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Clinicopathological, Genetic and Survival Advantages of Naevus-associated Melanomas: A Cohort Study

Xavier BOSCH-AMATE[1], Sebastian PODLIPNIK[1,2], Constanza RIQUELME-MC LOUGHLIN[1], Cristina CARRERA[1–3], Alicia BARREIRO-CAPURRO[1], Adriana GARCIA-HERRERA[4], Llucia ALOS[4], Josep MALVEHY[1–3] and Susana PUIG[1–3]

[1]Dermatology Department, Hospital Clinic of Barcelona, University of Barcelona, [2]Melanoma Group, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), [3]Biomedical Research Networking Center on Rare Diseases (CIBERER), ISCIII and [4]Pathology Department, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain

Several studies have suggested that naevus-associated melanomas differ from *de novo* melanomas, being thinner and with less ulceration; however, the prognostic implication is unclear. The objective of this study was to describe clinicopathological, genetic and survival characteristics of *de novo* and naevus-associated melanomas in a cohort of primary invasive cutaneous melanomas over a 20-year period. Of the 2,227 patients included in the study, 509 (22.86%) had naevus-associated melanomas. Compared with patients with *de novo* melanoma, they were younger, with a fairer phototype and a higher naevus count, tumours were predominantly the superficial spreading subtype, American Joint Committee on Cancer stage I, located on the trunk, and there were fewer signs of invasiveness (thinner Breslow index, less ulceration, lower mitotic index and less satellitosis). Germline mutational status did not show any significant association. As determined through univariate analysis, overall survival was significantly better in patients with naevus-associated melanoma (hazard ratio 0.64; 95% confidence interval 0.51–0.80, $p < 0.001$), but multivariate analysis did not support this prognostic indication (hazard ratio 0.94; 95% confidence interval 0.75–1.18, $p < 0.606$). Despite this, we conclude that naevus-associated and *de novo* melanomas should be considered as different subtypes of melanoma.

Key words: melanoma; naevus-associated; *de novo*; histopathological; genetic; prognosis; survival.

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Corr: Susana Puig, Melanoma Unit, Dermatology Department, Hospital Clinic Barcelona, Villarroel 170, ES-08036, Barcelona, Spain. E-mails: susipuig@gmail.com, spuig@clinic.cat, susipuig@ub.edu

SIGNIFICANCE

Several studies have suggested that naevus-associated melanomas differ from *de novo* melanomas, being thinner and less ulcerated; however, the prognostic implication is unclear. In the study cohort of 2,227 patients, there were 509 (22.86%) naevus-associated melanomas, and when compared with patients with *de novo* melanoma, they were younger with a fairer phototype, tumours were located on the trunk, and showed fewer signs of invasiveness. Germline mutational status did not show significant associations. Overall survival was not significantly better for naevus-associated melanoma on multivariate analysis. However, despite this finding, it is concluded that they should be considered as different types of melanoma.

The incidence of cutaneous melanoma is increasing worldwide (1, 2). In addition, it is an important healthcare problem, since it is one of the most frequent types of cancer affecting young adults (3).

To date, little is known about patient and/or tumour factors that give rise to melanoma in normal skin or in association with a naevus. In 1978, Clark proposed a carcinogenic evolution from dysplastic naevi to melanoma in patients with a family history of melanoma (4). However, the significance of this claim remains uncertain, as benign acquired naevi can also be found in association with melanomas, and not all melanomas appear from precursor lesions. Histopathological studies have revealed naevus-associated cells in approximately 10–50% of melanomas, and only 40–50% of these naevus cells had dysplastic features (5–11). In addition, it appears that the majority of melanomas arise *de novo* and not from precursor lesions (6, 12).

Naevus-associated melanomas (NAM) are more often of the superficial spreading subtype, affect young patients, are located on the trunk, have a thinner Breslow index, and absence of ulceration (5–9, 11, 13, 14). However, it remains unclear if there is a survival advantage in NAM compared with *de novo* melanomas (DNM) or if there are genetic differences between them (9, 13, 15).

The primary objective of this study was to examine both overall survival (OS) and melanoma-specific survival (MSS) in NAM compared with DNM. A secondary objective was to analyse the clinicopathological and genetic background of the tumours and patients by germline mutations in susceptibility genes, from a large cohort of prospectively followed patients with melanoma.

MATERIALS AND METHODS

Study design and setting

This cohort study included patients with melanoma seen at Hospital Clinic of Barcelona, Spain from January 1998 through December 2017. All variables were prospectively recorded, following the staging and follow-up protocols, in our centre (16, 17). This registry mainly includes patients of Mediterranean origin, living

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in the Catalonia region. Written informed consent was obtained from all patients. The study was approved by the Clinical Research Ethics Committee of Hospital Clinic of Barcelona (institutional review board number HCB/2015/0298). This study was performed following the 2015 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (18).

Participants and variables

As eligibility criteria, all patients diagnosed with invasive primary cutaneous melanomas without distant disease were included. If a patient had more than one melanoma, the one with worst prognosis, characterized by the highest American Joint Committee on Cancer (AJCC) stage, was included in the statistical analysis. Exclusion criteria were: patients with stage IV at the time of diagnosis (to avoid bias in survival); those with missing data that prevented a proper staging; patients who did not continue follow-up at our centre; and patients whose histology was not prospectively recorded in our database (**Fig. 1**).

The main outcome variable was overall survival, defined as the length of time from primary melanoma diagnosis to the date of death by any cause or last follow-up visit. The secondary outcome variable was melanoma-specific survival, calculated from the time of diagnosis of the primary melanoma to the time of death by melanoma or the last follow-up visit.

As independent variables, we prospectively included the patients' demographic (age and sex) and clinical (Fitzpatrick skin type, naevus count, eye and hair colour) characteristics. In addition, the tumour's location (and number of primary tumours) with the histopathological (histological subtype, Breslow index, ulceration status, mitotic index, presence of satellitosis and regression) and sentinel lymph node biopsy (SLNB) status were included, thus allowing the staging of the patient following the 8th edition of the AJCC guidelines. Histopathological variables were discussed in a weekly melanoma committee meeting of dermatologists and pathologists. The germline mutational status of *MC1R* gene was also recorded when present.

Statistical analysis

To determine which of the independent variables were associated with DNM or NAM Pearson's χ^2 test was used for categorical variables and trend test for ordinal variables. The linear model analysis of variance (ANOVA) was used to compare continuous independent variables.

Survival curves based on Kaplan–Meier methods were used to investigate differences in OS and MSS between *de novo* and naevus-associated melanomas. Curves were calculated using the "survfit" function in the "survival" package (v 3.1-12) and plotted with the "survminer" package (v 0.4.6) in R (19–21). A log-rank test was performed to test for a significant difference in outcome between the groups.

Univariate and multivariate survival analyses were performed using Cox's proportional hazards model. Models were fitted using the "coxph" function in the "survival" package (v 3.1-12) in R. Hazard ratio (HR) estimations were calculated for the effect of DNM or NAM on OS and MSS, adjusted for age at diagnosis, sex, AJCC stages and location of the primary tumour. The AJCC classification was used in the multivariate analysis since it includes the main prognostic factors (Breslow index, ulceration and SLNB status) and avoids multicollinearity. A Cox regression table for univariate and multivariate hazard ratios was calculated for better visualization of the data (22).

All statistical tests were 2-sided and a p-value ≤ 0.05 was considered significant. All statistical analyses were performed using the computing environment R (v 4.0.0) (23).

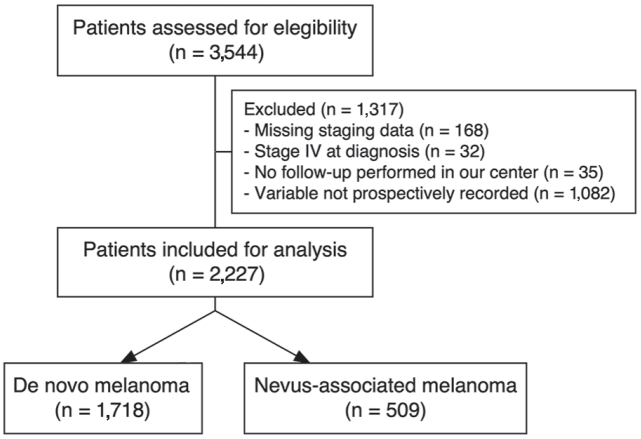

Fig. 1. Flowchart of the study cohort.

RESULTS

Data were available for 3,544 patients, but after applying exclusion criteria, a total of 2,227 patients were included for analysis. The median follow-up time of the cohort was 7.05 years (interquartile range (IQR) 3.2–13.9) (Fig. 1). Of the 2,227 melanomas, 509 were NAM (22.86%). The clinicopathological characteristics of the cohort are summarized in **Table I**.

The stratified analysis between NAM and DNM showed that NAM was related to younger age at presentation (49 vs 55 years, $p<0.001$), but without a sex predominance. Phenotypically, it was observed that patients with NAM had fairer skin types, more frequently exhibited blond-red hair colour (29.1% vs 23.5%, $p=0.018$), a higher naevus count (52.2% vs 36.7%, $p<0.001$) and presented more frequently in the setting of multiple primary melanomas (16.7% vs 12.6%, $p=0.019$). The histopathological assessment of the tumours showed that NAM were predominantly the superficial spreading subtype (80.7% vs 66.4%, $p<0.001$) and showed a lower criterion of invasiveness with a Breslow index that was 0.67 mm thinner (1.55 vs 2.22, $p<0.001$) and they were less proportionally ulcerated (13% vs 23.2%, $p<0.001$). As a result, a higher proportion of stage I melanomas (72.5% vs 60.3%, $p<0.001$) was observed in the NAM group. Of 2,227 patients included, 1,027 did not undertake an SLNB. Of these, in 814 (79.3%) cases it was not indicated based on tumour thickness and in 213 (20.7%) was medically indicated, but not performed, due to individual factors. Finally, the stratified analysis of *MC1R* germline mutations did not show statistically significant differences between the groups (Table I).

Survival analysis based on Kaplan–Meier curves revealed that NAM had statistically significant higher OS and MSS rates than DNM **(Fig. 2)**. Five-year OS in DNM and NAM was 82% (95% CI 80.1–84) and 88.4% (95% CI 85.5–91.4), respectively. Ten-year OS in DNM and NAM was 71.9% (95% CI 69.5–74.5) and 79.2% (95% CI 75.2–83.5), respectively. Five-year MSS in DNM and

Table I. Baseline characteristics of the cohort and comparison between *de novo* and naevus-associated melanoma

	De novo melanoma ($n = 1,718$)	Naevus-associated melanoma ($n = 509$)	Total ($n = 2,227$)	*p*-value
Age, years, mean (SD)	55.74 (17.27)	49.13 (16.76)	54.23 (17.38)	< 0.001
Sex, *n* (%)				0.444
Female	904 (52.6)	258 (50.7)	1,162 (52.2)	
Male	814 (47.4)	251 (49.3)	1,065 (47.8)	
Eye colour, *n* (%)				0.312
Brown-black	869 (62.4)	248 (57.8)	1,117 (61.3)	
Green	271 (19.5)	89 (20.7)	360 (19.8)	
Blue	238 (17.1)	88 (20.5)	326 (17.9)	
Other	14 (1.0)	4 (0.9)	18 (1.0)	
Missing values	326	80	406	
Hair colour, *n* (%)				0.018
Brown-black	1,063 (76.5)	307 (70.9)	1,370 (75.2)	
Blond-red	326 (23.5)	126 (29.1)	452 (24.8)	
Missing values	329	76	405	
Fitzpatrick skin type, *n* (%)				< 0.001
I	62 (4.4)	23 (5.2)	85 (4.6)	
II	594 (41.9)	226 (50.7)	820 (44.0)	
III	604 (42.6)	166 (37.2)	770 (41.3)	
IV–VI	158 (11.1)	31 (7.0)	189 (10.1)	
Missing values	300	63	363	
Naevus count, *n* (%)				< 0.001
< 50	647 (63.3)	179 (47.9)	826 (59.2)	
51–100	223 (21.8)	108 (28.9)	331 (23.7)	
> 100	152 (14.9)	87 (23.3)	239 (17.1)	
Missing values	696	135	831	
Histological subtype, *n* (%)				< 0.001
Superficial spreading	1,141 (66.4)	411 (80.7)	1,552 (69.7)	
Nodular	271 (15.8)	44 (8.6)	315 (14.1)	
Acral lentiginous	105 (6.1)	10 (2.0)	115 (5.2)	
Lentiginous malignant	90 (5.2)	6 (1.2)	96 (4.3)	
Other	111 (6.5)	38 (7.5)	149 (6.7)	
Melanoma location, *n* (%)				< 0.001
Trunk	757 (44.1)	310 (60.9)	1067 (47.9)	
Lower limbs	376 (21.9)	82 (16.1)	458 (20.6)	
Upper limbs	233 (13.6)	49 (9.6)	282 (12.7)	
Head and neck	209 (12.2)	49 (9.6)	258 (11.6)	
Acral	143 (8.3)	19 (3.7)	162 (7.3)	
Number of primary melanomas, *n* (%)				0.019
Single	1,501 (87.4)	424 (83.3)	1,925 (86.4)	
Multiple	217 (12.6)	85 (16.7)	302 (13.6)	
Breslow index, median (IQR)	1.19 (0.65–2.60)	1.00 (0.60–1.70)	1.10 (0.63–2.30)	< 0.001
Ulceration, *n* (%)				< 0.001
Absent	1,320 (76.8)	443 (87.0)	1,763 (79.2)	
Present	398 (23.2)	66 (13.0)	464 (20.8)	
Mitotic index, mean (SD)	2.35 (4.69)	1.70 (3.17)	2.21 (4.41)	0.006
Missing values, *n*	119	60	179	
Satellitosis, *n* (%)				0.010
Absent	1,591 (97.7)	444 (99.6)	2,035 (98.1)	
Present	38 (2.3)	2 (0.4)	40 (1.9)	
Missing values	89	63	152	
Regression, *n* (%)				0.002
< 50%	324 (32.1)	130 (37.4)	454 (33.5)	
> 50%	143 (14.2)	68 (19.5)	211 (15.5)	
None	542 (53.7)	150 (43.1)	692 (51.0)	
Missing values	709	161	870	
AJCC 8th edition, *n* (%)				< 0.001
IA	745 (43.4)	251 (49.3)	996 (44.7)	
IB	291 (16.9)	118 (23.2)	409 (18.4)	
IIA	165 (9.6)	39 (7.7)	204 (9.2)	
IIB	141 (8.2)	17 (3.3)	158 (7.1)	
IIC	65 (3.8)	6 (1.2)	71 (3.2)	
IIIA	51 (3.0)	21 (4.1)	72 (3.2)	
IIIB	61 (3.6)	20 (3.9)	81 (3.6)	
IIIC	183 (10.7)	33 (6.5)	216 (9.7)	
IIID	16 (0.9)	4 (0.8)	20 (0.9)	
SLNB status, *n* (%)				0.349
Negative	694 (74.7)	210 (77.5)	904 (75.3)	
Positive	235 (25.3)	61 (22.5)	296 (24.7)	
Not performed	789	238	1027	
MC1R status, *n* (%)				0.910
Variants	444 (68.5)	171 (68.1)	615 (68.4)	
Wild-type	204 (31.5)	80 (31.9)	284 (31.6)	
Not performed	1,070	258	1,328	

AJCC: American Joint Committee on Cancer; IQR: interquartile range; *MC1R*: melanocortin 1 receptor; SLNB: sentinel lymph node biopsy; SD: standard deviation.

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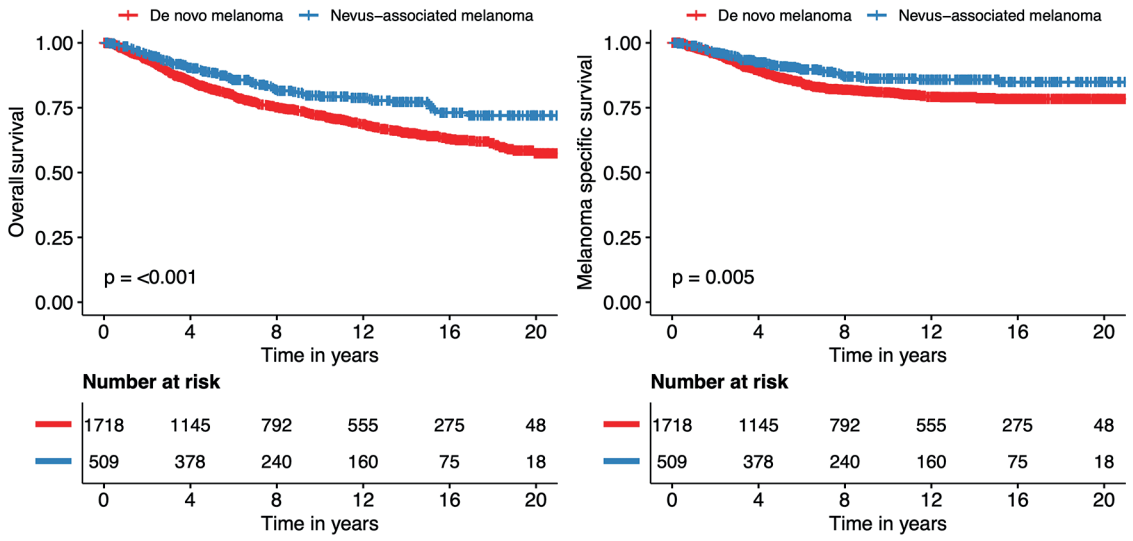

Fig. 2. Kaplan–Meier curves with log-rank estimation for overall survival and melanoma-specific survival comparing *de novo* and naevus-associated melanoma.

NAM was 86.5% (95% CI 84.7–88.3) and 90.9% (95% CI 88.3–93.6), respectively. Ten-year MSS in DNM and NAM was 80.9% (95% CI 78.7–83.1) and 86.3% (95% CI 82.9–89.8), respectively.

Univariate Cox regression analysis of OS showed that NAM was associated with a better prognosis than DNM (HR 0.64, 95% CI 0.51–0.80, $p<0.001$). Similarly, the univariate Cox regression model of MSS showed a protective factor in NAM compared with DNM (HR 0.67, 95% CI 0.50–0.89, $p=0.005$). However, multivariate Cox regression analysis including all the independent variables in the same model did not show any statistical differences in OS (HR 0.94, 95% CI 0.75–1.18, $p<0.606$) and MSS (HR 0.88, 95% CI 0.66–1.18, $p<0.391$) between NAM and DNM (**Table II**).

DISCUSSION

This study examined whether NAM and DNMs could be separated into 2 distinct entities with different clinicopathological, genetic and prognostic features.

In the study cohort, 22.86% of melanomas were NAM, showing a slightly lower percentage compared with a recent meta-analysis by Pampena et al. (6) (29.1%). This could be explained because all the melanoma histological subtypes and body locations were included in the analysis, unlike some studies cited in the meta-analysis, which only included superficial spreading melanoma, a subtype that is more predominant in NAM (5, 9).

Many histological features associated with better prognosis, such as lower Breslow thickness, less ulcera-

Table II. Univariate and multivariate analyses for overall survival and melanoma-specific survival

	Overall survival		Melanoma-specific survival	
	HR model 1 (univariate)	HR model 2 (multivariate)	HR model 3 (univariate)	HR model 4 (multivariate)
Type				
De novo melanoma	–	–	–	–
Naevus-associated melanoma	0.64 (0.51–0.80, $p<0.001$)	0.94 (0.75–1.18, $p=0.606$)	0.67 (0.50–0.89, $p=0.005$)	0.88 (0.66–1.18, $p=0.391$)
Age, years				
<45.5	–	–	–	–
45.5–63.3	1.78 (1.37–2.31, $p<0.001$)	1.35 (1.04–1.76, $p=0.024$)	1.44 (1.08–1.91, $p=0.012$)	1.00 (0.75–1.33, $p=0.989$)
>63.3	4.74 (3.76–5.99, $p<0.001$)	3.19 (2.50–4.06, $p<0.001$)	2.06 (1.57–2.72, $p<0.001$)	1.24 (0.93–1.65, $p=0.148$)
Sex				
Female	–	–	–	–
Male	1.93 (1.63–2.29, $p<0.001$)	1.49 (1.25–1.79, $p<0.001$)	1.91 (1.53–2.38, $p<0.001$)	1.41 (1.12–1.78, $p=0.004$)
AJCC				
I	–	–	–	–
II	3.80 (3.08–4.69, $p<0.001$)	2.76 (2.23–3.42 $p<0.001$)	7.01 (5.08–9.67, $p<0.001$)	5.87 (4.22–8.15, $p<0.001$)
III	6.25 (5.09–7.67, $p<0.001$)	5.28 (4.29–6.50, $p<0.001$)	14.49 (10.71–19.59, $p<0.001$)	13.06 (9.62–17.73, $p<0.001$)
Melanoma location				
Trunk	–	–	–	–
Lower limbs	0.85 (0.67–1.08, $p=0.193$)	0.97 (0.76–1.25, $p=0.827$)	0.70 (0.50–0.96, $p=0.028$)	0.74 (0.53–1.03, $p=0.076$)
Upper limbs	0.69 (0.50–0.96, $p=0.027$)	0.89 (0.64–1.23, $p=0.467$)	0.57 (0.37–0.88, $p=0.012$)	0.72 (0.46–1.12, $p=0.148$)
Head and neck	2.61 (2.08–3.28, $p<0.001$)	1.71 (1.35–2.16, $p<0.001$)	1.93 (1.42–2.63, $p<0.001$)	1.46 (1.06–2.01, $p=0.020$)
Acral	2.41 (1.85–3.15 $p<0.001$)	1.89 (1.44–2.48, $p<0.001$)	2.46 (1.78–3.41, $p<0.001$)	1.84 (1.32–2.57, $p<0.001$)

Univariate and multivariate Cox regression analyses of overall survival (models 1 and 2, respectively), and univariate and multivariate Cox regression analyses of melanoma-specific survival (models 3 and 4, respectively). Factors included in the multivariate model were age, sex, American Joint Committee on Cancer (AJCC) stage and melanoma location.
HR: hazard ratio.

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tion, lower mitotic index, less satellitosis, and a higher incidence of regression, are significantly more present in NAM than DNM. Furthermore, the proportion of patients classified as stage I by the AJCC were 72.5% and 60.3% for NAM and DNM, respectively. On the other hand, differences in SLNB status were not found when comparing both groups, which is consistent with other series, such as that by Lin et al. (9).

The phenotype of patients with NAM in our cohort was characterized by individuals with Fitzpatrick skin type I–II, red-blond-coloured hair and more than 50 naevi. This pattern has also been reported by other authors (14, 24, 25). Moreover, in the current study, patients with NAM were more likely to develop a second primary melanoma. Therefore, the surveillance and follow-up of these patients, with a higher melanoma risk, becomes especially important (26).

No significant differences between men and women were found in our cohort or in the literature (6). However, it was evident that NAMs were more frequent in younger patients. This could be explained by the fact that a higher number of naevi are more common in this age group (27, 28) as the number of naevi decreases as we get older. Another reason could be because melanomas in older individuals may result from cumulative sun damage (28). This could also explain why DNM were more frequent in locations with chronic sun exposure: upper and lower limbs, head and neck.

Recent molecular and genetic studies have described the mutational pathways in key melanocytic genes that convert benign naevi into melanomas (*BRAF*^{V600E}, *CDKN2A*, *TERT*) (28, 29). Therefore, these findings suggest that the pathophysiological pathways of NAM and DNM could be different.

It is difficult to demonstrate whether a DNM was originally associated with a naevus. Some authors have explained the absence of naevus cells arguing that invasive melanoma cells tend to engulf them (7). This could explain the thicker Breslow index associated with melanomas without naevi cells (misclassified histologically as DNM) (7, 30, 31), but this error of categorization would not explain any of the demographic, clinical or genetic differences between NAM and DNM. Other authors defend the view that DNM could arise without any precursor lesion, either by the rapid accumulation of mutations or from a melanocyte which already harboured genetic alterations and then a proliferation-initiating mutation in *MAPK* pathway triggered the appearance of the melanoma (28). These differences described at an early tumoural stage, could help us classify NAM and DNM as 2 different melanoma types.

No differences in *MC1R* germline mutational status were detected between NAM and DNM patients. It is interesting that, although we have related NAM to fair phenotype, the main gene related with this feature, *MC1R*, was not predominantly found in the NAM group. In contrast, in the study by Martin-Gorgojo et al. (8) a significantly increased prevalence of *MC1R* variants was shown in patients with NAM (dysplastic type). These differences could be explained by the fact that no subgroup analysis was performed in the NAM group. Interestingly, the same authors did not find differences in the prevalence of somatic mutations in *BRAF* or *NRAS* genes between the 2 groups studied (8).

The primary objective of this study was to examine OS and MSS in both groups as its prognostic significance is still unclear in the literature. As early as the 1960s, Cochran (32) reported that the 5-year survival rates were not statistically different. In contrast, in the 1980s, Rhodes et al. (33) and Friedman et al. (34) suggested a more favourable survival rate in NAM. Kaddu et al. (35) and Weatherhead et al. (15) did not find survival differences. Although Shitara et al. (36) did not carry out a 5-year survival analysis, they suggested a more favourable prognosis for NAM based on the lower Breslow thickness as a surrogate marker. Lin et al. (9) reported no survival differences; however, their study group consisted of patients who consecutively underwent SLNB. Cymerman et al. (13) studied survival in 2 melanoma cohorts and found that NAM had better OS in univariate analysis, but this difference remained significant in only one cohort in their multivariate analysis. Finally, Martin-Gorgojo et al. (8) found a higher overall survival for patients with NAM, but multivariate adjustment showed that these differences were dependent on other characteristics rather than just histological association with a preexisting naevus. Survival analysis in the current study using Kaplan–Meier curves and univariate analysis showed a significantly better OS and MSS in NAM than DNM. However, as with Martin-Gorgojo et al. (8), when we adjusted the presence of naevi cells with the other potential confounders in the multivariable analysis, no statistical significance was found in OS and MSS. Possible explanations for the difference in both OS and MSS in the univariable analysis could be that pathological misdiagnosis of a naevus as melanoma is more likely in NAM, or that invasion thickness could be overestimated in NAM because part of the naevus is added to the measurement, but based on the current data we believe that these differences are due to intrinsic characteristics of both melanoma types.

The findings of the current study support the theory that there are diverse genetic, molecular, and environmental factors in the pathways that can lead to the development of melanoma (12, 28). With the data from the current cohort differences in survival were found, but no difference in the multivariate analysis, so the difference found could be explained by the other clinicopathological characteristics that are included in our model. Currently, differentiating NAM from DNM does not change our daily clinical practice, but we believe that differentia-

ting them may allow us a better understanding of both diseases, identifying different risk factors, leading to better primary and secondary preventive strategies. Future developments will include new tools, such as artificial intelligence or machine learning, which will allow us to integrate all this data and carry out more personalized staging and management.

Limitations

A limitation of this study is that it is a single-centre retrospective cohort study. However, we consider that the results could have good external validity since we included all patients with invasive melanoma and performed a prospective follow-up for a long period, thus decreasing the risk of bias.

Conclusion

Of melanomas, 22.86% were NAM and clinicopathological features associated with better prognosis are significantly more present in NAM than in DNM. However, OS and MSS of patients with NAM lose significance in the multivariable analysis. Despite this, given all the data reported, although no differences in survival were found in the current study, it is appropriate to consider NAM and DNM as 2 different subtypes inside the large heterogeneous melanoma family.

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All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional research committee and with the Declaration of Helsinki 1964 and its later amendments or comparable ethics standards.

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