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Nevus count associations with pigmentary phenotype, histopathological melanoma characteristics and survival from melanoma

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This study, among a large population-based series of melanoma cases, showed that nevus count is associated with an increased risk of melanoma-specific death; however, no significant relationships between nevus count and histopathological tumor features were observed after adjustment for relevant covariates.

Conflict of interest statement: None declared.

Author Contributions

NJT and PAK designed the analytic question, interpreted the analysis of data, and prepared the manuscript.
NJT and PAK performed the analysis of data.
CBB and MB conceived and designed the GEM Study and also contributed to data collection and critical review of the manuscript.
All other authors (AEC, HAC, IO, KJB, LF, NET, RPG, RZ, SBG, SR, TD) contributed to data collection and critical review of the manuscript.

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Abstract

Although nevus count is an established risk factor for melanoma, relationships between nevus number and patient and tumor characteristics have not been well studied and the influence of nevus count on melanoma-specific survival is equivocal. Using data from the Genes, Environment, and Melanoma (GEM) study, a large population-based study of primary cutaneous melanoma, we evaluated associations between number of nevi and patient features, including sun-sensitivity summarized in a phenotypic index, and tumor characteristics, and we assessed the association of nevus count with melanoma-specific survival. Higher nevus counts were independently and positively associated with male gender and younger age at diagnosis and inversely associated with lentigo maligna histology. We observed a borderline significant trend of poorer melanoma-specific survival with increasing quartile of nevus count, but little or no association between number of nevi and pigmentary phenotypic characteristics or prognostic tumor features.

Introduction

Total body nevus count is a strong predictor of melanoma risk[1–3] and is a key feature of one of the postulated dual pathways for developing melanoma, which is further characterized by melanomas presenting on the trunk and a history of intermittent sun exposure[4, 5]. The relationships between number of nevi and the characteristics of melanoma patients, and their melanoma survival outcomes have not been well studied, and, for survival specifically, published results are inconsistent. A population-based case-control study of cutaneous melanoma in Connecticut found increased risk of melanoma-specific death (N_{cases}=528) in the highest category of nevus counts on the backs and arms of patients (>31 nevi; HR=2.1; 95% CI: 1.1, 4.1), but no statistically significant association overall (P_{trend}=0.10)[6]. A more recent report (Ribero *et al*. 2015) however found favorable prognostic features and better melanoma-specific survival (HR=0.43; 95% CI: 0.21, 0.89) associated with high total body nevus counts (>50 nevi) in 2,184 population- and hospital-based melanoma cases[7].

The aim of this study was to further assess associations between nevus counts and melanoma patient and tumor characteristics and melanoma-specific survival in a large population-based series of cutaneous melanomas arising from diverse geographic environments. We also aimed to explore specifically the nevus-associated pathway of the divergent pathway hypothesis[5, 8] by examining the relationship of nevus counts with a phenotypic index comprising measures of tanning, hair, and eye color. The divergent hypothesis proposes that higher nevus counts, younger age at diagnosis, and intermittently sun-exposed anatomical sites of melanoma, particularly the trunk, are markers of a distinct biological pathway, and that the alternative pathway is characterized by occurrence on sites of more continuous sun exposure and in people with comparatively few nevi[5, 8].

Methods

We used data from the Genes, Environment, and Melanoma (GEM) study—a population-based case-control study including a large series of primary cutaneous melanoma cases identified by study centers in Australia, Canada, Italy, and the United States as previously described[9, 10]. Human research ethical oversight committees at each GEM study site approved the study protocol, and written and signed informed consent was obtained from all participants.

Host variables including age, gender, and body site of melanoma were abstracted from pathology reports and confirmed during patient interviews. Histopathological data corresponding to 3,566 cases of primary cutaneous melanoma were collected via a centralized pathology review as previously published[11]. For patients with multiple primary melanomas (MPM), data corresponding to the thickest lesion according to Breslow thickness were used for the analysis and considered to be representative of the melanoma most likely to cause death.

Phenotypic data were available for 3,430 (96%) participants. A phenotypic index was created as previously described based on: tanning phenotype, hair color, and eye color[12]. Higher phenotypic scores correspond to more sun-sensitive phenotypes; lower scores indicate a more sun-resistant phenotype. Using a glossy-colored guide to aid in distinguishing nevi from other skin lesions, participants were asked to have a family member or friend count the number of nevi on their backs. GEM counts of nevi on the back are significantly correlated with participants' choice of a diagram that illustrated their total body nevus density[13], and have served as satisfactory proxy measures of total body nevus counts in other studies[14]. We log-transformed back nevus counts and used study center-specific distributions to dichotomize ln(counts) at the median number, and quartile measures were calculated in similar fashion. Pearson's or Mantel-Haenszel χ^2 and Student's t-tests were performed to compare categorical and continuous variables, respectively. Multivariable logistic regression was used to estimate the associations between study factors and nevus count, adjusting for factors that were statistically significantly associated with nevus count (α=0.05) in univariate analyses and study design variables: age, gender, presence of MPM and study center. Since Breslow thickness was not normally distributed among cases, values were log transformed for parametric testing when Breslow thickness was used as an adjustment term. Melanoma-specific survival was calculated from the diagnosis date of the index primary melanoma to the date of melanoma death or last follow-up, and adjusted hazard ratios with corresponding 95% confidence intervals were calculated using Cox proportional hazards models. Deaths not attributable to melanoma were censored. Hazards models were adjusted for a time-dependent variable to account for differences in follow-up time for GEM participants diagnosed with a second primary melanoma during the course of study recruitment[11].

Because nevus distributions between GEM study participants and those sampled by Ribero *et al*. (2015) were considerably different and to facilitate comparison, we created a dichotomous nevus variable using a study center-specific cutoff at the 70th percentile of (non-log-transformed) nevus count to create high (≥70th percentile nevi, 31%) and low

(<70th percentile nevi, 69%) nevus count categories representing proportions similar to those reported by Ribero *et al*. Two survival analyses were performed: first we evaluated melanoma-specific survival according to nevus counts among all GEM cases, and then repeated this analysis limited to GEM participants enrolled with a single primary melanoma. Covariates in these models were: gender, age at diagnosis, presence of mitoses, Breslow thickness, ulceration, site of primary melanoma, and GEM study center. Data on sentinel lymph node involvement were not available for GEM participants. In the analysis of all GEM cases, we included the abovementioned time-dependent variable and an indicator variable for MPM status; whereas in the analysis limited to GEM single primary melanomas, only an indicator variable was included for participants who developed MPM during the course of the study. All statistical tests were two-sided with an alpha level of 0.05 and were performed using SAS v9.3 (SAS Institute, Cary, NC).

Results

Univariate analyses of gender, age, ulceration, Breslow thickness, tumor infiltrating lymphocytes, site of primary melanoma, histological subtype, and phenotypic index showed statistically significant differences between cases with high and low nevus counts (Table 1). Age at melanoma diagnosis and gender remained significantly associated with nevus counts in multivariable regression models after adjustment; cases who were older at diagnosis were less likely to exhibit high nevus counts compared to younger cases (OR=0.48; 95% CI: 0.41, 0.57) and men were more likely to show high nevus counts compared to women (OR=1.76; 95%CI: 1.46, 2.11). We also observed a marginally statistically significant association between lower nevus counts and lentigo maligna melanomas (LMM) within histological subtype (OR=0.72; 95%CI: 0.54, 0.97) (Table 2). The lack of association of tumor characteristics with number of nevi in the multivariable model is explained by their confounding with age and gender.

When quartiles of nevi were examined, we observed a borderline significant trend of increasing risk for melanoma-specific death with increasing nevus counts (P_{trend}=0.06). A positive association between higher nevus counts and risk of melanoma death was also noted when the median cutoff was employed (HR=1.31; 95%CI: 0.98, 1.76), but that association was not statistically significant after adjusting for relevant covariates (Table 3).

Our recapitulation of analyses conducted by Ribero *et al*. (2015) showed no significant difference in survival between those at/above the study center-specific 70th percentile for nevus counts and those below the study center-specific 70th percentile via Kaplan-Meier estimates (Figure 1). However, the adjusted Cox model demonstrated a strong positive association between nevus count and melanoma-specific survival in the full GEM study population (≥70th percentile nevi vs. <70th percentile nevi—HR=1.59; 95%CI: 1.15, 2.18), as well as among single primary melanoma cases alone (HR=1.55; 95%CI: 1.03, 2.33) (results not shown). We conducted one further analysis utilizing the exact nevus coding of Ribero *et al*. (≥50 nevi vs. <50 nevi) and observed no statistically significant association between nevus counts and risk of melanoma-specific death (results not shown).

Discussion

Overall our results indicate that nevus count is not independently associated with prognostic tumor features, nor is it significantly associated with phenotypic index after adjustment for potential confounders. Higher nevus counts were independently associated with younger age at diagnosis and male gender among GEM study participants. The former observation is not unexpected, since nevi tend to involute and disappear with age in Caucasian populations[2, 15, 16] and similar findings among cutaneous melanoma patients have been reported[17]. Our results do not support a meaningful relationship between number of nevi and pigmentary phenotype, although previous studies have shown higher nevus counts among individuals with sun-sensitive phenotypes epitomized by lighter skin, hair and eyes, and a propensity for sun burning[18, 19]. Others, however, have reported higher nevus counts among individuals with darker phenotypic characteristics[20, 21]. The inconsistency in results may be due to a combination of factors, including heterogeneity of study populations, varying evaluation and classification of skin type, and measurement of nevi.

Our observation that LMM cases exhibited significantly fewer nevi compared to superficially spreading melanoma (SSM) cases is consistent with results reported by others[5, 22] and may be due to diminished proliferative activity of melanocytes in patients with LMM compared to those with SSM[23]. Moreover, LMM arises on chronically sun-damaged skin by definition[24] which supports the hypothesized pathway characterized by few nevi and chronic sun exposure to the site of lesion presentation[5].

A direct comparison of our multivariable model results for prognostic tumor factors to Ribero *et al.* is not possible since Ribero *et al.* did not report adjusted associations between nevus counts and tumor factors. However, comparing unadjusted estimates presented in Table 1 to those reported by Ribero *et al.*, we noted similar observations with respect to Breslow thickness (*i.e.* thinner lesions associated with higher nevus counts), ulceration (*i.e.* an inverse association between ulceration and number of nevi), and mitoses (*i.e.* an inverse association between mitoses and number of nevi). Although Ribero *et al.* reported a borderline statistically significant result for mitoses, our results, as well as others'[25], suggest no association.

Results of our survival analysis are in contrast to those reported by Ribero *et al.* (2015) who found improved melanoma-specific survival among patients with high nevus counts (>50 nevi) vs. those with low nevus counts (≤50 nevi) (HR=0.43; 95%CI: 0.21, 0.89). While it is possible that high nevus counts may contribute to biopsies and overdiagnosis of more indolent melanomas, which is consistent with a trend of steadily increasing melanoma incidence without concomitant increases in mortality[26], our estimates indicating poorer survival among cases with greater numbers of nevi would suggest otherwise. Although we do not report a statistically significant difference in survival according to nevus count, we noted consistently greater risk of melanoma death among those with higher nevus counts compared to those with lower nevus counts as evidenced by a borderline significant trend by nevus count quartile. Several factors may have contributed to differences between our results and those of others: importantly, data on sentinel lymph node status were not available for GEM study participants and we were unable to adjust survival analyses for this factor; our study included data from cases that arose in a more heterogeneous population; case sampling was different between the two studies; and distributions of nevus counts differed significantly between the study populations. Additionally, the present study used a self-reported indirect measure of total body nevus counts by considering only moles on the backs of cases, whereas in Ribero *et al.* (2015) study staff assessed total body nevus counts, although methods were slightly different at each study site.

Previous studies have demonstrated the elevated heritability of nevus counts, with as much as 50% of the genetic variance in nevus count attributable to a quantitative trait locus near the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene region[27–29], an established melanoma risk locus. It is possible that variation in the frequency and distribution of polymorphisms at *CDKN2A* between study populations could account for differences in nevus distributions, and thus differences in effect estimates. Moreover, the *CDKN2A* locus is not the only region purported to influence variation in nevus counts; a recent genome wide association study (GWAS) identified germline variation in the interferon regulatory factor 4 (*IRF4*) gene, involved in controlling pigmentation and also a putative melanoma risk locus[30], as being strongly associated with high nevus counts among adolescent twins[31]. Additionally, variants in the methylthioadenosine phosphorylase (*MTAP*) and phospholipase A2, group VI (*PLA2G6*) genes were also strongly associated with nevus count in a GWAS of 297,108 tag-SNPs among 1,524 twins[32]. Variation between study populations at these important pigmentation loci could also contribute to differences in effect estimates.

In summary, our results suggest that nevus count is associated with poorer melanoma-specific survival while demonstrating little or no association with pigmentary phenotypic characteristics and prognostic tumor features.

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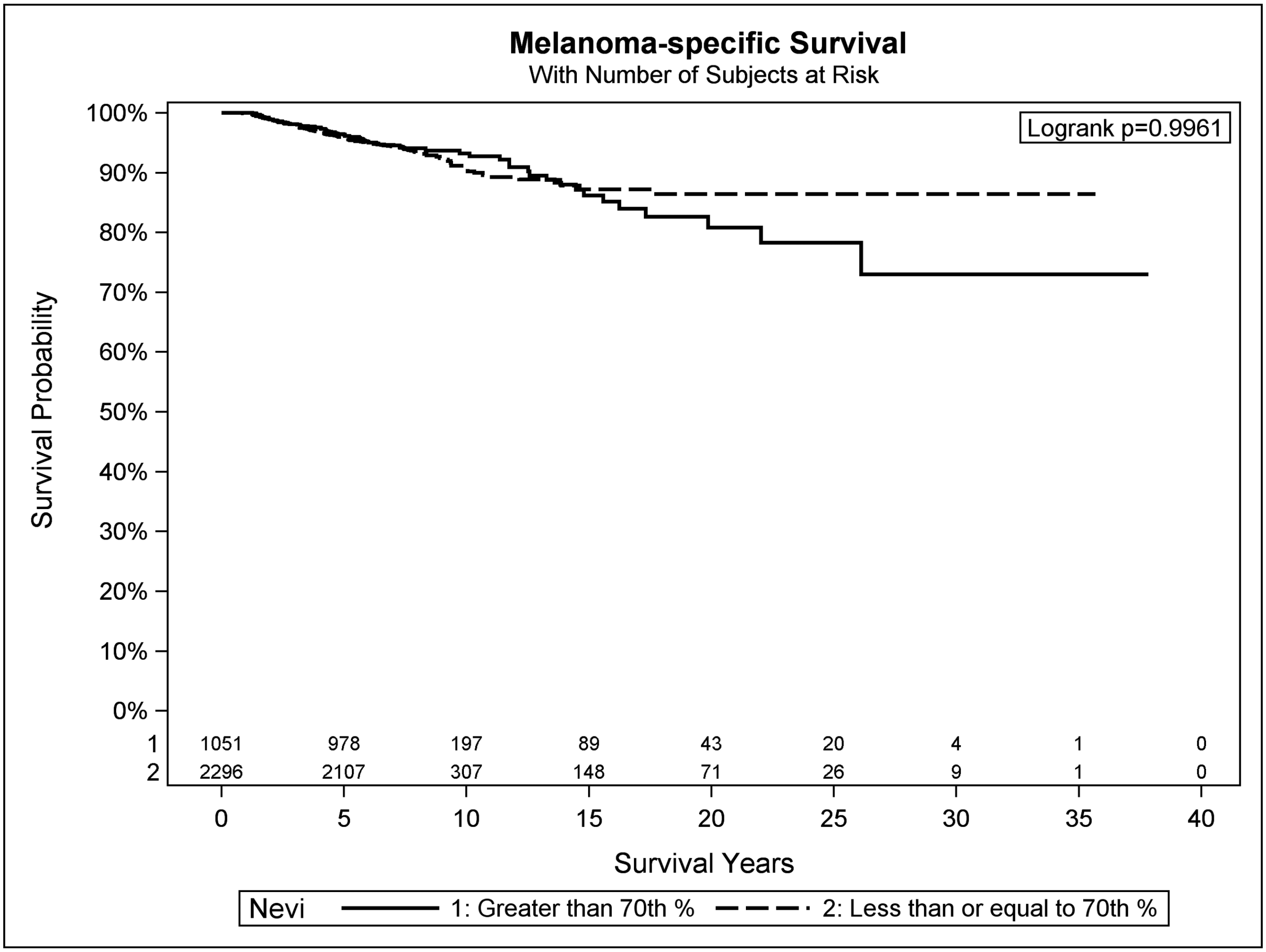
Melanoma-specific Survival
With Number of Subjects at Risk
Logrank p=0.9961
Survival Probability
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1 1051 978 197 89 43 20 4 1 0
2 2296 2107 307 148 71 26 9 1 0
0
5
10
15
20
25
30
35
40
Survival Years
Nevi
1: Greater than 70th %
2: Less than or equal to 70th %

Figure 1.

Table 1

Host and histopathological tumor characteristics among GEM study participants with high and low nevus counts

		Low nevus count*	**High nevus count***	**Total**	**P-value**
Gender	Female	835(49%)	632 (39%)	1,467	0.0001[1]
	Male	871 (51%)	1,009 (61%)	1,880	
Age (years)	Median (IQR)	62 (49–72)	54 (43–67)		<0.0001[2]
Age categorical (years)†	≤ Median	736 (43%)	969 (59%)	1,705	<0.0001[1]
	> Median	970 (57%)	672 (41%)	1,642	
Multiple primary melanomas	Single primary only	1,608 (94%)	1,519 (93%)	3,127	0.05[1]
	Multiple primaries	98 (6%)	122 (7%)	220	
Ulceration	Absent	1,220 (89%)	1,187 (92%)	2,407	0.007[1]
	Present	148 (11%)	100 (8%)	248	
Breslow thickness (mm)	Mean (SE)	1.39 (0.05)	1.21 (0.04)		0.02[3]
TILs	Absent	311 (23%)	251 (20%)	562	0.002[4]
	Nonbrisk	880 (64%)	817 (64%)	1,697	
	Brisk	175 (13%)	215 (17%)	390	
Site of primary	Head/Neck	303 (18%)	242 (15%)	545	<0.0001[1]
	Trunk	664 (39%)	821 (50%)	1,485	
	Limbs	739 (43%)	578 (35%)	1,317	
Mitoses	Absent	747 (54%)	737 (57%)	1,484	0.16[1]
	Present	626 (46%)	554 (43%)	1,180	
Regression	Absent	983 (70%)	926 (69%)	1,909	0.54[1]
	Present	424 (30%)	420 (31%)	844	
Histology	in situ	0	0	0	<0.0001[1]
	SSM	1,058 (62%)	1,133 (69%)	2,191	

		Low nevus count*	High nevus count*	Total	P-value
	NM	168 (10%)	148 (9%)	316	
	LMM	225 (13%)	131 (8%)	356	
	ALM	10 (<1%)	3 (<1%)	13	
	Other	39 (2%)	26 (1%)	65	
	NOS	206 (12%)	200 (12%)	406	
Phenotypic Index	Very low/Low	440 (27%)	437 (28%)	877	
	Medium	630 (38%)	660 (42%)	1,290	0.04[4]
	Very high/High	585 (35%)	489 (31%)	1,074	

[1] P-value calculated using Pearson's χ^2 test

[2] P-value calculated with Wilcoxon-Mann-Whitney test

[3] P-value calculated using t-test on natural log transformed Breslow depth

[4] P-value calculated using Mantel-Haenszel χ^2 test

[*] High and low nevus counts are defined as > or ≤ the median value of moles on the back respectively based on study center-specific median values.

[†] Age at diagnosis is defined as > or ≤ the median value of based on study center-specific median values.

Table 2

Associations between nevus count (high vs. low based on study center-specific median values) and host/tumor factors among GEM study participants utilizing multivariable logistic regression models

Factor	OR (95% CI)*	P-value
Age (> Median vs. ≤ Median)†	0.48 (0.41, 0.57)	<0.0001
Breslow depth (continuous)	1.00 (0.95, 1.05)	0.94
Gender (male vs. female)	1.76 (1.46, 2.11)	<0.0001
Site of primary		
Head/Neck	1.00	
Trunk	1.30 (1.00, 1.69)	0.05
Limbs	0.99 (0.76, 1.29)	0.93
Histology		
SSM	1.00	
NM	1.16 (0.85, 1.59)	0.34
LMM	0.72 (0.54, 0.97)	0.03
ALM	0.80 (0.19, 3.36)	0.76
Other	0.69 (0.38, 1.24)	0.22
NOS	0.78 (0.55, 1.09)	0.15
Ulceration (present vs. absent)	0.78 (0.57, 1.07)	0.12
Mitoses (present vs. absent)	0.90 (0.73, 1.10)	0.30
Phenotypic Index		
Very high/High	1.00	
Medium	1.20 (0.99, 1.45)	0.06
Low/Very low	1.13 (0.92, 1.39)	0.25

*Models adjusted for age, Breslow thickness, gender, ulceration, site of primary, mitoses, study center, histological subtype, multiple primary diagnoses, and phenotypic index

†Age at diagnosis is defined as > or ≤ the median value based on study center-specific median values.

Table 3

Cox proportional hazards analyses of melanoma-specific survival (n=3,347; melanoma-specific deaths=238) among invasive case participants of the GEM study

	Reduced Model			Fully Adjusted Model		
	HR (95%CI)	P-value	P_{trend}	HR (95%CI)	P-value	P_{trend}
Nevus count (continuous)[*]	0.97 (0.87, 1.07)	0.52		1.08 (0.96, 1.21)	0.22	
Nevus count[*] (Q2 vs. Q1)	0.96 (0.66, 1.39)	0.82	0.94	1.08 (0.71, 1.65)	0.73	0.06
Nevus count[*] (Q3 vs. Q1)	0.97 (0.67, 1.41)	0.50		1.30 (0.86, 1.95)	0.37	
Nevus count[*] (Q4 vs. Q1)	1.01 (0.69, 1.49)	0.95		1.47 (0.94, 1.29)	0.09	
Nevus count (> Median vs. ≤ Median)[*]	1.01 (0.78, 1.32)	0.93		1.31 (0.98, 1.76)	0.07	

[*] Models based on log-transformed nevus counts; reduced model adjusted for study design variables: age, gender, study center, multiple primary melanoma diagnoses and a time-dependent covariate accounting for differences in follow-up time for participants diagnosed with a second primary melanoma during the course of study recruitment; fully adjusted model additionally adjusted for Breslow thickness, ulceration, site of primary, mitoses, histological subtype, and phenotypic index. Quartiles and medians are based on study center-specific values.