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

Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2013 May ; 22(5): 987–992. doi:10.1158/1055-9965.EPI-13-0028.

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

Kristin L. White[1], **Robert A. Vierkant**[2], **Zachary C. Fogarty**[2], **Bridget Charbonneau**[3], **Matthew S. Block**[4], **Paul D.P. Pharoah**[5,6], **Georgia Chenevix-Trench**[7], **Mary Anne Rossing**[8,9], **Daniel W. Cramer**[10,11], **C. Leigh Pearce**[12], **Joellen M. Schildkraut**[13,14], **Usha Menon**[15], **Susanne Kruger Kjaer**[16,17], **Douglas A. Levine**[18], **Jacek Gronwald**[19], **Hoda Anton Culver**[20], **Alice S. Whittemore**[21], **Beth Y. Karlan**[22], **Diether Lambrechts**[23,24], **Nicolas Wentzensen**[25], **Jolanta Kupryjanczyk**[26], **Jenny Chang-Claude**[27], **Elisa V. Bandera**[28], **Estrid Hogdall**[17,29], **Florian Heitz**[30,31], **Stanley B. Kaye**[32], **Peter A. Fasching**[33,34], **Ian Campbell**[35,36], **Marc T. Goodman**[37], **Tanja Pejovic**[38,39], **Yukie Bean**[38,39], **Galina Lurie**[40], **Diana Eccles**[41], **Alexander Hein**[33], **Matthias W. Beckmann**[33], **Arif B. Ekici**[42], **James Paul**[43], **Robert Brown**[44], **James Flanagan**[44], **Philipp Harter**[30,31], **Andreas du Bois**[30,31], **Ira Schwaab**[45], **Claus K. Hogdall**[16], **Lene Lundvall**[16], **Sara H. Olson**[46], **Irene Orlow**[46], **Lisa E. Paddock**[47], **Anja Rudolph**[27], **Ursula Eilber**[27], **Agnieszka Dansonka-Mieszkowska**[26], **Iwona K. Rzepecka**[26], **Izabela Ziolkowska-Seta**[48], **Louise Brinton**[25], **Hannah Yang**[25], **Montserrat Garcia-Closas**[49], **Evelyn Despierre**[50], **Sandrina Lambrechts**[50], **Ignace Vergote**[50], **Christine Walsh**[22], **Jenny Lester**[22], **Weiva Sieh**[21], **Valerie McGuire**[21], **Joseph H. Rothstein**[21], **Argyrios Ziogas**[20], **Jan Lubiński**[19], **Cezary Cybulski**[19], **Janusz Menkiszak**[51], **Allan Jensen**[17], **Simon A. Gayther**[12], **Susan J. Ramus**[12], **Aleksandra Gentry-Maharaj**[15], **Andrew Berchuck**[52], **Anna H. Wu**[12], **Malcolm C. Pike**[12,46], **David Van Den Berg**[12], **Kathryn L. Terry**[10,11], **Allison F. Vitonis**[10], **Jennifer A. Doherty**[53], **Sharon Johnatty**[7], **Anna deFazio**[54], **AOCS/ACS**, **Honglin Song**[5], **Jonathan Tyrer**[5], **Thomas A. Sellers**[55], **Catherine M. Phelan**[55], **Kimberly R. Kalli**[4], **Julie M. Cunningham**[56], **Brooke L. Fridley**[57], and **Ellen L. Goode**[3]

[1]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA. [2]Department of Health Science Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA. [3]Department of Health Science Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA. [4]Department of Medical Oncology, Mayo Clinic, Rochester, MN, USA. [5]Department of Oncology, University of Cambridge, Cambridge, UK. [6]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. [7]Cancer Division, Queensland Institute of Medical Research, Herston, QLD, Australia. [8]Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. [9]Department of Epidemiology, University of Washington, Seattle, WA, USA. [10]Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. [11]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA. [12]Department of Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA. [13]Cancer Prevention, Detection and Control Research Program, Duke Cancer Institute, Durham, NC, USA. [14]Department of Community and Family Medicine, Duke University Medical Center, Durham, NC, USA. [15]Gynaecological Cancer Research Centre, UCL EGA Institute for

Address correspondence to: Ellen L. Goode, Ph.D., M.P.H., Department of Health Sciences Research, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA, Phone 507/266-7997; Fax 507/266-2478, egoode@mayo.edu.

The authors have no financial conflicts of interest.

Women's Health, London, UK. [16]The Juliane Marie Centre, Department of Obstetrics and Gynecology, Rigshospitalet, Copenhagen, Denmark. [17]Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark. [18]Memorial Sloan-Kettering Cancer Center, New York, NY, USA. [19]International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland. [20]Department of Epidemiology, Center for Cancer Genetics Research and Prevention, School of Medicine, University of California Irvine, Irvine, CA, USA. [21]Department of Health Research and Policy - Epidemiology, Stanford University School of Medicine, Palo Alto, CA, USA. [22]Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA. [23]Vesalius Research Center, University of Leuven, Belgium. [24]Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Leuven, Belgium. [25]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda MD, USA. [26]Department of Molecular Pathology, The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland. [27]German Cancer Research Center, Division of Cancer Epidemiology, Heidelberg, Germany. [28]The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA. [29]Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark. [30]Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Kliniken Wiesbaden, Wiesbaden, Germany. [31]Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte/ Evang. Huyssens-Stiftung/ Knappschaft GmbH, Essen, Germany. [32]Section of Medicine, The Institute of Cancer Research and the Royal Marsden Hospital, Sutton, UK. [33]University Hospital Erlangen, Department of Gynecology and Obstetrics, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center, Erlangen, Germany. [34]Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. [35]Cancer Genetics Laboratory, Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia. [36]Department of Pathology, University of Melbourne, Parkville, Victoria, Australia. [37]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA. [38]Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA. [39]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA. [40]Cancer Epidemiology Program, University of Hawaii Cancer Center, HI, USA. [41]Faculty of Medicine, University of Southampton, University Hospital Southampton, UK. [42]Institute of Human Genetics, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany. [43]The Beatson West of Scotland Cancer Centre, Glasgow, UK. [44]Department of Surgery and Cancer, Imperial College London, London, UK. [45]Institut für Humangenetik Wiesbaden, Wiesbaden, Germany. [46]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. [47]New Jersey Department of Health, Trenton, NJ, USA. [48]The Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland. [49]Division of Genetics and Epidemiology, Institute of Cancer Research, Sutton, UK and Breakthrough Breast Cancer Research Centre, London, UK. [50]Gynecologic Oncology, University Hospitals Leuven, Belgium and Department of Oncology, KU Leuven, Belgium. [51]Clinic of Gynaecological Surgery and Oncology, Pomeranian Medical University, Szczecin, Poland. [52]Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC, USA. [53]Section of Biostatistics and Epidemiology, The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA. [54]Department of Gynaecological Oncology, Westmead Hospital and Westmead Institute for Cancer Research, University of Sydney at the Westmead Millennium Institute, Westmead, Australia. [55]Department of Cancer Epidemiology, Division of Population Sciences, Moffitt Cancer Center, Tampa, FL, USA. [56]Department of Laboratory Medicine and Pathology, Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA. [57]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

defined by time to disease recurrence or death (377 additional events, including 273 among women with high-grade serous disease).

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. Rodriquez, M. King, U. Chandran, D. Gifkins, 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 Trails group and

SCOTROC1 investigators (SRO); I. Jacobs, M. Widschwendter, E. Wozniak, N. Balogun, A. Ryan and J. Ford (UKO); C. Pye (UKR); A. Amin Al Olama, K. Michilaidou, and K. Kuchenbäker (COGS). The Australian Ovarian Cancer Study (AOCS) Management Group (D Bowtell, G. Chenevix-Trench, A. deFazio, D. Gertig, A. Green, and P.M. Webb) gratefully acknowledges the contribution of all the clinical and scientific collaborators (see reference 9). The Australian Cancer Study (ACS) Management Group comprises A. Green, P. Parsons, N. Hayward, P.M. Webb, and D. Whiteman.

The COGS project is funded through a European Commission's Seventh Framework Programme grant (agreement number 223175 - HEALTH-F2-2009-223175). The Ovarian Cancer Association Consortium is supported by a grant from the Ovarian Cancer Research Fund thanks to donations by the family and friends of Kathryn Sladek Smith (PPD/RPCI.07). The scientific development and funding for this project were in part supported by the Genetic Associations and Mechanisms in Oncology (GAME-ON): a NCI Cancer Post-GWAS Initiative (U19-CA148112). G.C.-T. and P.M.W. are supported by the National Health and Medical Research Council. B.K. holds an American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN).

Funding of the constituent studies was provided by the American Cancer Society (CRTG-00-196-01-CCE); the California Cancer Research Program (00-01389V-20170, N01-CN25403, 2II0200); the Canadian Institutes for Health Research; Cancer Council Victoria; Cancer Council Queensland; Cancer Council New South Wales; Cancer Council South Australia; Cancer Council Tasmania; Cancer Foundation of Western Australia; the Cancer Institute of New Jersey; Cancer Research UK (C490/A6187, C490/A10119, C490/A10124, C536/A13086, C536/A6689); the Celma Mastry Ovarian Cancer Foundation; the Danish Cancer Society (94-222-52); the ELAN Program of the University of Erlangen-Nuremberg; the Eve Appeal; the Helsinki University Central Hospital Research Fund; Helse Vest; Imperial Experimental Cancer Research Centre (C1312/A15589); the Norwegian Cancer Society; the Norwegian Research Council; the Ovarian Cancer Research Fund; Nationaal Kankerplan of Belgium; the L & S Milken Foundation; the Polish Ministry of Science and Higher Education; the US National Cancer Institute (K07-CA095666, K07-CA143047, K22-CA138563, N01-CN55424, N01-PC067010, N01-PC035137, P01-CA017054, P01-CA087696, P30-CA072720, P30-CA15083, P50-CA105009, P50-CA136393, R01-CA014089, R01-CA016056, R01-CA017054, R01-CA049449, R01-CA050385, R01-CA054419, R01-CA058598, R01-CA058860, R01-CA061107, R01-CA061132, R01-CA063682, R01-CA064277, R01-CA067262, R01-CA071766, R01-CA074850, R01-CA076016, R01-CA080742, R01-CA080978, R01-CA083918, R01-CA087538, R01-CA092044, R01-095023, R01-CA106414, R01-CA122443, R01-CA61107, R01-CA112523, R01-CA114343, R01-CA126841, R01-CA136924, R01-CA149429, R03-CA113148, R03-CA115195, R37-CA070867, R37-CA70867, U01-CA069417, U01-CA071966 and Intramural research funds); the US Army Medical Research and Material Command (DAMD17-98-1-8659, DAMD17-01-1-0729, DAMD17-02-1-0666, DAMD17-02-1-0669, W81XWH-10-1-0280); the National Health and Medical Research Council of Australia (199600 and 400281); the German Federal Ministry of Education and Research of Germany Programme of Clinical Biomedical Research (01 GB 9401); the state of Baden-Württemberg through Medical Faculty of the University of Ulm (P.685); the Minnesota Ovarian Cancer Alliance; the Mayo Foundation; the Fred C. and Katherine B. Andersen Foundation; the Lon V. Smith Foundation (LVS-39420); the Polish Committee for Scientific Research (4P05C 028 14 and 2P05A 068 27); the Oak Foundation; the OHSU Foundation; the Mermaid I project; the Rudolf-Bartling Foundation; the UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge, Imperial College London, University College Hospital “Womens Health Theme” and the Royal Marsden Hospital; and WorkSafeBC.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians. 2011; 61:69–90. [PubMed: 21296855]
2. Bolton KL, Ganda C, Berchuck A, Pharaoh PD, Gayther SA. Role of common genetic variants in ovarian cancer susceptibility and outcome: progress to date from the Ovarian Cancer Association Consortium (OCAC). Journal of Internal Medicine. 2012; 271:366–378. [PubMed: 22443200]
3. Goode EL, Maurer MJ, Sellers TA, Phelan CM, Kalli KR, Fridley BL, et al. Inherited determinants of ovarian cancer survival. Clin Cancer Res. 2010; 16:995–1007. [PubMed: 20103664]
4. Goode EL, Chenevix-Trench G, Hartmann LC, Fridley BL, Kalli KR, Vierkant RA, et al. Assessment of hepatocyte growth factor in ovarian cancer mortality. Cancer Epidemiology, Biomarkers & Prevention. 2011; 20:1638–1648.
5. Peethambaram P, Fridley BL, Vierkant RA, Larson MC, Kalli KR, Elliott EA, et al. Polymorphisms in ABCB1 and ERCC2 associated with ovarian cancer outcome. Int J Mol Epidemiol Genet. 2011; 2:185–195. [PubMed: 21686133]
6. Pharoah PDP, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, et al. GWAS meta-analysis and replication identifies three novel common susceptibility loci for ovarian cancer. Nat Genet. in press.

7. Chung CC, Chanock SJ. Current status of genome-wide association studies in cancer. Hum Genet. 2011; 130:59–78. [PubMed: 21678065]

8. Diaz-Padilla I, Amir E, Marsh S, Liu G, Mackay H. Genetic polymorphisms as predictive and prognostic biomarkers in gynecological cancers: a systematic review. Gynecol Oncol. 2012; 124:354–365. [PubMed: 22063461]

9. http://www.aocstudy.org/.

Table 1

Participating Invasive Epithelial Ovarian Cancer Studies

Abbreviation	Name	Location	Case source	All Histologies			High-Grade Serous		
				N	N Deaths (%)	Person-years	N	N Deaths (%)	Person-years
SEA	Study of Epidemiology and Risk Factors in Cancer Heredity	UK: East Anglia and West Midlands	Population	1,341	426 (32%)	5,010	518	229 (44%)	1,595
AUS	Australian Ovarian Cancer Study/Australian Cancer Study (Ovarian Cancer)	Australia	Population	848	432 (51%)	2,796	498	313 (63%)	1,547
DOV	Diseases of the Ovary and their Evaluation	USA: 13 counties in western Washington state	Population	761	296 (39%)	2,280	435	193 (44%)	1,224
MAY	Mayo Clinic Ovarian Cancer Case-Control Study	USA: North Central (MN, SD, ND, IL, IA, WI)	Clinic	695	364 (52%)	1,858	497	297 (60%)	1,233
NEC	New England Case Control Study	USA: New Hampshire and Eastern Massachusetts	Population	671	334 (50%)	3,948	343	236 (69%)	1,573
USC	Los Angeles County Case-control studies of Ovarian Cancer-1	Los Angeles County	Population	638	273 (43%)	2,323	363	189 (52%)	1,263
NCO	North Carolina Ovarian Cancer Study	USA: Central and eastern North Carolina (48 counties)	Population	636	327 (51%)	2,708	366	240 (66%)	1,382
UKO	United Kingdom Ovarian Cancer Population Study	United Kingdom (England, Wales and Northern Ireland)	Population	620	200 (32%)	2,180	269	110 (41%)	941
MAL	MALignant OVArian Cancer	Denmark	Population	440	322 (73%)	2,046	183	158 (86%)	666
MSK	Memorial Sloan-Kettering Cancer Center	USA: New York City	Hospital	391	108 (28%)	1,070	302	84 (28%)	749
POC	Polish Ovarian Cancer Study	Poland: Szczecin, Poznan, Opole, Rzeszów	Population	355	203 (57%)	1,288	0	0	0
UCI	University of California Irvine Ovarian Study	USA: Southern California (Orange and San-Diego, Imperial Counties)	Population	275	90 (33%)	968	144	63 (44%)	456
STA	Genetic Epidemiology of Ovarian Cancer	USA: Six counties in the San Francisco Bay area	Population	257	142 (55%)	1,300	135	95 (70%)	581
LAX	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	USA: Southern California	Hospital	256	148 (58%)	1,050	201	127 (63%)	831
BEL	Belgian Ovarian Cancer Study	Belgium, University Hospital Leuven	Hospital	245	53 (22%)	307	173	46 (27%)	220
POL	Polish Ovarian Cancer Case Control Study	Poland, Warszaw and Lodz	Population	211	113 (54%)	746	60	40 (67%)	187
WOC	Warsaw Ovarian Cancer Study	Poland: Warsaw and central Poland	Clinic	201	85 (42%)	724	143	74 (52%)	498
GER	German Ovarian Cancer Study	Germany: two geographical regions in the states of Baden-Württemberg and Rhineland-Palatinate	Population	183	118 (65%)	907	75	59 (79%)	312

Abbreviation	Name	Location	Case source	All Histologies			High-Grade Serous		
				N	N Deaths (%)	Person-years	N	N Deaths (%)	Person-years
NJO	New Jersey Ovarian Cancer Study	USA: New Jersey (six counties)	Population	169	33 (20%)	316	80	24 (30%)	135
PVD	Danish Pelvic Mass Study	Denmark	Population	162	69 (43%)	438	121	58 (48%)	310
HSK	Dr. Horst Schmidt Kliniken	Germany	Clinic	141	84 (60%)	634	109	71 (65%)	463
RMH	Royal Marsden Hospital Ovarian Cancer Study	UK: London	Hospital	138	59 (43%)	1,000	0	0	0
SRO	Scottish Randomised Trial in Ovarian Cancer	Coordinated through clinical trials unit, Glasgow UK from patients recruited world-wide	Clinical trial	132	67 (51%)	231	94	47 (50%)	169
BAV	Bavarian Ovarian Cancer Cases and Controls	Southeast Germany	Population	85	34 (40%)	245	44	18 (41%)	119
SOC	Southampton Ovarian Cancer Study	United Kingdom, Wessex region	Hospital	74	33 (45%)	157	25	10 (40%)	47
HAW	Hawaii Ovarian Cancer Case-Control Study	USA: Hawaii	Population	60	27 (45%)	266	36	18 (50%)	145
ORE	Oregon Ovarian Cancer Registry	Portland, Oregon	Clinic	52	9 (17%)	123	34	6 (18%)	71
UKR	UK Familial Ovarian Cancer Registry	UK: National	Familial register	47	29 (62%)	254	0	0	0
	TOTAL			**10,084**	**4,478 (44%)**	**37,171**	**5,248**	**2,805 (53%)**	**16,717**

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.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2013 November 01.

Table 2

Association between SNPs and Ovarian Cancer Survival

				All Histologies (n=10,084)				High-Grade Serous (n=5,248)			
				Minimally Adjusted		Fully Adjusted		Minimally Adjusted		Fully Adjusted	
Gene	SNP	Min/Maj	MAF	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
PRKACB	rs12031680	A/C	0.34	1.02 (0.97–1.07)	0.41	1.02 (0.97–1.06)	0.42	1.00 (0.94–1.06)	1.00	1.01 (0.96–1.07)	0.62
	rs12405120	G/A	0.49	1.00 (0.96–1.05)	0.86	1.01 (0.96–1.05)	0.79	1.01 (0.96–1.06)	0.73	1.00 (0.95–1.06)	0.95
	rs1402694	G/A	0.44	0.99 (0.95–1.03)	0.65	0.98 (0.94–1.02)	0.39	0.98 (0.93–1.03)	0.40	1.00 (0.94–1.05)	0.87
	rs12129768	G/A	0.11	0.99 (0.93–1.06)	0.85	1.02 (0.95–1.09)	0.57	0.99 (0.91–1.08)	0.85	1.03 (0.94–1.12)	0.56
VHL	rs265318	C/A	0.11	1.02 (0.96–1.09)	0.55	1.05 (0.99–1.12)	0.12	1.04 (0.96–1.13)	0.31	1.06 (0.98–1.15)	0.18
	rs1678607	A/C	0.12	1.01 (0.95–1.07)	0.79	1.02 (0.96–1.08)	0.57	1.00 (0.92–1.08)	0.99	1.00 (0.92–1.08)	0.95
HGF	rs1800793	A/G	0.20	1.05 (0.99–1.10)	0.09	1.03 (0.98–1.08)	0.26	1.05 (0.99–1.12)	0.10	1.05 (0.98–1.12)	0.17
	rs2214825	A/G	0.23	1.06 (1.01–1.11)	0.03	1.04 (0.99–1.09)	0.10	1.06 (1.00–1.13)	0.05	1.06 (1.00–1.12)	0.07
ABCB1	rs2235023	A/G	0.07	0.98 (0.90–1.06)	0.54	0.98 (0.90–1.06)	0.59	0.98 (0.89–1.08)	0.72	1.00 (0.90–1.10)	0.96
	rs13237132	G/C	0.32	1.01 (0.96–1.05)	0.78	1.01 (0.97–1.06)	0.54	1.02 (0.97–1.08)	0.44	1.01 (0.96–1.07)	0.61
	rs12334183	G/A	0.20	0.99 (0.94–1.04)	0.58	0.98 (0.93–1.03)	0.37	0.96 (0.90–1.02)	0.21	0.95 (0.89–1.01)	0.12
	rs10264990	G/A	0.34	1.00 (0.96–1.04)	0.90	1.00 (0.96–1.05)	0.84	1.02 (0.96–1.08)	0.54	1.01 (0.96–1.07)	0.72
	rs4148732	G/A	0.14	1.01 (0.96–1.08)	0.63	1.01 (0.95–1.07)	0.73	1.03 (0.95–1.11)	0.47	0.99 (0.92–1.08)	0.89
CYP2C8	rs1934954	G/A	0.08	0.97 (0.90–1.05)	0.50	1.00 (0.93–1.08)	0.99	0.97 (0.88–1.07)	0.55	0.98 (0.89–1.08)	0.71
	rs11188148	G/A	0.12	0.99 (0.93–1.06)	0.81	1.00 (0.94–1.07)	0.98	0.97 (0.89–1.06)	0.52	0.98 (0.90–1.07)	0.68
	rs1934983	G/A	0.29	0.99 (0.95–1.04)	0.79	0.99 (0.95–1.04)	0.78	1.00 (0.94–1.06)	0.92	1.00 (0.94–1.06)	0.89
	rs2185571	A/G	0.29	0.99 (0.95–1.04)	0.71	0.99 (0.95–1.04)	0.67	0.99 (0.94–1.06)	0.86	0.99 (0.94–1.05)	0.82
IL18	rs549908	C/A	0.31	1.02 (0.98–1.07)	0.38	1.03 (0.98–1.08)	0.20	0.99 (0.94–1.05)	0.84	1.00 (0.94–1.05)	0.88
	rs5744247	C/G	0.10	0.95 (0.89–1.02)	0.17	0.96 (0.89–1.03)	0.23	0.98 (0.90–1.07)	0.68	0.99 (0.91–1.08)	0.88
	rs11214108	A/G	0.12	0.95 (0.89–1.02)	0.15	0.96 (0.90–1.03)	0.23	0.98 (0.90–1.06)	0.62	0.99 (0.92–1.08)	0.90
ERCC2	rs13181	C/A	0.38	0.99 (0.95–1.03)	0.64	0.99 (0.95–1.04)	0.71	0.98 (0.93–1.04)	0.52	0.98 (0.93–1.03)	0.43
	rs1799787	A/G	0.31	1.00 (0.95–1.04)	0.87	0.99 (0.95–1.04)	0.67	0.98 (0.92–1.04)	0.48	0.97 (0.92–1.03)	0.33
	rs238417	C/G	0.42	1.00 (0.96–1.04)	0.99	1.01 (0.97–1.06)	0.49	1.02 (0.97–1.08)	0.43	1.02 (0.96–1.07)	0.54
	rs238416	A/G	0.36	1.01 (0.97–1.05)	0.71	1.02 (0.97–1.06)	0.45	1.02 (0.97–1.08)	0.44	1.02 (0.96–1.07)	0.58

				All Histologies (n=10,084)				High-Grade Serous (n=5,248)			
				Minimally Adjusted		Fully Adjusted		Minimally Adjusted		Fully Adjusted	
Gene	**SNP**	**Min/Maj**	**MAF**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
	rs238415	C/G	0.40	1.00 (0.96–1.05)	0.86	1.02 (0.97–1.06)	0.46	1.02 (0.97–1.08)	0.43	1.02 (0.96–1.07)	0.56
	rs50872	A/G	0.24	1.01 (0.97–1.07)	0.56	1.02 (0.97–1.07)	0.50	1.06 (1.00–1.13)	0.05	1.07 (1.01–1.14)	0.03
ERCC1	rs735482	C/A	0.14	0.97 (0.91–1.03)	0.32	1.00 (0.94–1.06)	0.91	0.97 (0.90–1.05)	0.42	0.98 (0.91–1.06)	0.56

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.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2013 November 01.