Title

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Journal

JID Innovations, 1(1)

ISSN

2667-0267

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Publication Date

2021-03-01

DOI

10.1016/j.xjidi.2021.100002

Differences in Melanoma Between Canada and New South Wales, Australia: A Population-Based Genes, Environment, and Melanoma (GEM) Study

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In an effort to understand the difference between melanomas diagnosed in Australia (New South Wales) and Canada, where the incidence in New South Wales is almost three times greater than in Canada, and mortality is twice as high although survival is slightly more favorable, we had one pathologist review 1,271 melanomas from British Columbia and Ontario, Canada, to compare these to melanomas in New South Wales, Australia. We hypothesized that histopathologic characteristics might provide insight into divergent pathways to melanoma development. We found a number of differences in risk factors and tumor characteristics between the two geographic areas. There were higher mole counts and darker phenotypes in the Canadian patients, while the Australian patients had greater solar elastosis, more lentigo maligna melanomas, and more tumor infiltrating lymphocytes. We hypothesize that the differences observed may illustrate different etiologies — the cumulative exposure pathway among Australian patients and the nevus pathway among Canadian patients. This is one of the largest studies investigating the divergent pathway hypothesis and is particularly robust due to the evaluation of all lesions by one dermatopathologist.

JID Innovations (2021);**1:**100002 doi:10.1016/j.xjidi.2021.100002

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Abbreviation: TIL, tumor-infiltrating lymphocyte

Received 16 October 2020; revised 22 November 2020; accepted 7 December 2020; accepted manuscript published online 16 January 2021

Cite this article as: JID Innovations 2021;1:100002

INTRODUCTION

Melanoma incidence is greater at latitudes with high levels of ambient UVR (Baade et al., 2012). Canada's average estimated UVR levels are a little more than half those of New South Wales, Australia, at 16.11 kJ/m^2/day in Vancouver, British Columbia (49°N) and 19.11 kJ/m^2/day in Toronto, Ontario (44°N) compared with 32.21 kJ/m^2/day in Sydney, New South Wales, Australia (34°S) (Lee-Taylor et al., 2010). Melanoma incidence in New South Wales (67.5 per 100,000 males; 42.3, females) is almost three times higher than the estimated incidence in British Columbia (22.3, males; 18.7, females) and Ontario (28.5, males; 20.2, females) (Canadian Cancer Statistics Advisory Committee, 2019; Cancer Institute NSW, 2016). Australian melanoma mortality in the year 2000 (4.4 per 100,000 males; 2.2, females) was twice that in Canada (2.0, males; 1.1, females) (Australian Institute of Health and Welfare, 2012; Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2013), yet the five-year relative survival was slightly more favorable in Australia (2006–2010) than Canada (2006–2008) in men (88.5% vs. 85%) and women (93.6% vs. 92%).

We hypothesized that, given the substantial difference in UVR and melanoma incidence and the small difference in relative survival between New South Wales and Canada, patient and histopathologic characteristics in melanoma might differ between regions and give some insight into divergent pathways to melanoma development.

MATERIALS AND METHODS

Our study included 1,271 individuals from British Columbia and Ontario, Canada, and New South Wales, Australia, with first primary

Table 1. Univariate and Multivariable Logistic Regression (N = 1,271)

Characteristics	Canada (n = 546) n (%)	NSW (n = 725) n (%)	NSW versus Canada OR (95% CI) Univariate	*P*-value	NSW versus Canada OR (95 % CI) Multivariable	*P*-value
Patient characteristics						
Age at diagnosis						
<49	198 (36.3)	210 (29.0)	1 (Referent)	—	1 (Referent)	—
50–69	241 (44.1)	291 (40.1)	1.14 (0.88–1.47)	0.33	0.61 (0.43–0.85)	0.00
70+	107 (19.6)	224 (30.9)	1.97 (1.46–2.67)	<0.001	0.88 (0.57–1.34)	0.54
Missing	0	0	—	—	—	—
Sex						
Male	269 (49.3)	408 (56.3)	1.00 (Referent)	—	1.00 (Referent)	—
Female	277 (50.7)	317 (43.7)	0.75 (0.60–0.94)	0.01	0.64 (0.47–0.88)	0.006
Missing	0	0	—	—	—	—
Phenotypic index						
Dark	162 (29.7)	172 (23.7)	1.00 (Referent)	—	1.00 (Referent)	—
Medium	189 (34.6)	306 (42.2)	1.52 (1.15–2.02)	0.003	1.63 (1.15–2.29)	0.005
Fair	151 (27.7)	246 (33.9)	1.53 (1.14–2.06)	0.004	1.46 (1.03–2.09)	0.04
Missing	44 (8.1)	1 (0.1)	—	—	—	—
Mole count						
0–4	165 (30.2)	314 (43.3)	1.00 (Referent)	—	1.00 (Referent)	—
5–10	102 (18.7)	181 (25.0)	0.93 (0.69–1.27)	0.66	1.05 (0.72–1.53)	
11–25	127 (23.3)	137 (18.9)	0.57 (0.42–0.77)	<0.001	0.65 (0.45–0.94)	
>25	145 (26.6)	92 12.7)	0.33 (0.24–0.46)	<0.001	0.38 (0.26–0.57)	$P_{trend} < 0.001$
Missing	7 (1.3)	1 (0.1)	—	—	—	
Family history of melanoma						
Absent	484 (88.6)	588 (81.1)	1.00 (Referent)	—	1.00 (Referent)	—
Present	58 (10.6)	108 (14.9)	1.53 (1.09–2.16)	0.01	1.57 (1.04–2.37)	0.03
Missing	4 (0.7)	29 (0.04)	—	—	—	—
Ancestry						
Other	172 (31.5)	202 (27.9)	1.00 (Referent)	—	1.00 (Referent)	—
Northern European	367 (67.2)	513 (70.8)	1.19 (0.93–1.52)	0.16	1.12 (0.83–1.51)	0.45
Missing	7 (1.3)	10 (1.4)	—	—	—	—
Tumor characteristics						
Anatomic site						
Trunk	258 (47.3)	310 (42.8)	1.00 (Referent)	—	1.00 (Referent)	—
Head and neck	65 (11.9)	118 (16.3)	1.51 (1.07–2.13)	0.02	0.78 (0.47–1.31)	0.35
Arms	100 (18.3)	137 (18.9)	1.14 (0.84–1.55)	0.40	0.82 (0.54–1.26)	0.37
Legs	123 (22.5)	160 (22.0)	1.08 (0.81–1.44)	0.59	1.36 (0.92–2.02)	0.12
Missing	0	0	—	—	—	—
Histologic subtype						
Superficial spreading	376 (68.9)	485 (66.9)	1.00 (Referent)	—	1.00 (Referent)	—
Nodular	61 (11.2)	74 (10.2)	0.94 (0.65–1.35)	0.74	0.76 (0.45–1.28)	0.30
Lentigo maligna	36 (6.6)	95 (13.1)	2.05 (1.36–3.07)	0.001	1.37 (0.77–2.43)	0.29
Other	73 (13.4)	71 (9.8)	0.75 (0.53–1.07)	0.12	1.00 (0.56–1.79)	0.99
Missing	0	0	—	—	—	—
AJCC tumor stage (2018 edition)						
Stage 1a/1b	308 (56.4)	460 (63.5)	1.00 (Referent)	—	—	—
Stage 2a	94 (17.2)	110 (15.2)	0.78 (0.57–1.07)	0.12	—	—
Stage 2b/3a	44 (8.1)	69 (9.5)	1.05 (0.70–1.57)	0.81	—	—
Stage 3b/4a	36 (6.6)	41 (5.7)	0.76 (0.48–1.22)	0.26	—	—
Stage 4b	10 (1.8)	16 (2.2)	1.07 (0.48–2.39)	0.87	—	—
Missing	54 (9.9)	29 (4.0)	—	—	—	—
Breslow thickness						
0.1–1.00 mm	338 (61.9)	473 (65.2)	1.00 (Referent)	—	1.00 (Referent)	—
1.01–2.00 mm	124 (22.7)	136 (18.8)	0.78 (0.59–1.04)	0.09	0.82 (0.55–1.23)	0.34
2.01–4.00 mm	54 (9.9)	80 (11.0)	1.06 (0.73–1.54)	0.76	0.99 (0.54–1.79)	0.96
>4.00 mm	26 (4.8)	36 (5.0)	0.99 (0.59–1.67)	0.97	0.78 (0.35–1.74)	0.54
Missing	4 (0.7)	0	—	—	—	—

(*continued*)

Table 1. Continued

Characteristics	Canada (n = 546) n (%)	NSW (n = 725) n (%)	NSW versus Canada OR (95% CI) Univariate	*P*-value	NSW versus Canada OR (95 % CI) Multivariable	*P*-value
TILs						
Absent	160 (29.3)	111 (15.3)	1.00 (Referent)	—	1.00 (Referent)	—
Brisk	95 (17.4)	138 (19.0)	2.09 (1.47–2.99)	<0.001	2.07 (1.34–3.19)	0.001
Nonbrisk	238 (43.6)	447 (61.7)	2.71 (2.03–3.61)	<0.001	2.76 (1.96–3.90)	<0.001
Missing	53 (9.7)	29 (4.0)	—	—	—	—
Solar elastosis						
Absent	306 (56.0)	212 (29.2)	1.00 (Referent)	—	1.00 (Referent)	—
Present	191 (35.0)	459 (63.3)	3.47 (2.72–4.42)	<0.001	3.83 (2.75–5.34)	<0.001
Missing	49 (9.0)	54 (7.4)	—	—	—	—
Ulceration						
Absent	444 (81.3)	634 (87.4)	1.00 (Referent)	—	1.00 (Referent)	—
Present	48 (8.8)	62 (8.6)	0.90 (0.61–1.34)	0.62	0.82 (0.45–1.46)	0.50
Missing	54 (9.9)	29 (4.0)	—	—	—	—
Mitoses						
Absent	274 (50.2)	393 (54.2)	1.00 (Referent)	—	1.00 (Referent)	—
Present	220 (40.3)	303 (41.8)	0.96 (0.76–1.21)	0.73	1.07 (0.75–1.52)	0.72
Missing	52 (9.5)	29 (4.0)	—	—	—	—
Regression						
Absent	411 (75.3)	557 (76.8)	1.00 (Referent)	—	1.00 (Referent)	—
Present	98 (17.9)	137 (18.9)	1.03 (0.77–1.38)	0.83	0.91 (0.63–1.31)	0.60
Missing	37 (6.8)	31 (4.3)	—	—	—	—
Coexisting nevus						
Absent	322 (59.0)	457 (63.0)	1.00 (Referent)	—	1.00 (Referent)	—
Present	188 (34.4)	239 (33.0)	0.90 (0.71–1.14)	0.37	1.16 (0.86–1.56)	0.34
Missing	36 (6.6)	29 (4.0)	—	—	—	—

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; NSW, New South Wales; TIL, tumor-infiltrating lymphocyte.

The univariate logistic regression models exclude only missing values for each individual model.

The multivariable logistic regression model includes only individuals with complete data on all variables and is mutually adjusted for all patient and histopathological features except stage.

melanomas diagnosed in 2000, all reviewed by one dermatopathologist (LF) who conducted a standardized pathology review according to published criteria. Institutional review boards from all centers provided approval, and all subjects signed informed consent. Breslow thickness, histologic subtype, tumor-infiltrating lymphocytes (TILs), solar elastosis, ulceration, presence of mitoses, regression, and presence of a coexisting nevus were determined from the slide review. Age, sex, phenotypic index, back mole count, family history of melanoma, ancestry, and anatomic site was confirmed at interview. Classification of tumors followed the T-category of the American Joint Committee on Cancer tumor staging system (Gershenwald et al., 2017).

Variables were first compared between Canada and New South Wales using univariate logistic regression. Then, a multivariable logistic regression was modeled that mutually adjusted for all patient and tumor characteristics. Tests were two-sided, and $P < 0.05$ was considered statistically significant. Data were analyzed using Stata/SE 15.1 (StataCorp LLC, College Station, TX).

RESULTS

The results from the univariate and multivariable logistic regression analyses are presented in Table 1 and demonstrate a number of differences in the risk factors and tumor characteristics in Canada versus New South Wales. Most relevant to our thesis are the generally higher mole counts in Canadian cases and the somewhat darker phenotypes of these cases. Regarding tumor characteristics, the New South Wales cases are characterized by tumors that have markedly greater solar elastosis, a greater presence of lentigo maligna melanoma histology, and, importantly, considerably more evidence of TILs.

DISCUSSION

The divergent pathway theory of melanoma hypothesizes two pathways leading to melanoma development (Holman et al., 1983; Whiteman et al., 1998), one requiring high cumulative (chronic) sun exposure and the other high counts of cutaneous nevi, which are precursors to melanoma.

Melanomas attributed to the cumulative sun exposure pathway occur more commonly on the head and neck and are more likely to be lentigo maligna melanoma (Holman et al., 1983; Whiteman et al., 2003). Solar elastosis, a marker of cumulative UVR exposure, is associated with melanomas on the head and neck and lentigo maligna melanoma (Thomas et al., 2010). We found New South Wales melanomas to be associated with the head and neck, lentigo maligna melanoma, TILs, and solar elastosis, with TILs and solar elastosis remaining associated in multivariable analysis. In prior GEM analyses, the presence of TILs has been found to be associated with Breslow thickness, anatomic site, histologic subtype, and age (Thomas et al., 2013). Including those factors, as well as other patient and tumor characteristics, in

the presented model did not diminish the association of TILs with New South Wales melanomas.

The presence of TILs with cutaneous melanoma has consistently been associated with improved overall survival. In the larger GEM study population, death from melanoma is reduced 30% in the presence of nonbrisk TILs and 50% with brisk TILs (Thomas et al., 2013). The biological mechanism drawing TILs to some melanomas is not fully understood. Based on our observed association of New South Wales melanomas with TILs and solar elastosis, we speculate that cumulative sun exposure may be contributing. Melanomas with high UVR have increased numbers of DNA mutations (Pleasance et al., 2010). These mutations may cause more neoantigen formation, attracting TILs. This increase in TILs may contribute to the better relative survival observed in Australia.

Melanomas occurring along the nevus pathway are classically associated with a younger age and high nevus counts and found on unexposed skin such as the trunk (Olsen et al., 2009). Prior studies comparing Australia and England have documented a higher nevus density in Australia (Bataille et al., 1998). In this analysis, melanomas occurring in Canada were associated with higher counts of back nevi.

We hypothesize that the difference in melanoma between Canada and New South Wales identified here may illustrate different etiologies. That is, New South Wales melanomas develop disproportionately by way of the cumulative sun exposure pathway and Canadian melanomas develop disproportionately by the nevus pathway. Alternatively, there may be a similar baseline rate of melanoma development from nevi between the two regions, but additional melanomas develop in New South Wales because of the higher UVR exposure.

Our study is unique as we present one of the very largest studies investigating the divergent pathways of melanoma. One dermatopathologist reviewed all slides, enabling robust histologic analysis. By comparing patient and histopathological features between regions, we provide evidence for each pathway within the same study. These data may offer additional leads to the understanding of melanoma etiology and may help to target and appropriately screen individuals in New South Wales and Canada.

Data availability statement

Data can be requested from Nancy E. Thomas or Marianne Berwick after review by the GEM Steering Committee.

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ACKNOWLEDGMENTS

This work was conducted in Albuquerque, New Mexico, USA.

This work was supported by the National Cancer Institute at the National Institutions of Health (Award Number U01CA83180, R01CA112524, R01CA112524-05S2 to MB; R01CA112243, R01CA112243-05S1, K07CA098438, and R33CA10704339 to NET; P01 CA206980 to MB and NET; R01CA233524 to MB, NET, CBB, and HA-C; P30CA014089 to SBG; and P30CA118100 to MB), the National Institute of Environmental Health Sciences at the National Institutes of Health (P30 ES010126 to NET), and the University of Sydney Medical Foundation Program grant (to BKA). AEC received a National Health and Medical Research Council Career Development Fellowship (1147843).

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CONFLICT OF INTEREST

The authors disclose no potential conflicts of interest.

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