



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

Joseph Michael Yardman-Frank<sup>1</sup>, Elyssa Glassheim<sup>1</sup>, Anne Kricke<sup>2,3</sup>, Bruce K. Armstrong<sup>4,5</sup>, Loraine D. Marrett<sup>6</sup>, Li Luo<sup>7</sup>, Anne E. Cust<sup>2,3</sup>, Klaus J. Busam<sup>8</sup>, Irene Orlow<sup>9</sup>, Richard P. Gallagher<sup>10</sup>, Stephen B. Gruber<sup>11</sup>, Hoda Anton-Culver<sup>12</sup>, Stefano Rosso<sup>13</sup>, Roberto Zanetti<sup>13</sup>, Lidia Sacchetto<sup>13</sup>, Peter A. Kanetsky<sup>14</sup>, Terence Dwyer<sup>15</sup>, Alison Venn<sup>16</sup>, Julia Lee-Taylor<sup>17</sup>, Colin B. Begg<sup>9</sup>, Nancy E. Thomas<sup>18,19</sup> and Marianne Berwick<sup>20,21</sup>

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.

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<sup>1</sup>University of New Mexico School of Medicine, Albuquerque, New Mexico, USA; <sup>2</sup>Sydney School of Public Health Melanoma Institute Australia, University of Sydney, Sydney, Australia; <sup>3</sup>Melanoma Institute Australia, University of Sydney, Sydney, Australia; <sup>4</sup>Sydney School of Public Health, University of Sydney, Sydney, Australia; <sup>5</sup>Sax Institute, Sydney, New South Wales, Australia; <sup>6</sup>Prevention and Cancer Control, Cancer Care Ontario, Toronto, Ontario, Canada; <sup>7</sup>Division of Epidemiology, Biostatistics and Preventive Medicine, Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, USA; <sup>8</sup>Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York, USA; <sup>9</sup>Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA; <sup>10</sup>BC Cancer, Vancouver, British Columbia, Canada; <sup>11</sup>City of Hope, Duarte, California, USA; <sup>12</sup>Department of Epidemiology, University of California, Irvine, California, USA; <sup>13</sup>Piedmont Cancer Registry, Centre for Epidemiology and Prevention in Oncology in Piedmont, Turin, Italy; <sup>14</sup>Department of Cancer Epidemiology, Moffitt Cancer Center and Research Institute, Tampa, Florida, USA; <sup>15</sup>The George Institute, University of Oxford, Oxford, United Kingdom; <sup>16</sup>Menzies Research Institute, University of Tasmania, Hobart, Australia; <sup>17</sup>Atmospheric Chemistry Division, National Center for Atmospheric Research, Boulder, Colorado, USA; <sup>18</sup>Department of Dermatology, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, USA for the GEM Study Group; <sup>19</sup>Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, USA for the GEM Study Group; <sup>20</sup>Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, USA; and <sup>21</sup>Department of Dermatology, University of New Mexico, Albuquerque, New Mexico, USA

Correspondence: Marianne Berwick, Department of Internal Medicine, University of New Mexico, MSC08 4720, 1 University of New Mexico, Albuquerque, New Mexico 87131-0001. E-mail: mberwick@salud.unm.edu

Abbreviation: TIL, tumor-infiltrating lymphocyte

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## 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<sup>2</sup>/day in Vancouver, British Columbia (49°N) and 19.11 kJ/m<sup>2</sup>/day in Toronto, Ontario (44°N) compared with 32.21 kJ/m<sup>2</sup>/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)	<i>P</i> <sub>trend</sub> < 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		NSW versus Canada	
			OR (95% CI) Univariate	P-value	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 (Pleasant 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.

#### ORCIDs

Joseph Michael Yardman-Frank: <https://orcid.org/0000-0002-0073-0834>

Elyssa Glasheim: <https://orcid.org/0000-0001-5195-5112>

Anne Kricke: <https://orcid.org/0000-0002-7219-1227>

Bruce K. Armstrong: <https://orcid.org/0000-0001-8940-7525>

Loraine D. Marrett: <https://orcid.org/0000-0002-1062-2503>

Li Luo: <https://orcid.org/0000-0003-0728-8628>

Anne E. Cust: <https://orcid.org/0000-0002-5331-6370>

Klaus J. Busam: <https://orcid.org/0000-0003-0888-9601>

Irene Orlow: <https://orcid.org/0000-0001-6234-6961>

Richard P. Gallagher: <https://orcid.org/0000-0003-2365-0391>

Stephen B. Gruber: <https://orcid.org/0000-0001-8656-7822>

Hoda Anton-Culver: <https://orcid.org/0000-0002-9603-0110>

Stefano Rosso: <https://orcid.org/0000-0001-6816-2661>

Roberto Zanetti: <https://orcid.org/0000-0001-6498-4086>

Lidia Sacchetto: <https://orcid.org/0000-0001-6590-325X>

Peter A. Kanetsky: <https://orcid.org/0000-0002-5567-9618>

Terence Dwyer: <https://orcid.org/0000-0002-2091-7663>

Alison Venn: <https://orcid.org/0000-0001-7090-1398>

Julia Lee-Taylor: <https://orcid.org/0000-0003-0989-1113>

Colin B. Begg: <https://orcid.org/0000-0003-3772-1795>

Nancy E. Thomas: <https://orcid.org/0000-0002-2230-1328>

Marianne Berwick: <https://orcid.org/0000-0001-5062-2180>

#### AUTHOR CONTRIBUTIONS

Conceptualization: MB; Data Curation: MB; Formal Analysis: JMYF, AK, LL, NET, MB; Funding Acquisition: CBB, NET, MB; Investigation: AK, BKA, LDM, AEC, KJB, IO, RPG, SBG, HAC, SR, RZ, LS, PAK, TD, AV, JLT, CBB, NET, MB; Methodology: CBB, MB; Project Administration: MB; Resources: IO; Software: AK, NET; Supervision: MB; Validation: AK, BKA, LS, PAK, NET, MB; Visualization: JMYF; Writing - Original Draft Preparation: JMYF, EG; Writing - Review and Editing: JMYF, AK, BKA, AEC, IO, RPG, LS, PAK, NET, MB

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GEM Study Group: Coordinating Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA: Marianne Berwick (Principal Investigator [PI], currently at the University of New Mexico, Albuquerque, NM, USA); Colin Begg, PhD (co-PI); Irene Orlow, PhD, MS (co-Investigator); Klaus J. Busam, MD (Dermatopathologist); Pampa Roy, PhD (Senior Laboratory Technician); Ajay Sharma, MS (Laboratory Technician); Emily La Pilla, MS (Senior Laboratory Technician); Sarah Yoo (Senior Laboratory Technician); Jaipreet Rayar (Senior Research Technician); and Anne Reiner, MS (Biostatistician). University of New Mexico, Albuquerque, NM, USA: Marianne Berwick, MPH, PhD (PI); Li Luo, PhD (Biostatistician); and Tawny W. Boyce, MPH (Data Manager). Study Centers: The University of Sydney and The Cancer Council New South Wales, Sydney, Australia: Anne E. Cust, PhD (PI); Bruce K. Armstrong, MD, PhD (former PI); and Anne Kricke, PhD (former co-PI). Menzies Institute for Medical Research University of Tasmania, Hobart, Australia: Alison Venn (current PI); Terence Dwyer (PI, currently at University of Oxford, United Kingdom); and Paul Tucker (Dermatopathologist). British Columbia Cancer Research Centre, Vancouver, Canada: Richard P. Gallagher, MA (PI). Cancer Care Ontario, Toronto, Canada: Loraine D. Marrett, PhD (PI) and Lynn From, MD (Dermatopathologist). CPO, Center for Cancer Prevention, Torino, Italy: Roberto Zanetti, MD (PI); Stefano Rosso, MD, MSc (co-PI); and Lidia Sacchetto, PhD (Biostatistician). University of California, Irvine, CA, USA: Hoda Anton-Culver, PhD (PI). University of Michigan, Ann Arbor, MI, USA: Stephen B. Gruber, MD, MPH, PhD (PI, currently at University of Southern California, Los Angeles, CA, USA); Shu-Chen Huang, MS, MBA (co-Investigator, joint at USC-University of Michigan). University of North Carolina, Chapel Hill, NC, USA: Nancy E. Thomas, MD, PhD (PI); Kathleen Conway, PhD (co-Investigator); David W. Ollila, MD (co-Investigator); Pamela A. Groben, MD (Dermatopathologist); Sharon N. Edmiston, BA (Research Analyst); Honglin Hao (Laboratory Specialist); Eloise Parrish, MSPH (Laboratory Specialist); Jill S. Frank, MS (Research Assistant); David C. Gibbs, BS (Research Assistant, currently MD/PhD candidate at Emory University, Atlanta, GA, USA). University of Pennsylvania, Philadelphia, PA, USA: Timothy R. Rebbeck, PhD (former PI) and Peter A. Kanetsky, MPH, PhD (PI, currently at H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA). UV data consultants: Julia Lee-Taylor, PhD, and Sasha Madronich, PhD, National Centre for Atmospheric Research, Boulder, CO, USA.

#### CONFLICT OF INTEREST

The authors disclose no potential conflicts of interest.

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