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Article

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De Novo vs Nevus-Associated Melanomas: Differences in Associations With Prognostic Indicators and Survival

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Abstract

Background: Although 20% to 30% of melanomas are histopathologically 'nevus associated,' the majority of melanomas arise de novo, ie, in clinically normal skin with no associated nevus. We examined whether these forms of melanoma differed in their associations with clinical and histopathologic features and patient survival.

Methods: We analyzed two prospective cohorts from our institution with protocol-driven follow-up information (NYU1, n = 1024; NYU2, n = 1125). We used univariate and multivariable analyses to examine associations between de novo vs nevus-associated melanoma classification and age, anatomic site, tumor thickness, tumor ulceration, mitotic index, histological subtype, clinical stage, and survival. We tested the associations identified in NYU1 using NYU2 as a replication cohort. All tests of statistical significance were two-sided.

Results: In NYU1, de novo melanomas were associated with tumor thickness greater than 1.0 mm (odds ratio [OR] = 1.96, 95% confidence interval [CI] = 1.43 to 2.70, $P < .001$), ulceration (OR = 1.65, 95% CI = 1.10 to 2.54, $P = .02$), nodular subtype (OR = 3.26, 95% CI = 1.70 to 7.11, $P = .001$), greater than stage I (OR = 2.35, 95% CI = 1.65 to 3.40, $P < .001$), older age (OR = 1.64, 95% CI = 1.18 to 2.30, $P = .004$), and shorter overall survival (HR = 1.63, 95% CI = 1.22 to 2.18, $P < .001$). In NYU2, de novo melanoma was again statistically significantly associated with thickness greater than 1.0 mm (OR = 2.24, 95% CI = 1.72 to 2.93, $P < .001$), ulceration (OR = 2.88, 95% CI = 1.95 to 4.37, $P < .001$), nodular subtype (OR = 2.41, 95% CI = 1.75 to 3.37, $P < .001$), greater than stage I (OR = 2.42, 95% CI = 1.80 to 3.29, $P < .001$), older age (OR = 1.68, 95% CI = 1.31 to 2.17, $P < .001$), and shorter overall survival (HR = 2.52, 95% CI = 1.78 to 3.56, $P < .001$). In multivariable analysis, de novo classification was an independent, poor prognostic indicator in NYU2 (HR = 1.70, 95% CI = 1.19 to 2.44, $P = .004$). Male patients had a statistically significantly worse survival than female patients if their melanoma was de novo (NYU1, $P < .001$; NYU2, $P < .001$); unexpectedly, there was no sex difference in survival among patients with nevus-associated tumors.

Conclusions: These data suggest that de novo melanomas are more aggressive than nevus-associated melanomas. This classification scheme may also provide a useful framework for investigations into sex differences in melanoma outcomes.

Cutaneous melanoma is a malignant, melanocytic tumor that is often found in patients with increased numbers of melanocytic nevi, which are benign neoplasms. Whether nevi, especially clinically atypical nevi, are melanoma precursors is controversial (1). Pathology-based studies have found that 20% to 30% of melanomas contain nevus cells in histologic continuity with melanoma (2–9), suggesting direct transformation of a nevus into melanoma. Current models of melanoma pathogenesis often indicate

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a progression from normal melanocytes to melanoma, with nevi representing an intermediate step for certain melanoma subtypes (10,11). The majority of melanomas (70%–80%), however, arise de novo, ie, with no associated nevus, and the majority of melanoma patients lack clinically atypical nevi or increased numbers of nevi (12,13). In addition, the lifetime risk of an individual nevus transforming into melanoma has been estimated to be far less than one in 1000 (14).

At present, little is known about the host and/or tumor factors that cause melanoma to arise in normal skin vs in association with a nevus. The divergent pathway model of melanoma pathogenesis, based primarily on epidemiologic studies identifying differences in the sun exposure patterns and mole phenotypes of patients with different subtypes of melanoma (15–18), provides a conceptual framework regarding differences in nevus-associated and de novo melanoma. For example, melanomas removed from 'nevus-prone' patients, ie, those with increased numbers of nevi, were more frequently found in physical association with a nevus than melanomas arising in patients with few nevi (ie, 'nevus-resistant' patients) (19).

Whether the presence of an associated nevus has any prognostic significance for patient outcomes is uncertain. There is no consensus among the published studies, which are generally limited by small sample sizes, patient selection criteria, retrospective designs, and/or varying quality of the follow-up data (2–9,19–23). In the current study, we sought to examine differences between nevus-associated and de novo melanomas in two large cohorts of prospectively followed patients. We aimed to determine whether nevus-associated and de novo melanomas differ in their associations with histopathologic features and whether de novo vs nevus-associated classification is an independent prognostic variable for melanoma patient survival.

Methods

Patients

We studied two cohorts of melanoma patients with protocol-driven follow-up prospectively enrolled and treated at New York University Medical Center. The first cohort, NYU1, was comprised of patients with primary cutaneous melanoma enrolled between 1972 and 1982, with follow-up until 1993. Clinical and pathological data were collected in 415 fields, from which 11 variables were examined including age, sex, mole phenotype, primary tumor thickness, ulceration status, tumor anatomic site, tumor mitoses, histopathological subtype, histopathological association of melanoma with a nevus, clinical stage, and overall survival. Cause of death and patient status were determined at the date of last follow-up. Patient nevus phenotype was based on the number of nevi assessed by physician exam. Patients were classified as having none, few (1–25), some (26–100), or many (>100) melanocytic nevi, defined as melanocytic lesions larger than 2 mm in size. For analytical purposes, we adopted the mole phenotype scheme proposed by Whiteman et al. (17) and grouped patients as nevus-prone (ie, having 'some' or 'many' nevi) or nevus-resistant (ie, having 'none' or 'few' nevi). There were 1134 patients with available data. We excluded 86 patients where the de novo/nevus-associated classification was missing. Among the remaining patients: 20 had a second primary tumor and were excluded; three were excluded as their time to death information was missing; and three were excluded because of a time to death being 0 or less than 0.1 years. This process yielded a total of 1024 patients for the analyses.

The second cohort, NYU2, included patients prospectively enrolled in the NYU Interdisciplinary Melanoma Cooperative Group registry (24) between 2002 and 2009, with follow-up until 2013. Clinical and pathological variables were chosen in order to replicate the findings from the NYU1 cohort. Ten relevant variables were examined: age, sex, primary tumor thickness, ulceration status, tumor anatomic site, tumor mitoses, tumor histological subtype, histopathological association of melanoma with a nevus, clinical stage, and overall survival. Survival data was collected as of last patient follow-up. Patient nevus phenotype was not available for this cohort. There were 1164 patients with available data from this cohort. We excluded 30 patients missing the de novo/nevus-associated classification and nine patients with time to death of less than 0.1 year, so the analyses are based on 1125 patients. All patients were restaged according to the American Joint Committee on Cancer Melanoma staging system, 7th edition. Written informed consent was obtained from all patients in the NYU2 cohort (NYU IRB study #10362); such consent was not obtained from patients in the NYU1 cohort. Informed consent procedures/requirements were not in place during the time period of their enrollment, and by current standards the analysis of the de-identified data in the NYU1 patient cohort would not be considered human subjects research.

Statistical Analysis

Univariate analyses using chi square for categorical data and the Mann-Whitney test for continuous data were performed for all variables to determine if they were associated with de novo or nevus-associated melanoma. Patients lacking a de novo or nevus association classification ($n = 86$ for NYU1; $n = 30$ for NYU2) were excluded from these analyses. Univariate survival analysis was performed using Cox PH models and log-rank analyses to evaluate which variables were associated with survival. Multivariable logistic analysis was performed to determine which variables were statistically significantly associated with de novo vs nevus-associated subtype in the presence of other covariates. Finally, multivariable Cox PH regression analysis was used to construct survival models using all univariate variables and de novo/nevus-associated status. We used the cox.zph test in R to verify the proportional hazards assumption for using Cox PH models and concluded that the Cox PH models can be used in both NYU1 and NYU2. All analyses were performed using R. All tests of statistical significance were two-sided, and a P of less than .05 was considered statistically significant.

We chose to compare the two datasets separately rather than merging the data into one large analysis for three reasons: Firstly, there is a 20-year gap between the time when the last patient was enrolled in NYU1 and the first patient was enrolled in NYU2; secondly, analyzing the datasets separately is a more conservative approach. The sample size for each dataset is smaller than the combined dataset, so associations between the variables under study need to have higher effect size to achieve statistical significance; finally, analyzing these datasets separately allows us to test the reproducibility of our observations in the two independent datasets, providing increased confidence in the robustness of the associations we identified.

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Table 1. Patient demographic and tumor characteristics

Characteristics	NYU1 (1972-1982)		NYU2 (2002-2009)	
	Nevus-assoc (n = 198, 19.3%)	De novo (n = 826, 80.7%)	Nevus-assoc (n = 349, 31.0%)	De novo (n = 776, 69.0%)
Age, y				
Median (range)	46.0 (19–88)	54.0 (9–91)	55.0 (19–91)	61.0 (6–97)
Missing, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex, No. (%)				
Male	92 (46.5)	408 (49.4)	201 (57.6)	415 (53.5)
Female	106 (53.5)	418 (50.6)	148 (42.4)	361 (46.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary tumor thickness, mm				
No. (range)	1.0 (0.1–9.8)	1.4 (0.1–15)	0.7 (0.1–30)	1.0 (0.12–30)
0–1.00, No. (%)	105 (53.0)	297 (36.0)	238 (68.2)	381 (49.1)
1.00–2.00, No. (%)	51 (25.8)	215 (26.0)	70 (20.1)	169 (21.8)
2.00–4.00, No. (%)	24 (12.1)	170 (20.6)	26 (7.4)	138 (17.8)
>4.00, No. (%)	12 (6.1)	98 (11.9)	14 (4.0)	88 (11.3)
Missing, No. (%)	6 (3.0)	46 (5.6)	1 (0.3)	0 (0.0)
Primary tumor ulceration status, No. (%)				
Absent	164 (82.8)	613 (74.2)	317 (90.8)	600 (77.3)
Present	31 (15.7)	192 (23.2)	32 (9.2)	175 (22.6)
Missing	3 (1.5)	21 (2.5)	0 (0.0)	1 (0.1)
Primary tumor anatomic site, No. (%)				
Axial	89 (44.9)	293 (35.5)	182 (52.1)	253 (32.6)
Head/Neck	31 (15.7)	119 (14.4)	35 (10.0)	149 (19.2)
Extremity	75 (37.9)	410 (49.6)	132 (37.8)	374 (48.2)
Missing	3 (1.5)	4 (0.5)	0 (0.0)	0 (0.0)
Primary tumor mitosis, No. (%)				
Absent	74 (37.4)	298 (36.1)	168 (48.1)	271 (34.9)
Present	100 (50.5)	429 (51.9)	175 (50.1)	500 (64.4)
Missing	24 (12.1)	99 (12.0)	6 (1.7)	5 (0.6)
Primary tumor histologic subtype, No. (%)				
Superficial	164 (82.8)	555 (67.2)	249 (71.3)	419 (54.0)
Nodular	9 (4.5)	101 (12.2)	58 (16.6)	236 (30.4)
Acral	4 (2.0)	19 (2.3)	2 (0.6)	32 (4.1)
Lentigo	7 (3.5)	41 (5.0)	11 (3.2)	33 (4.3)
Others	4 (2.0)	34 (4.1)	24 (6.9)	49 (6.3)
Missing	10 (5.1)	76 (9.2)	5 (1.4)	7 (0.9)
AJCC* stage at pathological diagnosis, No. (%)				
I	147 (74.2)	450 (54.5)	281 (80.5)	489 (63.0)
II	34 (17.2)	224 (27.1)	30 (8.6)	173 (22.3)
III/IV	12 (6.1)	108 (13.1)	38 (10.9)	114 (14.7)
Missing	5 (2.5)	44 (5.3)	0 (0.0)	0 (0.0)

*AJCC = American Joint Committee on Cancer.

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Results

Table 1 describes the baseline characteristics of patients in both cohorts. In the NYU1 cohort, 48.8% of patients were male and the median age was 53 years. The median tumor thickness was 1.3 mm, 21.8% of tumors were ulcerated, 51.7% had a mitotic index >1, 10.7% were of the nodular histotype, and 19.3% of melanomas were nevus-associated. In the NYU2 cohort, 54.8% of patients were male, and the median age was 59 years. The median tumor thickness was 0.9mm, 18.4% of tumors were ulcerated, 60.0% had a mitotic index of 1 or greater, 26.1% were of the nodular histotype, and 31.0% were nevus-associated. In univariate (Table 2) and multivariable survival analyses (Table 3; Supplementary Table 1, available online), well-established prognostic factors for melanoma survival (ie, age, tumor thickness, ulceration, mitotic index, and anatomic site on the trunk) were found to be statistically significantly associated with survival in both NYU1 and NYU2, demonstrating that these cohorts are typical of melanoma cohorts studied elsewhere.

To investigate whether melanomas arising in association with a melanocytic nevus had a different outcome than those arising without an associated nevus (ie, de novo) we first tested the potential association of 'nevus-associated' or de novo classification with other histopathological variables and then examined survival outcomes. We found that de novo melanomas were statistically significantly associated with several variables conferring poor outcomes (Table 4). For example, in univariate analysis of the NYU1 cohort, de novo melanomas were associated with tumor thickness greater than 1.0 mm (odds ratio [OR] = 1.96, 95% confidence interval [CI] = 1.43 to 2.70, $P < .001$), ulceration (OR = 1.65, 95% CI = 1.10 to 2.54, $P = .02$), nodular subtype (OR = 3.26, 95% CI = 1.70 to 7.11, $P = .001$), greater than stage I (OR = 2.35, 95% CI = 1.65 to 3.40, $P < .001$), older age (OR = 1.64, 95% CI = 1.18 to 2.30, $P = .004$). These observations

Table 2. Univariate survival analysis

Variable	NYU1			NYU2		
	HR (95% CI)	HR (95% CI), IQR	P*	HR (95% CI)	HR (95% CI), IQR	P*
Sex						
Female vs Male	0.65 (0.53 to 0.79)		<.001	0.64 (0.50 to 0.83)		.001
Age, y	1.04 (1.03 to 1.05)	2.84 (2.35 to 3.42)	<.001	1.04 (1.03 to 1.05)	2.61 (2.11 to 3.23)	<.001
Primary tumor thickness, mm	1.31 (1.27 to 1.36)	1.57 (1.48 to 1.67)	<.001	1.13 (1.11 to 1.15)	1.23 (1.19 to 1.26)	<.001
Primary tumor ulceration						
Present vs absent	2.46 (1.99 to 3.04)		<.001	4.56 (3.56 to 5.85)		.001
Primary tumor mitotic index						
Present vs absent	1.99 (1.57 to 2.54)		<.001	3.45 (2.46 to 4.83)		.001
Primary tumor histological type						
Nodular vs superficial spreading/other	1.68 (1.26 to 2.24)		<.001	2.95 (2.30 to 3.78)		.001
AJCC stage at pathological diagnosis						
III/IV vs I/II	3.50 (2.74 to 4.47)		<.001	4.87 (3.76 to 6.30)		.001
Primary tumor anatomic site						
Extremity vs axial/head & neck	0.69 (0.56 to 0.84)		<.001	0.72 (0.56 to 0.93)		.01
De novo/nevus-associated						
De novo vs nevus-associated	1.63 (1.22 to 2.18)		<.001	2.52 (1.78 to 3.56)		.001

*Based on two-sided Wald test for univariate Cox PH model. Hazard ratio per interquartile range for continuous covariates (age and tumor thickness). AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; IQR = interquartile range.

Table 3. Multivariable survival analysis of traditional prognostic indicators

Variable	NYU1			NYU2		
	HR (95% CI)	HR (95% CI), IQR	P*	HR (95% CI)	HR (95% CI), IQR	P*
Age, y	1.04 (1.03 to 1.05)	2.51 (2.04 to 3.08)	<.001	1.04 (1.03 to 1.05)	2.49 (2.00 to 3.09)	<.001
Primary tumor thickness, mm	1.22 (1.16 to 1.28)	1.40 (1.29 to 1.51)	<.001	1.09 (1.07 to 1.12)	1.16 (1.11 to 1.20)	<.001
Primary tumor ulceration						
Present vs absent	1.50 (1.15 to 1.96)		.003	2.49 (1.89 to 3.28)		<.001
Primary tumor mitotic index,						
Present vs absent	1.32 (1.01 to 1.73)		.04	1.97 (1.37 to 2.83)		<.001
Primary tumor anatomic site						
Extremity vs axial/head and neck	0.57 (0.46 to 0.72)		<.001	0.67 (0.52 to 0.87)		.003

*Based on two-sided Wald test for Cox PH model. Hazard ratio per interquartile range for continuous covariates (age and tumor thickness). CI = confidence interval; HR = hazard ratio; IQR = interquartile range.

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were also found in the NYU2 replication cohort, where de novo melanomas were associated with thickness greater than 1.0 mm (OR = 2.24, 95% CI = 1.72 to 2.93, $P < .001$), ulceration (OR = 2.88, 95% CI = 1.95 to 4.37, $P < .001$), nodular subtype (OR = 2.41, 95% CI = 1.75 to 3.37, $P < .001$), greater than stage I (OR = 2.42, 95% CI = 1.80 to 3.29, $P < .001$), older age (OR = 1.68, 95% CI = 1.31 to 2.17, $P < .001$). In both cohorts, de novo melanomas were statistically significantly associated with anatomic location on the extremities (NYU1 HR = 1.66, 95% CI = 1.18 to 2.34, $P = .01$; NYU2, HR = 3.05, CI = 2.03 to 4.67, $P<.001$), a location that, in several survival models, has been associated with better outcomes than location on the trunk (25–29). The presence of tumor mitoses was statistically significantly associated with de novo classification in NYU2 only. Incidentally, de novo melanomas were statistically significantly associated with the nevus-resistant mole phenotype in NYU1 (OR = 1.80, 95% CI = 1.28 to 2.51, $P < .001$); nevus phenotype was not available for NYU2.

Next we examined whether melanomas arising de novo had a worse survival outcome compared with nevus-associated melanomas. In both the NYU1 and NYU2 cohorts, we found that patients with de novo melanomas had shorter overall survivals than patients whose melanomas arose in association with a melanocytic nevus (Figure 1). In a univariate proportional hazards analysis for survival, we found that de novo classification was statistically significantly associated with worse survival in both the NYU1 (HR = 1.63, 95% CI = 1.22 to 2.18, $P < .001$) and NYU2 cohorts (HR = 2.52, 95% CI = 1.78 to 3.56, $P < .001$) (Table 2). In multivariable analysis including tumor thickness, ulceration, mitotic index, and anatomic site, de novo classification was an independent predictor of poor survival outcome in the NYU2 cohort (HR = 1.70, 95% CI = 1.19 to 2.44, $P = .004$); there was a trend in the same direction in the NYU1 cohort (HR = 1.27, 95% CI = 0.93 to 1.75, $P = .14$) (Table 5; Supplementary Table 2, available online).

We also examined whether there were differences in the associations between traditional prognostic variables and survival for patients classified with either de novo or nevus-associated melanomas. In both cohorts, we found that increasing tumor thickness, ulceration, and clinical stage were prognostic indicators of short survival irrespective of tumor association with a nevus (Supplementary Figures 1, 2, and 5, respectively, available online). Unexpectedly, the associations between survival and sex differed for patients with de novo vs nevus-associated melanomas. In both cohorts, male patients had a statistically significantly worse survival than female patients if their melanoma

Table 4. Univariate analysis of factors associated with de novo melanoma

Characteristics	NYU1		NYU2	
	OR (95% CI)	P*	OR (95% CI)	P*
Age, y		<.001		<.001
Sex				
Male	1.00 (Referent)	.51	1.00 (Referent)	.22
Female	0.89 (0.65 to 1.21)		1.18 (0.92 to 1.53)	
Primary tumor thickness, mm				
0–1.00	1.00 (Referent)	<.001	1.00 (Referent)	<.001
1.00–2.00	1.49 (1.02 to 2.18)		1.51 (1.09 to 2.09)	
2.00–4.00	2.49 (1.56 to 4.12)		3.30 (2.13 to 5.27)	
>4	2.85 (1.56 to 5.69)		3.89 (2.23 to 7.29)	
Primary tumor ulceration status				
Absent	1.00 (Referent)	.02	1.00 (Referent)	<.001
Present	1.65 (1.10 to 2.54)		2.88 (1.95 to 4.37)	
Primary tumor anatomic site				
Axial	1.00 (Referent)	.01	1.00 (Referent)	<.001
Head/neck	1.16 (0.74 to 1.87)		3.05 (2.03 to 4.67)	
Extremity	1.66 (1.18 to 2.34)		2.04 (1.55 to 2.68)	
Primary tumor histologic subtype				
Superficial	1.00 (Referent)	.003	1.00 (Referent)	<.001
Nodular	3.26 (1.70 to 7.11)		2.41 (1.75 to 3.37)	
Acral	1.36 (0.50 to 4.87)		8.86 (2.65 to 59.17)	
Lentigo	1.70 (0.79 to 4.24)		1.76 (0.90 to 3.74)	
Others	2.43 (0.95 to 8.41)		1.21 (0.73 to 2.05)	
AJCC stage at pathological diagnosis				
I	1.00 (Referent)	<.001	1.00 (Referent)	<.001
II	2.14 (1.44 to 3.26)		3.30 (2.21 to 5.08)	
III/IV	2.90 (1.61 to 5.72)		1.72 (1.17 to 2.58)	
Primary tumor mitosis				
Absent	1.00 (Referent)	.78	1.00 (Referent)	<.001
Present	1.07 (0.76 to 1.49)		1.68 (1.31 to 2.17)	

*Based on two-sided Chi-square test (categorical variables) or Wilcoxon test (continuous variables). AJCC = American Joint Committee on Cancer; CI = confidence interval; OR = odds ratio.

was de novo (NYU1, $P < .001$; NYU2, $P < .001$), but there was no difference in survival if their tumor was nevus-associated (Figure 2).

Finally, to address potential confounding because of the positive association between de novo melanomas and nodular melanomas, which are known to be an aggressive melanoma subtype, we repeated the analysis excluding patients diagnosed with nodular melanomas. In both the NYU1 and NYU2 cohorts, all associations remained statistically significant except for the association of ulceration with de novo melanoma in the NYU1 cohort. As expected, ulceration was found more often in de novo melanomas than nevus-associated melanomas; however, the association did not reach statistical significance ($P = .19$) (Supplementary Table 3, available online).

Discussion

We found that de novo melanomas were statistically significantly associated with older age at diagnosis, fewer nevi, anatomic location on the extremities, thicker tumors, ulceration, nodular subtype, higher stage, and shorter overall survival in both the NYU1 and NYU2 cohorts. The two cohorts were recruited decades apart and histopathologic slides were interpreted by different pathologists, suggesting that these are robust associations. In addition, these findings indicate that de novo melanomas may represent a more aggressive form of melanoma than nevus-associated melanomas, as the de novo classification was an independent prognostic indicator of short survival in multivariable analysis in the NYU2 cohort and it trended in the same direction in the NYU1 cohort.

Although several studies have attempted to determine if differences in etiology and prognosis exist between de novo and nevus-associated melanomas, to our knowledge no prior studies have definitively found de novo melanomas to be a prognostic indicator for shorter survival. Most of the prior studies have used Breslow thickness as a surrogate marker for patient outcome instead of survival, and the results have largely been inconclusive. Two studies found that nevus-associated melanomas were thicker than de novo melanomas, two studies found they were thinner, and two studies found no difference (20,22,23,30–32). Possible reasons for these discrepancies include the possibility that advanced melanomas may obliterate underlying nevus cells as they progress and/or inconsistencies in the measurement of thickness because of nonstandardized measures of evaluation of the associated nevus component.

Few studies have specifically analyzed survival outcomes with respect to nevus-associated and de novo classification of melanomas. A recent study by Lin et al. did not find statistically significant differences between de novo and nevus-associated melanoma with respect to tumor thickness and survival; however, their patient group was assembled from a retrospective chart review of consecutively seen patients who underwent sentinel lymph node biopsy (21). The median tumor thickness

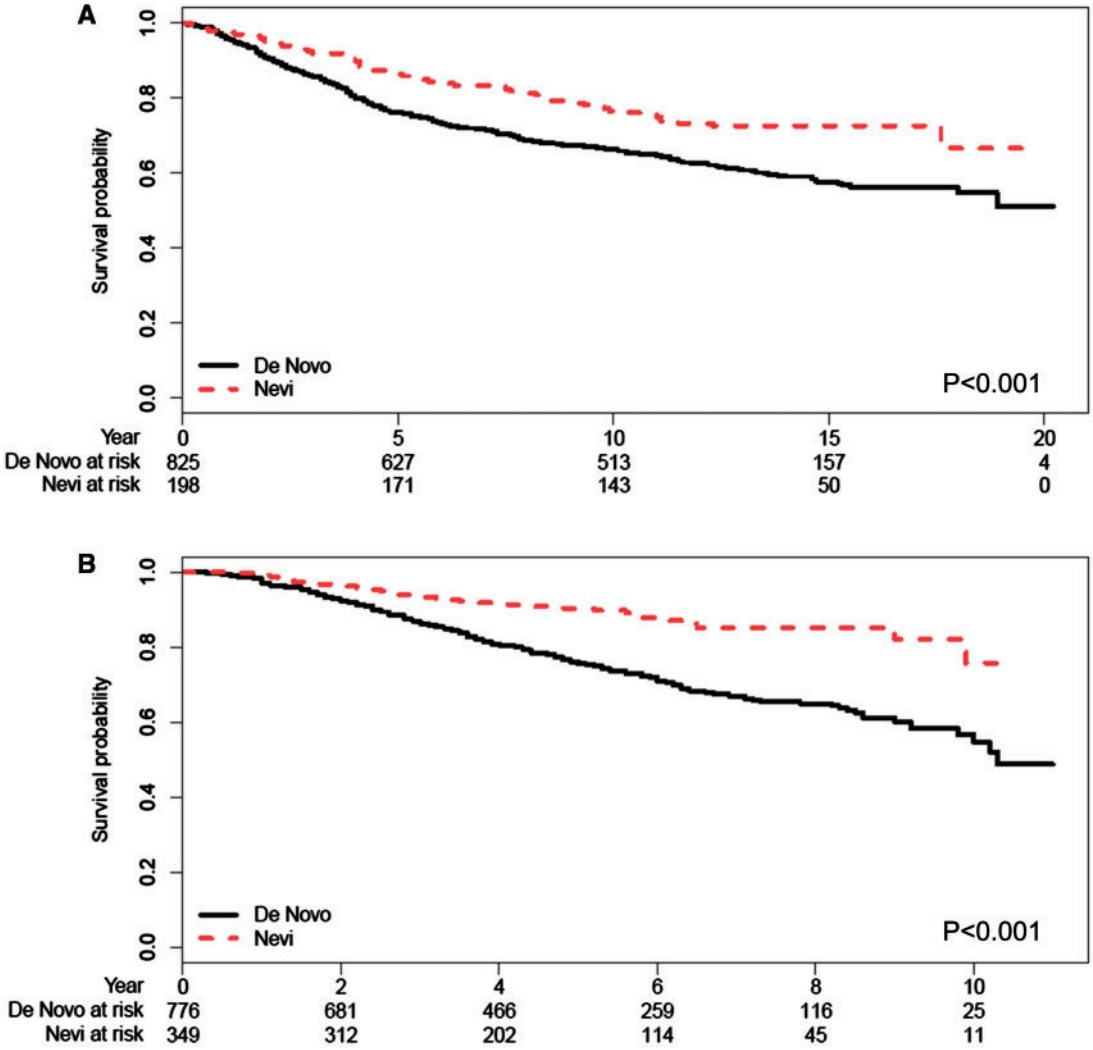

Figure 1. Overall survival stratified by de novo (**solid lines**) or nevus-associated (**dashed lines**) melanoma classification. **A)** NYU1 cohort. **B)** NYU2 cohort. **Tables** of the numbers of patients at risk at different time points are given below each graph. *P* values are calculated based on two-sided log-rank test.

Table 5. Multivariable survival analysis including de novo vs nevus-associated classification

	NYU1			NYU2		
Variable	HR (95% CI)	HR (95% CI), IQR	*P**	HR (95% CI)	HR (95% CI), IQR	*P**
Age, y	1.04 (1.03 to 1.05)	2.53 (2.04 to 3.13)	<.001	1.03 (1.03 to 1.04)	2.34 (1.88 to 2.91)	<.001
Primary tumor thickness, mm	1.22 (1.16 to 1.28)	1.39 (1.28 to 1.51)	<.001	1.10 (1.07 to 1.12)	1.17 (1.12 to 1.21)	<.001
Primary tumor ulceration						
Present vs absent	1.49 (1.14 to 1.95)		.003	2.32 (1.75 to 3.07)		<.001
Primary tumor mitotic index						
Present vs absent	1.32 (1.01 to 1.73)		.04	1.87 (1.30 to 2.69)		<.001
Primary tumor anatomic site						
Extremity vs axial/head and neck	0.57 (0.45 to 0.72)		<.001	0.65 (0.50 to 0.85)		.001
De novo/nevus-associated						
De novo vs nevus-associated	1.27 (0.93 to 1.75)		.14	1.70 (1.19 to 2.44)		.004

*Based on two-sided Wald test for Cox PH model. Hazard ratio per interquartile range for continuous covariates (age and tumor thickness). CI = confidence interval; HR = hazard ratio; IQR = interquartile range.

of their group was 1.7 mm, much higher than the tumor thicknesses of either the NYU1 or NYU2 cohorts. Interestingly, they did make similar observations to ours with respect to the patient and tumor characteristics associated with either nevus-associated or de novo melanoma classification (eg, patient age, anatomic site of the melanoma, histopathologic subtype, and ulceration). A small, retrospective study by Kaddu et al. also failed to find a difference in survival between patients classified with nevus-associated and de novo melanomas (30). In contrast to our prospectively recruited cohort design, both of these

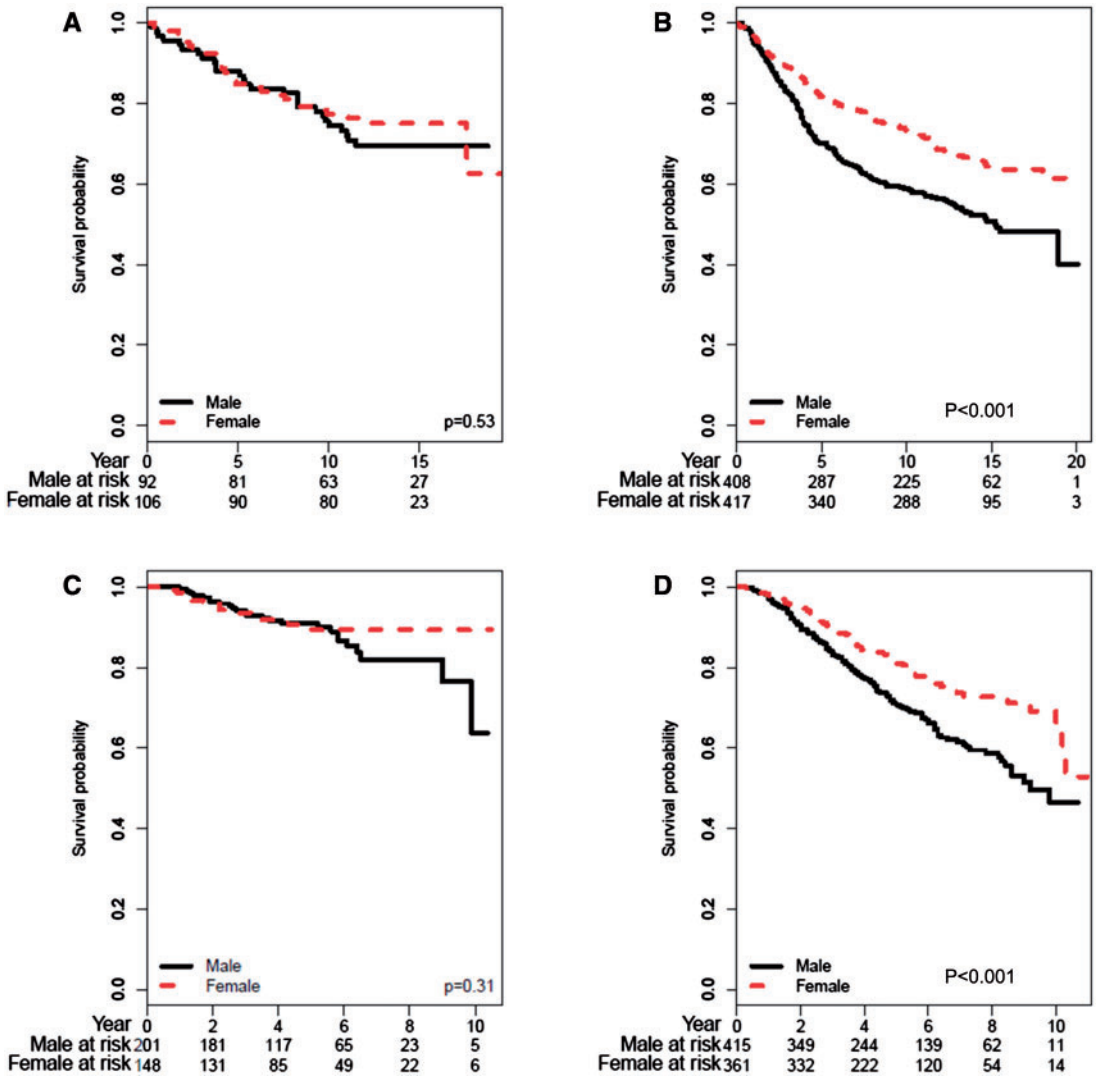

Figure 2. Overall survival analyses for nevus-associated and de novo melanoma patients stratified by sex (**solid lines** = male; **dashed lines** = female). **A)** NYU1 = nevus-associated patients. **B)** NYU1 = de novo patients. **C)** NYU2 = nevus-associated patients. **D)** NYU2 = de novo patients. **Tables** of the numbers of patients at risk at different time points are given below each graph. *P* values are calculated based on two-sided log-rank test.

studies are retrospective investigations, limiting their ability to conduct a statistically robust survival analysis. A prospective study conducted by investigators from our institution was published in 1983. These investigators performed a preliminary analysis of 557 patients from the NYU1 dataset. They found poorer disease-free survival for de novo melanomas; however, the impact of this finding was limited by the shorter follow-up time and small number of patient recurrences. Importantly, no multivariable survival analysis was described (20).

Unexpectedly, we found that the association between sex and survival was dependent upon whether a patient's melanoma was de novo or nevus-associated. In both cohorts, men had a statistically significantly worse survival than women among patients with de novo melanomas; however, there was no difference in survival between men and women who were diagnosed with nevus-associated melanoma. Several melanoma studies have found that male patients have worse survival than female patients, which suggests that important sex-associated biological differences exist (33–40). Additionally, recent analyses of Surveillance, Epidemiology, and End Results data demonstrate that men have poorer survival than women for most cancer types (41). Related hypotheses potentially worth exploring include sex differences in immune function, the potential effects of male vs female hormones on tumor cells and/or immune function, and the possible differences in how these (or other) factors may interact with a patient's underlying susceptibility to developing nevus-associated or de novo melanoma tumors. It is also possible that nevus-associated melanomas are intrinsically less aggressive because of their genotypic or phenotypic characteristics so that potential sex-related differences in host responses to these tumors are not manifested. Of note, we performed a formal statistical test of the interaction of sex and de novo vs nevus-associated melanomas on survival; however, the interaction term did not achieve statistical significance (data not shown).

These findings suggest there are potentially important differences in the biology of nevus-associated and de novo melanomas. Our results are largely consistent with the two-pathway (ie, divergent pathway) model for the development of melanoma on sun-exposed skin (reviewed in [16]). This model

reconciles epidemiologic differences in the sun exposure patterns and anatomic distribution of melanomas by incorporating a concept related to an individual's propensity to develop melanocytic nevi (ie, nevus-prone vs nevus-resistant). In this model, nevus-prone patients have increased numbers of melanocytic nevi and develop melanomas at younger ages that are more likely to arise in association with a melanocytic nevus, on axial locations, of the superficial spreading subtype, and with frequent BRAF mutations. Conversely, nevus-resistant patients have fewer nevi and develop melanomas at older ages that are more likely to arise de novo, be of nodular subtype, and be associated with NRAS mutations. These clinical features are also shared by the recently described 'high-mitotic-rate melanomas,' which, notably, are statistically significantly more likely to arise de novo than in association with a nevus (42). Other potential biological differences include sex-specific variations in the host response to de novo melanoma. Moving forward, it may be useful to use the nevus-associated vs de novo classification in analyses of melanoma risk factors, tumor biology, and response to therapy.

Strengths of our study include the analysis of two large, prospectively ascertained patient cohorts, enrolled decades apart by different investigators at a single institution. We had multiple clinical and histopathologic features available for analysis, along with lengthy survival data. This enabled us to use a second patient cohort to test associations identified in the initial cohort. Nearly all the associations were strongly statistically significant in both multivariable and univariate analyses in both cohorts. One weakness of our study is that the initial cohort was enrolled prior to the advent of sentinel node biopsy. For this reason, we were not able to include an analysis of sentinel node biopsy results in this analysis.

In summary, de novo melanoma classification was associated with several adverse histopathologic features in primary cutaneous melanoma and appears to be an independent predictor of poor outcome in multivariable analysis. De novo melanomas are more likely to possess molecular characteristics associated with poor survival compared with nevus-associated melanomas and may differ in their molecular pathogenesis as suggested by the divergent pathway model. As sex-specific survival differences were only observed among the patients with de novo melanomas, the de novo vs nevus-associated melanoma classification scheme may be helpful for investigations into sex-specific differences in melanoma survival.

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