Research Article

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Site-Specific Determinants of Cutaneous Melanoma: A Case–Case Comparison of Patients with Tumors Arising on the Head or Trunk

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Abstract

Background: Cutaneous melanomas have been hypothesized to arise through different pathways according to phenotype, body site, and sun exposure. To further test this hypothesis, we explored associations between phenotype and melanoma at different sites using a case–case comparative approach.

Methods: Melanoma patients ($n = 762$) aged 18 to 79 years and diagnosed from 2007 to 2010 were ascertained from pathology laboratories in Brisbane, Australia. Patients reported phenotypic information and a dermatologist counted melanocytic nevi and solar keratoses. We compared data for patients with trunk melanoma ($n = 541$, the reference group), head/neck melanoma ($n = 122$), or lentigo maligna melanoma (LMM) of the head/neck ($n = 69$). ORs and 95% confidence intervals were calculated using classical or polytomous logistic regression models.

Results: Compared with trunk melanoma patients, those with head/neck melanoma were significantly less likely to have high nevus counts (≥135: OR = 0.27; $P_{trend} = 0.0004$). Associations between category of nevus count and LMM head/neck were weaker and significantly different (≥135: OR = 1.09; $P_{trend} = 0.69$; $P_{homogeneity} = 0.02$). Patients with head/neck melanoma were more likely than those with truncal melanoma to have high solar keratosis counts (≥7: OR = 1.78, $P_{trend} = 0.04$). Again, associations with LMM head/neck were weaker, albeit not significantly different (≥7: OR = 1.61; $P_{trend} = 0.42$; $P_{homogeneity} = 0.86$).

Conclusion: Trunk melanomas are more strongly associated with nevus counts than head/neck melanomas, but are less strongly associated with number of solar keratoses, a marker of chronic sun exposure.

Impact: These findings underscore the notion that melanomas on the trunk typically arise through a causal pathway associated with nevus propensity, whereas melanomas on the head/neck arise through a pathway associated with cumulative sun exposure. *Cancer Epidemiol Biomarkers Prev; 22(12); 2222–31. ©2013 AACR.*

Introduction

Melanomas of the skin are caused principally by sunlight, but there is accumulating evidence that the pattern or dose required to cause melanoma varies according to the characteristics of the host and the anatomical location of the target cell, the melanocyte. We have previously proposed a model for the development of melanoma that recognizes the complex interactions between host characteristics, anatomical site, and sun exposure (1). This model extends earlier models for melanoma development (2, 3) by acknowledging that melanoma risk is heterogeneous within populations. Although at least one earlier model previously postulated that differences in tanning response might underlie differences in melanoma susceptibility (3), we hypothesize that individual risk is determined, at least in part, by the capacity for a person's melanocytes to proliferate following sun exposure.

Specifically, we predict that people with inherently highly proliferative melanocytes (characterized phenotypically by the presence of many nevi) require only modest levels of sun exposure to initiate melanoma development (especially early in life; ref. 4), after which host factors supervene to drive the process. In contrast, people whose melanocytes have a low proclivity to proliferate

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(characterized by very few nevi) require high doses of sun exposure to drive melanoma development.

Based on this hypothesis, melanomas arising among people with proliferative melanocytes should occur most often on body sites with large nevocyte populations such as the trunk, whereas melanomas occurring among the less proliferative group would be more likely to occur on habitually sun-exposed body sites such as the head or neck. Evidence in favor of this proposition has been published, although studies to date (1, 5, 6) have been small and/or have had incomplete reporting of key phenotypic features. Here, we report the findings of a study designed to test formally the hypothesis that melanomas arising on the trunk differ from melanomas arising on the head or neck in the strength of their associations with particular phenotypes, even after accounting for other factors known or suspected to influence these associations.

Materials and Methods

We used a case–case study design to test our hypothesis, in which one group of patients with melanoma served as the reference group to which other groups of patients were compared. Patients with incident diagnoses of invasive primary cutaneous melanoma were prospectively ascertained from diagnoses made in the main pathology laboratories serving southern Queensland (viz. Queensland Medical Laboratory, Sullivan Nicolaides Pathology, IQ Pathology). Approval to undertake the study was granted by the Human Research Ethics Committee of the Queensland Institute of Medical Research.

Patients

Eligible patients were those residents of greater Brisbane (defined by postcode of primary place of residence at the time of diagnosis) who were aged 18 to 79 years and were diagnosed for the first time with a primary invasive cutaneous melanoma between April 1, 2007 and September 30, 2010. We included patients with melanomas of superficial spreading, nodular, or unspecified subtypes arising on the chest, abdomen, back, and shoulders (group 1, "trunk," the reference group) or on the face, ears, head, or neck (group 2, "head or neck"); and separately, we included those with lentigo maligna melanoma (LMM) arising on the head or neck (group 3). This latter group was chosen as a "chronic sun exposure control group," because the LMM subtype is widely accepted as being caused by chronic sun exposure and because the presence of solar elastosis features in some histological criteria for LMM. For clarity of presentation, we hereafter refer to these groups as "trunk melanoma" (group 1), "head/neck melanoma" (group 2), and "LMM head/neck" (group 3).

Patients with metastatic disease or a previous diagnosis of melanoma were not eligible for this study. Potentially eligible patients were identified prospectively at each of the laboratories by the diagnosing dermatopathologists. At the time of diagnosis, a note was included into the computer-generated histology report sent to the treating doctor. The note briefly informed the doctor about the study and asked them to notify the laboratory if their patient was not to be contacted. If no objection was received within 4 weeks, a letter was sent by the pathology laboratory to the patient, seeking the patient's permission to release their contact details to the research team. Patients were asked to respond either by reply-paid mail, telephone, or email. If no response was received within 2 weeks, a second letter was sent. Patients granting permission to be contacted were then approached by a study nurse to obtain detailed consent and to formally enroll them into the study. The median (25th percentile, 75th percentile) interval between date of histological diagnosis and receipt of questionnaire was 84 days (68, 111), and between diagnosis and clinical examination was 102 days (81, 133).

Of 1,472 potentially eligible patients identified, 8 were uncontactable, 4 deceased, treating doctors denied permission to contact 2 patients, and 2 patients were too ill to participate. Invitations were therefore sent to 1,456 patients, of whom 808 (55%) responded with written consent to participate, 181 (12%) declined, and the remainder did not respond. We excluded patients with tumors at ineligible sites ($n = 33$), those with unclear information on site ($n = 6$) and those with multiple primary melanomas at different body sites ($n = 2$). We further excluded one patient with acral-lentiginous melanoma. The final study sample comprised 766 melanoma patients, with full clinical examination data available for 762 patients.

Data collection

Participants completed a detailed questionnaire and then underwent a clinical examination by a dermatologist. In addition to basic demographic details (including place of birth and age at migration to Australia if applicable, years of schooling, educational level, places of residence), participants were asked to report self-assessments of their phenotypic characteristics including their hair color as a teenager; tendency to burn after acute sun exposure; ability to tan after chronic sun exposure; facial freckling as a teenager (using a 4-category pictorial scale); and nevus burden as a teenager (using a 4-category pictorial scale). To assess their extent of actinic sun damage, we asked participants to report the number of solar keratoses ("sunspots") that had been treated. We also asked about prior treatment for "skin cancers." For both prior solar keratoses and prior skin cancers, participants separately recorded responses for the number of lesions that had been treated by freezing, creams, excision, and other means.

After completing the questionnaire, each participant was examined by a single dermatologist (M.B. Davis), who recorded hair and eye color and counted the number of melanocytic nevi (defined as brown to black pigmented macules or papules of any size which are darker than the

surrounding skin). Using a standard international protocol (7), nevi were counted on the back, neck, face, and upper limbs (left and right), and classified according to size (2–5 mm or >5 mm) using a transparent plastic stencil. Freckling density on the face and upper limbs was recorded using a standard 4-category scale. The numbers of solar keratoses (defined as superficial, rough scaly areas with erythematous background and ill-defined margins) were counted on the dorsum of hands and forearms, and on forehead, cheek, nose, and chin.

Statistical analysis

The aim of this analysis was to quantify the risks of head/neck melanoma and LMM head/neck, relative to the risk of trunk melanoma associated with phenotypic markers of melanocytic proliferation (nevus number), sun sensitivity (skin type), and cumulative sun exposure (solar keratoses and keratinocytic cancers). We categorized numbers of total nevi and nevi 2 to 5 mm at approximate quartile cutpoints, and numbers of nevi >5 mm and solar keratoses at approximate tertile cutpoints because of skewed distributions for these variables. We summed self-reported numbers of treated "sunspots" and "skin cancers" across variables for different treatments and categorized these numbers at approximate tertile cutpoints. We then calculated ORs and 95% confidence intervals (CI) as estimates of relative risk using polytomous logistic regression models. Homogeneity tests (8) were used to compare risk estimates between head/neck melanoma and LMM head/neck.

The reference group in all analyses was patients with melanoma arising on the trunk, to which we compared separately the groups with head/neck melanoma and LMM head/neck. All models were adjusted for age in years and sex. We considered several adjustments for age in the multivariate model. After assessing continuous age, quartiles of age, and an additional age-squared term, we selected continuous age for all of the reported analyses, as the model fit was best with this adjustment. Because of considerable correlations between many of the potentially confounding variables, we built multivariable models through a backward elimination process using all factors present in Table 1, setting a threshold for inclusion of $P = 0.15$. For the latter analyses, final models included age (continuous) and self-reported number of nevi as a teenager, as well as the main effects (counts of nevi and solar keratoses) that were included *a priori* into the model.

In addition, we analyzed associations with site-specific numbers of nevi, and we stratified all multivariable results according to median age and sex. Where relevant, we performed tests for linear trend using an ordinal score for each factor. Missing data occurred in <0.5% of observations for key exposures, and were imputed to the median value for continuous variables, and to the modal value for categorical variables. Statistical analyses were performed using the SAS statistical package, version 9.2 (SAS Institute, Inc.).

Results

Of the 762 patients included in the primary analysis, 541 had melanoma on the trunk, 122 had melanoma on the head/neck, and 69 had LMM on the head/neck. The majority of truncal (88%) or head or neck (85%) tumors were of the superficial spreading or nodular type of melanoma.

Age, sex, and self-reported phenotype

Patients with trunk melanoma were younger on average (mean: 56.5 years) than those with head/neck melanoma (mean: 57.6 years) or LMM head/neck (mean: 66.6 years). LMM head/neck patients were significantly older than trunk melanoma patients, but head/neck melanoma patients were not ($P_{homogeneity} < 0.0001$; Table 1).

Compared with trunk melanoma patients, those with head/neck melanoma were significantly less likely to self-report having many moles as a teenager (OR = 0.37; 95% CI, 0.17–0.83 for many vs. none; $P_{trend} = 0.0003$) or a skin that deeply tans when first exposed to the sun in summer (OR = 0.29; 95% CI, 0.13–0.66 for deep vs. no tan; $P_{trend} = 0.0003$), but significantly more likely to report having many facial freckles as a teenager (OR = 2.00; 95% CI, 1.04–3.85), although the trend was not statistically significant ($P_{trend} = 0.06$).

LMM head/neck patients were significantly less likely than patients with trunk melanoma to have red hair than black/dark brown hair as a teenager (OR = 0.39; 95% CI, 0.16–0.94), and to report having many nevi as a teenager ($P_{trend} = 0.0007$). Although head/neck melanoma patients were more likely to report heavy facial freckling as a teenager, LMM head/neck patients were less likely to do so (OR = 0.14; 95% CI, 0.02–1.08; $P_{trend} = 0.08$); the difference between head/neck melanoma and LMM head/neck was statistically significant ($P_{homogeneity} = 0.01$). Adult freckling density as assessed during clinical examination was not significantly associated with anatomic site or histological type of melanoma (data not shown).

Counts of nevi and solar keratoses from the clinical examination

Total nevus counts were lower for patients with head/neck melanoma (mean: 70.8) or LMM head/neck (mean: 59.9) than those with truncal melanoma (mean: 108.5). In models adjusted for age and sex, we observed a strong inverse association between category of nevus count and risk of head/neck melanoma compared with truncal melanoma (ORs of 0.74, 0.45, and 0.21 across quartiles of increasing nevus count, $P_{trend} < 0.0001$; Table 2). We observed similar results for total numbers of nevi 2 to 5 mm and >5 mm. Associations with LMM head/neck were weaker (ORs of 0.99, 0.56, and 0.61; $P_{trend} = 0.09$), and there was suggestive, although not statistically significant, evidence that the ORs for head/neck melanoma and LMM head/neck were different ($P_{homogeneity} = 0.06$ for the highest category of nevus count).

Table 1. Age- and sex-adjusted ORs and 95% CIs for self-reported factors in relation to risk of head/neck melanoma and LMM head/neck, compared with trunk melanoma ($n = 732$)

		Head or neck ($n = 122$)		LMM head or neck ($n = 69$)		
	Trunk ($n = 541$) *n* (%)	*n* (%)	Age- and sex-adjusted OR[a] (95% CI)	*n* (%)	Age- and sex-adjusted OR[a] (95% CI)	*P*-value[b]
Age (years)						
<50	156 (28.8)	35 (28.7)	1.00 (reference)	2 (2.9)	1.00 (reference)	–
50–59	129 (23.8)	21 (17.2)	0.80 (0.44–1.45)	14 (20.3)	8.93 (1.97–40.39)	
60–69	153 (28.3)	37 (30.3)	1.19 (0.70–2.03)	27 (39.1)	14.60 (3.37–63.23)	
≥70	103 (19.0)	29 (23.8)	1.42 (0.80–2.52)	26 (37.7)	21.14 (4.83–92.58)	
P_{trend}			0.14		<0.0001	0.001
Age (continuous)			1.01 (0.99–1.02)		1.07 (1.05–1.10)	<0.0001
Sex						
Male	370 (68.4)	76 (62.3)	1.00 (reference)	51 (73.9)	1.00 (reference)	–
Female	171 (31.6)	46 (37.7)	1.39 (0.90–2.13)	18 (26.1)	1.21 (0.67–2.19)	0.72
Hair color as a teenager[c]						
Black/dark brown	165 (30.5)	40 (33.1)	1.00 (reference)	29 (42.0)	1.00 (reference)	–
Light brown	180 (33.3)	36 (29.7)	0.82 (0.50–1.35)	26 (37.7)	0.82 (0.46–1.47)	0.99
Blond	122 (22.6)	25 (20.7)	1.08 (0.59–1.98)	7 (10.1)	0.53 (0.22–1.30)	0.20
Red/auburn/strawberry	74 (13.7)	20 (16.5)	0.85 (0.49–1.48)	7 (10.1)	0.39 (0.16–0.94)	0.15
Eye color						
Brown	348 (64.3)	75 (61.5)	1.00 (reference)	42 (60.9)	1.00 (reference)	–
Green/hazel	108 (20.0)	32 (26.2)	1.36 (0.85–2.19)	18 (26.1)	1.74 (0.94–3.24)	0.54
Blue/gray	85 (15.7)	15 (12.3)	0.84 (0.46–1.55)	9 (13.0)	1.13 (0.52–2.47)	0.56
Number of moles as a teenager						
None	89 (14.5)	31 (25.4)	1.00 (reference)	23 (33.3)	1.00 (reference)	–
Few	216 (39.9)	61 (50.0)	0.80 (0.48–1.34)	37 (53.6)	0.93 (0.51–1.70)	
Some	160 (29.6)	20 (16.4)	0.34 (0.18–0.65)	8 (11.6)	0.33 (0.14–0.79)	
Many	76 (14.0)	10 (8.2)	0.37 (0.17–0.83)	1 (1.5)	0.10 (0.01–0.75)	
P_{trend}			0.0003		0.0007	0.55
Number of freckles on face as a teenager						
None	190 (35.1)	37 (30.3)	1.00 (reference)	29 (42.0)	1.00 (reference)	–
Few	213 (39.4)	44 (36.1)	1.08 (0.66–1.74)	31 (44.9)	1.16 (0.66–2.04)	
Some	92 (17.0)	22 (18.0)	1.21 (0.67–2.18)	8 (11.6)	0.72 (0.31–1.69)	
Many	46 (8.5)	19 (15.6)	2.00 (1.04–3.85)	1 (1.5)	0.14 (0.02–1.08)	
P_{trend}			0.06		0.08	0.01
Burning reaction of skin						
Never/rarely burns	47 (8.7)	11 (9.0)	1.00 (reference)	6 (8.7)	1.00 (reference)	–
Sometimes burns	172 (31.8)	28 (23.0)	0.73 (0.34–1.59)	20 (29.0)	1.29 (0.48–3.46)	
Mostly burns	141 (26.0)	37 (30.3)	1.17 (0.55–2.50)	25 (36.2)	2.14 (0.80–5.68)	
Always burns	181 (33.5)	46 (37.7)	1.09 (0.52–2.30)	18 (26.1)	1.19 (0.43–3.26)	
P_{trend}			0.26		0.68	0.71
Tanning reaction of skin						
No tan	51 (9.4)	21 (17.2)	1.00 (reference)	6 (8.7)	1.00 (reference)	–
Light tan	139 (25.7)	43 (35.3)	0.76 (0.41–1.41)	27 (39.1)	1.69 (0.64–4.45)	
Moderate tan	257 (47.5)	47 (38.5)	0.46 (0.25–0.84)	27 (39.1)	0.89 (0.34–2.33)	
Deep tan	94 (17.4)	11 (9.0)	0.29 (0.13–0.66)	9 (13.0)	0.81 (0.26–2.49)	
P_{trend}			0.0003		0.14	0.30
Total number of treated sunspots						
<2	198 (36.6)	40 (32.8)	1.00 (reference)	9 (13.0)	1.00 (reference)	–
2–19	192 (35.5)	42 (34.4)	1.06 (0.63–1.78)	30 (43.5)	1.99 (0.90–4.42)	
≥20	151 (27.9)	40 (32.8)	1.29 (0.73–2.28)	30 (43.5)	1.89 (0.83–4.34)	
P_{trend}			0.38		0.21	0.67

(Continued on the following page)

Table 1. Age- and sex-adjusted ORs and 95% CIs for self-reported factors in relation to risk of head/neck melanoma and LMM head/neck, compared with trunk melanoma ($n = 732$) (Cont'd)

		Head or neck ($n = 122$)		LMM head or neck ($n = 69$)		
	Trunk ($n = 541$) *n* (%)	*n* (%)	Age- and sex-adjusted OR[a] (95% CI)	*n* (%)	Age- and sex-adjusted OR[a] (95% CI)	*P*-value[b]
Total number of treated skin cancers						
0	242 (44.7)	55 (45.1)	1.00 (reference)	14 (20.3)	1.00 (reference)	–
1–3	127 (23.5)	21 (17.2)	0.67 (0.38–1.18)	23 (33.3)	1.91 (0.92–3.95)	
≥4	172 (31.8)	46 (37.7)	1.06 (0.65–1.75)	32 (46.4)	1.51 (0.74–3.07)	
P_{trend}			0.81		0.38	0.59

[a]Results from polytomous logistic regression models.

[b]Test for homogeneity in age- and sex-adjusted estimates between head/neck melanoma and LMM head/neck.

[c]The "other" category of hair color as a teenager was excluded ($n = 1$).

In contrast, solar keratosis counts were significantly higher on average in patients with head/neck melanomas (mean: 15.9) or LMM head/neck (mean: 12.1) than those with truncal melanoma (mean: 10.2). In age- and sex-adjusted analyses, patients with head or neck melanomas were significantly more likely than those with truncal melanoma to have ≥7 solar keratoses (OR = 2.58; 95% CI, 1.35–4.94; $P_{trend} = 0.002$); ORs for LMM head/neck patients were lower (≥7 solar keratoses: OR = 1.82; 95% CI, 0.72–4.56), but not significantly so ($P_{homogeneity} = 0.54$; Table 2).

Table 2. Age- and sex-adjusted ORs and 95% CIs for clinically observed factors in relation to risk of head/neck melanoma and LMM head/neck, compared with trunk melanoma ($n = 732$)

		Head or neck ($n = 122$)		LMM head or neck ($n = 69$)		
	Trunk ($n = 541$) *n* (%)	*n* (%)	Age- and sex-adjusted OR[a] (95% CI)	*n* (%)	Age- and sex-adjusted OR[a] (95% CI)	*P*-value[b]
Total number of nevi						
<35	125 (23.1)	47 (38.5)	1.00 (reference)	29 (42.0)	1.00 (reference)	–
35–64	122 (22.6)	35 (28.7)	0.74 (0.44–1.24)	21 (30.4)	0.99 (0.51–1.90)	
65–134	145 (26.8)	26 (21.3)	0.45 (0.26–0.80)	12 (17.4)	0.56 (0.25–1.26)	
≥135	149 (27.5)	14 (11.5)	0.21 (0.10–0.42)	7 (10.1)	0.61 (0.25–1.48)	
P_{trend}			<0.0001		0.09	0.17
Number of nevi 2–5 mm						
<30	121 (22.4)	42 (34.4)	1.00 (reference)	27 (39.1)	1.00 (reference)	–
30–54	122 (22.5)	39 (32.0)	0.89 (0.53–1.49)	20 (29.0)	1.01 (0.52–1.97)	
55–119	150 (27.7)	26 (21.3)	0.46 (0.26–0.82)	15 (21.7)	0.80 (0.38–1.67)	
≥120	148 (27.4)	15 (12.3)	0.25 (0.12–0.51)	7 (10.1)	0.59 (0.22–1.58)	
P_{trend}			<0.0001		0.26	0.10
Number of nevi >5 mm						
<4	151 (27.9)	52 (42.6)	1.00 (reference)	29 (42.0)	1.00 (reference)	–
4–13	191 (35.3)	49 (40.2)	0.75 (0.48–1.18)	32 (46.4)	1.02 (0.58–1.80)	
≥14	199 (36.8)	21 (17.2)	0.31 (0.18–0.55)	8 (11.6)	0.35 (0.15–0.83)	
P_{trend}			<0.0001		0.03	0.54
Total number of solar keratoses						
0	191 (35.3)	34 (27.9)	1.00 (reference)	8 (11.6)	1.00 (reference)	–
1–6	182 (33.6)	33 (27.0)	1.24 (0.68–2.27)	26 (37.7)	1.67 (0.70–4.00)	
≥7	168 (31.1)	55 (45.1)	2.58 (1.35–4.94)	35 (50.7)	1.82 (0.72–4.56)	
P_{trend}			0.002		0.28	0.28

[a]Results from polytomous logistic regression models.

[b]Test for homogeneity in age- and sex-adjusted estimates between head/neck melanoma and LMM head/neck.

Table 3. Multivariable-adjusted ORs and 95% CIs for self-reported and clinically observed factors in relation to risk of head/neck melanoma and LMM head/neck, compared with trunk melanoma ($n = 732$)

	Multivariable OR[a] (95% CI)		
	Head or neck ($n = 122$)	LMM head or neck ($n = 69$)	*P*-value[b]
Age (continuous)	0.98 (0.96–1.00)	1.05 (1.02–1.09)	0.0001
Present total number of nevi			
<35	1.00 (reference)	1.00 (reference)	–
35–64	0.76 (0.45–1.28)	1.06 (0.56–2.01)	
65–134	0.51 (0.28–0.91)	0.66 (0.29–1.48)	
≥135	0.27 (0.13–0.57)	1.09 (0.44–2.71)	
P_{trend}	0.0004	0.69	0.06
Present total number of solar keratoses			
0	1.00 (reference)	1.00 (reference)	–
1–6	1.04 (0.56–1.93)	1.53 (0.62–3.74)	
≥7	1.78 (0.93–3.41)	1.61 (0.63–4.07)	
P_{trend}	0.04	0.42	
Number of moles as a teenager			
None	1.00 (reference)	1.00 (reference)	–
Few	0.94 (0.56–1.59)	0.97 (0.53–1.78)	
Some	0.52 (0.26–1.00)	0.35 (0.14–0.86)	
Many	0.67 (0.28–1.59)	0.10 (0.01–0.79)	
P_{trend}	0.06	0.002	0.19

[a]Results from the multivariable polytomous logistic regression model, adjusted for all covariates presented in the table.
[b]Test for homogeneity in multivariable estimates between head/neck melanoma and LMM head/neck.

To control for potential confounding, we fitted logistic regression models including terms for age and self-reported nevus burden in adolescence, as selected by backward selection. In this model, patients with head/neck melanoma remained significantly less likely than those with trunk melanoma to have high nevus counts (ORs of 0.76, 0.51, and 0.27 across quartiles of increasing nevus count, $P_{trend} = 0.0004$; Table 3).

ORs associated with solar keratosis counts also remained higher in head/neck melanoma or LMM head/neck compared with truncal melanoma patients, although less strongly than in age- and sex-adjusted models (head/neck melanoma: OR = 1.78; 95% CI, 0.93–3.41 for ≥7 solar keratoses, $P_{trend} = 0.04$; LMM head/neck: OR = 1.61; 95% CI, 0.63–4.07).

Site-specific nevus counts

We compared the counts of nevi at specific anatomical sites across groups of melanoma patients and observed generally similar patterns of association as for the global counts (i.e., generally lower counts for patients with head/neck melanoma compared with trunk melanoma; Supplementary Table S1). There was no evidence of heterogeneity according to anatomic site, although associations were stronger for nevus counts on the trunk (back and shoulders, anterior trunk) than on the head or neck and upper limbs in the fully adjusted model.

Stratified analyses

In analyses stratified by median age (Supplementary Table S2) and sex (Supplementary Table S3), we observed no significant heterogeneity in associations between melanoma group and counts for nevi or solar keratoses.

Discussion

We have confirmed that head/neck melanoma patients were significantly less likely to have high nevus counts, but significantly more likely to have high solar keratosis counts than truncal melanoma patients. Exploring LMM of the head or neck as a separate "chronic sun exposure" comparison group, we found significantly weaker associations with nevus counts than for head or neck melanoma, as compared with truncal melanoma.

Our study provides a direct and independent test of the *a priori* hypothesis (1) on the causal heterogeneity of cutaneous melanoma according to anatomical site, and is the largest study to date that has formally tested this hypothesis. A particular strength of the study was that phenotype was recorded through clinical examination by a single dermatologist, which ensures minimal misclassification and objective measurement of nevus and solar keratosis counts (although misclassification cannot be ruled out completely, as solar keratosis count has been suggested to have low reliability; refs. 9, 10). Incident melanoma patients were recruited rapidly following

diagnosis, thus minimizing the delay between diagnosis and solar keratosis counts, and likely minimizing biased recall of self-reported numbers of treated sunspots and skin cancers. More generally, our findings are unlikely to be explained by systematic recall bias, because this was a case-only study in which all participants had been diagnosed with invasive melanoma and patients were not aware of the tested hypotheses. However, a few limitations should be considered in the interpretation of our data. By design, our case–case comparison study did not include a disease-free control group. This approach was favored as it reduced some known biases when comparing one group of cases with another; however, the penalty was that we could not estimate risks of exposures relative to the general population. Thus, care must be exercised when interpreting our findings; in particular, it is essential to know that all risks were estimated relative to patients with melanomas of the trunk. Then, the response rate was suboptimal, because we were unable to contact patients directly (as required under Australia's Privacy Act). This is unlikely to lead to biased conclusions however, because all participants were cases and response rates were similar across the 3 case groups. Also, despite the large sample size, some analyses were statistically underpowered, and thus we cannot rule out the play of chance in some of our findings. Although we considered numerous potentially confounding factors, there is the possibility of residual confounding arising from errors in measurement and the role of other, unmeasured, factors. The potential role of confounding by age is particularly difficult to control, because age is a strong positive determinant of solar keratoses, and an inverse determinant of nevi, as well as being associated with the outcomes. We addressed this issue by adjusting for several different age terms, and also through stratification according to age, and our findings were essentially unchanged across models. Also, although power was limited in some analyses, it is unlikely that effects were only explained by differences in age distributions of participants with trunk versus head/neck melanoma. Finally, it is possible that reporting errors, particularly for past exposures such as treatments of solar keratoses or skin cancer, may have introduced misclassification into our study. The reliability of many of the items used in this study has been tested within a prospective cohort study of 43,794 Queensland residents currently being undertaken by the investigators (11). In that larger study, we performed reliability analyses on 114 participants surveyed on 2 occasions (average interval 188 days), and found agreement for items asking about numbers of previous skin cancers treated by surgery and numbers of solar keratoses treated by cryotherapy (the commonest modalities for these lesions in Queensland) were 0.79 (95% CI, 0.71–0.88) and 0.83 (95% CI, 0.76–0.90), respectively (12).

Our finding that melanomas arising on the head or neck are less likely to have high nevus counts than trunk melanomas corroborates our previous results in an independent, substantially smaller case series ($n = 306$), where patients with head/neck melanoma or LMM were significantly less likely to have high nevus counts than trunk melanoma patients (1). We had also observed similar findings in 3 previous independent analyses from our group: a familial case-study of melanoma (13), a pooled analysis of 10 case–control studies (6), and a follow-up study of 4 samples of melanoma patients (14). Other previous studies (15–18), although not all (5, 19–21), generally reported similar findings, including a meta-analysis of 24 observational studies involving 16,180 melanoma cases (15). In the latter, an increase in 5 common nevi resulted in an odds of 1.50 for head/neck melanoma, and of 1.72 for trunk melanoma, but this difference was not statistically significant. Similarly, actinic damage indicators were associated with higher odds of LMM versus superficial spreading or nodular melanoma, and of usually versus occasionally sun exposed sites, although no significant heterogeneity was detected.

With respect to site-specific nevi, we found lower nevus counts at all body sites in patients with head/neck melanoma compared with trunk melanoma, and similar findings were reported in previous studies (15, 22–25). Our results were similar for small and large nevi, thus ruling out a differential effect according to size of nevi.

Few studies have explored numbers of solar keratoses or markers of actinic damage in relation to body site of melanoma. The present findings confirm our previous observations that patients with head/neck melanoma or LMM are more likely than trunk melanoma patients to have high numbers of solar keratoses or actinic lesions (1). Two previous pooled analyses of case–control studies also reported that the number of solar keratoses on the face (26), or any solar keratoses (27), respectively, better predicted head or neck as compared with trunk melanoma.

Among previous studies investigating nevi or solar keratosis distributions by anatomic site of melanoma, 3 analyzed LMM as a separate subgroup (1, 6, 27), 4 excluded LMMs from the analysis (5, 13, 16, 23), 7 combined all histological types in the analysis (14, 15, 17, 19, 20, 24, 26), and 4 reported no information on histology (18, 21, 22, 25). Thus, because our study focuses on anatomic site among non-LMM tumors, and includes LMM of the head or neck as a third comparative group in all analyses, our study offers a stronger design to explore site-specific pathways in the etiology of melanoma than most previous studies.

A potential limitation is that we considered non-LMM melanomas of the head or neck as a homogenous group; however, there have been suggestions that melanomas of the scalp may differ in etiology or prognosis from those arising on the face (28). We had limited statistical power to explore possible differences between melanomas of the scalp and face, because nearly 80% of head/neck melanomas in our sample occurred on the face. Analyses stratifying by subsite found essentially the same risk estimates for facial melanoma as observed for head/neck melanomas overall, but there were too few scalp melanomas to permit meaningful interpretation (data not shown).

It has been observed previously that melanomas on the head or neck and LMM occurred at an older age as compared with trunk melanoma or other histological subtypes (6, 13, 16, 18, 19, 26). Our data only weakly confirm this, and our result for head/neck melanoma was not statistically significant. Also, although we expected a stronger positive association between tumor site and age in univariate analyses, we observed an inverse association when numbers of nevi and solar keratoses, which strongly associate with age, were also included in the model.

When exploring self-reported pigmentary traits, we found that, compared with trunk melanoma patients, head/neck melanoma patients were less likely to report high numbers of nevi as a teenager or deep tanning of skin after first summer sun exposure, but more likely to report high facial freckling as a teenager. In contrast, LMM head/neck patients were less likely to report high facial freckling and red hair as a teenager. These results are consistent with our previous finding of a higher freckling burden during adolescence in head/neck melanoma patients than in trunk melanoma or LMM patients (1). Conversely, in a recent meta-analysis, light hair or eyes were associated with melanomas of the superficial spreading and nodular types, but not with LMM, and freckling was associated with both head or neck and trunk melanomas (15). Previous studies showed that red hair and lower skin sensitivity to the sun were more strongly associated with head or neck than with trunk melanoma in an early case–control study (19). Although we did not find an association with red hair, we observed an inverse association between tanning reaction of skin and head/neck melanoma, compared with trunk melanoma.

The findings reported here support the hypothesis that cutaneous melanomas develop through complex pathways that seem to differ according to the phenotype of the host and the anatomical site of the target cell (4, 29). Recent population-based data also support this hypothesis, describing 2 peaks for melanoma diagnosis: early-onset melanomas were associated with trunk/lower extremities, superficial spreading melanoma, and female sex (which we refer to as the "nevus pathway"; ref. 1), and late-onset melanomas were associated with the head or neck, LMM, and male sex ("chronic sun exposure pathway"; refs. 30 and 31). However, within the "chronic sun exposure pathway," disentangling the effect of the head/neck body site from that of the LMM subtype has long been a challenge, given the high prevalence of LMM on the head or neck. An unexpected finding in our study was that, within the head/neck body site, other non-LMM subtypes were more strongly associated with markers of chronic sun exposure than the LMM subtype.

The notion that pigment cells at different body sites have different potentials for proliferation (and possibly malignant transformation) is suggested by epidemiological studies of the natural history of nevi in young children, showing different rates of acquisition of nevi for the face versus the trunk (32–35). These observations have been inferred to implicate melanocytes of the trunk, in the presence of nevi, as being more unstable and having a higher tendency for proliferation and progression than melanomas of the head or neck (32, 36).

Molecular studies also strongly suggest heterogeneous melanoma development pathways. Melanomas arising on the trunk more frequently harbor mutations in *BRAF* (37–45) than melanomas of the head or neck (46). *BRAF*-mutant melanomas have also been shown to be associated with younger age (41, 45, 47), higher numbers of nevi (45, 47), lower numbers of solar keratoses (41, 47), histological evidence of a preexisting, or contiguous nevus (47, 48), all consistent with a "nevus pathway." In contrast, p53 expression is more frequent in melanomas arising on the head or neck than at other sites (49), and nevus density is lower in p53-expressing melanomas (50).

In conclusion, we have shown that the prevalences of nevi and solar keratoses differ between patients with head/neck melanoma or LMM head/neck and patients with truncal melanoma. Our data suggest that melanomas arising on the trunk are more strongly associated with nevus propensity, whereas melanomas arising on the head or neck and LMM head/neck are more strongly associated with cumulated sun exposure. These findings support the hypothesis of causal heterogeneity for melanoma. Further exploration of this hypothesis will help enhance our knowledge of the etiology of melanomas arising at different body sites and inform approaches to melanoma prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Kvaskoff, N. Pandeya, A.C. Green, L. Westacott, D.C. Whiteman
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