



## Nevus Count Associations with Thinner Nodular or Superficial Spreading Melanoma

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Cutaneous melanoma (CM) accounts for 90% of deaths from skin cancer and models suggest continuous increases in melanoma incidence through 2031 (1). Breslow thickness is an important adverse staging and prognostic factor; however, the nodular (NM) histologic subtype was independently associated with higher mortality risk among thin ( $\leq 1$  mm) melanomas (2). Further distinct characteristics associated with NM compared to SSM even among thinner tumors include a higher mitotic rate (3), and the difficulty to detect thinner melanoma by skin self-examination (4).

Total-body melanocytic nevus counts and dysplastic nevi are important established phenotypic markers of melanoma risk, representing surrogate markers of underlying genetic factors and environmental sun exposure. The recognition of nevus count associations with melanoma subtypes, and particularly with NM, may contribute to the understanding of the biology as well as the earlier detection of this aggressive melanoma subtype. This multicenter study aimed to examine the association of concomitant melanocytic nevi counts in patients with melanoma of the nodular type compared to the superficial spreading melanoma (SSM) histological type, and how this may differ by Breslow thickness.

### METHODS

Pooled data were collected from 3 cross-sectional surveys among 4 dermatology-based melanoma referral centers at Stanford University and University of Michigan in the US, at the University of Athens and collaborating centers in Greece, and at the University of Szeged in Hungary. Consecutive, newly-diagnosed patients aged  $\geq 18$  years, with primary invasive melanoma of the NM and SSM subtype, were included.

The same structured questionnaire was used, based on the study by Swetter et al. (5). Accepted criteria for histopathologic classification of SSM vs NM subtype were employed (6). The number of common melanocytic nevi  $\geq 2$  mm in diameter and clinically atypical nevi (CAN) on the whole body, was recorded by clinical examination by a dermatologist. The number of common nevi was recorded as either of 3 categories: zero or  $< 20$ , 20–50 nevi or  $> 50$  nevi. A clinically atypical nevus was defined as a nevus  $\geq 5$  mm in diameter, with variable pigmentation and an irregular or diffuse edge. Institutional review board/ethics approval and informed patient consent was obtained at all sites.

For the statistical analysis, for thinner melanoma, the use of a  $\leq 2$  mm cut-off was used since only 4 NMs in the entire data set were diagnosed with thickness  $\leq 1$  mm, which precluded any reliable

analysis. To investigate the association of thinner melanoma with every nevus variable (number of common nevi, presence of CAN, number of CAN), multiple logistic regression analysis was carried out including statistically significant variables from the univariate analysis. Each nevus variable was investigated in a separate logistic model. Stratified analyses for nevi were conducted by stratifying the data into patients aged  $< 50$  and  $\geq 50$  years, since nevi involute with age. All *p*-values were two-sided and the significance level was  $< 0.05$ . Analyses were carried out using STATA, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

### RESULTS

Of 713 patients, 158 had NM and 555 had SSM. Patient and melanoma characteristics by NM or SSM histological type are presented in Table S1<sup>1</sup>. NM were significantly thicker compared to SSM (median Breslow: 2.94 mm vs 0.85 mm respectively,  $p < 0.001$ ). Overall, there was no association of the NM or SSM type with common nevi counts ( $p = 0.826$ ), the presence of clinically atypical nevi ( $p = 0.289$ ), or the number of atypical nevi ( $p = 0.529$ ). Among the 158 patients with NM, 50 (32%) had at least one CAN. Total nevi counts were not associated with the location of melanoma on the head/neck, trunk or extremities (data not shown).

In multivariate logistic analysis adjusted for age, sex, thickness and country, there was no association of NM compared to SSM (reference) with nevi counts (odds ratio [OR] (confidence interval) [CI] 0.93 (0.55–1.58)) or with the number of atypical nevi (OR (95% CI) 0.81 (0.46–1.45)). Similarly, there were no nevus associations in the multivariate analysis for thicker NM ( $> 2$  mm) compared to thinner NM ( $\leq 2$  mm), or for thicker SSM compared to thinner SSM (data not shown).

Lower nevus counts were more frequent in older patients. Patients with NM  $\geq 50$  years old compared to younger patients more frequently had lower ( $< 20$ ) nevus counts ( $p = 0.003$ ), and less frequently had any CAN present ( $p < 0.001$ ). Similar findings were found for SSM (data not shown). Age-stratified multivariate logistic regression analysis showed that for patients  $\geq 50$  years old, the presence of fewer nevi (0–20) com-

<sup>1</sup><https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3142>

pared to 20–50 nevi was significantly more likely to be associated with thicker compared to thinner NM (OR (95% CI 3.37 (1.07–10.60)). On the other hand, this association of lower number of nevi was not present for thicker compared to thinner SSM in patients of the same age category ( $\geq 50$  years old) (OR (95% CI 0.59 (0.29–1.17)) (Table SII<sup>1</sup>).

## DISCUSSION

In this study, we evaluated the association of the NM or SSM subtype with nevus counts, as well as the likelihood of thicker versus thinner melanoma with nevus counts by melanoma subtype. Total nevus counts or the number of CAN were not associated overall with NM compared to SSM (reference) after adjustment for Breslow thickness. Lower nevus counts were associated with thicker compared to thinner NM in individuals older than 50 years old, whereas this association was not shown for SSM.

A meta-analysis of 24 observational studies examined the association of nevus counts with histological subtype. It included 16,180 cases and reported similar nevi counts associated with melanoma of each histological subtype, without heterogeneity among RRs: 1.31 and 1.32 for NM and SSM, respectively (although NM was not directly compared to SSM) (7). Interestingly, higher nevus counts have been associated with thinner melanoma (8, 9), better survival rates independently of Breslow thickness (8) and, more recently, with melanoma associated histologically with a nevus (10). A previous age-stratified study reported that for individuals younger than 60 years, the presence of more than 50 total nevi was associated with thinner melanoma, although the histological subtype was not investigated (9). The detection of thicker melanomas in patients with lower nevus counts may be a result of lower skin cancer awareness because of lower nevus counts (9), or due to a more aggressive behavior of melanoma (8, 9). Our study showed that thicker melanomas were associated with lower nevus counts in older patients only for the NM and not for the SSM subtype, supporting the hypothesis of a distinct more aggressive biological pathway for NM. Nevus counts decrease with age via yet unknown mechanisms of involution (11), and a GWAS study for nevus density reported that the contribution of genetic factors in nevus density is stronger for older compared to younger individuals (12).

Limitations of our study include the lack of central histopathology review and the inclusion of only 158 NM, of which only 49 NM were diagnosed in patients younger than 50 years old, so these findings should be replicated with greater numbers of NM patients. However, there was a statistically significant association detected despite the low number included. A strength of the study is the inclusion of rigorous data by 3 international melanoma referral centers.

In summary, our findings showed that when analysing nodular versus superficial spreading melanoma, total nevus counts were not significantly associated with the histological subtype, and that thicker NM was associated with lower nevus counts in middle-aged and older individuals. This finding may raise skin cancer awareness for individuals aged 50 and above with a low risk nevus phenotype. Furthermore, our results suggest that age-specific factors may act in concert with nevus pathways to modulate aggressive melanoma features warranting further investigation.

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