, were analyzed. The characteristics of this database have been described previously.[9]

For the purposes of the present study, patients diagnosed with cutaneous melanoma between January 1, 1990, and

May 31, 2009, were included. Patients with metastatic melanoma from an unknown primary tumor and those whose primary melanoma was diagnosed prior to this period were excluded.

A total of 981 patients were included, of whom 47 had more than 1 cutaneous melanoma.

To identify the risk factors associated with developing a first melanoma in association with a nevus in our population, we considered all 981 patients diagnosed with cutaneous melanoma. To study the risk factors associated with developing a second melanoma in association with a nevus, we selected the 47 patients diagnosed with more than 1 cutaneous melanoma.

Patients with 1 melanoma were classified according to whether or not a nevus was detected in the histology study. A nevus-associated melanoma was defined as a melanoma in which histology revealed nests, cords, or isolated strands of cytologically benign nevus cells in the dermis adjacent to or beneath the melanoma.[10] If nevus cells were not detected, the melanoma was classified as de novo melanoma with no associated melanocytic lesion. For patients diagnosed with more than 1 melanoma, the second melanoma was classified in the same way according to whether it was associated with a nevus or not.

For the comparative analysis, the following variables were used:

1. Epidemiological: sex, age (<40, 40-60, or >60 y), and site of melanoma (head/neck, arms, legs, and acral locations)
2. Phenotypical: phototype (I-II/III-IV), eye color (dark/light), hair color (dark/chestnut, blond, or redhead), and number of melanocytic (<20, 20-50, 51-100, and >100) or dysplastic (≥1/none) nevi
3. Environmental: years of sun exposure (0, ≤20, >20 y) and history of severe sunburn both in general (0, 1-5, 6-10, >10) and at the melanoma site (none, mild, severe)
4. Familial: first- or second-degree relative with a history of melanoma (yes or no)
5. Histologic: traces of nevus, Breslow thickness (≤1.00 mm, 1.01-4.00 mm, >4.00 mm), and histologic subtype of the first melanoma (superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma)

Data collection and classification has been described previously.[9]

The differences between the distributions of each variable in each of the categories were evaluated using the Pearson χ^2 test. Odds ratios (OR) were calculated by both univariate and multivariate logistic regression. The relative importance of the prognostic factors was assessed using the Wald χ^2 statistic for the ratio of each prognostic factor in the regression model. The factors with larger χ^2 values were more significant in each model. The value of the χ^2 statistic was used to order the prognostic factors, as its interpretation was independent of the classification of the covariate. The *P* values used for comparing groups were adjusted for multiple comparisons using the Bonferroni correction. The statistical analysis was performed with the SPSS statistical package, version 15.0.

Results

Of the 981 patients selected for the study, 456 were men (46.5%) and 525 were women (53.5%). The median age at diagnosis was 54 years (interquartile range, 40-67 y) and the median duration of follow-up was 46 months (interquartile range, 19-90 mo). Of the group of selected patients, 297 (30.3%) developed a nevus-associated melanoma and 684 (69.7%) presented with de novo melanoma.

During follow-up, 47 patients developed a second melanoma. In 11 patients (24.4%), this second melanoma was associated with a nevus and in 34 (75.6%), it appeared de novo. In 2 cases, in which the second melanoma was excised in another center, it was not possible to retrieve information on the presence of nevus cells adjacent to the melanoma.

Analysis of factors related to the presence of nevus-associated in the general group of 981 patients diagnosed with melanoma (Table 1) showed that for the 2 groups—nevus-associated melanoma and de novo melanoma—the proportion of younger and older patients was different. Thus, younger patients tended to belong to the group with nevus-associated melanomas (*P*=.0016). For example, 35.4% of the nevus-associated melanomas were reported in patients under 40 years of age compared to 19.4% of de novo melanomas. Likewise, patients aged over 60 years were 66% less likely to develop nevus-associated melanomas compared to patients under 40 years (OR=0.34; 95% confidence interval [CI], 0.24-0.49).

The presence of clinically dysplastic nevi also showed a statistically significant association with the development of nevus-associated melanomas (*P*=.0016). Whereas 30.2% of the patients with nevus-associated melanomas had at least 1 dysplastic nevus, only 18.2% of the patients with de novo melanoma had such a nevus. Patients with a dysplastic nevus were at almost twice the risk of developing nevus-associated melanoma compared to patients with no dysplastic nevi (OR=1.94; 95% CI, 1.04-2.71).

Nevus-associated melanomas were not distributed evenly according to site (*P*=.0016): more than half were located on the trunk (54.9%) whereas only a third (33.8%) of de novo melanomas were located at this site.

Finally, the analysis by histologic subtypes of melanoma revealed that superficial spreading melanomas were more frequent in patients who developed nevus-associated melanomas—79.1% versus 60.9% for patients with de novo melanoma (*P*=.0016). The risk that a patient with nevus-associated melanoma developed a superficial spreading melanoma was 3.55 compared to lentigo maligna melanoma (OR=3.55; 95% CI, 1.57-8.01).

No significant group differences were observed in terms of phototype, eye color, hair color, number of melanocytic nevi, sex, number of severe sunburns (both in general and at the melanoma site), years of chronic sun exposure, tumor thickness, or family history of melanoma (Table 1). For the assessment of the number of nevi as a risk factor for developing nevus-associated melanoma, post-hoc categories of ≥20 nevi versus <20 and >50 versus ≤50 were established. After applying the Bonferroni correction, there were no significant differences, although the ratio was greater when the cutoff was set at 20 melanocytic nevi.

Table 1 Differences in the Epidemiological Characteristics, Phenotype, Environmental Factors, Family History of Melanoma, and Histological Findings Between Patients With a First Melanoma Associated With a Nevus and Those With a De Novo First Melanoma

	First Melanoma Associated With a Nevus				
Characteristic	**No, %**	**Yes, %**	**P[a]**	**OR**	**95% CI for the OR**
Epidemiological					
Sex					
Male	319 (46.6)	137 (46.1)	NS	1.02	0.78-1.34
Female	365 (53.4)	160 (53.9)			
Age, y					
<40	133 (19.4)	105 (35.4)	.0016	1	1
40-60	266 (39.1)	115 (38.7)		0.55	0.39-0.77
>60	285 (41.7)	77 (25.9)		0.34	0.24-0.49
Site					
Head/neck	125 (18.3)	32 (10.8)	.0016	1	1
Arms	98 (14.3)	45 (15.2)		1.79	1.06-3.03
Trunk	231 (33.8)	163 (54.9)		2.76	1.78-4.27
Legs	160 (23.4)	45 (15.2)		1.10	0.66-1.83
Acral	70 (10.2)	12 (4.0)		0.67	0.32-1.38
Phenotypic					
Phototype					
III-IV	231 (35.8)	119 (40.6)	NS	1.23	1
I-II	415 (64.2)	174 (59.4)			0.93-1.63
Eyes					
Dark	371 (61.8)	179 (66.5)	NS	1	1
Light	229 (38.2)	90 (33.5)		0.815	0.60-1.10
Hair color					
Dark/chestnut	463 (78.3)	203 (77.5)	NS	1	1
Blond	111 (18.8)	48 (18.3)		0.98	0.68-1.44
Red	17 (2.9)	11 (4.2)		1.48	0.68-3.21
Melanocytic nevi					
<20	362 (70.4)	139 (57.7)	NS	1	1
20-50	61 (11.9)	39 (16.2)		1.66	1.06-2.60
51-100	62 (12.1)	33 (13.7)		1.39	0.87-2.20
>100	29 (5.6)	30 (12.4)		2.70	1.56-4.65
Dysplastic nevi					
None	495 (81.7)	192 (69.8)	.0016	1	1
At least 1	111 (18.2)	83 (30.2)		1.94	1.40-2.71
Environmental factors					
Years of sun exposure					
No	391 (76.2)	192 (83.1)	NS	1	1
≤20 y	46 (9.0)	20 (8.7)		0.89	0.51-1.54
>20 y	76 (14.8)	19 (8.2)		0.51	0.30-0.87
Sunburn at the melanoma site					
No	171 (34.6)	55 (24.9)	NS	1	1
Mild	205 (41.5)	103 (46.6)		1.56	1.06-2.30
Severe	118 (23.9)	63 (28.5)		1.66	1.08-2.55

Table 1 *(Continued)*

Characteristic	First Melanoma Associated With a Nevus				
	No, %	Yes, %	P[a]	OR	95% CI for the OR
Severe sunburns					
0	299 (50.4)	108 (41.5)	NS	1	1
1-5	189 (31.9)	100 (38.5)		1.46	1.06-2.03
6-10	63 (10.6)	40 (15.4)		1.76	1.12-2.77
>10	42 (7.1)	12 (4.6)		0.79	0.40-1.56
Family history of melanoma					
No	603 (94.2)	274 (95.8)	NS	1	1
Yes	37 (5.8)	12 (4.2)		0.714	0.37-1.4
Histology					
Breslow thickness					
≤1.00 mm	277 (43.4)	138 (51.5)	NS	1	1
1.01-4.00 mm	272 (42.6)	115 (42.9)		0.85	0.63-1.14
>4.00 mm	89 (13.9)	15 (5.6)		0.34	0.19-0.60
Histologic classification					
LMM	44 (6.5)	7 (2.4)	.0016	1	1
SSM	414 (60.9)	234 (79.1)		3.55	1.57-8.01
NM	154 (22.6)	48 (16.2)		1.95	0.83-4.63
ALM	38 (5.6)	3 (1.0)		0.5	0.12-2.05
Others	30 (4.4)	4 (1.4)		0.84	0.22-3.11

Abbreviations: ALM, acral lentiginous melanoma; CI, confidence interval; LMM, lentigo maligna melanoma; NM, nodular melanoma; NS, not significant; OR, odds ratio; SSM, superficial spreading melanoma.
[a]After Bonferroni correction.

In the sex-adjusted multivariate analysis, only age, site, and histologic subtype remained in the model as independent predictors of nevus-associated melanoma (Table 2). When ordered by importance using the χ^2 statistic (Wald test), it was observed that truncal site, age less than 40 years, and superficial spreading histologic subtype were the characteristics most strongly associated with nevus-associated melanoma.

For the study of factors related to developing a second nevus-associated melanoma, only those variables significant in the univariate analysis of developing nevus-associated melanoma and whether a nevus was detected in association with the first melanoma were included in the model.

The analysis of the 47 patients diagnosed with more than 1 melanoma showed that a first melanoma histologically associated with a nevus was the only factor predictive of developing a second nevus-associated melanoma (P=.042) (Table 3). Of the patients who developed a second nevus-associated melanoma, 62.5% had also shown this association in the first melanoma, whereas only 16.2% of patients who had developed a first de novo melanoma developed a second nevus-associated melanoma. The risk of developing a second nevus-associated melanoma when the first melanoma had been associated with a nevus was 9.51 compared to patients who presented with a first de novo melanoma (OR=9.91; 95% CI, 1.60-56.56).

Table 2 Sex-Adjusted Multivariate Model With Variables Significantly Associated With Presenting a First Nevus-Associated Melanoma.

Variable	OR	95% CI for the OR
Age, y		
<40	1	1
40-60	0.58	0.41-0.83
>60	0.45	0.30-0.66
Site		
Head/neck	1	1
Arms	1.34	0.77-2.35
Trunk	1.98	1.23-3.19
Legs	0.79	0.45-1.37
Acral	0.77	0.31-1.87
Histologic classification		
LMM	1	1
SSM	2.14	0.90-5.10
NM	1.34	0.54-3.31
ALM	0.65	0.13-3.38
Others	0.48	0.12-1.87

Abbreviations: ALM, acral lentiginous melanoma; CI, confidence interval; LMM, lentigo maligna melanoma; NM, nodular melanoma; OR, odds ratio; SSM, superficial spreading melanoma.

Table 3 Comparison of the Characteristics Associated With Development of a First Nevus-Associated Melanoma in Patients Who Developed a Second Melanoma Associated With a Nevus and Those Who Developed a Second De Novo Melanoma

	Second Melanoma Associated With a Nevus		
Characteristic	**No (%)**	**Yes (%)**	***P*[a]**
Age, y			
<40	8 (23.5)	2 (18.2)	NS
40-60	15 (44.1)	4 (36.4)	
>60	11 (32.4)	5 (45.5)	
Dysplastic nevi			
None	17 (51.5)	2 (20)	NS
≥1	16 (48.5)	8 (80)	
Site			
Head/neck	7 (20.6)	4 (36.4)	NS
Arms	3 (8.8)	2 (18.2)	
Trunk	17 (50.0)	4 (36.4)	
Legs	6 (17.6)	0 (0)	
Acral	1 (2.9)	1 (9.1)	
Histologic classification			
LMM	3 (8.8)	0 (0)	NS
SSM	23 (67.6)	7 (70)	
NM	7 (20.6)	2 (20)	
ALM	0 (0)	1 (10)	
Others	1 (2.9)	0 (0)	
Nevus associated with first melanoma			
No	31 (83.8)	6 (16.2)	.042
Yes	3 (37.5)	5 (62.5)	

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; NS, not significant; SSM, superficial spreading melanoma.
[a]After Bonferroni correction.

In contrast to the risk of developing a nevus-associated melanoma in the overall group of 981 patients, the occurrence of a second nevus-associated melanoma compared to de novo melanoma was not associated with younger age, presence of clinically dysplastic nevi, truncal site, or superficial spreading subtypes.

Discussion

The present study was based on the premise that patients already diagnosed with a first melanoma are at greater risk than the general population of developing a second cutaneous melanoma,[5,7,11] and that many of these patients form part of the group described by Whiteman et al[1] as characterized by the presence of multiple nevi (reflecting instability of melanoma cells). The aim of this study was therefore to investigate clinical, epidemiological, and histologic characteristics that might help identify patients previously diagnosed with a first cutaneous melanoma who were at greater risk of developing a second melanoma associated with a preexisting nevus. These would be the patients who would benefit most from close follow-up of their benign melanocytic lesions.

When analyzing the results of this study, a number of limitations should be remembered. To investigate the risk factors associated with developing a second nevus-associated melanoma, we selected and analyzed data from patients diagnosed with cutaneous melanoma between 1990 and 2009. Data were collected retrospectively between 1990 and 1999 and prospectively from 2000 onwards. To assess whether a survival bias might affect the results of the study, thereby apparently increasing survival, all data from patients with diagnosis between 1990 and 1999 and those from patients with diagnosis between 2000 and 2009 were compared, and no significant differences were found (data not shown). An additional consideration is that data were collected using standard criteria and by the same observer in all cases. We assume that recall bias may have been present when patients were reporting the overall number of sunburns, the number of sunburns at the site of the melanoma, and the severity of these burns. Likewise, we should assume that there may be a bias in the classification given that not all histologic diagnoses were confirmed in a second study, although these diagnoses had been reviewed prior to inclusion in the database. In addition, there is the possibility that the histologic study failed to detect the presence of a nevus in some nevus-associated melanomas, which were therefore subsequently reported as de novo melanomas. In such cases, the nevus cells may have been absent because they had been destroyed by the melanoma itself or because they were not present in the sections studied given that the whole paraffin-embedded block was not used for histologic study. We also note that the *P* values may be considered more robust after application of the Bonferroni correction for multiple comparisons.

In our study, 30.3% of patients with cutaneous melanoma developed nevus-associated melanomas. This percentage is close to that reported in similar studies.[1,3] Of the variables analyzed, age less than 40 years at diagnosis, truncal site, and superficial spreading melanoma were the only factors found to be associated with nevus-associated melanoma, with truncal site showing the strongest association.

Other authors have reported the same 3 risk factors for development of nevus-associated melanoma.[1,10] The findings of Bevona et al[3] also agree with our study in that the variable most strongly associated with development of nevus-associated melanoma was truncal site versus other sites. In another study, variables significantly associated with development of nevus-associated melanoma were a high density of nevi and, as in our study, truncal site and superficial spreading melanoma, but not younger age of presentation.[4]

A number of studies have shown the increased risk of developing new melanomas in patients who have been previously diagnosed with cutaneous melanoma.[5-8] These second melanomas may appear both at the time of diagnosis of the first melanoma (synchronous lesions) or

during subsequent follow-up of the patient (metachronous lesions).[11,12] Second melanomas are usually thinner with a lower Clark level and show less ulceration compared to first melanomas. Given this greater risk, lifetime follow-up is recommended for patients diagnosed with cutaneous melanoma.

As shown by the present study, second melanomas, like first melanomas, present more frequently as de novo lesions although they may also occur in association with a nevus, but with a slightly lower proportion (24.4% vs 30.3%). Risk factors associated with developing a second melanoma associated with a preexisting nevus have not yet been studied, and this study is the first to investigate such factors.

In our study, our initial hypothesis was that the second nevus-associated melanoma was going to have the same risk factors as those observed for development of the first nevus-associated melanoma. In addition, we wanted to investigate whether having a certain type of nevus-associated melanoma might influence in any way whether the second melanoma was associated with a nevus. We therefore selected those variables that were significant in the univariate analysis of risk factors for presenting a second melanoma after the first melanoma. In addition, the model also included whether the first melanoma was associated with a nevus in the model. Of all the variables, only those patients who had presented a first nevus-associated melanoma were at greater risk of developing a second melanoma associated with a preexisting nevus. It seems likely that the lack of significance of the variables initially associated with developing a first nevus-associated melanoma might be explained by the small sample size. In any case, in our series, the most important factor was development of a first melanoma associated with a nevus. This factor was significant with the sample size available. Due to sample size limitations, we did not initially consider a separate analysis of the type of nevus (congenital nevus, acquired melanocytic nevus, or acquired dysplastic nevus, or other types) associated with melanoma. A post-hoc analysis using this classification did not reveal any differences (data not shown), although the low number of cases in each category makes interpretation of these results uncertain.

The data obtained in the 2 parts of the study support the hypothesis that there is a pathogenic pathway in the development of cutaneous melanoma resulting from melanocyte instability. This pathway—which would explain why melanoma develops in younger patients, with multiple nevi, and at sites not chronically exposed to sunlight, such as the trunk—is probably implicated in melanomas associated with nevi.

In conclusion, melanomas associated with nevi tend to present on the trunk and in younger patients, and are of the superficial spreading subtype. Of the patients who developed a second melanoma, the strongest predictor of an association with a nevus was having a first nevus-associated melanoma. Thus, patients who have a first nevus-associated melanoma and have multiple nevi would be those who would benefit most from extensive, regular follow-up of the melanocytic lesions, particularly with digital dermoscopy in reference hospitals. In certain patients with few nevi, it might be interesting to evaluate whether preventative excision could reduce the incidence of second melanomas, although such an approach has not been shown to be effective in the general population.

Conflict of Interest

The authors declare that they have no conflict of interest.

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