Nodular melanoma is less likely than superficial spreading melanoma to be histologically associated with a naevus

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The known Primary cutaneous melanomas may arise de novo or in association with a pre-existing naevus. Understanding the initial presentation of superficial spreading and nodular melanoma subtypes is vital for facilitating their early detection.

The new Most melanomas develop without a pre-existing naevus, particularly nodular melanomas, melanomas in patients over 70 years of age, and amelanotic/hypomelanotic melanomas.

The implications It is important for public health campaigns to emphasise the importance of detecting suspicious de novo lesions, as well as changing lesions.

Abstract

Objectives: To determine the frequency of naevus-associated melanoma among superficial spreading and nodular subtypes; and to investigate associations between naevus-associated melanoma and other clinico-pathological characteristics.

Design, setting and participants: Cross-sectional study of all patients with nodular and superficial spreading melanomas diagnosed between 1994 and 2015 at the Victorian Melanoma Service, Melbourne.

Methods and main outcome measures: Clinical and pathological characteristics of naevus-associated and de novo melanomas were assessed in univariable and multivariable logistic regression analyses.

Results: Of 3678 primary melanomas, 1360 (37.0%) were histologically associated with a naevus and 2318 (63.0%) were de novo melanomas; 71 of 621 nodular (11.4%) and 1289 of 3057 superficial spreading melanomas (42.2%) were histologically associated with a naevus. In multivariable analyses, the odds of being associated with a naevus were higher for melanomas located on the trunk (v head and neck: adjusted odds ratio [OR], 2.27; 95% CI, 1.73–2.96; $P < 0.001$), while the odds were lower for thicker tumours (adjusted OR, 0.75 per millimetre increase in Breslow thickness; 95% CI, 0.69–0.81; $P < 0.001$), amelanotic/hypomelanotic melanomas (adjusted OR, 0.68; 95% CI, 0.48–0.97; $P = 0.035$), and older age (patients 70 years or older v patients under 30 at diagnosis: adjusted OR, 0.28; 95% CI, 0.20–0.40; $P < 0.001$). After adjusting for confounders, the odds of an associated naevus was three times as high for superficial spreading melanomas as for nodular melanomas (adjusted OR, 3.05; 95% CI, 2.24–4.17; $P < 0.001$).

Conclusion: Melanomas are most likely to arise in the absence of a pre-existing naevus, particularly nodular melanomas. Public health campaigns should therefore emphasise the detection of suspicious de novo lesions, as well as of changing lesions.

Although only 10–15% of all invasive melanomas are nodular melanomas, this subtype is the predominant contributor to melanoma-related deaths.[1] Nodular melanomas often elude early detection and account for a disproportionately high number of thick primary melanomas, partly because of their atypical clinical presentation (Box 1).[1-3] Superficial spreading melanoma is the most common melanoma subtype, accounting for 55–65% of all melanomas (Box 2).[1]

Nodular melanomas often do not conform to the classical ABCDE criteria used to alert doctors and patients to the possibility of superficial spreading melanoma.[1,3,4] In contrast to superficial spreading melanoma, characterised by a radial growth phase followed by invasion into the dermis, nodular melanoma is characterised by early vertical growth. Nodular melanoma is also associated with more rapid vertical growth,[5] so that improving diagnostic accuracy of nodular melanoma is crucial.[1] Understanding the initial presentation of both these melanoma subtypes is vital for their early detection.

Primary cutaneous melanomas may arise de novo or in association with a pre-existing naevus. Based on histological assessment, naevus-associated melanomas are estimated to represent 19–58% of all cutaneous melanomas.[6-17] A clinical history of a longstanding precursor pigmented lesion is reported by patients for 40–45% of all biopsy-proven melanomas.[11] However, a reported precursor pigmented lesion may be a slowly progressing early melanoma or a benign naevus, so that this information is not always reliable.[16] Indeed, it has been reported that about one-third of patients without histological evidence of a naevus erroneously recall a pre-existing naevus.[18]

A correlation between various clinical and pathological characteristics and naevus-associated and de novo melanoma has been reported in several studies.[6,9,12,14-17,19] Earlier studies have reported that nodular melanomas typically arise de novo and are only infrequently associated with a contiguous naevus.[6,12,15] The aim of our study was to determine the frequency of naevus-associated melanoma among superficial spreading and nodular melanoma subtypes, which together account for about 70% of invasive melanomas and are the most common radial and vertical growth phase melanoma subtypes. Accurately understanding how often superficial spreading and nodular melanoma subtypes present as new or changing lesions may inform advice on how to detect these melanoma subtypes at their earliest presentation. Our secondary aim was to investigate the association between naevus-associated melanoma and other clinical and pathological characteristics, allowing us to determine whether there are any confounders of the potential relationship between naevus association and superficial spreading and nodular melanoma subtypes.

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1 Nodular melanoma with five dermal and subcutaneous satellite deposits. Breslow thickness, 6.4 mm, Clark level IV (invasion into the reticular dermis), ulcerated with seven mitoses; arose de novo on the left posterior lower leg of a 66-year-old man

2 Superficial spreading melanoma. Breslow thickness, 1 mm, Clark level IV, non-ulcerated with one mitosis; arose within a pre-existing naevus on the left lower back of a 39-year-old man

3 Clinical and pathological characteristics of naevus-associated and de novo melanoma

Characteristic	All	Naevus-associated	De novo	P
All melanomas	3678	1360 (37.0%)	2318 (63.0%)	
Histological subtype				< 0.001
Superficial spreading	3057	1289 (42.2%)	1768 (57.8%)	
Nodular	621	71 (11%)	550 (88.6%)	
Amelanosis/hypomelanosis				< 0.001
Yes	283	45 (16%)	238 (84.1%)	
No	3395	1315 (38.7%)	2080 (61.3%)	
Breslow thickness				< 0.001
≤ 1.0 mm	1997	964 (48.3%)	1033 (51.7%)	
1.01−4.0 mm	1357	357 (26.3%)	1000 (73.7%)	
> 4.0 mm	279	36 (13%)	243 (87.1%)	
Sex				0.29
Men	1943	735 (37.8%)	1208 (62.2%)	
Women	1735	625 (36.0%)	1110 (64.0%)	
Anatomic location				< 0.001
Head and neck	485	111 (22.9%)	374 (77.1%)	
Upper extremities	799	265 (33.2%)	534 (66.8%)	
Lower extremities	968	283 (29.2%)	685 (70.8%)	
Trunk	1395	688 (49.3%)	707 (50.7%)	
Age group				< 0.001
< 30 years	253	137 (54.2%)	116 (45.8%)	
30−49 years	1213	545 (44.9%)	668 (55.1%)	
50−69 years	1488	516 (34.7%)	972 (65.3%)	
≥ 70 years	709	158 (22.3%)	551 (77.7%)	
Fitzpatrick skin type*				0.46
I	1020	362 (35.5%)	658 (64.5%)	
II	1549	580 (37.4%)	969 (62.6%)	
III/IV	1008	383 (38.0%)	625 (62.0%)	
Personal history of melanoma				0.04
Yes	518	210 (40.5%)	308 (59.5%)	
No	3013	1077 (35.7%)	1936 (64.3%)	
Family history of melanoma				0.17
Yes	827	323 (39.1%)	504 (60.9%)	
No	2843	1035 (36.4%)	1808 (63.6%)	

* I = always burns, never tans; II = burns easily, tans poorly; III = burns moderately, then develops a light tan; IV = burns minimally to rarely, then develops a moderate tan; V = rarely burns, tans darkly easily; VI = never burns, always tans darkly. ◆

Methods

The Victorian Melanoma Service (VMS) is a statewide, multidisciplinary tertiary referral service based at the Alfred Hospital in Melbourne; it reviews about one-quarter of new melanoma cases in Victoria. The VMS database includes data on all patients treated at the service. Data for all patients with nodular melanomas and superficial spreading melanomas diagnosed at the VMS during 1994−2015 were included in this study.

An expert VMS dermatopathologist provided histopathological review of each melanoma. Tumour histological subtype was classified according to the World Health Organization classification system as superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral lentiginous melanoma, or desmoplastic melanoma. Our study assessed only the superficial spreading and nodular melanoma subtypes. The histopathological review recorded the presence or absence of an associated naevus for each melanoma. Data for patients were excluded from our

study if information on the presence or absence of an associated naevus was not recorded.

The anatomic location of the primary tumour was categorised into the following groups: head and neck, trunk, and extremities. Patient-related variables were recorded by the treating doctor during the patients' initial presentation.

Clinical and pathological characteristics extracted from the database included age, sex, Fitzpatrick skin type, personal history of melanoma, family history of melanoma, anatomic location of the primary tumour, Breslow thickness, histological subtype and amelanosis/hypomelanosis as assessed by the patient and family.

4 Univariable and multivariable logistic regression analysis of the clinical and pathological characteristics of naevus-associated melanoma

Characteristic	Univariable analysis		Multivariable analysis*	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Histological subtype				
Superficial spreading	5.65 (4.37–7.31)	< 0.001	3.05 (2.24–4.17)	< 0.001
Nodular	1		1	
Amelanosis/hypomelanosis				
Yes	0.30 (0.22–0.41)	< 0.001	0.68 (0.48–0.97)	0.035
No	1		1	
Breslow thickness				
Per millimetre increase	0.62 (0.58–0.67)	< 0.001	0.75 (0.69–0.81)	< 0.001
Sex				
Men	1.09 (0.94–1.24)	0.30	1.18 (1.00–1.39)	0.049
Women	1		1	
Age group				
< 30 years	1		1	
30–49 years	0.69 (0.53–0.91)	0.008	0.63 (0.46–0.86)	0.003
50–69 years	0.45 (0.34–0.59)	< 0.001	0.42 (0.31–0.57)	< 0.001
≥ 70 years	0.24 (0.18–0.33)	< 0.001	0.28 (0.20–0.40)	< 0.001
Anatomic location				
Head and neck	1		1	
Extremities	1.51 (1.20–1.92)	0.001	1.05 (0.80–1.37)	0.71
Trunk	3.28 (2.59–4.15)	< 0.001	2.27 (1.73–2.96)	< 0.001
Fitzpatrick skin type				
I	1		1	
II	1.09 (0.92–1.28)	0.30	0.98 (0.82–1.18)	0.83
III–IV	1.11 (0.93–1.33)	0.20	0.98 (0.80–1.20)	0.85
Personal history of melanoma				
Yes	1.23 (1.02–1.48)	0.04	1.17 (0.94–1.45)	0.16
No	1		1	
Family history of melanoma				
Yes	1.12 (0.95–1.31)	0.17	1.05 (0.87–1.26)	0.61
No	1		1	

CI = confidence interval. * Adjusted for all other covariates in this table. ◆

Amelanosis/hypomelanosis describes melanomas with no or little pigment apparent to visual inspection.[20]

For statistical analysis, Breslow thickness was analysed as a continuous variable. Age was classified into ordinal groups (< 30, 30–49, 50–69, ≥ 70 years). Clinical and pathological characteristics of naevus-associated melanomas and de novo melanomas were compared in χ^2 tests, and in univariable and multivariable logistic regression analyses; $P < 0.05$ was defined as statistically significant. Effect modification was assessed by calculating the strata-specific association between the proportion of naevus-associated melanoma and superficial spreading and nodular subtypes for multiple covariates (Breslow thickness, age, sex, amelanosis/hypomelanosis). All statistical analyses were performed in Stata 13 (StataCorp).

Ethics approval

Institutional ethics approval to conduct a cross-sectional study based on data from the prospectively maintained database at the VMS was granted by the Alfred Hospital (project number, 38/16).

Results

The study included 3678 primary cutaneous melanomas, of which 3260 were invasive and 418 in situ melanomas; 3057 primary melanomas (83.1%) were classified as superficial spreading melanoma (including all in situ tumours) and 621 (16.9%) as nodular melanoma. The median age of the patients was 54 years (interquartile range, 42–66 years); 53% were men. Of the 3678 melanomas, 1360 (37.0%) were histologically associated with a naevus, and 2318 (63.0%) were de novo; 71 of 621 nodular melanomas (11%) and 1289 of 3057 superficial spreading melanomas (42.2%) were histologically associated with a naevus. The clinical and pathological characteristics of naevus-associated and de novo melanoma are summarised in Box 3.

Univariable analysis

Thicker melanomas were less likely to be associated with a naevus (odds ratio [OR], 0.62 per mm increase in Breslow thickness; 95% confidence interval [CI], 0.58–0.67; $P < 0.001$). Melanomas on the trunk (OR, 3.28; 95% CI, 2.59–4.15; $P < 0.001$) and extremities (OR 1.51; 95% CI, 1.20–1.92; $P = 0.001$) were significantly more likely to be associated with a naevus than head and neck melanomas (Box 4).

The odds of a melanoma being naevus-associated declined with age (v patients under 30: 30–49 years, OR, 0.69; 95% CI, 0.53–0.91; $P = 0.008$; 50–69 years, OR, 0.45; 95% CI, 0.34–0.59; $P < 0.001$; 70 years or older, OR, 0.24; 95% CI, 0.18–0.33; $P < 0.001$). The odds of amelanotic/hypomelanotic melanomas being associated with a naevus were 70% lower than for pigmented melanomas (OR, 0.30; 95% CI, 0.22–0.41; $P < 0.001$) (Box 4).

Multivariable analysis

After adjusting for Breslow thickness, amelanosis/hypomelanosis, anatomic location, age, sex, personal and family history of melanoma, and Fitzpatrick skin type, the odds of being associated with a naevus were 3.05 times as high for superficial spreading melanomas as for nodular melanomas (OR, 3.05; 95% CI, 2.24–4.17, $P < 0.001$) (Box 4).

In the multivariable model, the inverse relationship between melanoma being naevus-associated and patient age remained (v patients under 30: 30–49 years, OR, 0.63; 95% CI, 0.46–0.86; $P = 0.003$; 50–69 years, OR, 0.42; 95% CI, 0.31–0.57; $P < 0.001$; 70 years or older, OR, 0.28; 95% CI, 0.20–0.40; $P < 0.001$). The odds of a melanoma being associated with a naevus declined by 25% for each 1 mm increase in Breslow thickness (OR, 0.75 per mm increase; 95% CI, 0.69–0.81; $P < 0.001$) (Box 4).

The relationship between anatomic location of the primary tumour on the trunk and being associated with a naevus was confirmed in the multivariable model: the odds of being associated with a naevus was 2.27 times higher for trunk melanomas than for melanomas on the head and neck region (OR, 2.27; 95% CI, 1.73–2.96;

$P < 0.001$). Further, the odds of being associated with a naevus were 32% lower for amelanotic/hypomelanotic melanomas than for pigmented melanomas (OR, 0.68; 95% CI, 0.48–0.97; $P = 0.035$) (Box 4).

The strata-specific association between the proportion of naevus-associated melanomas and age group was the same for superficial spreading and nodular melanomas ($P = 0.88$), suggesting no effect modification by histologic subtype (Box 5, A). Further, there was no effect modification by sex ($P = 0.27$), amelanotic/hypomelanotic status ($P = 0.79$), and Breslow thickness ($P = 0.96$) (Box 5, B-D).

Discussion

In this study, we investigated the frequencies of naevus-associated melanoma among superficial spreading and nodular melanoma subtypes in a large and well characterised Australian cohort, and also examined clinical and pathological characteristics of naevus-associated melanomas. We found that 11.4% of nodular melanomas and 42.2% of superficial spreading melanomas were associated with a pre-existing naevus. After controlling for known confounders, nodular melanomas were significantly less likely than superficial spreading melanomas to be histologically associated with a naevus.

Previous studies have also found that nodular melanomas are less likely than other subtypes to be associated with a pre-existing naevus.[6,9,12,16,17,19] A recent cross-sectional study in Brazil found that 8.7% of nodular melanomas were associated with a benign naevus.[14] Similarly, a retrospective analysis in the United States identified that 35.4% of superficial spreading and 11.3% of nodular melanomas were naevus-associated,[9] while an earlier study in Victoria found that only 2.7% of nodular melanomas were histologically associated with a pre-existing naevus.[7]

We also determined that the odds of an amelanotic/hypomelanotic melanoma being associated with a naevus were 32% lower than for pigmented melanomas. Amelanotic/hypomelanotic melanomas have been associated with the nodular subtype, head and neck location, and increased Breslow thickness.[21-24] After controlling for potentially confounding covariates, we found an independent association between amelanotic/hypomelanotic melanoma and de novo development. This association has been reported by only one previous study: Thomas and colleagues[21] compared the clinico-pathological features and survival of amelanotic and pigmented melanomas, and were the first to find a relationship between amelanosis and the absence of a pre-existing naevus (OR, 0.6; 95% CI, 0.4–1.0; $P = 0.03$).[21] Their study assessed amelanosis histologically, while we assessed reports by patients and their families. Our study therefore

5 Proportion of superficial spreading and nodular melanomas associated with pre-existing naevi, according to A. age group; B. sex; C. amelanosis/hypomelanosis; and D. Breslow thickness
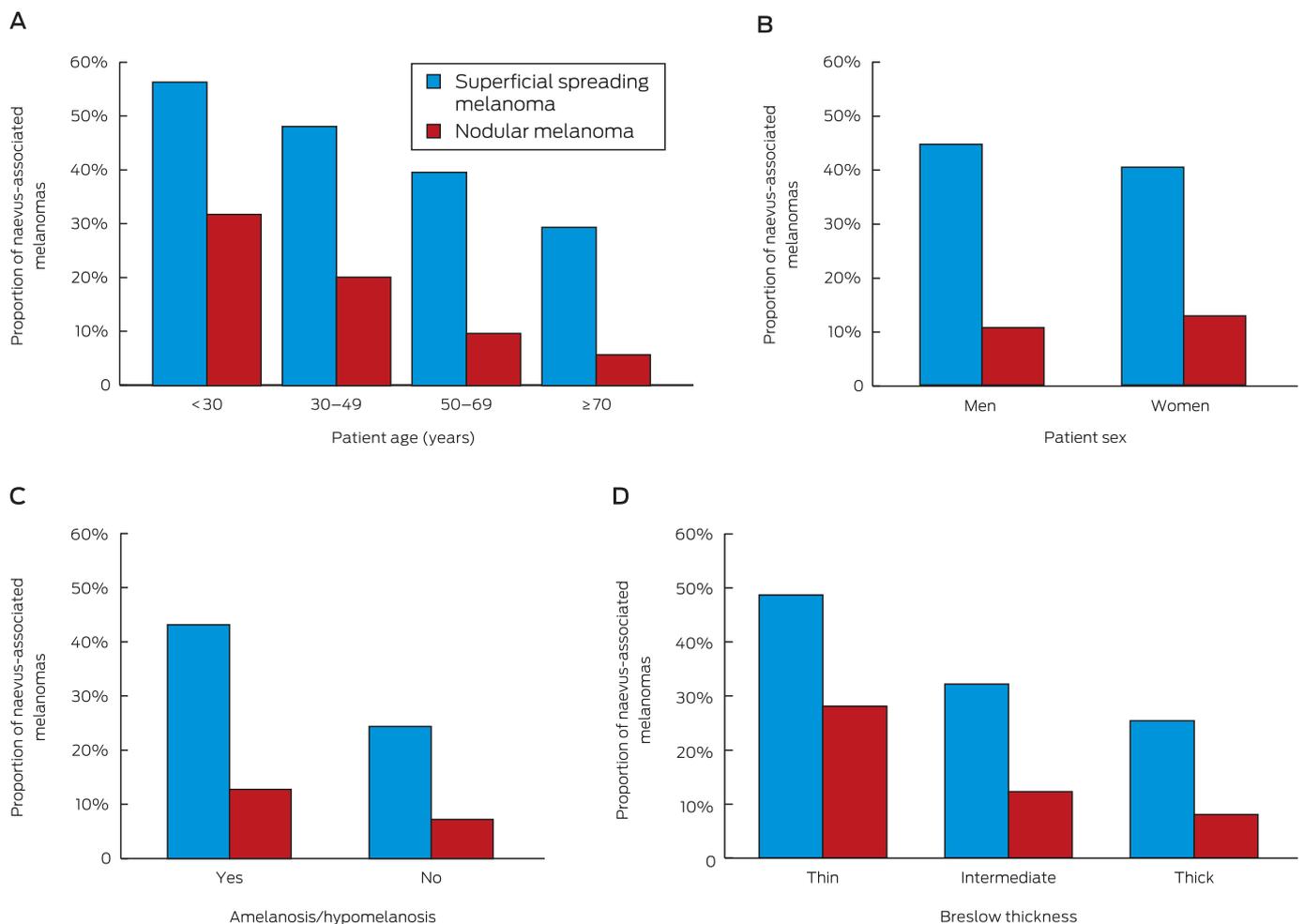
contributes to the limited literature on an independent relationship between amelanosis/hypomelanosis and the absence of a pre-existing naevus.

We found that the odds of a melanoma being with associated with a naevus declined with increasing tumour thickness. It is possible that thick melanomas obliterate pre-existing naevus cells, and this contributes to the inverse relationship between the Breslow thickness of a melanoma and its being associated with a naevus. In fact, the odds ratios from the multivariate analysis indicated a weaker associations between naevus-associated melanoma and Breslow thickness and histological subtype than in the univariate analysis, which suggests that these covariates are mutually confounded. The inverse relationship between Breslow thickness and the presence of a pre-existing naevus remained in the multivariate analysis; this indicates that Breslow thickness was independently and inversely associated with naevus-associated melanoma, and that this relationship was not completely explained by the difference between nodular and superficial spreading melanoma subtypes.

An inverse relationship between tumour thickness and the presence of an associated pre-existing naevus has been reported in previous studies: Shitara and colleagues[14] found that the median Breslow thickness of naevus-associated melanomas was significantly lower than for de novo melanomas, while Sagebiel[10] reported that 65% of nodular and superficial spreading melanomas less than 1.69 mm thick, 46% of those 1.70–3.60 mm thick, and 32% of tumours more than 3.60 mm thick were histopathologically associated with benign naevus cells. Nonetheless, a recent prospective, single centre, observational study found that naevus-associated melanomas were more frequently associated with in situ tumours than invasive tumours; for invasive melanomas, however, being associated with a naevus was not related to tumour thickness.[16]

There is accumulating evidence for the aetiological heterogeneity of de novo naevus-associated melanomas.[12,25] Whitehead and colleagues proposed a divergent pathway for cutaneous melanoma, premised on the propensity of the host to develop naevi.[25,26] The first pathway describes naevus-prone individuals, in whom melanomas often arise in association with naevi, and require only modest amounts of sun exposure, after which tumour progression is predominantly driven by host factors. The second pathway describes individuals with a low propensity for developing naevi; these individuals are more likely to have de novo melanomas, and melanoma development requires a high degree of cumulative sun exposure.[25,26]

Consistent with this hypothesis, earlier observational studies found an association between naevus-associated melanoma and anatomic sites of intermittent sun exposure, such as the trunk.[6,9,12,14-16,19] Accordingly, melanomas on sites associated with cumulative sun exposure, such as the head and neck, are less likely to be associated with a pre-existing naevus.[6,9,12,14,25] This is consistent with our results, as the odds of a trunk melanoma being associated with a naevus were 2.27 times as high as for melanomas on the head and neck. Further, we found that naevus-associated melanomas were more common in younger patients, consistent with one previous study,[9] although others have not found this association.[12,16]

Limitations of our study include likely referral bias, as the VMS is a statewide tertiary referral service to which patients with more advanced or aggressive disease are more likely to have been referred. A further limitation is that it may be difficult to histologically recognise the presence of a naevus in association with a melanoma, particularly dysplastic naevi and naevoid melanomas, despite the review of all melanomas by a dermatopathologist. The possibility of a fortuitous collision event — the coincidental coexistence of an adjacent naevus — must be acknowledged as a nondifferential error. Nonetheless, the strengths of our study include the large sample size and the prospectively collected data in the VMS database, providing a clinically and histologically well characterised cohort of patients.

Conclusion

Consistent with earlier research, our study found that the vast majority of nodular melanomas arise in the absence of a pre-existing naevus. Melanoma development in association with a naevus was positively and independently associated with the superficial spreading melanoma subtype, location of the melanoma on the trunk, younger patient age, thinner primary tumours, and pigmented melanomas.

Most public education campaigns have focused the attention of people on observing suspicious changes in pre-existing naevi.[7] While this message is undeniably important, it may be similarly imperative to emphasise the detection of suspicious de novo lesions, as melanomas of all subtypes are most likely to arise as new lesions. This is particularly the case for nodular melanoma, which contributes a disproportionately high fraction of thick primary tumours and melanoma-related deaths.[1,3]

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