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Analysis of Over 10,000 Cases Finds No Association between Previously-Reported Candidate Polymorphisms and Ovarian Cancer Outcome


¹Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA. ²Department of Health Science Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA. ³Department of Health Science Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA. ⁴Department of Medical Oncology, Mayo Clinic, Rochester, MN, USA. ⁵Department of Oncology, University of Cambridge, Cambridge, UK. ⁶Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. ⁷Cancer Division, Queensland Institute of Medical Research, Herston, QLD, Australia. ⁸Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. ⁹Department of Epidemiology, University of Washington, Seattle, WA, USA. ¹⁰Obstetrics and Gynecology Epidemiology Program, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA. ¹¹Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA. ¹²Department of Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA. ¹³Cancer Prevention, Detection and Control Research Program, Duke Cancer Institute, Durham, NC, USA. ¹⁴Department of Community and Family Medicine, Duke University Medical Center, Durham, NC, USA. ¹⁵Gynaecological Cancer Research Centre, UCL EGA Institute for Cancer Research, London, UK.
Women's Health, London, UK. The Juliane Marie Centre, Department of Obstetrics and Gynecology, Rigshospitalet, Copenhagen, Denmark. Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark. Memorial Sloan-Kettering Cancer Center, New York, NY, USA. International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland. Department of Epidemiology, Center for Cancer Genetics Research and Prevention, School of Medicine, University of California Irvine, Irvine, CA, USA. Department of Health Research and Policy - Epidemiology, Stanford University School of Medicine, Palo Alto, CA, USA. Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Vesalius Research Center, University of Leuven, Belgium. Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Leuven, Belgium. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda MD, USA. Department of Molecular Pathology, The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland. German Cancer Research Center, Division of Cancer Epidemiology, Heidelberg, Germany. The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA. Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark. Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Kliniken Wiesbaden, Wiesbaden, Germany. Department of Gynecology and Gynecologic Oncology, Klinikum Essen-Mitte/ Evang. Huysse-Stiftung/ Knappschaft GmbH, Essen, Germany. Section of Medicine, The Institute of Cancer Research and the Royal Marsden Hospital, Sutton, UK. University Hospital Erlangen, Department of Gynecology and Obstetrics, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center, Erlangen, Germany. Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. Cancer Genetics Laboratory, Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia. Department of Pathology, University of Melbourne, Parkville, Victoria, Australia. Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA. Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA. Cancer Epidemiology Program, University of Hawaii Cancer Center, HI, USA. Faculty of Medicine, University of Southampton, University Hospital Southampton, UK. Institute of Human Genetics, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany. The Beatson West of Scotland Cancer Centre, Glasgow, UK. Department of Surgery and Cancer, Imperial College London, London, UK. Institut für Humangenetik Wiesbaden, Wiesbaden, Germany. Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. New Jersey Department of Health, Trenton, NJ, USA. Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland. Division of Genetics and Epidemiology, Institute of Cancer Research, Sutton, UK and Breakthrough Breast Cancer Research Centre, London, UK. Gynecologic Oncology, University Hospitals Leuven, Belgium and Department of Oncology, KU Leuven, Belgium. Clinic of Gynaecological Surgery and Oncology, Pomeranian Medical University, Szczecin, Poland. Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC, USA. Section of Biostatistics and Epidemiology, The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA. Department of Gynaecological Oncology, Westmead Hospital and Westmead Institute for Cancer Research, University of Sydney at the Westmead Millennium Institute, Westmead, Australia. Department of Cancer Epidemiology, Division of Population Sciences, Moffitt Cancer Center, Tampa, FL, USA. Department of Laboratory Medicine and Pathology, Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA. Biostatistics and Informatics Shared Resource, University of Kansas Medical Center, Kansas City, KS, USA.
Abstract

**Background**—Ovarian cancer is a leading cause of cancer-related death among women. In an effort to understand contributors to disease outcome, we evaluated single-nucleotide polymorphisms (SNPs) previously associated with ovarian cancer recurrence or survival, specifically in angiogenesis, inflammation, mitosis, and drug disposition genes.

**Methods**—Twenty-seven SNPs in VHL, HGF, IL18, PRKACB, ABCB1, CYP2C8, ERCC2, and ERCC1 previously associated with ovarian cancer outcome were genotyped in 10,084 invasive cases from 28 studies from the Ovarian Cancer Association Consortium with over 37,000 observed person-years and 4,478 deaths. Cox proportional hazards models were used to examine the association between candidate SNPs and ovarian cancer recurrence or survival with and without adjustment for key covariates.

**Results**—We observed no association between genotype and ovarian cancer recurrence or survival for any of the SNPs examined.

**Conclusions**—These results refute prior associations between these SNPs and ovarian cancer outcome and underscore the importance of maximally powered genetic association studies.

**Impact**—These variants should not be used in prognostic models. Alternate approaches to uncovering inherited prognostic factors, if they exist, are needed.

INTRODUCTION

In 2012, ovarian cancer was estimated to be the seventh leading cause of female cancer-related deaths worldwide (1). Despite standardized treatment approaches, inter-individual variation in outcomes exists; understanding the source of this variation, including potential inherited factors, is of high importance (2). Our prior studies of over 400 candidate genes in biological pathways that are relevant to ovarian cancer suggested association between ovarian cancer outcome and inherited variation in certain genes (3–5). These include the angiogenesis genes VHL (3) and HGF (4), taxol efflux and metabolism genes ABCB1 and CYP2C8 (5), DNA repair genes ERCC2 and ERCC1 (5), the inflammation gene IL18 (3), and the mitosis gene PRKACB (4). Here, we sought to confirm prior associations (p<0.05) between ovarian cancer outcome and 27 single-nucleotide polymorphisms (SNPs) in these genes using a much larger sample size than the discovery studies.

MATERIALS AND METHODS

A total of 10,084 women with invasive epithelial ovarian cancer (over 37,000 person-years follow-up) including 5,248 high-grade serous cases were examined. Participants from 28 studies (Table 1) in the Ovarian Cancer Association Consortium (OCAC) were genotyped on a custom Illumina iSelect BeadArray using centralized genotype calling and quality control procedures, as previously described (6). In brief, we excluded SNPs and samples with call rate < 95%; we restricted to women with > 90% predicted European ancestry and estimated principal components (PCs) representing European substructure (6).

Cox proportional hazards regression modeling accounting for left truncation and censoring at 10 years following diagnosis was used to estimate per-allele hazard ratios (HRs) and 95% confidence intervals (CIs) for associations with death from any cause for all cases and for high-grade serous cases. Two models were assessed: a minimally adjusted model including covariates for age at diagnosis, five population substructure PCs, and study site, and a fully adjusted model which additionally included histology (for analyses of all cases only), tumor stage, tumor grade, and oral contraceptive use as these covariates were associated with survival in these data (p<0.05). Analyses were also conducted with a recurrence endpoint...
RESULTS

Overall, there were no associations between SNPs and ovarian cancer survival in either the minimally or fully adjusted models; Table 2 shows HRs, 95% CIs, and p-values for all cases and high-grade serous cases. No heterogeneity across studies was observed (p-values>0.05). SNP rs2214825 in HGF was significantly associated with survival in the minimally adjusted model (p=0.03), although not in the fully adjusted model (Table 2). After excluding 2,015 women who contributed to the original report (4), no association was seen at p<0.05 (minimally adjusted HR=1.04, 95% CI=0.98–1.10, p=0.19). Additionally, in ERCC2, SNP rs50872 conferred a slightly increased risk of death among women with high-grade serous disease (p=0.03) in the fully adjusted model, but this association was not statistically significant at α=0.05 in the minimally adjusted model, and, after excluding 497 women in the original report (5), no statistically significant association was seen (fully adjusted HR=1.06, 95% CI=1.00–1.14, p=0.06). Near identical results were seen for these SNPs in analysis of time to recurrence. On the whole, while these candidates showed promise with large effect sizes (i.e., HRs >1.23 or <0.82) in earlier reports (3–5), our very large scale study refutes association at these loci with 95% CIs excluding prior risk estimates.

DISCUSSION

Here, we aimed to confirm the relationship between previously-associated SNPs and ovarian cancer outcome using a sample of over 10,000 women from 28 studies participating in the OCAC. Results of this analysis did not confirm the associations originally observed (3–5). While associations with other SNPs may exist, we report no consistent associations between these 27 SNPs and ovarian cancer outcome and believe it critical to disseminate results to reduce the possibility of publication bias. These null results highlight the necessity of large-scale replication of initial SNP associations, as the most likely explanation for non-replication is that initial false positive findings resulted from chance in smaller studies. Studies of SNPs and cancer outcome have been less fruitful than cancer susceptibility studies (7). This may be due to several challenges: lack of a large collection of homogeneous cases due to missing baseline clinical data, inability to verify chemotherapeutic or surgical data to evaluate whether SNP effects arise only in certain clinical contexts, and inconsistent follow-up methods leading to variable completeness of endpoints (8). Although ovarian cancer has high mortality rate and a generally uniform treatment compared to other cancers, there is a trade-off in expected power between the larger sample sizes of observational studies and the detailed data available from clinical trials. We propose that utilization of both study designs, including detailed tumor characteristics and coordination with animal and mechanistic studies, is the best path forward for the identification of predictive and prognostic factors in ovarian cancer outcomes.

Acknowledgments

We thank all the individuals who took part in this study and all the researchers, clinicians and technical and administrative staff who have made possible the many studies contributing to this work. In particular, we thank: D. Bowtell, A. deFazio, D. Gertig, A. Green, P. Parsons, N. Hayward, P. Webb and D. Whiteman (AUS); G. Peuteman, T. Van Brussel and D. Smeets (BEL); the staff of the genotyping unit, S. LaBoissière and F. Robidoux (Genome Quebec); T. Koehler (GER); G.S. Keeney, S. Windebank, C. Hilker and J. Vollenweider (MAY); L. Rodriguez, M. King, U. Chandran, D. Giffins, and T. Puvananayagam (NJO); M. Sherman, A. Hutchinson, N. Szeszenia-Dabrowska, B. Peplonska, W. Zatonski, A. Soni, P. Chao and M. Stagner (POL); C. Luccarini, P. Harrington, the SEARCH team, and ECRIC (SEA); the Scottish Gynaecological Clinical Trials group and...
REFERENCES


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<th>Abbreviation</th>
<th>Name</th>
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<th>High-Grade Serous</th>
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<td></td>
<td></td>
<td></td>
<td>N</td>
<td>Person-years</td>
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<td>UK: East Anglia and West Midlands</td>
<td>Population</td>
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<td>426 (32%)</td>
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<td>Australia</td>
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<td>432 (51%)</td>
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<td>Diseases of the Ovary and their Evaluation</td>
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<td>761</td>
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<td>1,224</td>
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<td>MAY</td>
<td>Mayo Clinic Ovarian Cancer Case-Control Study</td>
<td>USA: North Central (MN, SD, ND, IL, IA, WI)</td>
<td>Clinic</td>
<td>695</td>
<td>364 (52%)</td>
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<td>NEC</td>
<td>New England Case Control Study</td>
<td>USA: New Hampshire and Eastern Massachusetts</td>
<td>Population</td>
<td>671</td>
<td>334 (50%)</td>
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<td>USC</td>
<td>Los Angeles County Case-control studies of Ovarian Cancer-1</td>
<td>Los Angeles County</td>
<td>Population</td>
<td>638</td>
<td>273 (43%)</td>
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<td>1,263</td>
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<td>NCO</td>
<td>North Carolina Ovarian Cancer Study</td>
<td>USA: Central and eastern North Carolina (48 counties)</td>
<td>Population</td>
<td>636</td>
<td>327 (51%)</td>
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<td>UKO</td>
<td>United Kingdom Ovarian Cancer Population Study</td>
<td>United Kingdom (England, Wales and Northern Ireland)</td>
<td>Population</td>
<td>620</td>
<td>200 (32%)</td>
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<td>MAL</td>
<td>MALignant OVArian Cancer</td>
<td>Denmark</td>
<td>Population</td>
<td>440</td>
<td>322 (73%)</td>
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<tr>
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<td></td>
<td>666</td>
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<tr>
<td>MSK</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>USA: New York City</td>
<td>Hospital</td>
<td>391</td>
<td>108 (28%)</td>
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<tr>
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<tr>
<td>POC</td>
<td>Polish Ovarian Cancer Study</td>
<td>Poland: Szczecin, Poznan, Opole, Rzeszow</td>
<td>Population</td>
<td>355</td>
<td>203 (57%)</td>
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<td></td>
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<td>0</td>
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<tr>
<td>UCI</td>
<td>University of California Irvine Ovarian Study</td>
<td>USA: Southern California (Orange and San-Diego, Imperial Counties)</td>
<td>Population</td>
<td>275</td>
<td>90 (33%)</td>
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<tr>
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<tr>
<td>STA</td>
<td>Genetic Epidemiology of Ovarian Cancer</td>
<td>USA: Six counties in the San Francisco Bay area</td>
<td>Population</td>
<td>257</td>
<td>142 (55%)</td>
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<td>581</td>
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<td>LAX</td>
<td>Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute</td>
<td>USA: Southern California</td>
<td>Hospital</td>
<td>256</td>
<td>148 (58%)</td>
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<td>831</td>
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<tr>
<td>BEL</td>
<td>Belgian Ovarian Cancer Study</td>
<td>Belgium, University Hospital Leuven</td>
<td>Hospital</td>
<td>245</td>
<td>53 (22%)</td>
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<td>220</td>
</tr>
<tr>
<td>POL</td>
<td>Polish Ovarian Cancer Case Control Study</td>
<td>Poland, Warszaw and Lodz</td>
<td>Population</td>
<td>211</td>
<td>113 (54%)</td>
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<td>187</td>
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<td>WOC</td>
<td>Warsaw Ovarian Cancer Study</td>
<td>Poland: Warsaw and central Poland</td>
<td>Clinic</td>
<td>201</td>
<td>85 (42%)</td>
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<td></td>
<td>498</td>
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<tr>
<td>GER</td>
<td>German Ovarian Cancer Study</td>
<td>Germany: two geographical regions in the states of Baden-Württemberg and Rhineland-Palatinate</td>
<td>Population</td>
<td>183</td>
<td>118 (65%)</td>
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<td>Name</td>
<td>Location</td>
<td>Case source</td>
<td>All Histologies</td>
<td>High-Grade Serous</td>
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<tr>
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<td>------------------------------------</td>
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<tr>
<td>NJO</td>
<td>New Jersey Ovarian Cancer Study</td>
<td>USA: New Jersey (six counties)</td>
<td>Population</td>
<td>169</td>
<td>33 (20%)</td>
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<tr>
<td>PVD</td>
<td>Danish Pelvic Mass Study</td>
<td>Denmark</td>
<td>Population</td>
<td>162</td>
<td>69 (43%)</td>
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<tr>
<td>HSK</td>
<td>Dr. Horst Schmidt Kliniken</td>
<td>Germany</td>
<td>Clinic</td>
<td>141</td>
<td>84 (60%)</td>
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<tr>
<td>RMH</td>
<td>Royal Marsden Hospital Ovarian Cancer Study</td>
<td>UK: London</td>
<td>Hospital</td>
<td>138</td>
<td>59 (43%)</td>
</tr>
<tr>
<td>SRO</td>
<td>Scottish Randomised Trial in Ovarian Cancer</td>
<td>Coordinated through clinical trials unit, Glasgow UK from patients recruited world-wide</td>
<td>Clinical trial</td>
<td>132</td>
<td>67 (51%)</td>
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<tr>
<td>BAV</td>
<td>Bavarian Ovarian Cancer Cases and Controls</td>
<td>Southeast Germany</td>
<td>Population</td>
<td>85</td>
<td>34 (40%)</td>
</tr>
<tr>
<td>SOC</td>
<td>Southampton Ovarian Cancer Study</td>
<td>United Kingdom, Wessex region</td>
<td>Hospital</td>
<td>74</td>
<td>33 (45%)</td>
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<tr>
<td>HAW</td>
<td>Hawaii Ovarian Cancer Case-Control Study</td>
<td>USA: Hawaii</td>
<td>Population</td>
<td>60</td>
<td>27 (45%)</td>
</tr>
<tr>
<td>ORE</td>
<td>Oregon Ovarian Cancer Registry</td>
<td>Portland, Oregon</td>
<td>Clinic</td>
<td>52</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>UKR</td>
<td>UK Familial Ovarian Cancer Registry</td>
<td>UK: National</td>
<td>Familial register</td>
<td>47</td>
<td>29 (62%)</td>
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<tr>
<td>TOTAL</td>
<td></td>
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<td>10,084</td>
<td>4,478 (44%)</td>
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</table>

All cases are of European ancestry; grade is missing for UCI, RMH, and UKR, thus excluded from high grade serous analysis; person-years indicates person-years at risk accounting for left truncation and right censoring at 10 years.
### Table 2

Association between SNPs and Ovarian Cancer Survival

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Min/Maj</th>
<th>MAF</th>
<th>Minimally Adjusted HR (95% CI)</th>
<th>p</th>
<th>Fully Adjusted HR (95% CI)</th>
<th>p</th>
<th>Minimally Adjusted HR (95% CI)</th>
<th>p</th>
<th>Fully Adjusted HR (95% CI)</th>
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<tr>
<td>PRKACB</td>
<td>rs12031680 A/C</td>
<td>0.34</td>
<td>1.02 (0.97–1.07)</td>
<td>0.41</td>
<td>1.02 (0.97–1.06)</td>
<td>0.42</td>
<td>1.00 (0.94–1.06)</td>
<td>1.00</td>
<td>1.01 (0.96–1.07)</td>
<td>0.62</td>
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<td>rs12405120 G/A</td>
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<td>1.00 (0.96–1.05)</td>
<td>0.86</td>
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<td>1.00 (0.95–1.06)</td>
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<td>rs1402694  G/A</td>
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<td>0.99 (0.95–1.03)</td>
<td>0.65</td>
<td>0.98 (0.94–1.02)</td>
<td>0.39</td>
<td>0.98 (0.93–1.03)</td>
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<td></td>
<td>rs12129768 G/A</td>
<td>0.11</td>
<td>0.99 (0.93–1.06)</td>
<td>0.85</td>
<td>1.02 (0.95–1.09)</td>
<td>0.57</td>
<td>0.99 (0.91–1.08)</td>
<td>0.85</td>
<td>1.03 (0.94–1.12)</td>
<td>0.56</td>
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<td>VHL</td>
<td>rs265318   C/A</td>
<td>0.11</td>
<td>1.02 (0.96–1.09)</td>
<td>0.55</td>
<td>1.05 (0.99–1.12)</td>
<td>0.12</td>
<td>1.04 (0.96–1.13)</td>
<td>0.31</td>
<td>1.06 (0.98–1.15)</td>
<td>0.18</td>
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<td></td>
<td>rs1678607  A/C</td>
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### All Histologies (n=10,084)

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SNPs are listed by rsid in chromosomal order; Min/Maj, minor/major allele; MAF, minor allele frequency; HR, hazard ratio represent the relative risk of death per-allele (0, 1, 2 copies of the minor allele); 95% CI, 95% confidence interval; P, P-values < 0.05 are bold; fully adjusted Cox model adjusted for age at diagnosis, population substructure principal components, study site, histology (for analyses of all cases only), tumor stage (I, II, III, unknown), tumor grade (grade 1, grade 2, grade 3, grade 4, unknown), and oral contraceptive use (yes, no, unknown); minimally adjusted Cox model adjusted for age at diagnosis, population substructure principal components, and study site.