Table 2. Odds ratios with 95% confidence intervals for congenital abnormalities, low birth weight, and premature birth in children fathered by men treated with azathioprine, cyclosporine, methotrexate, or mycophenolate mofetil within the last 90 d before and after conception

<table>
<thead>
<tr>
<th></th>
<th>Exposed n/N (%)</th>
<th>Unexposed n/N (%)</th>
<th>Crude OR (95% CI)</th>
<th>P-Value</th>
<th>Adjusted OR† (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any immunosuppressants</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>34/480 (7.1)</td>
<td>31,204/417,154 (7.5)</td>
<td>0.94 (0.67–1.34)</td>
<td>0.740</td>
<td>0.94 (0.66–1.35)</td>
<td>0.751</td>
</tr>
<tr>
<td>Low birth weight (&lt;2,500 g)</td>
<td>23/480 (4.8)</td>
<td>22,066/417,154 (5.3)</td>
<td>0.90 (0.59–1.37)</td>
<td>0.626</td>
<td>0.87 (0.56–1.35)</td>
<td>0.543</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk)</td>
<td>25/480 (5.2)</td>
<td>18,947/417,154 (4.5)</td>
<td>1.15 (0.77–1.73)</td>
<td>0.484</td>
<td>1.13 (0.74–1.71)</td>
<td>0.581</td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>21/335 (6.3)</td>
<td>32,217/417,229 (7.5)</td>
<td>0.83 (0.53–1.29)</td>
<td>0.400</td>
<td>0.85 (0.55–1.33)</td>
<td>0.486</td>
</tr>
<tr>
<td>Low birth weight (&lt;2,500 g)</td>
<td>18/335 (5.4)</td>
<td>22,071/417,229 (5.3)</td>
<td>1.02 (0.63–1.64)</td>
<td>0.945</td>
<td>1.04 (0.64–1.70)</td>
<td>0.867</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk)</td>
<td>18/335 (5.4)</td>
<td>18,954/417,229 (4.5)</td>
<td>1.19 (0.74–1.92)</td>
<td>0.466</td>
<td>1.13 (0.68–1.87)</td>
<td>0.642</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>7/67 (10.5)</td>
<td>31,231/417,567 (7.5)</td>
<td>1.44 (0.66–3.16)</td>
<td>0.358</td>
<td>1.45 (0.66–3.19)</td>
<td>0.350</td>
</tr>
<tr>
<td>Low birth weight (&lt;2,500 g)</td>
<td>&lt;3/67 (not shown)</td>
<td>22,087/417,567 (5.3)</td>
<td>0.55 (0.14–2.25)</td>
<td>0.407</td>
<td>0.58 (0.14–2.39)</td>
<td>0.454</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk)</td>
<td>4/67 (6.0)</td>
<td>18,968/417,567 (4.5)</td>
<td>1.34 (0.493.67)</td>
<td>0.575</td>
<td>1.40 (0.51–3.85)</td>
<td>0.520</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Congenital abnormality</td>
<td>6/81 (7.4)</td>
<td>31,232/417,553 (7.5)</td>
<td>0.99 (0.43–2.27)</td>
<td>0.980</td>
<td>0.85 (0.34–2.10)</td>
<td>0.718</td>
</tr>
<tr>
<td>Low birth weight (&lt;2,500 g)</td>
<td>3/81 (3.7)</td>
<td>22,086/417,553 (5.3)</td>
<td>0.69 (0.22–2.18)</td>
<td>0.526</td>
<td>0.43 (0.11–1.77)</td>
<td>0.244</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk)</td>
<td>4/81 (4.9)</td>
<td>18,968/417,553 (4.5)</td>
<td>1.09 (0.40–2.98)</td>
<td>0.864</td>
<td>1.13 (0.41–3.10)</td>
<td>0.813</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight (&lt;2,500 g)</td>
<td>0/6 (0.0)</td>
<td>31,238/417,628 (7.5)</td>
<td>not applicable</td>
<td>0.69</td>
<td>0.69 (0.22–2.18)</td>
<td>0.526</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk)</td>
<td>0/6 (0.0)</td>
<td>18,972/417,628 (4.5)</td>
<td>not applicable</td>
<td>0.69</td>
<td>0.69 (0.22–2.18)</td>
<td>0.526</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
†Adjusted for mother’s age (below 25 y, 25–29 y, and 30 y or more), parity (1 or more than 1), maternal smoking (yes/no), and sex of the child in a logistic regression model.

statistical analysis. They provided administrative, technical, or material support. All authors supervised the study.

**Alexander Egeberg**, Gunnar H. Gislason, and Alexander Nast

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**SUPPLEMENTARY MATERIAL**

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.03.030.

**REFERENCES**


Renehan et al., 2015. TO THE EDITOR

TO THE EDITOR

Obesity is a known risk factor for cancer development (Arnold et al., 2016; Basen-Engquist and Chang, 2011; Renehan et al., 2015) and death

Association between Body Mass Index, C- Reactive Protein Levels, and Melanoma Patient Outcomes


**Abbreviations:** BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DFS, disease-free survival; HR, hazard ratio; MSS, melanoma-specific survival; OS, overall survival; SNP, single-nucleotide polymorphism

**CrossMark**
Categorical BMI (‡30 kg/m²) versus <30 kg/m²)

- **BMI**: 1.20 (1.09–1.31) *P*-value = 0.0002
- **Logarithmic CRP**: 1.26 (1.12–1.41) *P*-value = 0.0002
- **Age**: 1.01 (1.00–1.03) *P*-value = 0.0261

**Stage: III/IV versus I/II**

- **BMI**: 4.63 (3.54–6.04) *P*-value <0.0001
- **Logarithmic CRP**: 1.56 (1.25–1.94) *P*-value <0.0001

**Multi-variable analysis adjusted for CRP**

- **BMI**: 1.26 (1.12–1.41) *P*-value = 0.0002
- **Logarithmic CRP**: 1.21 (1.10–1.34) *P*-value = 0.0001
- **Age**: 1.04 (1.03–1.05) *P*-value <0.0001

**Abbreviations**: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio.

1 *P*-value from the Student *t*-test for the association between categorical variables and BMI.

2 Correlation measured using BMI and logarithmic CRP levels.

Elevated BMI was associated with poorer overall survival (OS) (hazard ratio [HR] = 1.20 per 5 kg/m² increase in BMI, 95% confidence interval [CI] 1.11–1.29, *P* < 0.0001). In the multi-variable analysis, after adjustment for age, sex, and stage, increased BMI remained associated with poorer OS (HR = 1.14, 95% CI 1.06–1.23, *P* < 0.0001).

Elevated BMI was associated with shorter overall survival (OS) (hazard ratio [HR] = 1.20 per 5 kg/m² increase in BMI, 95% confidence interval [CI] 1.11–1.29, *P* < 0.0001). In the multi-variable analysis, after adjustment for age, sex, and stage, increased BMI remained associated with poorer OS (HR = 1.14, 95% CI 1.06–1.23, *P* < 0.0001)
We next excluded patients whose first BMI measurement or blood draw was performed more than 1 year after diagnosis and again assessed the relationship between BMI and melanoma outcomes for the remaining 760 patients. We observed the same pattern of associations as in the full patient cohort (Supplementary Tables S2 and S3 online).

Although underweight patients in our population tended to have a lower risk of death than did normal-weight patients (HR close to 0, likely because sample size was small; Supplementary Table S4 online), overweight patients had a trend toward an elevated risk of disease recurrence and death. These risks were significantly increased in patients who were obese (P < 0.05).

Previously validated BMI-associated SNPs were assessed for association with melanoma risk and patient outcomes. None of the 82 examined SNPs significantly predicted any outcome after correction for multiple testing (P = 0.05/82 = 6.10 × 10⁻⁴) (Supplementary Table S5 online). Fifteen SNPs from different gene regions reached nominal significance (P < 0.05) in predicting BMI. In addition, several BMI-associated SNPs were associated with melanoma risk or outcome (P < 0.05). In particular, the C allele in the rs17782313 SNP (within MC4R, the melanocortin 4 receptor) was nominally associated with increased BMI (beta coefficient = 0.65, P = 0.0249), showed a trend toward association with elevated CRP (beta coefficient = 0.13, P = 0.0653), and was associated with poorer OS (HR = 1.11, 95% CI 1.00–1.23, P = 0.0422) and poorer MSS (HR = 1.16, 95% CI 1.03–1.30, P = 0.0135), but not DFS (HR = 1.08, 95% CI 0.95–1.22, P = 0.237), among patients with stage I/II melanoma (Supplementary Table S5 online).

To our knowledge, this investigation is the first to report associations between elevated BMI and poorer melanoma patient outcomes after adjustment for sex, age, and stage. A previous population-based cohort study detected no association between elevated BMI and melanoma mortality (Calle et al., 2003), but that study was small, did not assess melanoma stage or recurrence, and did not include biomarker data. Furthermore, because prior investigations have identified strong associations between obesity and elevated levels of inflammatory markers, including CRP (Ellulu et al., 2016; Oba et al., 2016), our finding that the outcome associations identified in the current investigation were weakened or became insignificant after adjustment for CRP suggests that systemic inflammation and/or metabolic syndrome may be involved in BMI-associated melanoma progression. Finally, our data suggest that genetic variations underlying elevated BMI and CRP might also contribute to poorer melanoma patient survival. Further investigation is needed to confirm these findings and to determine whether control of body weight and/or interventions to reduce chronic inflammation and metabolic syndrome could be beneficial to patients with melanoma.

All individuals gave written informed consent to participate under an Institutional Review Board-approved protocol.

CONFLICT OF INTEREST

JEG claims a consulting role for Merck. JW claims roles for the following companies: Honoraria for Dana Oncology, H. Lee Moffitt Cancer Center and Research Institute; Consulting or Advisory Role for Genentech, GlaxoSmithKline, Novartis; Speakers’ Bureau for Illumina, Bristol-Myers Squibb, Dava Oncology; Research Funding for Genentech, GlaxoSmithKline, Bristol-Myers Squibb; Travel, Accommodations, Expenses for Bristol-Myers Squibb. JP Morgan. All other authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank the individuals who volunteered to participate in this project. We also thank Dr Amy Ninetto in the Department of Scientific Publications at The University of Texas MD Anderson Cancer Center who edited the manuscript. This work was supported by the National Cancer Institute of the National Institutes of Health through SPORE grant P50 CA093459 and Cancer Center Support Grant P30 CA016672 (Clinical Trials Support Resource), as well as by philanthropic contributions to The University of Texas MD Anderson Cancer Center Moon Shots Program, The University of Texas MD Anderson Cancer Center Various Donors Melanoma and Skin Cancers Priority Program Fund; the Miriam and Jim Mulva Research Fund; the McCarty Skin Cancer Research Fund and the Marit Peterson Fund for Melanoma Research.

Shenyang Fang1, Yuling Wang1, Yifang Dang1, Andrew Gagel1, Merrick I. Ross1, Jeffrey E. Gershenson1, Janice N. Cormier2, Jennifer Wargo1, Lauren E. Haydu1, Michael A. Davies1, Jennifer L. McQuade2, Dawen Sui1, Roland L. Bassett1, John D. Reveille1
Postzygotic Mutations in Beta-Actin Are Associated with Becker’s Nevus and Becker’s Nevus Syndrome

TO THE EDITOR

Becker’s nevus is a cutaneous hamartoma affecting approximately 1 in 200 individuals (Tymen et al., 1981). Becker’s nevus appears in childhood as a unilateral tan patch, increasing in size over time. The nevus is often associated with flat-topped rete ridges, basilar hyperpigmentation, and smooth muscle hypertrophy (Figure 1b). In rare cases, termed Becker’s nevus syndrome, nevus can be accompanied by musculoskeletal abnormalities, unilateral breast hypoplasia, mental retardation, developmental delay, and cardiomyopathy (Danarti et al., 2004; Dasegowa et al., 2014; Happle and Koopman, 1997). Although most Becker’s nevi are innocuous, rapid onset during adolescence presents significant cosmetic distress. Despite prevalence of Becker’s nevi, the pathogenesis remains unknown.

A 13-year-old girl presented with hyperpigmented patches overlying her arms, legs, torso and back, and unilateral left breast and pectoralis muscle hypoplasia (Figure 1c). Lesional skin biopsy revealed epidermal acanthosis with flat-tipped rete ridges, basilar hyperpigmentation, and smooth muscle hypertrophy (Figure 1d). Her presentation was characteristic of Becker’s nevus syndrome. To identify genetic alterations underlying her condition, biopsies from a pigmented patch and adjacent nonlesional skin were subjected to exome-sequencing, along with seven independent biopsies of nonsyndromic Becker’s nevi, and an additional adjacent nonlesional skin (Supplementary Materials and Methods online; Supplementary Tables S1–S4 online). This study was approved by the institutional review board of Stanford University. Patients and parents of minors signed consent for skin biopsies performed for this study, and provided verbal consent for publication of photos. For research conducted on preexisting paraffin-embedded samples, signed consent was waived by Stanford institutional review board.

Our analysis identified an ACTB point mutation (c.C439T, p.R147C) in the index case absent from adjacent normal skin. An additional five of seven nonsyndromic Becker’s nevi contained a point mutation affecting the same codon resulting in ACTB c.C439T, p.R147C or c.C439A, p.R147S (Figure 2a, Supplementary Table S1). These variants

REFERENCES


Abbreviation: Hh, Hedgehog

Supplementary Material

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.04.007.