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Impact of naevus association on survival for nodular and superficial spreading melanomas.

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Running head: Impact of naevus association on survival in melanoma.

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There is much speculation surrounding the role of common and dysplastic naevi as an intermediary precursor in the pathogenesis of cutaneous melanoma.^{1,2} It is well recognised that the majority of invasive cutaneous melanomas arise de novo and a smaller proportion are associated with a pre-existing naevus, however the biologic and prognostic significance of naevus-associated status remains unclear.

The studies that have compared survival outcomes between naevus-associated and de novo melanomas have produced conflicting results.³⁻⁶ Superficial spreading melanoma (SSM) and nodular melanoma together account for approximately 70% of all invasive melanomas and represent the most common radial and vertical growth phase melanoma subtypes. Therefore, the aim of this study

was to determine the prognosis of naevus-associated and de novo melanoma among these two melanoma subtypes.

Institutional ethics approval was obtained to conduct a retrospective cohort study of histologically confirmed NM and SSM, either arising de novo or associated with a naevus. The study was conducted at The Victorian Melanoma Service (VMS) from 2002 to 2015 with data linkage to the Victorian Cancer Registry for survival outcome. Independent expert VMS dermatopathologists provided histopathological review of each melanoma. The presence or absence of an associated naevus was assessed microscopically on hematoxylin and eosin stained sections and recorded. Our study was restricted to include SSM and NM.

The clinical features obtained included age, sex, date of diagnosis and tumour anatomic site. The pathological characteristics that were extracted from the database included Breslow thickness (millimetre), naevus-association status, presence of ulceration and mitosis (mm^2). Melanoma-specific-survival was analysed by multivariable Cox proportional hazards regression models. Statistical significance was determined as $p \leq 0.05$. All statistical analyses were performed using statistical software Stata version 14 (StataCorp LP, College Station, Texas, USA).

In this cohort of 1831 primary cutaneous melanomas, 54% were male and 46% female. The median Breslow thickness was 0.94mm. Table 1 describes the baseline characteristics of the patient cohort. In this study, 639 (34.9%) melanomas were histologically associated with a naevus and 1192 (65.1%) arose de novo. Of the total primary cutaneous melanomas, 325 (17.7%) were NM and 1506 (82.3%) were SSM. The proportion of NM and SSM that were histologically associated with a naevus were 35/325 (10.8%) and 604/1506 (40.1%), respectively.

During the follow up period, 263 (14.4%) participants had died. Of these, 166 (63.1%) died from melanoma, 81 (30.8%) died from other causes and 16 (6.1%) had an unknown cause of death.

In the univariate analysis, naevus-associated melanomas demonstrated a reduced risk of death from melanoma compared to de novo melanomas (Hazard Ratio [HR] 0.46, 95% confidence interval [CI] 0.32-0.67, $p < 0.001$). In univariate analysis, patients aged ≥ 50 years (HR 2.33, 95% CI 1.62-3.35, $p < 0.001$), males (HR 2.20, 95% CI 1.58-3.05, $p < 0.001$), Breslow thickness (mm) (HR 1.31, per every 1mm increase in thickness, 95% CI 1.26-1.36, $p < 0.001$), NM subtype (HR 2.84, 95% CI 2.06-3.92, $p < 0.001$), head and neck location (HR compared to upper extremities 3.13, 95% CI 1.90-5.14, $p < 0.001$), ulceration (HR 4.87, 95% CI 3.57-6.64, $p < 0.001$) and mitotic count 5-9/ mm^2 (HR compared to $< 5/\text{mm}^2$ 2.72, 95% CI 1.73-4.30, $p < 0.001$) were associated with poorer melanoma-specific

survival. When adjusted for Breslow thickness, anatomic location, subtype, age, sex, ulceration and mitoses, the melanoma-specific survival benefit of naevus-associated melanoma was no longer statistically significant (adjusted HR 0.65, 95% CI 0.39-1.05, $p=0.08$).

The prognostic implications of naevus-associated melanomas remains unclear. In our study, the poorer prognosis of patients with de novo melanoma was explained to a considerable degree by confounding variables. This is consistent with two smaller retrospective studies by Lin *et al* and Kaddu *et al* which demonstrated no difference in survival outcome between naevus-associated and de novo melanomas when adjusted for confounders.^{3,4}

In contrast, other studies have shown that histological naevus association confers a survival benefit over melanomas that arise de novo.⁵ However in Cymerman *et al.*'s large prospective study, de novo melanoma classification remained an independent predictor of poorer survival compared to naevus-associated melanomas in only one of two cohorts.⁵ Sheen *et al.*'s retrospective study demonstrated improved recurrence-free survival amongst naevus-associated compared to de novo melanomas, however the study's predominant melanoma subtype was ALM (70.9%), limiting generalisability of the results.⁶

Strengths of our study include the large size of the cohort and independent pathology review by an expert dermatopathologist. A limitation is that we did not include the less common melanoma subtypes, such as ALM and lentigo maligna melanoma. This represents an area for future research, alongside investigating the mutational characteristics of de novo and naevus-associated melanomas. Our study demonstrated that de novo melanomas confer a worse prognosis than naevus-associated melanomas. However, with adjustments, much of the observed effect on prognosis was accounted for by other clinicopathological characteristics. Therefore, in our study, naevus-association status was not observed to be an independent predictor of survival.

References

1. Rhodes AR, Sober AJ, Day CL *et al.* The malignant potential of small congenital nevocellular nevi: an estimate of association based on histologic study of 234 primary cutaneous melanomas. *J Am Acad Dermatol.* 1982;6:230-241.
2. Hastrup N, Osterling A, Drzewiecki KT, Hou-Jensen K. The presence of dysplastic nevus remnants in malignant melanomas: a population based study of 551 malignant melanomas. *Am J Dermatopathol.* 1991;13:378-85.
3. Lin WM, Luo S, Muzikansky A *et al.* Outcome of patients with de novo versus nevus-associated melanoma. *J Am Acad Dermatol.* 2017;72(1):54058.
4. Kaddu S, Smolle J, Zenahilk P, Hofmann-Wellenhof R, Kerl H. Melanoma with benign melanocytic naevus components: reappraisal of clinicopathological features and prognosis. *Melanoma Res.* 2002;12(3):271-278.
5. Cymerman RM, Shao Y, Wang K *et al.* De Novo vs. Nevus-Associated Melanomas: Differences in Associations with Prognostic Indicators and Survival [published online 27 May 2016]. *J Natl Cancer Inst.* doi: 10.1093/jnci/djw121.
6. Sheen YS, Liao YH, Lin MH *et al.* Clinicopathological features and prognosis of patients with de novo versus nevus-associated melanoma in Taiwan [published online 4 May, 2017]. *PLoS One.* doi: 10.1371/journal.pone.0177126.

Tables

Table 1 Patient demographic and tumour characteristics of naevus associated and de novo melanomas.

Clinicopathological characteristics	Naevus associated (n= 639, %=34.9)	De Novo (n = 1192, % =65.1)
Age (years)	51	59
Median, Interquartile range	39.5 – 63.5	47 – 70
Sex		
Male	347 (54.3%)	625 (52.4%)
Female	292 (45.7%)	567 (47.6%)
Primary tumour thickness (mm)		
0-1	430 (67.3%)	510 (42.8%)
1-4	190 (29.7%)	540 (45.3%)

>4	19 (3.0%)	142 (11.9%)
Anatomical location		
Head and neck	52 (8.1%)	219 (18.4%)
Upper extremity	122 (19.1%)	261 (21.9%)
Trunk	319 (49.9%)	338 (28.3%)
Lower extremity	146 (22.9%)	375 (31.4%)
Primary tumour histologic subtype		
Nodular melanoma	35 (5.5%)	290 (24.3%)
Superficial spreading melanoma	604 (94.5%)	902 (75.7%)
Survival status		
Alive	575 (90.0%)	993 (83.3%)
Deceased		
- Melanoma	37 (5.8%)	129 (10.8%)
- Other malignancy	8 (1.2%)	20 (1.7%)
- Other cause	14 (2.2%)	39 (3.3%)
- Unknown	5 (0.8%)	11 (0.9%)

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