

## No Evidence That Genetic Variation in the Myeloid-Derived Suppressor Cell Pathway Influences Ovarian Cancer Survival

Lara E. Sucheston-Campbell<sup>1</sup>, Rikki Cannioto<sup>2</sup>, Alyssa I. Clay<sup>3</sup>, John Lewis Etter<sup>2</sup>, Kevin H. Eng<sup>4</sup>, Song Liu<sup>4</sup>, Sebastiano Battaglia<sup>5</sup>, Qiang Hu<sup>4</sup>, J. Brian Szender<sup>6</sup>, Albina Minlikeeva<sup>2</sup>, Janine M. Joseph<sup>2</sup>, Paul Mayor<sup>6</sup>, Scott I. Abrams<sup>7</sup>, Brahm H. Segal<sup>7,8</sup>, Paul K. Wallace<sup>9</sup>, Kah Teong Soh<sup>9</sup>, Emese Zsiros<sup>6</sup>, Hoda Anton-Culver<sup>10</sup>, Elisa V. Bandera<sup>11</sup>, Matthias W. Beckmann<sup>12</sup>, Andrew Berchuck<sup>13</sup>, Line Bjorge<sup>14,15</sup>, Amanda Bruegl<sup>16</sup>, Ian G. Campbell<sup>17,18</sup>, Shawn Patrice Campbell<sup>16</sup>; Georgia Chenevix-Trench<sup>19</sup>, on behalf of the Australian Ovarian Cancer Study; Daniel W. Cramer<sup>20,21</sup>, Agnieszka Dansonka-Mieszkowska<sup>22</sup>, Fanny Dao<sup>23</sup>, Brenda Diergaarde<sup>24</sup>, Thilo Doerk<sup>25</sup>, Jennifer A. Doherty<sup>26</sup>, Andreas du Bois<sup>27,28</sup>, Diana Eccles<sup>29,30</sup>, Svend Aage Engelholm<sup>31</sup>, Peter A. Fasching<sup>12</sup>, Simon A. Gayther<sup>32,33</sup>, Aleksandra Gentry-Maharaj<sup>34</sup>, Rosalind M. Glasspool<sup>35</sup>, Marc T. Goodman<sup>36,37</sup>, Jacek Gronwald<sup>38</sup>, Philipp Harter<sup>27</sup>, Alexander Hein<sup>12</sup>, Florian Heitz<sup>27,28</sup>, Peter Hillemanns<sup>25</sup>, Claus Høgdall<sup>39</sup>, Estrid V.S. Høgdall<sup>40,41</sup>, Tomasz Huzarski<sup>38</sup>, Allan Jensen<sup>40</sup>, Sharon E. Johnatty<sup>19</sup>, Audrey Jung<sup>42,43</sup>, Beth Y. Karlan<sup>44</sup>, Reudiger Klapdor<sup>25</sup>, Tomasz Kluz<sup>45</sup>, Bożena Konopka<sup>22</sup>, Susanne Krüger Kjær<sup>39,40</sup>, Jolanta Kupryjanczyk<sup>22</sup>, Diether Lambrechts<sup>46</sup>, Jenny Lester<sup>44</sup>, Jan Lubiński<sup>38</sup>, Douglas A. Levine<sup>23</sup>, Lene Lundvall<sup>47</sup>, Valerie McGuire<sup>48</sup>, Iain A. McNeish<sup>49</sup>, Usha Menon<sup>34</sup>, Francesmary Modugno<sup>24,50,51</sup>, Roberta B. Ness<sup>52</sup>, Sandra Orsulic<sup>44</sup>, James Paul<sup>35</sup>, Celeste Leigh Pearce<sup>53,54</sup>, Tanja Pejovic<sup>16,55</sup>, Paul Pharoah<sup>56,57</sup>, Susan J. Ramus<sup>58,59</sup>, Joseph Rothstein<sup>48</sup>, Mary Anne Rossing<sup>60,61</sup>, Matthias Rübner<sup>12</sup>, Joellen M. Schildkraut<sup>62</sup>, Barbara Schmalfeldt<sup>63</sup>, Ira Schwaab<sup>64</sup>, Nadeem Siddiqui<sup>65</sup>, Weiva Sieh<sup>66,67</sup>, Piotr Sobiczewski<sup>68</sup>, Honglin Song<sup>56</sup>, Kathryn L. Terry<sup>20,21</sup>, Els Van Nieuwenhuysen<sup>69</sup>, Adriaan Vanderstichele<sup>69</sup>, Ignace Vergote<sup>69</sup>, Christine S. Walsh<sup>44</sup>, Penelope M. Webb<sup>70</sup>, Nicolas Wentzensen<sup>71</sup>, Alice S. Whittemore<sup>48</sup>, Anna H. Wu<sup>54</sup>, Argyrios Ziogas<sup>72</sup>, Kunle Odunsi<sup>6</sup>, Jenny Chang-Claude<sup>42,43</sup>, Ellen L. Goode<sup>73</sup>, and Kirsten B. Moysich<sup>2</sup>

### Abstract

**Background:** The precise mechanism by which the immune system is adversely affected in cancer patients remains poorly understood, but the accumulation of immunosuppressive/promotorigenic myeloid-derived suppressor cells (MDSCs) is thought to be a prominent mechanism contributing to immunologic tolerance of malignant cells in epithelial ovarian cancer (EOC). To this end, we hypothesized genetic variation in MDSC pathway genes would be associated with survival after EOC diagnoses.

**Methods:** We measured the hazard of death due to EOC within 10 years of diagnosis, overall and by invasive subtype, attributable to SNPs in 24 genes relevant in the MDSC pathway in 10,751 women diagnosed with invasive EOC. Versatile Gene-based Association Study and the admixture likelihood

method were used to test gene and pathway associations with survival.

**Results:** We did not identify individual SNPs that were significantly associated with survival after correction for multiple testing ( $P < 3.5 \times 10^{-5}$ ), nor did we identify significant associations between the MDSC pathway overall, or the 24 individual genes and EOC survival.

**Conclusions:** In this well-powered analysis, we observed no evidence that inherited variations in MDSC-associated SNPs, individual genes, or the collective genetic pathway contributed to EOC survival outcomes.

**Impact:** Common inherited variation in genes relevant to MDSCs was not associated with survival in women diagnosed with invasive EOC. *Cancer Epidemiol Biomarkers Prev*; 26(3); 420–4. ©2016 AACR.

<sup>1</sup>College of Pharmacy, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio. <sup>2</sup>Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York. <sup>3</sup>Cancer Genetic Epidemiology, Division of Epidemiology, Mayo Clinic, Rochester, Minnesota. <sup>4</sup>Department of Biostatistics and Bioinformatics, Roswell Park Cancer Institute, Buffalo, New York. <sup>5</sup>Department of Cancer Genetics, Roswell Park Cancer Institute, Buffalo, New York. <sup>6</sup>Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, New York. <sup>7</sup>Department of Immunology, Roswell Park Cancer Institute, Buffalo, New York.

<sup>8</sup>Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York. <sup>9</sup>Department of Flow & Image Cytometry, Roswell Park Cancer Institute, Buffalo, New York. <sup>10</sup>Genetic Epidemiology Research Institute, School of Medicine, University of California Irvine, Irvine, California. <sup>11</sup>Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey. <sup>12</sup>Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany. <sup>13</sup>Department of Obstetrics and

## Introduction

Survival after a diagnosis of epithelial ovarian cancer (EOC) has seen only modest improvements in recent decades, making the identification of novel mechanisms and pathways associated with EOC prognosis imperative. EOC is associated with immunosuppressive pathways, including regulatory T cells and myeloid-derived suppressor cells (MDSC) that can be barriers to antitumor immunity and adversely affect clinical outcomes. To this end, MDSCs suppress the antigen-specific T-cell response by both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, and elevated concentrations of MDSCs have been detected in the peripheral blood of cancer patients when compared with normal controls (1, 2). We hypothesized that common inherited genetic variation in genes involved in the MDSC pathway is associated with survival following ovarian cancer diagnosis.

## Materials and Methods

We conducted a pooled analysis utilizing individual-level data from 28 studies in the Ovarian Cancer Association Consortium to assess the association of genes in the MDSC-associated pathway with EOC survival. Participants included 11,034 women ages 18 years and older with a histologically confirmed primary diagnosis of invasive EOC, fallopian tube cancer, or primary peritoneal cancer who were genotyped on the Illumina iSelect array designed for the Collaborative Oncological Gene-environment Study (3). Clinical, epidemiologic, and follow-up data were made available for all analyses.

To assess the association between invasive EOC outcome and inherited variation in the MDSC pathway, we conducted SNP, gene, and pathway-based analyses of 24 candidate genes relevant to the biology of MDSCs, as established from an extensive literature review utilizing the PubMed database (*ARG1*, *CD274*,

Gynecology, Duke University Medical Center, Durham, North Carolina.<sup>14</sup>Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway.<sup>15</sup>Department of Clinical Science, Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway.<sup>16</sup>Department of Obstetrics & Gynecology, Oregon Health & Science University, Portland, Oregon.<sup>17</sup>Cancer Genetics Laboratory, East Melbourne, Australia.<sup>18</sup>Department of Pathology, University of Melbourne, Parkville, Victoria, Australia.<sup>19</sup>Genetics and Computational Biology Department, QIMR Berghofer Medical Research Institute, Herston, Australia.<sup>20</sup>Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Boston, Massachusetts.<sup>21</sup>Harvard T. H. Chan School of Public Health, Boston, Massachusetts.<sup>22</sup>Department of Pathology and Laboratory Diagnostics, the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland.<sup>23</sup>Gynecologic Oncology, Laura and Isaac Pearlmuter Cancer Center, NYU Langone Medical Center, New York, New York.<sup>24</sup>Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania.<sup>25</sup>Department of Obstetrics and Gynecology, Hannover Medical School, Hannover, Niedersachsen, Germany.<sup>26</sup>Department of Epidemiology, The Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire.<sup>27</sup>Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte/Evang. Huysens-Stiftung/Knappschaft GmbH, Essen, Germany.<sup>28</sup>Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Kliniken Wiesbaden, Wiesbaden, Germany.<sup>29</sup>Faculty of Medicine, University of Southampton, Southampton, United Kingdom.<sup>30</sup>Wessex Clinical Genetics Service, Southampton University Hospitals Trust, Southampton, United Kingdom.<sup>31</sup>Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.<sup>32</sup>Center for Cancer Prevention and Translational Genomics, Cedars-Sinai Medical Center, Los Angeles, California.<sup>33</sup>Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, California.<sup>34</sup>Women's Cancer, Institute for Women's Health, University College London, London, United Kingdom.<sup>35</sup>The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom.<sup>36</sup>Cancer Prevention and Control, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California.<sup>37</sup>Department of Biomedical Sciences, Community and Population Health Research Institute, Cedars-Sinai Medical Center, Los Angeles, California.<sup>38</sup>Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland.<sup>39</sup>Department of Gynaecology, Rigshospitalet, University of Copenhagen, Herlev, Denmark.<sup>40</sup>Department of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark.<sup>41</sup>Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark.<sup>42</sup>Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany.<sup>43</sup>University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Heidelberg, Germany.<sup>44</sup>Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California.<sup>45</sup>Clinic of Obstetrics and Gynecology, Institute of Midwifery and Emergency Medicine, Faculty of Medicine, University of Rzeszów, Rzeszów, Poland.<sup>46</sup>Department of Oncology, Laboratory for Translational Genetics, Vesalius Research Center, University of Leuven, Leuven, Belgium.<sup>47</sup>Department of Gynecology, The Juliane Marie Centre, Rigshospitalet, Univer-

sity of Copenhagen, Copenhagen, Denmark.<sup>48</sup>Department of Health Research and Policy - Epidemiology, Stanford University School of Medicine, Stanford, California.<sup>49</sup>Institute of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Beatson Institute for Cancer Research, Glasgow, United Kingdom.<sup>50</sup>Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.<sup>51</sup>Ovarian Cancer Center of Excellence, Womens Cancer Research Program, Magee-Womens Research Institute and University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania.<sup>52</sup>The University of Texas School of Public Health, Houston, Texas.<sup>53</sup>Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan.<sup>54</sup>Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California.<sup>55</sup>Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon.<sup>56</sup>Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Cambridge, United Kingdom.<sup>57</sup>Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge, United Kingdom.<sup>58</sup>School of Women's and Children's Health, University of New South Wales, New South Wales, Australia.<sup>59</sup>The Kinghorn Cancer Centre, Garvan Institute of Medical Research, New South Wales, New South Wales, Australia.<sup>60</sup>Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington.<sup>61</sup>Department of Epidemiology, University of Washington, Seattle, Washington.<sup>62</sup>Department of Public Health Sciences, The University of Virginia, Charlottesville, Virginia.<sup>63</sup>Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.<sup>64</sup>Praxis für Humangenetik, Wiesbaden, Germany.<sup>65</sup>Department of Gynaecological Oncology, Glasgow Royal Infirmary, Glasgow, United Kingdom.<sup>66</sup>Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, New York.<sup>67</sup>Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York.<sup>68</sup>Department of Gynecologic Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland.<sup>69</sup>Division of Gynecologic Oncology, Department of Obstetrics and Gynaecology and Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium.<sup>70</sup>Population Health Department, QIMR Berghofer Medical Research Institute, Herston, Australia.<sup>71</sup>Division of Cancer Epidemiology and Genetics, NCI, Bethesda, Maryland.<sup>72</sup>Department of Epidemiology, University of California Irvine, Irvine, California.<sup>73</sup>Department of Health Science Research, Mayo Clinic, Rochester, Minnesota.

L.E. Sucheston-Campbell and R. Cannioto are first co-authors of this article.

**Corresponding Author:** Kirsten B. Moysich, Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. Phone: 716-845-8004; Fax: 716-845-8125; E-mail: kirsten.moysich@roswellpark.org

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**Table 1.** Clinical characteristics of invasive EOC cases from the Ovarian Cancer Association Consortium analyzed for association with MDSC genetic variation

Patient characteristics	Vital status at last follow-up		Total invasive EOC cases N = 10,751
	Alive n = 5,243 (48.8%)	Deceased n = 5,508 (51.2%)	
Age at diagnosis			
<50 years	1,627 (59.1%)	1,125 (40.9%)	2,752
50–69 years	3,100 (47.4%)	3,445 (52.6%)	6,545
70+ years	516 (35.5%)	938 (64.5%)	1,454
Histology			
Serous	2,765 (39.7%)	4,207 (60.3%)	6,972
High-grade serous	2,210 (38.2%)	3,568 (61.8%)	5,578
Mucinous	504 (72.1%)	197 (27.9%)	701
Endometrioid	1,058 (68.7%)	485 (31.3%)	1,543
Clear cell	529 (67.1%)	260 (32.9%)	789
Mixed cell	215 (56.7%)	166 (43.3%)	381
Undifferentiated/poorly differentiated	92 (42.6%)	124 (57.4%)	216
Unknown epithelial	70 (49.6%)	69 (50.3%)	139
Grade			
Well differentiated	757 (70.5%)	316 (29.3%)	1,073
Moderately differentiated	1,107 (50.6%)	1,079 (49.4%)	2,186
Poorly differentiated	2,185 (42.4%)	2,969 (57.6%)	5,154
Undifferentiated	284 (46.8%)	323 (53.2%)	607
Unknown	583 (58.1%)	419 (41.9%)	1,002
Stage			
Localized	1,393 (81.3%)	320 (18.7%)	1,713
Regional	1,314 (66.4%)	665 (33.6%)	1,979
Distant	2,109 (34.3%)	4,034 (65.7%)	6,134
Unknown	178 (55.5%)	143 (44.5%)	321

CSF2, CSF3, EIF2AK4, FLT3, IL10RA, IL13RA2, IL4, IL4R, IL5RA, IL6R, IDO, IRF8, KITLG, MMP1, MMP12, MMP3, MMP9, NOS2A, PSME4, STAT1, STAT3, and VEGFA). SNP selection and quality control were performed as described previously, yielding a total of 736 SNPs for analyses (4). We calculated the effective number of independent SNPs tested; this value was used in a Bonferroni correction to determine single-SNP significance (4). We utilized Cox proportional hazards regression models adjusted for age, tumor stage, and grade to estimate HRs and 95% confidence intervals (CI) representing SNP associations with EOC overall and by invasive histotype. Survival time was defined as the time from diagnosis of invasive EOC until death from any cause or time of last follow-up. Analyses accommodated left truncation to account for prevalent cases where appropriate and right censoring was done at >10 years follow-up time. Analyses and graphics were done using R (<https://www.r-project.org>). Gene- and pathway-based tests of association with hazard of death were performed using Versatile Gene-based Association Study and the admixture likelihood method, respectively (5, 6).

## Results

The clinical characteristics of the study population are presented in Table 1. As expected, the majority of patients were diagnosed with serous EOCs, had poorly differentiated tumors, and were diagnosed with distant disease.

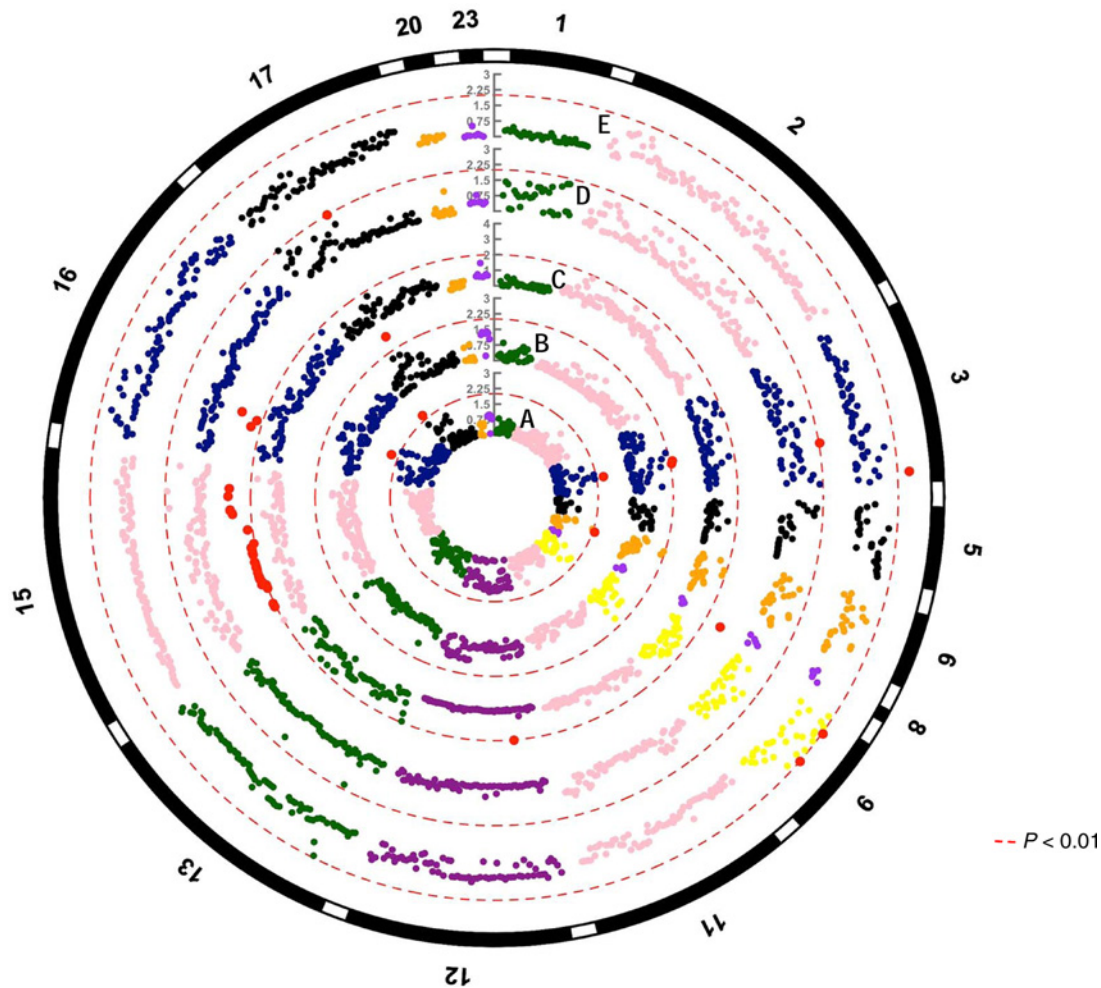
We considered  $P < 3.5 \times 10^{-5}$  as the threshold for significance, based on a Bonferroni correction for the estimated number of independent SNPs ( $n = 288$ ) across five histotypes. Single SNP associations for EOC overall and by invasive histotype are shown in circular Manhattan style plots in Fig. 1 with SNPs showing  $P < 0.01$  highlighted in red. The most significant single SNP was the C allele of rs6492925 in EIF2AK4 on chromosome 15, with a reduction in hazard of death in

women with mucinous tumors (HR = 0.57; 95% CI, 0.42–0.78;  $P = 3.7 \times 10^{-4}$ ).

The most significant gene-based associations for all invasive ovarian cancer cases (KITLG,  $P = 0.07$ ), high-grade serous (VEGFA,  $P = 0.11$ ), mucinous (EIF2AK4,  $P = 0.015$ ), endometrioid (CSF,  $P = 0.02$ ), and clear cell (CD274,  $P = 0.037$ ) did not pass multiple test correction threshold set for testing the 24 genes. Taken together, the 24 genes showed no significant association with any histotype; mucinous cell tumors showed the most significant MDSC pathway association with survival ( $P = 0.11$ ).

## Discussion

Assuming genotyping captures, on average, 70% of the variation in each gene for tests of association with overall EOC and given the proportion of events at 51%, our study had 80% power at  $P < 3.5 \times 10^{-5}$  to detect an HR of 1.11 to 1.24 for minor allele frequencies between 40% and 10%, respectively. We conducted a well-powered, hypothesis-driven study to evaluate a role for common inherited variation in MDSC pathway genes with EOC survival; we observed no evidence of an association at the SNP, gene or pathway level with EOC survival. To date, neither genome wide analyses of single SNP association with progression-free survival nor copy number variation with overall survival showed significant findings and did not report suggestive associations in these genes (7, 8). It is possible that rare variation in MDSC-associated genes not captured by these analyses could be correlated with EOC outcomes or that the magnitude of effect sizes was below detection. In addition, recent work has identified an expanding list of genes associated with MDSCs; thus, future studies should consider the importance of this emerging knowledge of MDSC biology.



**Figure 1.**

These five concentric circles are circular standard Manhattan plots. The chromosome is on the outer circle,  $-\log_{10} P$  values are on the y-axis (vertical), with each circle representing the  $P$  value from single SNP tests of association with overall survival adjusted for age, stage, and grade. **A-E**, The Manhattan plots are as follows: all ovarian cancer cases (**A**); high-grade serous (**B**); mucinous cell (**C**); endometrioid (**D**); and clear cell (**E**). The red dashed line designates  $P = 0.01$ ,  $-\log_{10}(P \text{ value}) = 2$ , with all red-colored SNPs above that line reflecting SNPs  $P < 0.01$ .

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P.A. Fasching reports receiving commercial research grants from Amgen and Novartis and has received speakers bureau honoraria from Novartis and Pfizer. No potential conflicts of interest were disclosed by the other authors.

### Authors' Contributions

**Conception and design:** L.E. Sucheston-Campbell, E. Zsiros, H. Anton-Culver, M.W. Beckmann, S.A. Engelholm, A. Ziogas, E.L. Goode, K.B. Moysich

**Development of methodology:** L.E. Sucheston-Campbell, P. Mayor, P.K. Wallace, S.A. Engelholm, T. Huzarski, K.B. Moysich

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** P. Mayor, P.K. Wallace, K.T. Soh, E. Zsiros, H. Anton-Culver, E.V. Bandera, M.W. Beckmann, A. Berchuck, L. Bjorge, I.G. Campbell, G. Chenevix-Trench, D.W. Cramer, A. Dansonka-Mieszkowska, F. Dao, B. Diergaard, T. Doerk, A. du Bois, D. Eccles, S.A. Engelholm, P.A. Fasching, S.A. Gayther, A. Gentry-Maharaj, R.M. Glasspool, M.T. Goodman, J. Gronwald, P. Harter, A. Hein, F. Heitz, P. Hillemanns, C. Høgdall, T. Huzarski, A. Jensen, B.Y. Karlan, R. Klapdor, T. Kluz, B. Konopka, S.K. Kjær, J. Kupryjanczyk, D. Lambrechts, J. Lester, D.A. Levine, V. McGuire, U. Menon,

F. Modugno, R.B. Ness, S. Orsulic, J. Paul, T. Pejovic, P. Pharoah, S.J. Ramus, M.A. Rossing, M. Rübner, J.M. Schildkraut, N. Siddiqui, P. Sobiczewski, H. Song, K.L. Terry, E. Van Nieuwenhuysen, A. Vanderstichele, I. Vergote, C.S. Walsh, P.M. Webb, N. Wentzensen, A.S. Whittemore, A.H. Wu, A. Ziogas, K. Odunsi, J. Chang-Claude, E.L. Goode, K.B. Moysich

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** L.E. Sucheston-Campbell, A.I. Clay, J.L. Etter, K.H. Eng, S. Liu, S. Battaglia, Q. Hu, J.B. Szender, P. Mayor, S.I. Abrams, B.H. Segal, P.K. Wallace, D. Lambrechts, R.B. Ness, P. Pharoah, M.A. Rossing, B. Schmalfeldt, W. Sieh, I. Vergote, A. Ziogas, K. Odunsi, K.B. Moysich

**Writing, review, and/or revision of the manuscript:** L.E. Sucheston-Campbell, R. Cannioto, A.I. Clay, J.L. Etter, K.H. Eng, S. Battaglia, J.B. Szender, A. Minlikeeva, J.M. Joseph, P. Mayor, S.I. Abrams, B.H. Segal, P.K. Wallace, K.T. Soh, E. Zsiros, H. Anton-Culver, E.V. Bandera, M.W. Beckmann, A. Berchuck, L. Bjorge, A. Bruegl, G. Chenevix-Trench, D.W. Cramer, B. Diergaard, J.A. Doherty, A. du Bois, D. Eccles, P.A. Fasching, A. Gentry-Maharaj, R.M. Glasspool, M.T. Goodman, J. Gronwald, P. Harter, F. Heitz, P. Hillemanns, C. Høgdall, E.V.S. Høgdall, A. Jensen, S.E. Johnatty, A. Jong, B.Y. Karlan, R. Klapdor, T. Kluz, B. Konopka, S.K. Kjær, D. Lambrechts, L. Lundvall, V. McGuire, I.A. McNeish, U. Menon, F. Modugno, R.B. Ness, C.L. Pearce, P. Pharoah, S.J. Ramus, M.A. Rossing, B. Schmalfeldt, N. Siddiqui,

Sucheston-Campbell et al.

W. Sieh, H. Song, I. Vergote, P.M. Webb, N. Wentzensen, A.H. Wu, K. Odunsi, J. Chang-Claude, E.L. Goode, K.B. Moysich

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** L.E. Sucheston-Campbell, R. Cannioto, J.L. Etter, J.M. Joseph, A. Berchuck, S.P. Campbell, G. Chenevix-Trench, A. Dansonka-Mieszkowska, T. Doerk, S.A. Engelholm, C. Høgdall, E.V.S. Høgdall, S.E. Johnatty, B.Y. Karlan, T. Kluz, D. Lambrechts, J. Lester, F. Modugno, S.J. Ramus, J. Rothstein, I. Schwaab

**Study supervision:** L.E. Sucheston-Campbell, S. Battaglia, P. Mayor, M.W. Beckmann, S.K. Kjær, F. Modugno, K.B. Moysich

**Other (pathologist, clinical geneticist):** J. Lubiński

**Other (acquisition of clinical information):** P. Sobczewski

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