Cross-Cancer Genome-Wide Association Study of Endometrial Cancer and Epithelial Ovarian Cancer Identifies Genetic Risk Regions Associated with Risk of Both Cancers

Dylan M. Glubb[1], Deborah J. Thompson[2], Katja K.H. Aben[3,4], Ahmad Alsulimani[5], Frederic Amant[6], Daniela Annibali[6], John Attia[7,8], Aurelio Barricarte[9,10,11], Matthias W. Beckmann[12], Andrew Berchuck[13], Marina Bermisheva[14], Marcus Q. Bernardini[15], Katharina Bischof[16,17], Line Bjorge[16,17], Clara Bodelon[18], Alison H. Brand[19,20], James D. Brenton[21], Louise A. Brinton[18], Fiona Bruinsma[22], Daniel D. Buchanan[23,24,25,26], Stefanie Burghaus[12], Ralf Butzow[27], Hui Cai[28], Michael E. Carney[29], Stephen J. Chanock[30], Chu Chen[31], Xiao Qing Chen[1], Zhihua Chen[32], Linda S. Cook[33,34], Julie M. Cunningham[35], Immaculata De Vivo[36,37], Anna deFazio[19,38], Jennifer A. Doherty[39], Thilo Dörk[40], Andreas du Bois[41,42], Alison M. Dunning[43], Matthias Dürst[44], Todd Edwards[45], Robert P. Edwards[46,47], Arif B. Ekici[48], Ailith Ewing[2], Peter A. Fasching[12,49], Sarah Ferguson[15], James M. Flanagan[50], Florentia Fostira[51], George Fountzilas[52], Christine M. Friedenreich[34], Bo Gao[38,53], Mia M. Gaudet[54], Jan Gawełko[55], Aleksandra Gentry-Maharaj[56], Graham G. Giles[22,24,57], Rosalind Glasspool[58], Marc T. Goodman[59], Jacek Gronwald[60], Holly R. Harris[61,62], Philipp Harter[41], Alexander Hein[12], Florian Heitz[41], Michelle A.T. Hildebrandt[63], Peter Hillemanns[40], Estrid Høgdall[64,65], Claus K. Høgdall[66], Elizabeth G. Holliday[7,8], David G. Huntsman[67,68,69,70], Tomasz Huzarski[71,72], Anna Jakubowska[60,73], Allan Jensen[64], Michael E. Jones[74], Beth Y. Karlan[75], Anthony Karnezis[76], Joseph L. Kelley[47], Elza Khusnutdinova[14,77], Jeffrey L. Killeen[78], Susanne K. Kjaer[64,79], Rüdiger Klapdor[80], Martin Köbel[81], Bozena Konopka[82], Irene Konstantopoulou[51], Reidun K. Kopperud[16,17], Madhuri Koti[83], Peter Kraft[37,84], Jolanta Kupryjanczyk[82], Diether Lambrechts[85,86], Melissa C. Larson[87], Loic Le Marchand[88], Shashikant Lele[89], Jenny Lester[75], Andrew J. Li[90], Dong Liang[91], Clemens Liebrich[92], Loren Lipworth[93], Jolanta Lissowska[94], Lingeng Lu[95], Karen H. Lu[96], Alessandra Macciotta[97], Amalia Mattiello[98], Taymaa May[15], Jessica N. McAlpine[99], Valerie McGuire[100], Iain A. McNeish[101,102], Usha Menon[56], Francesmary Modugno[47,103], Kirsten B. Moysich[5], Heli Nevanlinna[104], Kunle Odunsi[89], Håkan Olsson[105], Sandra Orsulic[90], Ana Osorio[106,107], Domenico Palli[108], Tjoung-Won Park-Simon[40], Celeste L. Pearce[109,110], Tanja Pejovic[111,112], Jennifer B. Permuth[113], Agnieszka Podgorska[82], Susan J. Ramus[114,115], Timothy R. Rebbeck[116,117], Marjorie J. Riggan[13], Harvey A. Risch[95], Joseph H. Rothstein[118,119], Ingo B. Runnebaum[44], Rodney J. Scott[7,120,121], Thomas A. Sellers[113], Janine Senz[67,68], Veronica Wendy Setiawan[122], Nadeem Siddiqui[123], Weiva Sieh[118,119], Beata Spiewankiewicz[124], Rebecca Sutphen[125], Anthony J. Swerdlow[74,126], Lukasz Michael Szafron[127], Soo Hwang Teo[128,129], Pamela J. Thompson[59], Liv Cecilie Vestrheim Thomsen[16,17], Linda Titus[130], Alicia Tone[15], Rosario Tumino[131], Constance Turman[37], Adriaan Vanderstichele[132], Digna Velez Edwards[133], Ignace Vergote[132], Robert A. Vierkant[87], Zhaoming Wang[18], Shan Wang-Gohrke[134], Penelope M. Webb[135]; for the OPAL Study Group[135] and for the AOCS Group[38,136], Emily White[62,137], Alice S. Whittemore[100,138], Stacey J. Winham[87], Xifeng Wu[63], Anna H. Wu[122], Drakoulis Yannoukakos[51], Amanda B. Spurdle[1], and Tracy A. O'Mara[1]

[1]Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [2]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. [3]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands. [4]Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands. [5]Division of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York. [6]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University Hospitals KU Leuven, University of Leuven, Leuven, Belgium. [7]Hunter Medical Research Institute, John Hunter Hospital, Newcastle, New South Wales, Australia. [8]Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia. [9]CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain. [10]Navarra Public Health Institute, Pamplona, Spain. [11]Navarra Institute for Health Research (IdiSNA), Pamplona, Spain. [12]Department of Gynecology and Obstetrics, Comprehensive Cancer Center ER-EMN, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany. [13]Department of Gynecologic Oncology, Duke University Hospital, Durham, North Carolina. [14]Institute of Biochemistry and Genetics, Ufa Federal Research Centre of the Russian Academy of Sciences, Ufa, Russia. [15]Division of Gynecologic Oncology, University Health Network, Princess Margaret Hospital, Toronto, Ontario, Canada. [16]Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway. [17]Centre for Cancer Biomarkers CCBIO, Department of Clinical Science, University of Bergen, Bergen, Norway. [18]Division of Cancer Epidemiology and Genetics, NCI, Bethesda, Maryland. [19]Department of Gynaecological Oncology, Westmead Hospital, Sydney, New South Wales, Australia. [20]University of Sydney, Sydney, New South Wales, Australia. [21]Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK.

ABSTRACT

Background: Accumulating evidence suggests a relationship between endometrial cancer and ovarian cancer. Independent genome-wide association studies (GWAS) for endometrial cancer and ovarian cancer have identified 16 and 27 risk regions, respectively, four of which overlap between the two cancers. We aimed to identify joint endometrial and ovarian cancer risk loci by performing a meta-analysis of GWAS summary statistics from these two cancers.

Methods: Using LDScore regression, we explored the genetic correlation between endometrial cancer and ovarian cancer. To identify loci associated with the risk of both cancers, we implemented a pipeline of statistical genetic analyses (i.e., inverse-variance meta-analysis, colocalization, and M-values) and performed analyses stratified by subtype. Candidate target genes were then prioritized using functional genomic data.

Results: Genetic correlation analysis revealed significant genetic correlation between the two cancers ($r_G = 0.43$, $P = 2.66 \times 10^{-5}$). We found seven loci associated with risk for both cancers ($P_{\text{Bonferroni}} < 2.4 \times 10^{-9}$). In addition, four novel subgenome-wide regions at 7p22.2, 7q22.1, 9p12, and 11q13.3 were identified ($P < 5 \times 10^{-7}$). Promoter-associated HiChIP chromatin loops from immortalized endometrium and ovarian cell lines and expression quantitative trait loci data highlighted candidate target genes for further investigation.

Conclusions: Using cross-cancer GWAS meta-analysis, we have identified several joint endometrial and ovarian cancer risk loci and candidate target genes for future functional analysis.

Impact: Our research highlights the shared genetic relationship between endometrial cancer and ovarian cancer. Further studies in larger sample sets are required to confirm our findings.

Introduction

Epithelial ovarian cancer accounts for ∼90% of ovarian tumors and is commonly divided into five major histotypes: high-grade serous, low-grade serous, mucinous, clear cell, and endometrioid (1). Herein, "ovarian cancer" refers to epithelial types of this disease. On both histologic and molecular levels, it is evident that ovarian cancer is a highly heterogeneous disease. Endometrial cancer (cancer of the uterine lining) is a comparatively understudied gynecologic cancer, although it ranks fifth for cancer incidence in women globally (2). Endometrial cancer also has several histotypes, the most common being endometrioid (∼80% of cases) but also includes serous, mucinous, and clear cell.

Comparison of the epidemiology and histopathology of endometrial cancer and ovarian cancer has identified a number of similarities suggesting that shared molecular mechanisms underlie the pathology of these two diseases. Both cancers are hormone related, with epidemiologic studies showing concordant direction of effect in relation to exposure to estrogen and progesterone (reviewed by Cramer; ref. 3).

[22]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia. [23]Department of Clinical Pathology, The University of Melbourne, Melbourne, Victoria, Australia. [24]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. [25]Genomic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Victoria, Australia. [26]University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Parkville, Victoria, Australia. [27]Department of Pathology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. [28]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee. [29]John A. Burns School of Medicine, Department of Obstetrics and Gynecology, University of Hawaii, Honolulu, Hawaii. [30]Division of Cancer Epidemiology and Genetics, NCI, NIH, Department of Health and Human Services, Bethesda, Maryland. [31]Epidemiology Program, Fred Hutchinson Cancer Research Center, Seattle, Washington. [32]Department of Biostatistics, Moffitt Cancer Center, Tampa, Florida. [33]University of New Mexico Health Sciences Center, University of New Mexico, Albuquerque, New Mexico. [34]Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Alberta, Canada. [35]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota. [36]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [37]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [38]Centre for Cancer Research, The Westmead Institute for Medical Research, The University of Sydney, Sydney, New South Wales, Australia. [39]Huntsman Cancer Institute, Department of Population Health Sciences, University of Utah, Salt Lake City, Utah. [40]Gynaecology Research Unit, Hannover Medical School, Hannover, Germany. [41]Department of Gynecology and Gynecologic Oncology, Ev. Kliniken Essen-Mitte (KEM), Essen, Germany. [42]Praxis für Humangenetik, Wiesbaden, Germany. [43]Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK. [44]Department of Gynaecology, Jena University Hospital- Friedrich Schiller University, Jena, Germany. [45]Division of Epidemiology, Center for Human Genetics Research, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee. [46]Ovarian Cancer Center of Excellence, Women's Cancer Research Program, Magee-Women's Research Institute and University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania. [47]Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. [48]Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany. [49]David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, Los Angeles, California. [50]Division of Cancer and Ovarian Cancer Action Research Centre, Department of Surgery and Cancer, Imperial College London, London, UK. [51]Molecular Diagnostics Laboratory, INRASTES, National Centre for Scientific Research "Demokritos," Athens, Greece. [52]Second Department of Medical Oncology, EUROMEDICA General Clinic of Thessaloniki, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece. [53]The Crown Princess Mary Cancer Centre Westmead, Sydney-West Cancer Network, Westmead Hospital, Sydney, New South Wales, Australia. [54]Department of Population Science, American Cancer Society, Atlanta, Georgia. [55]Institute of Nursing and Health Sciences, Medical Faculty, University of Rzeszów, Rzeszów, Poland. [56]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London, UK. [57]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. [58]Department of Medical Oncology, Beatson West of Scotland Cancer Centre and University of Glasgow, Glasgow, UK. [59]Samuel Oschin Comprehensive Cancer Institute, Cancer Prevention and Genetics Program, Cedars-Sinai Medical Center, Los Angeles, California. [60]Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland. [61]Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington. [62]Department of Epidemiology, University of Washington, Seattle, Washington. [63]Department of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, Texas. [64]Department of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark. [65]Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark. [66]The

Protective factors for both types of cancer include early menopause (4, 5), late age of menarche (6, 7), longer periods of breastfeeding (8, 9), and longer use of contraceptives that include progesterone (refs. 10, 11; i.e., factors that decrease exposure to unopposed estrogen). Although more strongly associated with endometrial cancer risk, higher body mass index (BMI) has been reported to be associated with increased risk of both cancers (12, 13).

The histotypes of endometrial cancer mirror those of ovarian cancer, albeit with varied frequencies observed across the two cancers. For example, serous histology is found in ∼70% of ovarian tumors, compared with 10% of endometrial tumors, while endometrioid histology is found in ∼10% of ovarian tumors and 80% of endometrial tumors. Clear cell and mucinous histologies are found in a relatively low frequency in both ovarian and endometrial tumors. Common

Juliane Marie Centre, Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. [67]British Columbia's Ovarian Cancer Research (OVCARE) Program, BC Cancer, Vancouver General Hospital, and University of British Columbia, Vancouver, BC, Canada. [68]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada. [69]Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada. [70]Department of Molecular Oncology, BC Cancer Research Centre, Vancouver, BC, Canada. [71]Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland. [72]Department of Genetics and Pathology, University of Zielona Góra, Zielona Góra, Poland. [73]Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University, Szczecin, Poland. [74]Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK. [75]David Geffen School of Medicine, Department of Obstetrics and Gynecology, University of California at Los Angeles, Los Angeles, California. [76]Department of Pathology and Laboratory Medicine, UC Davis Medical Center, Sacramento, California. [77]Department of Genetics and Fundamental Medicine, Bashkir State University, Ufa, Russia. [78]Department of Pathology, Kapiolani Medical Center for Women and Children, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii. [79]Department of Gynaecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. [80]Clinics of Obstetrics and Gynaecology, Hannover Medical School, Hannover, Germany. [81]Department of Pathology and Laboratory Medicine, University of Calgary, Foothills Medical Center, Calgary, Alberta, Canada. [82]Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland. [83]Departments of Biomedical and Molecular Sciences and Obstetrics and Gynaecology, Cancer Biology and Genetics Division, Queen's Cancer Research Institute, Queen's University, Kingston, Ontario, Canada. [84]Program in Genetic Epidemiology and Statistical Genetics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts. [85]VIB Center for Cancer Biology, Leuven, Belgium. [86]Laboratory for Translational Genetics, Department of Human Genetics, University of Leuven, Leuven, Belgium. [87]Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota. [88]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii. [89]Department of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, New York. [90]Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California. [91]College of Pharmacy and Health Sciences, Texas Southern University, Houston, Texas. [92]Clinics of Gynaecology, Cancer Center Wolfsburg, Wolfsburg, Germany. [93]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee. [94]Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Cancer Center, Oncology Institute, Warsaw, Poland. [95]Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut. [96]Department of Gynecologic Oncology and Clinical Cancer Genetics Program, University of Texas MD Anderson Cancer Center, Houston, Texas. [97]Evangelische Kliniken Essen-Mitte Klinik für Gynäkologie und gynäkologische Onkologie, Essen, Germany. [98]Dipertimento Di Medicina Clinca e Chirurgia, Federico II University, Naples, Italy. [99]British Columbia's Ovarian Cancer Research (OVCARE) Program–Gynecologic Tissue Bank, Department of Obstetrics and Gynecology, University of British Columbia, Vancouver General Hospital and BC Cancer, Vancouver, BC, Canada. [100]Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California. [101]Division of Cancer and Ovarian Cancer Action Research Centre, Department Surgery and Cancer, Imperial College London, London, UK. [102]Institute of Cancer Sciences, University of Glasgow, Glasgow, UK. [103]Womens Cancer Research Center, Magee-Women's Research Institute and Hillman Cancer Center, Pittsburgh, Pennsylvania. [104]Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. [105]Department of Cancer Epidemiology, Clinical Sciences, Lund University, Lund, Sweden. [106]Centro de Investigación en Red de Enfermedades Raras (CIBERER), Madrid, Spain. [107]Human Cancer Genetics Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain. [108]Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy. [109]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan. [110]Department of Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California. [111]Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, Oregon. [112]Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon. [113]Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, Florida. [114]School of Women's and Children's Health, Faculty of Medicine, University of NSW Sydney, Sydney, New South Wales, Australia. [115]Adult Cancer Program, Lowy Cancer Research Centre, University of NSW Sydney, Sydney, New South Wales, Australia. [116]Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [117]Dana-Farber Cancer Institute, Boston, Massachusetts. [118]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York. [119]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, New York. [120]Division of Molecular Medicine, Pathology North, John Hunter Hospital, Newcastle, New South Wales, Australia. [121]Discipline of Medical Genetics, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle, Callaghan, New South Wales, Australia. [122]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California. [123]Department of Gynaecological Oncology, Glasgow Royal Infirmary, Glasgow, UK. [124]Tytus Chałbiński Specialist Hospital in Radom, Warsaw, Poland. [125]Epidemiology Center, College of Medicine, University of South Florida, Tampa, Florida. [126]Division of Breast Cancer Research, The Institute of Cancer Research, London, UK. [127]Department of Immunology, the Maria Sklodowska-Curie Institute–Oncology Center, Warsaw, Poland. [128]Breast Cancer Research Programme, Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia. [129]Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. [130]Geisel School of Medicine, Dartmouth College, Hanover, New Hampshire. [131]Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department for Gynecology with the Center for Oncologic Surgery Charité Campus Virchow-Klinikum, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Berlin, Germany. [132]Division of Gynecologic Oncology, Department of Obstetrics and Gynaecology and Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium. [133]Division of Quantitative Sciences, Department of Obstetrics and Gynecology, Department of Biomedical Sciences, Women's Health Research, Vanderbilt University Medical Center, Nashville, Tennessee. [134]Department of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany. [135]Population Health Department, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [136]Peter MacCallum Cancer Center, Melbourne, Victoria, Australia. [137]Fred Hutchinson Cancer Research Center, Seattle, Washington. [138]Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, California.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Tracy A. O'Mara, Genetics and Computational Biology Department, QIMR Berghofer Medical Research Institute, Brisbane, Queensland 4006, Australia. Phone: 61-7-3362-0389; E-mail: tracy.omara@qimrberghofer.edu.au

Cancer Epidemiol Biomarkers Prev 2021;30:217–28

doi: 10.1158/1055-9965.EPI-20-0739

features have been observed in similar histotypes regardless of the organ of origin. Tumors with serous histology from both the endometrium and ovary are characterized by somatic defects in the tumor suppressor gene, *TP53* (14, 15). Endometrioid endometrial and endometrioid ovarian tumors have both been found to contain somatic alterations in *PTEN, PIK3CA, ARID1A, PPP2R1A*, and *CTNNB1*, although the frequencies of these mutations vary by tissue type (reviewed by McConechy and colleagues; ref. 16). Methylation profiling has found endometrioid endometrial and endometrioid ovarian tumors cluster together (17), and similar gene-expression patterns have been observed for clear cell endometrial and clear cell ovarian tumors (18). Further, there is increasing evidence that clear cell and endometrioid ovarian tumors arise in part from endometriosis (reviewed by King and colleagues; ref. 19). Endometriosis is a chronic disease affecting reproductive-aged women, in which endometrium grows outside of the uterus, suggesting these ovarian cancer subtypes and endometrial cancer develop from similar precursor endometrial epithelial cells.

Some, but not all, germline cancer risk variants are also shared between endometrial cancer and ovarian cancer. Lynch syndrome, characterized by germline pathogenic variants in the mismatch-repair genes (i.e., *MLH1, MSH2*, and *MSH6*), is associated with 40% to 60% and 8% to 15% lifetime risks of endometrial cancer and ovarian cancer, respectively (20). Additionally, separate genome-wide association studies (GWAS) of the two cancer types have identified four genetic risk regions common to both cancers (21, 22).

Meta-analyses of GWAS data sets across etiologically related diseases have successfully been used to increase statistical power and identify novel genetic risk regions (23, 24). Hence, in the current study, we have performed a joint meta-analysis of the largest endometrial cancer and ovarian cancer GWAS data sets to identify novel genetic loci associated with risk of both cancers, including risk variation specific to less common ovarian cancer subtypes. To identify candidate target genes at such loci, we have intersected risk variation with chromatin looping data enriched for promoter–enhancer interactions. We have also assessed associations between risk variation and gene expression to provide evidence of candidate target gene regulation and reveal further candidate genes.

Materials and Methods

GWAS data sets

GWAS summary statistics were obtained from the latest meta-analyses performed by the Endometrial Cancer Association Consortium (ECAC; ref. 21) and the Ovarian Cancer Association Consortium (OCAC; ref. 22). Because of the low number of nonendometrioid endometrial cancer available in ECAC, summary statistics were provided for all endometrial cancer risks (including all endometrial cancer cases), and analyses were restricted to endometrioid cases only. OCAC summary statistics were available for all ovarian cancer risks (including all ovarian cancer cases), as well as analyses were restricted to eight different subtypes: endometrioid histology, serous (including borderline, high-grade, and low-grade serous cases), serous high-grade histology, serous low-grade histology, serous borderline histology, serous low-grade and borderline cases combined, clear cell histology, and mucinous histology. Sample sizes for each study and subgroups analyzed are provided in **Table 1**. Details on genotyping, quality control, and imputation have been previously described (21, 22). Data for approximately 10 million genetic variants (imputation quality score > 0.4 and minor allele frequency > 0.01) were available for both cancers for the present study.

Genetic correlation analyses

Genetic correlation (i.e., the estimated proportion of variance shared between two traits due to genetic factors) between endometrial cancer and ovarian cancer was assessed using linkage disequilibrium (LD) score regression (25). Genetic correlation was also assessed between each of the ovarian cancer subtypes analyzed by OCAC and all endometrial cancer as well as restricted to endometrioid endometrial cancer. For this analysis, the complete set of GWAS variants were pruned to the HapMap3 variant list (∼1 million variants) to provide variants with high confidence imputation scores. The major histocompatibility complex (MHC) region was removed from this analysis because of its complex LD structure.

Cross-cancer GWAS meta-analyses

To identify joint endometrial and ovarian cancer genetic risk variants, summary statistics from ECAC and OCAC were combined by inverse-variance meta-analysis, adjusting for unknown sample overlap using MTAG (26). Because of the significant heterogeneity in risk estimates observed for genetic variants across ovarian cancer subtypes (22), we additionally performed meta-analysis combining results from ECAC (all endometrial cancer or endometrioid endometrial cancers) with summary statistics from each of the nine ovarian cancer subtypes analyzed by OCAC (listed in **Table 1**). To minimize false positives, output variants were restricted to those meeting the following criteria: (i) concordant direction of effect on risk of both cancers; (ii) no significant heterogeneity in risk estimates between the

Table 1. Details of samples included in the meta-analysis, by histotype.

Phenotype	ECAC (*N*)	OCAC (*N*)
All cases[a]	12,906	23,342
Endometrioid cases	8,578	2,810
Serous cases	NA	16,003
Serous high-grade cases	NA	13,037
Serous low-grade cases	NA	1,012
Serous borderline cases	NA	1,954
Serous low-grade and borderline cases	NA	2,966
Clear cell cases	NA	1,366
Mucinous cases	NA	2,566
Controls	108,979	40,941

Abbreviations: ECAC, Endometrial Cancer Association Consortium; *N*, sample counts; NA, not available; OCAC, Ovarian Cancer Association Consortium.
[a]"All cases" also includes those with unknown or mixed histology.

two cancers ($P_{het} > 0.05$); and (iii) associated with each cancer at nominal significance ($P < 0.05$). Counts of variants meeting these criteria are provided in Supplementary Table S1. M-values (27) were generated for variants reaching suggestive evidence of association ($P < 5 \times 10^{-7}$) using METASOFT (28). This analysis assesses whether an effect is observed for the variant in each study contributing to the meta-analysis. Variants with a posterior probability for an effect in each study (M-value > 0.9) were retained for further consideration.

Loci containing variants with suggestive evidence of association ($P < 5 \times 10^{-7}$) that met all the above criteria in the meta-analysis were further evaluated for colocalization by GWAS-PW (29), using all genetic variants at the query locus. Query loci were defined using LD from the European 1000 Genomes Phase I reference panel (30) and coordinates provided in Supplementary Table S3. GWAS-PW estimates Bayes factors and posterior probabilities of association (PPA) for four models: (i) a locus associates with risk of endometrial cancer only; (ii) a locus associates with risk of ovarian cancer only; (iii) a locus contains a risk signal that associates with risk of both endometrial and ovarian cancers; or (iv) a locus contains two risk signals that associate independently with risk of either endometrial or ovarian cancer. Risk signals located in loci that were classified as meeting model (iii) were considered to be joint endometrial and ovarian cancer signals (PPA > 0.5).

Cell culture

IOSE11 (immortalized ovarian surface epithelial; ref. 31) cells were gifted from Prof S Gayther (Cedars-Sinai Medical Center). Cells were authenticated using STR profiling and confirmed to be negative for *Mycoplasma* contamination. IOSE11 were grown in 1:1 MCDB105: Medium 199 with 15% FBS and antibiotics (100 IU/mL penicillin and 100 μg/mL streptomycin).

HiChIP library generation

IOSE11 cells (∼80% confluent on 10-cm tissue culture plates) were washed with PBS and fixed at room temperature in 1% formaldehyde in PBS. After 10 minutes, the reaction was quenched by washing with 125 mmol/L glycine in PBS and then adding fresh glycine-PBS. Cells were removed from the dish with a cell scraper and washed with PBS before storing cell pellets at −80°C. HiChIP libraries were generated as previously described (32). Sequencing libraries were generated using HiChIP libraries and the Nextera DNA preparation kit (Illumina). Size selection was performed using Ampure XP beads to capture 300 to 700 bp fragments. Two independent sequencing libraries were pooled to provide 25 μL of library at ≥10 nmol/L for Illumina HiSeq4000 (AGRF) paired-end sequencing with read lengths of 75 bp.

HiChIP bioinformatics analyses

HiChIP reads (fastq files) were aligned to the human reference genome (hg19) using HiC-Pro v2.9.0 (33) and default settings used to filter for valid interactions as previously (32). IOSE11 HiChIP reads and valid interactions can be downloaded from GEO (accession GSE155328; https://www.ncbi.nlm.nih.gov/geo/). All valid interactions from Hi-Pro were processed by the hichipper pipeline v0.7.0 (34) as previously described (32). Chromatin interactions were filtered using a minimum distance of 5 kb and a maximum of 2 Mb. The final set of chromatin loops used were interactions supported by a minimum of two unique paired-end tags and with a Mango (35) q-value < 5%. Promoter-associated chromatin loops were defined as HiChIP loops with anchors within ±3 kb of a transcription start site. Promoter-associated chromatin looping data were also available from our previous analysis of a normal immortalized endometrial cell line (E6E7hTERT; ref. 32).

Credible candidate risk variants

Using 100:1 log likelihood ratios, "credible variants" (CV) were identified at each of the joint endometrial and ovarian cancer risk regions. To identify genes that could be distally regulated by a CV, intersections of CVs with promoter-associated chromatin loops were performed using bedtools v2.28.0. Identification of genes whose expression is associated with a CV was performed by lookup of publicly available eQTL databases, including precomputed eQTL results from 336 endometrial and 318 ovarian tumors from The Cancer Genome Atlas (https://albertlab.shinyapps.io/tcga_eqtl; ref. 36) and from 101 noncancerous uterus samples and 122 ovarian tissue samples from GTEx (data release v7; http://gtexportal.org; ref. 37). Additionally, due to the substantially increased power the sample size provided over solid tissue analyses, we accessed eQTL results from 31,684 whole-blood samples (http://eqtlgen.org; ref. 38). Genes were considered potential targets if their expression associated with CVs that had P values within two orders of magnitude of the best eQTL variant in any of these eQTL data sets.

Results

Significant genetic correlation was observed between all endometrial cancer and all ovarian cancer ($r_G = 0.43$, $P = 2.66 \times 10^{-5}$; **Table 2**). When broken down by ovarian cancer subtype, we observed significant correlation between endometrial cancer and the following subgroups: endometrioid ($r_G = 0.53$, $P = 7.0 \times 10^{-3}$), serous ($r_G = 0.42$, $P = 1.0 \times 10^{-4}$), and high-grade serous ovarian cancers ($r_G = 0.44$, $P = 1.0 \times 10^{-4}$). These correlations remained significant, although attenuated, when using endometrioid endometrial cancers only (**Table 2**).

Seven genetic loci displaying evidence of a joint association with risk of both endometrial cancer (all or endometrioid histology) and ovarian cancer (all or one of the subtypes; i.e., PPA > 0.5 for GWAS-PW model iii), passed Bonferroni correction for multiple testing ($5 \times 10^{-8}/17$ tests $= 2.9 \times 10^{-9}$; **Table 3**). Three of these loci belong to regions that have previously been reported as being associated with risk of both cancers (8q24, 17q12, and 17q21.32), although the 17q21.32 region had not been reported to be associated with the specific subtypes of ovarian cancer found in this meta-analysis (**Table 3**). One of the seven loci (2p16.1) has been previously reported as being associated with risk of endometrial cancer, but not with ovarian cancer risk. The three remaining loci (5p15.33, 9q34.2, and 10p12.31) have been previously reported as associated with risk of all ovarian cancer and serous ovarian cancer but not with endometrial cancer risk below GWAS significance levels; however, associations between endometrial cancer and variants in the 5p15.33 (*TERT*) region have been reported in a candidate-region study (39). Additionally, we identified four novel loci with sub-GWAS significance levels ($P < 5 \times 10^{-7}$) that had not been previously reported as being associated with risk of either cancer at genome-wide levels of significance (7p22.2, 7q22.1, 9p12, and 11q13.3; **Fig. 1**).

We identified a total of 22 candidate target genes at the 11 identified joint endometrial and ovarian cancer risk loci using a number of approaches (**Table 4**; Supplementary Table S2). Log likelihood ratios identified a median of 20 CVs per locus (range, 1–73; Supplementary Table S3). Using H3K27Ac-associated chromatin looping data from normal immortalized ovarian surface epithelial cells and the same data previously generated from a normal immortalized endometrium cell line (32), we intersected CVs coincident with putative enhancers

Table 2. Genetic correlations between epithelial ovarian cancer subtypes and endometrial cancer (all and endometrioid) from LD score regression analysis.

Ovarian cancer subtype (40,941 controls)	All endometrial cancer (12,906 cases, 180,979 controls)		Endometrioid endometrial cancer (8,578 cases, 46,126 controls)	
	r_G (SE)	*P*	r_G (SE)	*P*
Clear cell (1,366 cases)	0.13 (0.21)	0.53	0.05 (0.23)	0.82
Endometrioid (2,810 cases)	**0.53 (0.20)**	**7.00E−03**	**0.45 (0.22)**	**0.04**
Mucinous (2,566 cases)	0.03 (0.16)	0.85	−0.12 (0.18)	0.51
Serous (16,003 cases)	**0.42 (0.11)**	**1.00E−04**	**0.37 (0.11)**	**9.00E−04**
Serous borderline (1,954 cases)	0.49 (0.56)	0.4	0.68 (0.72)	0.34
Serous HG (13,137 cases)	**0.44 (0.11)**	**1.00E−04**	**0.39 (0.12)**	**8.00E−04**
Serous LG and borderline (2,966 cases)	0.28 (0.25)	0.25	0.32 (0.28)	0.25
All ovarian (23,342 cases)	**0.43 (0.10)**	**2.66E−05**	**0.36 (0.11)**	**1.40E−03**

Note: Results with a significant genetic correlation ($P < 0.05$) have been bolded. The genetic heritability could not be estimated for one ovarian cancer subtype (serous low grade); therefore, it could not be included in the genetic correlation analyses.
Abbreviations: HG, high grade; LG, low grade; r_G, genetic correlation estimate; SE, standard error.

(marked by H3K27Ac) belonging to promoter-associated loops. We found looping between such enhancers and the promoters of 14 genes (at five of the 11 loci) to be common to both immortalized endometrium and ovarian surface epithelial cell lines (e.g., **Fig. 1**). Four of the 14 candidate target genes identified by chromatin looping also had a CV located in the promoter, indicating potential to regulate expression (**Table 4**). An additional five genes were identified as candidate targets with CVs located in the corresponding promoters (**Table 4**). Interrogation of five relevant public eQTL databases revealed CVs to be associated with the expression of four genes (*ABO, BCL11A, HOXB2*, and *SNX11*), highlighting them as candidate targets. One of these, *SNX11*, had also been identified through the chromatin looping analyses and a CV was located in its promoter. Notably, we observed that increased expression of *ABO* associated with risk allele of CVs at the 9q34.2 locus in all five eQTL data sets: blood, noncancerous uterine and ovarian tissues, and endometrial and ovarian tumors.

Discussion

In this study, we have performed the first cross-cancer GWAS analysis of endometrial cancer and ovarian cancer. Genetic correlation analyses found significant correlation between the two cancers, particularly between all endometrial cancer (and its endometrioid subtype) and the serous (high- and low-grade combined) or endometrioid ovarian cancer subtypes. Our pipeline of genetic analyses, stratifying by subtype, allowed us to identify seven joint endometrial cancer and ovarian cancer genetic risk loci. Three of these loci were located in regions that had been previously associated with both cancers, one was located in a known endometrial cancer risk region and the remaining three were located in known ovarian cancer risk regions. Four novel genetic risk loci for these two cancers did not reach the statistical threshold for significance but were highlighted as of potential interest, requiring further study to confirm their status.

Joint endometrial and ovarian cancer risk loci are located in the 8q24.21 and 5p15.33 regions, previously described as "cancer GWAS nexus regions" (40) because genetic variation at these regions has been associated with many different types of cancer. 8q24.21 has been previously identified as a genetic risk region for both endometrial cancer and ovarian cancer (21, 22). CVs in a putative enhancer at the 8q24.21 joint endometrial and ovarian cancer risk locus showed evidence of chromatin looping to the promoter of the pan-cancer *MYC* oncogene in the endometrial and ovarian cell lines. A previous study of the 5p15.33 multicancer risk region, containing the *TERT* gene, identified two independent signals for ovarian cancer risk: one (lead variant rs7705526) associated with serous borderline ovarian cancer risk and the other (lead variant rs10069690) associated with serous invasive ovarian cancer risk (41). Although not previously associated with risk of endometrial cancer at genome-wide significance, a candidate fine-mapping study of 5p15.33 did highlight three independent endometrial cancer risk signals at this locus at study-wide significance (39), one of which was shared with the serous borderline ovarian cancer risk signal. The present analysis identified this signal as a joint endometrial and ovarian cancer risk signal, with CVs in the *TERT* promoter highlighting this gene as a likely target. Moreover, TERT has been heavily implicated in cancer development (reviewed in Yuan and colleagues; ref. 42) and has oncogenic interactions with MYC (reviewed in Pestana and colleagues; ref. 43).

Our results suggest, at a subgenome-wide significance level, a potential joint endometrial and ovarian cancer risk signal at another cancer GWAS nexus region, 11q13.3. Originally identified as a prostate cancer risk locus, 11q13.3 also contains risk signals for melanoma, breast cancer, and renal cancer (https://www.ebi.ac.uk/gwas/). Although the results from the present study require validation, the identification of a shared endometrial and ovarian cancer risk signal at 11q13.3 provides further evidence that this region is important for cancer development. At this locus, chromatin looping data showed that CVs in a putative enhancer looped to the promoters of *MYEOV* and *CCND1*. *CCND1* (encoding cyclin D1) is of particular interest as it is frequently amplified in human cancers and has been identified as a pan-cancer driver gene (44). Cyclin D1 is considered an oncogene due to its central role in cell-cycle regulation, and ability to promote cell proliferation (45). *CCND1* has been found to be significantly mutated

Table 3. Results from GWAS meta-analysis of endometrial cancer and epithelial ovarian cancer.

Region	ECAC phenotype	OCAC phenotype	Lead variant	Chr:Pos (hg19)	EA/OA	Freq EA (ECAC/OCAC)	OncoArray INFO Score (ECAC/OCAC)	Endometrial cancer			Ovarian cancer			Meta-analysis		
								OR (95% CI)	*P* value	*M*-value	OR (95% CI)	*P* value	*M*-value	OR (95% CI)	*P* value	Model 3 PPA
Known endometrial and ovarian cancer risk regions																
8q24.21	Endometrioid	All	rs10103314	8:129560744	C/A	0.13/0.13	1.00/0.99	0.86 (0.82–0.91)	9.05E−08	1.00	0.85 (0.82–0.88)	4.91E−16	1.00	0.85 (0.82–0.88)	1.49E−20	0.90
17q12	All	Clear cell	rs11263763	17:36103565	A/G	0.55/0.52	1.00/1.00	1.15 (1.12–1.19)	4.01E−20	1.00	1.25 (1.15–1.35)	3.46E−08	1.00	1.16 (1.13–1.2)	2.46E−24	1.00
17q12	Endometrioid	Clear cell	rs11263763	17:36103565	A/G	0.55/0.52	1.00/1.00	1.15 (1.11–1.19)	1.23E−14	1.00	1.25 (1.15–1.35)	3.46E−08	1.00	1.17 (1.13–1.21)	2.20E−19	1.00
17q21.32	All	Clear cell	rs882380	17:46294236	A/C	0.61/0.60	0.99/0.97	1.10 (1.06–1.13)	4.66E−09	1.00	1.09 (1.00–1.18)	0.04	0.94	1.10 (1.06–1.13)	1.91E−09	0.85
17q21.32	*Endometrioid*	*Clear cell*	*rs882380*	*17:46294236*	*A/C*	*0.61/0.60*	*0.99/0.97*	*1.11 (1.07–1.15)*	*1.25E−08*	*1.00*	*1.09 (1.00–1.18)*	*0.04*	*0.94*	*1.11 (1.07–1.15)*	*4.67E−09*	*0.90*
17q21.32	All	Endometrioid	rs882380	17:46294236	A/C	0.61/0.60	0.99/0.97	1.10 (1.06–1.13)	4.66E−09	1.00	1.09 (1.03–1.15)	3.44E−03	0.99	1.09 (1.06–1.13)	2.90E−10	0.91
17q21.32	Endometrioid	Endometrioid	rs882380	17:46294236	A/C	0.61/0.60	0.99/0.97	1.11 (1.07–1.15)	1.25E−08	1.00	1.09 (1.03–1.15)	3.44E−03	0.99	1.11 (1.07–1.14)	6.91E−10	1.00
17q21.32	*All*	*Serous borderline*	*rs12950225*	*17:46145200*	*G/A*	*0.58/0.57*	*1.00/1.00*	*1.08 (1.05–1.12)*	*1.98E−07*	*1.00*	*1.10 (1.03–1.18)*	*5.64E−03*	*0.99*	*1.09 (1.06–1.12)*	*1.26E−08*	*1.00*
17q21.32	Endometrioid	Serous borderline	rs882380	17:46294236	A/C	0.61/0.60	0.99/0.97	1.11 (1.07–1.15)	1.25E−08	1.00	1.15 (1.07–1.23)	9.56E−05	1.00	1.12 (1.08–1.16)	2.88E−11	0.99
17q21.32	All	Serous LG and borderline	rs882380	17:46294236	A/C	0.61/0.60	0.99/0.97	1.10 (1.06–1.13)	4.66E−09	1.00	1.14 (1.08–1.21)	6.73E−06	1.00	1.11 (1.08–1.14)	3.10E−12	0.98
17q21.32	All	Serous LG	rs882380	17:46294236	A/C	0.61/0.60	0.99/0.97	1.10 (1.06–1.13)	4.66E−09	1.00	1.12 (1.02–1.23)	0.02	0.96	1.10 (1.07–1.13)	1.84E−09	0.99
Known endometrial cancer risk regions																
2p16.1	All	Clear cell	rs148261157	2:60897579	A/G	0.04/0.04	0.89/0.87	1.26 (1.16–1.36)	3.39E−08	1.00	1.37 (1.11–1.69)	3.18E−03	0.99	1.27 (1.18–2.78)	1.85E−09	0.96
2p16.1	*Endometrioid*	*Clear cell*	*rs7579014*	*2:60707894*	*A/G*	*0.64/0.63*	*0.99/0.98*	*1.10 (1.06–1.14)*	*6.16E−07*	*1.00*	*1.13 (1.04–1.22)*	*4.24E−03*	*0.99*	*1.10 (1.07–1.57)*	*2.92E−08*	*0.71*
Known ovarian cancer risk regions																
5p15.33	All	All	rs7725218	5:1282414	A/G	0.36/0.35	0.97/0.94	1.07 (1.04–1.11)	1.12E−05	1.00	1.10 (1.07–1.13)	1.76E−11	1.00	1.09 (1.07–1.11)	2.71E−14	1.00
5p15.33	Endometrioid	All	rs7726159	5:1282319	A/C	0.34/0.34	0.98/0.94	1.08 (1.04–1.12)	7.90E−05	1.00	1.10 (1.07–1.13)	1.04E−11	1.00	1.09 (1.07–1.12)	5.23E−14	1.00
5p15.33	All	Serous	rs6897196	5:1280938	G/A	0.40/0.39	1.00/0.98	1.07 (1.03–1.10)	6.46E−05	0.99	1.11 (1.08–1.15)	2.07E−11	1.00	1.09 (1.07–1.12)	2.21E−13	1.00
5p15.33	Endometrioid	Serous	rs7725218	5:1282414	A/G	0.36/0.35	0.97/0.94	1.08 (1.04–1.12)	6.12E−05	0.99	1.13 (1.09–1.16)	1.5E−13	1.00	1.11 (1.08–1.14)	1.40E−15	1.00
5p15.33	All	Serous HG	rs7725218	5:1282414	A/G	0.36/0.35	0.97/0.94	1.07 (1.04–1.11)	1.12E−05	1.00	1.12 (1.09–1.16)	4.4E−12	1.00	1.10 (1.07–1.12)	1.07E−14	1.00
5p15.33	Endometrioid	Serous HG	rs7725218	5:1282414	A/G	0.36/0.35	0.97/0.94	1.08 (1.04–1.12)	6.12E−05	0.99	1.12 (1.09–1.16)	4.4E−12	1.00	1.10 (1.08–1.13)	2.34E−14	1.00
5p15.33	*All*	*Serous LG and borderline*	*rs2853672*	*5:1292983*	*A/C*	*0.48/0.49*	*1.00/1.00*	*0.94 (0.91–0.96)*	*1.30E−05*	*1.00*	*0.88 (0.83–0.93)*	*5.72E−06*	*1.00*	*0.92 (0.90–0.95)*	*1.03E−08*	*1.00*
5p15.33	*Endometrioid*	*Serous LG and borderline*	*rs2853672*	*5:1292983*	*A/C*	*0.48/0.49*	*1.00/1.00*	*0.93 (0.89–0.96)*	*2.27E−05*	*1.00*	*0.88 (0.83–0.93)*	*5.72E−06*	*1.00*	*0.91 (0.88–0.94)*	*7.20E−09*	*1.00*
9q34.2	All	All	rs635634	9:136155000	T/C	0.20/0.20	1.00/1.00	1.06 (1.02–1.10)	1.48E−03	0.99	1.10 (1.07–1.14)	3.08E−09	1.00	1.09 (1.06–1.11)	3.46E−10	0.91
9q34.2	All	Serous	rs687289	9:136137106	A/G	0.35/0.34	1.00/1.00	1.07 (1.03–1.10)	6.39E−05	1.00	1.10 (1.06–1.13)	1.35E−08	1.00	1.08 (1.06–1.11)	4.15E−11	0.80
10p12.31	All	All	rs564819152	10:21820650	G/A	0.32/0.32	1.00/0.97	1.05 (1.02–1.08)	2.55E−03	0.97	1.09 (1.06–1.12)	2.52E−10	1.00	1.08 (1.05–1.10)	8.73E−11	0.99
10p12.31	All	Serous	rs7090708	10:21929179	G/A	0.33/0.33	1.00/0.99	1.05 (1.02–1.08)	2.6E−03	0.96	1.09 (1.06–1.13)	1.92E−08	1.00	1.07 (1.05–1.10)	3.62E−09	0.99
10p12.31	*All*	*Serous HG*	*rs7090708*	*10:21929179*	*G/A*	*0.33/0.33*	*1.00/0.99*	*1.05 (1.02–1.08)*	*2.6E−03*	*0.92*	*1.10 (1.07–1.14)*	*5.02E−08*	*1.00*	*1.07 (1.05–1.10)*	*7.63E−09*	*0.99*
Novel regions																
7p22.2	*All*	*All*	*rs13221982*	*7:3865621*	*C/T*	*0.06/0.06*	*0.98/0.98*	*1.13 (1.06–1.21)*	*1.32E−04*	*1.00*	*1.12 (1.06–1.18)*	*6.85E−05*	*1.00*	*1.13 (1.08–1.18)*	*1.57E−07*	*0.90*
9p12	*Endometrioid*	*Serous LG and borderline*	*rs2475339*	*9:10262484*	*T/C*	*0.83/0.83*	*0.99/0.99*	*0.89 (0.85–0.93)*	*8.64E−07*	*1.00*	*0.90 (0.84–0.97)*	*4.50E−03*	*0.99*	*0.89 (0.86–0.93)*	*4.36E−08*	*0.94*
7q22.1	*All*	*Serous borderline*	*rs139380031*	*7:98911827*	*A/C*	*0.03/0.03*	*0.97/0.95*	*0.77 (0.70–0.85)*	*5.98E−07*	*1.00*	*0.77 (0.61–0.97)*	*0.03*	*0.95*	*0.77 (0.70–0.85)*	*1.28E−07*	*0.57*
11q13.3	*Endometrioid*	*All*	*rs7118966*	*11:69019272*	*C/T*	*0.24/0.25*	*1.00/1.00*	*0.93 (0.89–0.97)*	*4.30E−04*	*0.99*	*0.94 (0.91–0.97)*	*1.96E−05*	*1.00*	*0.93 (0.91–0.96)*	*1.25E−07*	*0.82*

Note: Italicized results meet suggestive association ($P < 5 \times 10^{-7}$).

Abbreviations: CI, Confidence interval; EA, Effect allele; EAF, Effect allele frequency; HG, High grade; LG, Low grade; OA, Other allele; OR, Odds ratio; PPA, Posterior probability of association.

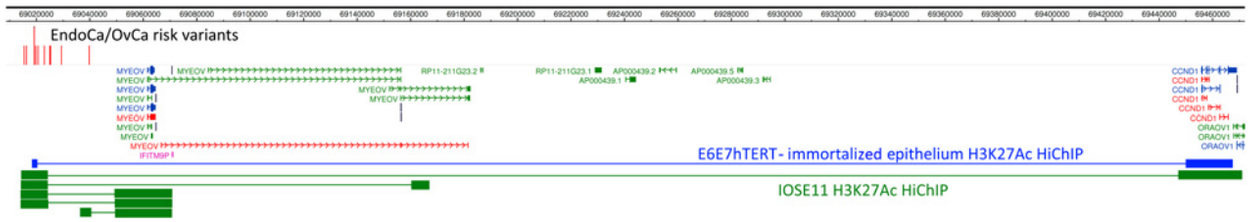

Figure 1.
Promoter-associated chromatin looping by HiChIP identifies candidate target genes at the 11q13.3 locus. Promoter-associated loops were intersected with joint endometrial and ovarian cancer risk CVs (colored red), revealing chromatin loops that interact with the promoter of *CCDN1* in both an immortalized endometrium epithelial cell line (E6E7hTERT, colored blue) and an immortalized ovarian surface epithelial cell line (IOSE11, colored green).

in gynecologic (including endometrial and ovarian cancers) and breast cancers (46). The results of our analyses provide additional support that *CCND1* is important in the development of endometrial cancer and ovarian cancer.

Our analysis identified the 17q12 region as a joint endometrial and ovarian cancer risk region, associating with clear cell ovarian cancer. The 17q12 region, containing *HNF1B*, has been previously associated with risk of endometrial cancer and ovarian cancer (47–50). Significant heterogeneity in risk estimates has been observed across ovarian cancer histotypes at this locus. The minor allele of the lead ovarian cancer risk variant previously identified at this region associated with increased serous (high- and low-grade combined) ovarian cancer risk but decreased clear cell ovarian cancer risk (49, 50). Further genotyping had resolved this region into two risk signals for ovarian cancer risk: one in intron 1 of *HNF1B* for clear cell ovarian cancer risk (rs11651775; the same signal for endometrial cancer risk) and another in intron 3 for serous ovarian cancer risk (rs7405776; ref. 50). Our results confirm that joint endometrial and ovarian cancer risk variants at 17q12 map to the same signal as that for that previously reported for endometrial cancer and the clear cell ovarian subtype. *HNF1B* is a likely target of endometrial and ovarian cancer risk variation, with CVs located in its promoter region. We have previously demonstrated that these variants affect activity of the *HNF1B* promoter (47), which may lead to increased secretion of insulin, a risk factor for endometrial cancer (51).

The 17q21.32 region is a known shared endometrial (21) and ovarian cancer (22) risk region. The joint endometrial and ovarian cancer signal found in the present study (lead SNP rs882380) is the same as that previously identified for endometrial cancer, but is independent of the signal previously found for all invasive and high-grade serous ovarian cancer risk (lead SNP rs7207826, r^2 = 0.06 with rs882380). The joint endometrial and ovarian cancer signal associates specifically with risk of clear cell, endometrioid, serous low-grade, serous low-grade and borderline combined, and serous borderline ovarian cancer subtypes. Clear cell, endometrioid, and serous low-grade ovarian cancers are often referred to as endometriosis-associated ovarian cancers due to the increased risk of these ovarian cancer subtypes with endometriosis (52). Epidemiologic and molecular data provide strong evidence that clear cell and endometrioid ovarian cancer arise in part from endometriosis (reviewed by King and colleagues; ref. 19). The joint endometrial and ovarian cancer signal identified in the present study at 17q21.32 was also found in a joint GWAS analysis of endometrial cancer and endometriosis (53), and subsequently found to be associated with endometriosis risk independently (54). Five candidate target genes were identified at this locus, all of which we had previously found to be candidate targets of the original endometrial cancer signal through chromatin looping studies (32).

Another potential joint endometrial and ovarian cancer signal, 9p12, associated with risk of serous low-grade ovarian cancer, has also been previously identified as a joint endometrial cancer and

Table 4. Candidate target genes at joint endometrial cancer and epithelial ovarian cancer risk loci.

Region	Candidate target gene/s (evidence)
Known endometrial and ovarian cancer risk regions	
8q24.21	*MYC* (chromatin looping)
17q12	*HNF1B* (promoter CV)
17q21.32	*CBX1* (chromatin looping), *HOXB2* (blood eQTL), *HOXB8* (chromatin looping), *MIR1203* (promoter CV), *SNX11* (blood eQTL, promoter CV, chromatin looping)
Known endometrial cancer risk regions	
2p16.1	*BCL11A* (UCEC eQTL)
Known ovarian cancer risk regions	
5p15.33	*TERT* (promoter CV)
9q34.2	*ABO* (blood eQTL, UCEC and OVCA eQTL, uterus and ovary eQTL), *CACFD1* (promoter CV)
10p12.31	*CASC10* (promoter CV, chromatin looping), *MIR1915* (promoter CV, chromatin looping), *MLLT10* (promoter CV, chromatin looping), *SKIDA1* (chromatin looping)
Novel regions	
7q22.1	*CYP3A43* (promoter CV)
7p22.2	*COX19* (chromatin looping), *ENSG00000229043* (chromatin looping), *GPER1* (chromatin looping), *ZFAND2A* (chromatin looping)
9p12	Nil
11q13.3	*CCND1* (chromatin looping), *MYEOV* (chromatin looping)

endometriosis risk locus (53). These findings at 17q21.32 and 9p12 add to the body of evidence for the relationship between endometriosis and specific ovarian cancer subtypes (19, 52), and provide further support for shared genetic etiology between endometriosis and endometrial cancer (53). CVs at the 9p12 joint risk locus were located intronic to *PTPRD*, but no candidate target genes were identified. PTPRD is involved in the STAT3 pathway, which has been implicated as a potential target for both endometrial cancer (55) and ovarian cancer (56).

The 2p16.1 region is a known endometrial cancer risk locus and was found to be associated with the risk of clear cell ovarian cancer only. Interestingly, we previously found evidence that this locus may have a stronger association with risk of nonendometrioid endometrial cancer, with the strongest effect observed for clear cell endometrial cancer subtype (128 cases and 26,638 controls; rs148261157; OR, 2.36; 95% CI, 1.07-5.19; ref. 21). *BCL11A* was identified as a candidate target gene through eQTL analysis of endometrial tumors. We had previously found that *BCL11A* was a candidate target gene at the endometrial cancer risk locus through chromatin looping studies in endometrial cancer cells (32). The eQTL finding suggested that reduced expression of *BCL11A* may increase endometrial/clear cell ovarian cancer risk. Indeed, some studies have shown that *BCL11A* acts as a proto-oncogene (57, 58); however, others suggest that overexpression of *BCL11A* results in anticancer effects (59). Notably, *BCL11A* has been found to be mutated in clear cell ovarian cancer (60, 61), providing further evidence that *BCL11A* may underlie the risk association with endometrial cancer and clear cell ovarian cancer at this locus.

The 9q34.2 region is a known ovarian cancer risk locus that is highly pleiotropic, having been previously associated with gastric and pancreatic cancers, in addition to a wide range of traits including blood cell counts, the tumor marker CEA (carcinoembryonic antigen), bone mineral density, and levels of angiogenic proteins (https://www.ebi.ac.uk/gwas/). eQTL data from normal, tumor endometrial, and ovarian tissue, as well as blood, provide evidence that *ABO* is a regulatory target of CVs at this locus. *ABO* encodes an enzyme that determines human ABO blood group antigens. It is not immediately apparent how *ABO* may mediate cancer risk but its encoded glycosyltransferase can affect cell recognition and adhesion, and activation of T and natural killer cells (reviewed by Arend; ref. 62).

The 10p12.31 region is another known ovarian cancer risk locus that is also pleiotropic, having been previously associated with breast cancer as well as with traits related to obesity such as BMI, body fat percentage, and physical activity (https://www.ebi.ac.uk/gwas/). *MLLT10* was identified as a candidate target gene at this locus, through chromatin looping analysis and localization of a CV to its promoter, and is a partner gene for chromosomal rearrangements that result in leukemia (63). Another biologically relevant candidate target gene at this locus is *MIR1915*, whose expression is upregulated by p53 in response to DNA damage, leading to increased apoptosis (64).

Two of the subgenome-wide significant endometrial/ovarian cancer risk regions (7q22.1 and 7p22.2) may relate to circulating hormone levels or regulation. At 7q22.1, GWAS have previously revealed associations with androgen and progesterone levels (65). The sole candidate target gene at this locus, *CYP3A43*, encodes a cytochrome P450 enzyme that may be involved in androgen metabolism (66) and is upregulated in ovarian tumors (67). At 7p22.2, the candidate target gene *GPER1*, identified through chromatin looping, encodes an estrogen receptor that induces endometrial and ovarian cancer cell proliferation in response to estrogen (reviewed in Prossnitz and Barton; ref. 68). Further, it appears that androgen can also bind to GPER1 to stimulate cancer cell growth (69).

Despite these findings, the present study does have some limitations. The low numbers of nonendometrioid endometrial cancers meant we could not explore the relationship of these endometrioid histotypes with ovarian cancer. Another limitation was the use of cell lines to model chromatin looping that occurs in tissue, with chromatin looping potentially affected by the immortalization and 2D-culturing processes of cell lines, or mutations gained through passaging. As only one endometrial and one ovarian cell line were used, these experiments should be repeated in additional endometrial and ovarian cell lines, representing tumor subtypes. One of the four regions previously identified to be associated with both cancers, located at 1p34, was not identified in the present analysis. This locus was originally found in a combined analysis of the OCAC with a cohort of *BRCA1/2* carriers with ovarian cancer (70), which was not included in the present study, perhaps explaining why it was not identified as a joint endometrial and ovarian cancer locus. Future analysis of this region, in the context of *BRCA1/2* carrier status will be required to explore how this region affects endometrial cancer and ovarian cancer risk.

In summary, using endometrial and ovarian cancer GWAS summary statistics, we have identified seven joint risk loci for these cancers, with an additional four novel potential risk regions at a sub-GWAS significance level. Further studies are required to validate these findings in larger sample sets. Notably, we also found significant genetic correlation between the two cancers, supported by the observed epidemiologic and histopathologic similarities. These findings support the need for larger GWAS of endometrial and ovarian cancer, in particular focusing on their minor subtypes to further explore shared genetic etiology. Integration of CVs with chromatin looping and eQTL data has identified several plausible candidate target genes, including those at potentially novel risk loci. Although the role of these genes in endometrial and ovarian cancer development should be explored in future studies, the current findings provide insights into the shared biology of endometrial and ovarian cancer.

Authors' Disclosures

D.M. Glubb reports grants from National Health and Medical Research Council and QIMR Berghofer Medical Research Institute during the conduct of the study. D.J. Thompson reports other from Genomics plc (since the completion of the work in this paper, the author left the University of Cambridge and is now employed by Genomics plc) outside the submitted work. M.Q. Bernardini reports personal fees from AstraZeneca outside the submitted work. A. deFazio reports grants from National Health and Medical Research Council of Australia, Cancer Council New South Wales, Cancer Council Victoria, Cancer Council of South Australia, Cancer Council of Queensland, Cancer Council Tasmania, Cancer Foundation of Western Australia, and Cancer Institute New South Wales during the conduct of the study, as well as grants from AstraZeneca outside the submitted work. A. du Bois reports personal fees from AstraZeneca, GSK/Tesaro, Roche, Genmab/Seattle Genetics, Zodiac, and BIOCAD outside the submitted work. P.A. Fasching reports grants and personal fees from Novartis, as well as personal fees from Pfizer, Daiichi-Sankyo, AstraZeneca, Eisai, Merck Sharp & Dohme, Cepheid, Lilly, Pierre Fabre, and Seattle Genetics outside the submitted work. G. Fountzilas reports personal fees from Pfizer (advisory board), Sanofi (advisory board), Roche (advisory board), and AstraZeneca (honoraria) outside the submitted work and Genprex, Daiichi-Sankyo, and ARIAD stock ownership. G.G. Giles reports grants from National Health and Medical Research Council (paid to author's institution Cancer Council Victoria) during the conduct of the study. R. Glasspool reports grants from Sanofi-Aventis (some of the data used in this work were derived from clinical samples that were originally collected in an investigator initiated clinical trial supported by Sanofi-Aventis) during the conduct of the study. P. Harter reports grants and personal fees from AstraZeneca, Roche, and Tesaro/GSK; personal fees from Sotio, Immunogen, Stryker, Clovis, Zai Lab, Merck Sharp & Dohme, and Lilly; and grants from Genmab, European Union, DKH, and DFG outside the submitted work. M.E. Jones reports grants from Breast Cancer Now (research finding charity: program grant) during the conduct of the study. B.Y. Karlan reports grants from Ovarian Cancer Research Fund

outside the submitted work. R. Klapdor reports nonfinancial support from Intuitive Surgical outside the submitted work. P. Kraft reports grants from NIH during the conduct of the study. M.C. Larson reports grants from Mayo Clinic during the conduct of the study and grants from Mayo Clinic outside the submitted work. L. Le Marchand reports grants from NCI (to author's institution) during the conduct of the study. D. Liang reports grants from Texas Southern University during the conduct of the study. V. McGuire reports grants from Stanford University during the conduct of the study. I.A. McNeish reports personal fees from Clovis Oncology, AstraZeneca, Tesaro, Roche, and Scancell and grants from AstraZeneca outside the submitted work. U. Menon reports other from Abcodia (shares in Abcodia given to her by UCL) outside the submitted work. F. Modugno reports grants from NCI and Department of Defense during the conduct of the study. H. Nevanlinna reports personal fees from AstraZeneca (honorarium) outside the submitted work. K. Odunsi reports funding from AstraZeneca and Tesaro Pharma. S. Orsulic reports grants from NIH/NCI, Department of Defense, and Ovarian Cancer Research Alliance outside the submitted work and has a patent for US010253368 issued and a patent for EU2908913 issued. T.-W. Park-Simon reports personal fees and other from Roche (advisory role, expert testimony, clinical trials, travel), AstraZeneca (advisory role, expert testimony, clinical trials, travel), Daichii (advisory role, expert testimony, clinical trials, travel), Tesaro (advisory role, expert testimony, clinical trials, travel), Novartis (advisory role, expert testimony, clinical trials, travel), Pfizer (advisory role, expert testimony, clinical trials, travel), Merck Sharp & Dohme (advisory role, expert testimony), and Lilly (advisory role, expert testimony, clinical trials, travel) outside the submitted work. C.L. Pearce reports grants from NIH and Department of Defense during the conduct of the study. J.H. Rothstein reports grants from NIH during the conduct of the study. A.J. Swerdlow reports grants from Breast Cancer Now, during the conduct of the study. L.C.V. Thomsen reports personal fees from Bayer and AstraZeneca, as well as other from AstraZeneca (financial support to a researcher-initiated trial) outside the submitted work. L. Titus reports grants from NIH/NCI during the conduct of the study. I. Vergote reports grants, personal fees, and other from Amgen (fees for consulting paid to author's university, corporate-sponsored research and accommodation, travel expenses) and Roche NV (fees for consulting paid to author's university, corporate-sponsored research and accommodation, travel expenses); personal fees and other from AstraZeneca NV/UK/Belux (fees for consulting paid to author's university, accommodation, travel expenses), Genmab A/S,B.V,US (fees for consulting paid to author's university and contracted research; KU Leuven), Merck Sharp & Dohme Belgium (fees for consulting paid to author's university and accommodation, travel expenses), Oncoinvent AS (fees for consulting paid to author's university and contracted research; KU Leuven), and Tesaro Inc./Bio GmbH (fees for consulting paid to author's university and accommodation, travel expenses); and personal fees (consulting paid to author's university) from Clovis Oncology Inc., Carrick Therapeutics, Debiopharm International SA, F. Hoffman-La Roche Ltd., GSK Pharmaceuticals NV, Immunogen Inc., Millennium Pharmaceuticals, Octimet Oncology NV, Pharmamar-Doctaforum Servicios SL, Sotio a.s., Deciphera Pharmaceuticals, and Verastem Oncology, outside the submitted work. P.M. Webb reports grants from National Health and Medical Research Council of Australia and Brisbane Women's Club during the conduct of the study, as well as grants from Astra Zeneca (to support an unrelated study of ovarian cancer) outside the submitted work. X. Wu reports grants from The University of Texas MD Anderson Cancer Center during the conduct of the study. D. Yannoukakos reports grants from AstraZeneca outside the submitted work. T.A. O'Mara reports grants from National Health and Medical Council of Australia, Cancer Australia, Cure Cancer Australia, and CanToo Foundation during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

D.M. Glubb: Conceptualization, formal analysis, funding acquisition, investigation, methodology, writing–original draft, writing–review and editing. **D.J. Thompson:** Conceptualization, resources, data curation, methodology, writing–original draft, writing–review and editing. **K.K.H. Aben:** Resources, writing–review and editing. **A. Alsulimani:** Resources, writing–review and editing. **F. Amant:** Resources, writing–review and editing. **D. Annibali:** Resources, writing–review and editing. **J. Attia:** Resources, writing–review and editing. **A. Barricarte:** Resources, writing–review and editing. **M.W. Beckmann:** Resources, writing–review and editing. **A. Berchuck:** Resources, writing–review and editing. **M. Bermisheva:** Resources, writing–review and editing. **M.Q. Bernardini:** Resources, writing–review and editing. **K. Bischof:** Resources, writing–review and editing. **L. Bjorge:** Resources, writing–review and editing. **C. Bodelon:** Resources, writing–review and editing. **A.H. Brand:** Resources, writing–review and editing. **J.D. Brenton:** Resources, writing–review and editing. **L.A. Brinton:** Resources, writing–review and editing. **F. Bruinsma:** Resources, writing–review and editing. **D.D. Buchanan:** Resources, writing–review and editing. **S. Burghaus:** Resources, writing–review and editing. **R. Butzow:** Resources, writing–review and editing. **H. Cai:** Resources, writing–review and editing. **M.E. Carney:** Resources, writing–review and editing. **S.J. Chanock:** Resources, writing–review and editing. **C. Chen:** Resources, writing–review and editing. **X.Q. Chen:** Resources, writing–review and editing. **Z. Chen:** Resources, writing–review and editing. **L.S. Cook:** Resources, writing–review and editing. **J.M. Cunningham:** Resources, writing–review and editing. **I. De Vivo:** Resources, writing–review and editing. **A. deFazio:** Resources, writing–review and editing. **J.A. Doherty:** Resources, writing–review and editing. **T. Dörk:** Resources, writing–review and editing. **A. du Bois:** Resources, writing–review and editing. **A.M. Dunning:** Resources, writing–review and editing. **M. Durst:** Resources, writing–review and editing. **T. Edwards:** Resources, writing–review and editing. **R.P. Edwards:** Resources, writing–review and editing. **A.B. Ekici:** Resources, writing–review and editing. **A. Ewing:** Resources, writing–review and editing. **P.A. Fasching:** Resources, writing–review and editing. **S. Ferguson:** Resources, writing–review and editing. **J.M. Flanagan:** Resources, writing–review and editing. **F. Fostira:** Resources, writing–review and editing. **G. Fountzilas:** Resources, writing–review and editing. **C.M. Friedenreich:** Resources, writing–review and editing. **B. Gao:** Resources, writing–review and editing. **M.M. Gaudet:** Resources, writing–review and editing. **J. Gawełko:** Resources, writing–review and editing. **A. Gentry-Maharaj:** Resources, writing–review and editing. **G.G. Giles:** Resources, writing–review and editing. **R. Glasspool:** Resources, writing–review and editing. **M.T. Goodman:** Resources, writing–review and editing. **J. Gronwald:** Resources, writing–review and editing. **H.R. Harris:** Resources, writing–review and editing. **P. Harter:** Resources, writing–review and editing. **A. Hein:** Resources, writing–review and editing. **F. Heitz:** Resources, writing–review and editing. **M.A.T. Hildebrandt:** Resources, writing–review and editing. **P. Hillemanns:** Resources, writing–review and editing. **E. Høgdall:** Resources, writing–review and editing. **C.K. Høgdall:** Resources, writing–review and editing. **E.G. Holliday:** Resources, writing–review and editing. **D.G. Huntsman:** Resources, writing–review and editing. **T. Huzarski:** Resources, writing–review and editing. **A. Jakubowska:** Resources, writing–review and editing. **A. Jensen:** Resources, writing–review and editing. **M.E. Jones:** Resources, writing–review and editing. **B.Y. Karlan:** Resources, writing–review and editing. **A. Karnezis:** Resources, writing–review and editing. **J.L. Kelley:** Resources, writing–review and editing. **E. Khusnutdinova:** Resources, writing–review and editing. **J.L. Killeen:** Resources, writing–review and editing. **S.K. Kjaer:** Resources, writing–review and editing. **R. Klapdor:** Resources, writing–review and editing. **M. Köbel:** Resources, writing–review and editing. **B. Konopka:** Resources, writing–review and editing. **I. Konstantopoulou:** Resources, writing–review and editing. **R.K. Kopperud:** Resources, writing–review and editing. **M. Koti:** Resources, writing–review and editing. **P. Kraft:** Resources, writing–review and editing. **J. Kupryjanczyk:** Resources, writing–review and editing. **D. Lambrechts:** Resources, writing–review and editing. **M.C. Larson:** Resources, writing–review and editing. **L. Le Marchand:** Resources, writing–review and editing. **S. Lele:** Resources, writing–review and editing. **J. Lester:** Resources, writing–review and editing. **A.J. Li:** Resources, writing–review and editing. **D. Liang:** Resources, writing–review and editing. **C. Liebrich:** Resources, writing–review and editing. **L. Lipworth:** Resources, writing–review and editing. **J. Lissowska:** Resources, writing–review and editing. **L. Lu:** Resources, writing–review and editing. **K.H. Lu:** Resources, writing–review and editing. **A. Macciotta:** Resources, writing–review and editing. **A. Mattiello:** Resources, writing–review and editing. **T. May:** Resources, writing–review and editing. **J.N. McAlpine:** Resources, writing–review and editing. **V. McGuire:** Resources, writing–review and editing. **I.A. McNeish:** Resources, writing–review and editing. **U. Menon:** Resources, writing–review and editing. **F. Modugno:** Resources, writing–review and editing. **K.B. Moysich:** Resources, writing–review and editing. **H. Nevanlinna:** Resources, writing–review and editing. **K. Odunsi:** Resources, writing–review and editing. **H. Olsson:** Resources, writing–review and editing. **S. Orsulic:** Resources, writing–review and editing. **A. Osorio:** Resources, writing–review and editing. **D. Palli:** Resources, writing–review and editing. **T.-W. Park-Simon:** Resources, writing–review and editing. **C.L. Pearce:** Resources, writing–review and editing. **T. Pejovic:** Resources, writing–review and editing. **J.B. Permuth:** Resources, writing–review and editing. **A. Podgorska:** Resources, writing–review and editing. **S.J. Ramus:** Resources, writing–review and editing. **T.R. Rebbeck:** Resources, writing–review and editing. **M.J. Riggan:** Resources, writing–review and editing. **H.A. Risch:** Resources, writing–review and editing. **J.H. Rothstein:** Resources, writing–review and editing. **I.B. Runnebaum:** Resources, writing–review and editing. **R.J. Scott:** Resources, writing–review and editing. **T.A. Sellers:** Resources, writing–review and editing. **J. Senz:** Resources, writing–review and editing. **V.W. Setiawan:** Resources, writing–review and editing.

N. Siddiqui: Resources, writing–review and editing. **W. Sieh:** Resources, writing–review and editing. **B. Spiewankiewicz:** Resources, writing–review and editing. **R. Sutphen:** Resources, writing–review and editing. **A.J. Swerdlow:** Resources, writing–review and editing. **L.M. Szafron:** Resources, writing–review and editing. **S.H. Teo:** Resources, writing–review and editing. **P.J. Thompson:** Resources, writing–review and editing. **L.C.V. Thomsen:** Resources, writing–review and editing. **L. Titus:** Resources, writing–review and editing. **A. Tone:** Resources, writing–review and editing. **R. Tumino:** Resources, writing–review and editing. **C. Turman:** Resources, writing–review and editing. **A. Vanderstichele:** Resources, writing–review and editing. **D. Velez Edwards:** Resources, writing–review and editing. **I. Vergote:** Resources, writing–review and editing. **R.A. Vierkant:** Resources, writing–review and editing. **Z. Wang:** Resources, writing–review and editing. **S. Wang-Gohrke:** Resources, writing–review and editing. **P.M. Webb:** Resources, writing–review and editing. **E. White:** Resources, writing–review and editing. **A.S. Whittemore:** Resources, writing–review and editing. **S.J. Winham:** Resources, writing–review and editing. **X. Wu:** Resources, writing–review and editing. **A.H. Wu:** Resources, writing–review and editing. **D. Yannoukakos:** Resources, writing–review and editing. **A.B. Spurdle:** Conceptualization, resources, supervision, writing–original draft, writing–review and editing. **T.A. O'Mara:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, writing–original draft, project administration, writing–review and editing.

Acknowledgments

We thank ECAC and OCAC for provision of summary statistics to perform this study. We thank Siddhartha Kar for his helpful discussions and advice for designing the genetic analysis approaches. Full acknowledgments and funding for ECAC and OCAC can be found in the Supplementary Note. T.A. O'Mara is supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (APP1111246) and Investigator Fellowship (APP1173170). A.B. Spurdle is supported by an NHMRC Senior Research Fellowship (APP1061779) and Investigator Fellowship (APP1177524). This work was supported by a Cancer Australia PdCCRS Project Grant, funded by Cure Cancer Australia and the CanToo Foundation (#1138084), NHMRC project grants (APP1158083 and APP1109286), QIMR Berghofer Medical Research Institute Near Miss Funding, and a special purpose donation gratefully received from Sarah Stork.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 13, 2020; revised July 31, 2020; accepted October 22, 2020; published first November 3, 2020.

References

1. Koshiyama M, Matsumura N, Konishi I. Recent concepts of ovarian carcinogenesis: type I and type II. Biomed Res Int 2014;2014:934261.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
3. Cramer DW. The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin North Am 2012;26:1–12.
4. Braem MGM, Onland-Moret NC, van den Brandt PA, Goldbohm RA, Peeters PHM, Kruitwagen RFPM, et al. Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. Am J Epidemiol 2010;172:1181–9.
5. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010;127:442–51.
6. Gong TT, Wang YL, Ma XX. Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. Sci Rep 2015;5:14051.
7. Gong TT, Wu QJ, Vogtmann E, Lin B, Wang YL. Age at menarche and risk of ovarian cancer: a meta-analysis of epidemiological studies. Int J Cancer 2013;132:2894–900.
8. Danforth KN, Tworoger SS, Hecht JL, Rosner BA, Colditz GA, Hankinson SE. Breastfeeding and risk of ovarian cancer in two prospective cohorts. Cancer Causes Control 2007;18:517–23.
9. Jordan SJ, Na R, Johnatty SE, Wise LA, Adami HO, Brinton LA, et al. Breastfeeding and endometrial cancer risk: an analysis from the Epidemiology of Endometrial Cancer Consortium. Obstet Gynecol 2017;129:1059–67.
10. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371:303–14.
11. Maxwell GL, Schildkraut JM, Calingaert B, Risinger JI, Dainty L, Marchbanks PA, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. Gynecol Oncol 2006;103:535–40.
12. Jenabi E, Poorolajal J. The effect of body mass index on endometrial cancer: a meta-analysis. Public Health 2015;129:872–80.
13. Leitzmann MF, Koebnick C, Danforth KN, Brinton LA, Moore SC, Hollenbeck AR, et al. Body mass index and risk of ovarian cancer. Cancer 2009;115:812–22.
14. Vang R, Levine DA, Soslow RA, Zaloudek C, Shih Ie-M, Kurman RJ. Molecular alterations of TP53 are a defining feature of ovarian high-grade serous carcinoma: a rereview of cases lacking TP53 mutations in The Cancer Genome Atlas Ovarian Study. Int J Gynecol Pathol 2016;35:48–55.
15. Schultheis AM, Martelotto LG, De Filippo MR, Piscuglio S, Ng CKY, Hussein YR, et al. TP53 Mutational spectrum in endometrioid and serous endometrial cancers. Int J Gynecol Pathol 2016;35:289–300.
16. McConechy MK, Ding J, Senz J, Yang W, Melnyk N, Tone AA, et al. Ovarian and endometrial endometrioid carcinomas have distinct CTNNB1 and PTEN mutation profiles. Mod Pathol 2014;27:128–34.
17. Kolbe DL, DeLoia JA, Porter-Gill P, Strange M, Petrykowska HM, Guirguis A, et al. Differential analysis of ovarian and endometrial cancers identifies a methylator phenotype. PLoS One 2012;7:e32941.
18. Zorn KK, Bonome T, Gangi L, Chandramouli GV, Awtrey CS, Gardner GJ, et al. Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. Clin Cancer Res 2005;11:6422–30.
19. King CM, Barbara C, Prentice A, Brenton JD, Charnock-Jones DS. Models of endometriosis and their utility in studying progression to ovarian clear cell carcinoma. J Pathol 2016;238:185–96.
20. Lu KH, Broaddus RR. Gynecologic cancers in lynch syndrome/HNPCC. Fam Cancer 2005;4:249–54.
21. O'Mara TA, Glubb DM, Amant F, Annibali D, Ashton K, Attia J, et al. Identification of nine new susceptibility loci for endometrial cancer. Nat Commun 2018;9:3166.
22. Phelan CM, Kuchenbaecker KB, Tyrer JP, Kar SP, Lawrenson K, Winham SJ, et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet 2017;49:680–91.
23. Cheng THT, Thompson D, Painter J, O'Mara T, Gorman M, Martin L, et al. Meta-analysis of genome-wide association studies identifies common susceptibility polymorphisms for colorectal and endometrial cancer near SH2B3 and TSHZ1. Sci Rep 2015;5:17369.
24. Kar SP, Beesley J, Amin Al Olama A, Michailidou K, Tyrer J, Kote-Jarai Z, et al. Genome-wide meta-analyses of breast, ovarian, and prostate cancer association studies identify multiple new susceptibility loci shared by at least two cancer types. Cancer Discov 2016;6:1052–67.
25. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 2015;47:291–5.
26. Turley P, Walters RK, Maghzian O, Okbay A, Lee JJ, Fontana MA, et al. Multi-trait analysis of genome-wide association summary statistics using MTAG. Nat Genet 2018;50:229–37.
27. Han B, Eskin E. Interpreting meta-analyses of genome-wide association studies. PLoS Genet 2012;8:e1002555.
28. Han B, Eskin E. Random-effects model aimed at discovering associations in meta-analysis of genome-wide association studies. Am J Hum Genet 2011;88:586–98.
29. Pickrell JK, Berisa T, Liu JZ, Ségurel L, Tung JY, Hinds DA. Detection and interpretation of shared genetic influences on 42 human traits. Nat Genet 2016;48:709–17.
30. Berisa T, Pickrell JK. Approximately independent linkage disequilibrium blocks in human populations. Bioinformatics 2016;32:283–5.

31. Lawrenson K, Benjamin E, Turmaine M, Jacobs I, Gayther S, Dafou D. In vitro three-dimensional modelling of human ovarian surface epithelial cells. Cell Prolif 2009;42:385–93.
32. O'Mara TA, Spurdle AB, Glubb DM, Endometrial Cancer Association C. Analysis of promoter-associated chromatin interactions reveals biologically relevant candidate target genes at endometrial cancer risk loci. Cancers 2019; 11:1440.
33. Servant N, Varoquaux N, Lajoie BR, Viara E, Chen CJ, Vert JP, et al. HiC-Pro: an optimized and flexible pipeline for Hi-C data processing. Genome Biol 2015;16: 259.
34. Lareau CA, Aryee MJ. hichipper: a preprocessing pipeline for calling DNA loops from HiChIP data. Nat Methods 2018;15:155–6.
35. Phanstiel DH, Boyle AP, Heidari N, Snyder MP. Mango: a bias-correcting ChIA-PET analysis pipeline. Bioinformatics 2015;31:3092–8.
36. Lim YW, Chen-Harris H, Mayba O, Lianoglou S, Wuster A, Bhangale T, et al. Germline genetic polymorphisms influence tumor gene expression and immune cell infiltration. Proc Natl Acad Sci U S A 2018;115:E11701–10.
37. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. Nat Genet 2013;45:580–5.
38. Võsa U, Claringbould A, Westra H, Bonder MJ, Deelen P, Zeng B, et al. Unraveling the polygenic architecture of complex traits using blood eQTL metaanalysis. bioRxiv 2018;447367.
39. Carvajal-Carmona LG, O'Mara TA, Painter JN, Lose FA, Dennis J, Michailidou K, et al. Candidate locus analysis of the TERT-CLPTM1L cancer risk region on chromosome 5p15 identifies multiple independent variants associated with endometrial cancer risk. Hum Genet 2015;134: 231–45.
40. Chung CC, Magalhaes WC, Gonzalez-Bosquet J, Chanock SJ. Genome-wide association studies in cancer–current and future directions. Carcinogenesis 2010; 31:111–20.
41. Bojesen SE, Pooley KA, Johnatty SE, Beesley J, Michailidou K, Tyrer JP, et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet 2013;45:371–84.
42. Yuan X, Larsson C, Xu D. Mechanisms underlying the activation of TERT transcription and telomerase activity in human cancer: old actors and new players. Oncogene 2019;38:6172–83.
43. Pestana A, Vinagre J, Sobrinho-Simoes M, Soares P. TERT biology and function in cancer: beyond immortalisation. J Mol Endocrinol 2017;58: R129–46.
44. Bailey MH, Tokheim C, Porta-Pardo E, Sengupta S, Bertrand D, Weerasinghe A, et al. Comprehensive characterization of cancer driver genes and mutations. Cell 2018;173:371–85.
45. Tashiro E, Tsuchiya A, Imoto M. Functions of cyclin D1 as an oncogene and regulation of cyclin D1 expression. Cancer Sci 2007;98:629–35.
46. Berger AC, Korkut A, Kanchi RS, Hegde AM, Lenoir W, Liu W, et al. A comprehensive pan-cancer molecular study of gynecologic and breast cancers. Cancer Cell 2018;33:690–705.
47. Painter JN, O'Mara TA, Batra J, Cheng T, Lose FA, Dennis J, et al. Fine-mapping of the HNF1B multicancer locus identifies candidate variants that mediate endometrial cancer risk. Hum Mol Genet 2015;24:1478–92.
48. Spurdle AB, Thompson DJ, Ahmed S, Ferguson K, Healey CS, O'Mara T, et al. Genome-wide association study identifies a common variant associated with risk of endometrial cancer. Nat Genet 2011;43:451–4.
49. Pharoah PDP, Tsai Ya-Yu, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet 2013;45:362–70.
50. Shen H, Fridley BL, Song H, Lawrenson K, Cunningham JM, Ramus SJ, et al. Epigenetic analysis leads to identification of HNF1B as a subtype-specific susceptibility gene for ovarian cancer. Nat Commun 2013;4:1628.
51. O'Mara TA, Glubb DM, Kho PF, Thompson DJ, Spurdle AB. Genome-wide association studies of endometrial cancer: latest developments and future directions. Cancer Epidemiol Biomarkers Prev 2019;28:1095–102.
52. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol 2012;13:385–94.
53. Painter JN, O'Mara TA, Morris AP, Cheng THT, Gorman M, Martin L, et al. Genetic overlap between endometriosis and endometrial cancer: evidence from cross-disease genetic correlation and GWAS meta-analyses. Cancer Med 2018;7: 1978–87.
54. Nilufer R, et al. Large-scale genome-wide association meta-analysis of endometriosis reveals 13 novel loci and genetically-associated comorbidity with other pain conditions. bioRxiv 2018;406967.
55. Chen CL, Hsieh FC, Lieblein JC, Brown J, Chan C, Wallace JA, et al. Stat3 activation in human endometrial and cervical cancers. Br J Cancer 2007;96: 591–9.
56. Yoshikawa T, Miyamoto M, Aoyama T, Soyama H, Goto T, Hirata J, et al. JAK2/STAT3 pathway as a therapeutic target in ovarian cancers. Oncol Lett 2018;15: 5772–80.
57. Khaled WT, Choon Lee S, Stingl J, Chen X, Raza Ali H, Rueda OM, et al. BCL11A is a triple-negative breast cancer gene with critical functions in stem and progenitor cells. Nat Commun 2015;6:5987.
58. Lazarus KA, Hadi F, Zambon E, Bach K, Santolla M-F, Watson JK, et al. BCL11A interacts with SOX2 to control the expression of epigenetic regulators in lung squamous carcinoma. Nat Commun 2018;9:3327.
59. Luc S, Huang J, McEldoon JL, Somuncular E, Li D, Rhodes C, et al. Bcl11a deficiency leads to hematopoietic stem cell defects with an aging-like phenotype. Cell Rep 2016;16:3181–94.
60. Itamochi H, Oishi T, Oumi N, Takeuchi S, Yoshihara K, Mikami M, et al. Whole-genome sequencing revealed novel prognostic biomarkers and promising targets for therapy of ovarian clear cell carcinoma. Br J Cancer 2017;117:717–24.
61. Er TK, Su YF, Wu CC, Chen CC, Wang J, Hsieh TH, et al. Targeted next-generation sequencing for molecular diagnosis of endometriosis-associated ovarian cancer. J Mol Med 2016;94:835–47.
62. Arend P. Position of human blood group O(H) and phenotype-determining enzymes in growth and infectious disease. Ann N Y Acad Sci 2018;1425:5–18.
63. Meyer C, Hofmann J, Burmeister T, Gröger D, Park TS, Emerenciano M, et al. The MLL recombinome of acute leukemias in 2013. Leukemia 2013;27: 2165–76.
64. Nakazawa K, Dashzeveg N, Yoshida K. Tumor suppressor p53 induces miR-1915 processing to inhibit Bcl-2 in the apoptotic response to DNA damage. FEBS J 2014;281:2937–44.
65. Ruth KS, Campbell PJ, Chew S, Lim EeM, Hadlow N, Stuckey BGA, et al. Genome-wide association study with 1000 genomes imputation identifies signals for nine sex hormone-related phenotypes. Eur J Hum Genet 2016;24: 284–90.
66. Domanski TL, Finta C, Halpert JR, Zaphiropoulos PG. cDNA cloning and initial characterization of CYP3A43, a novel human cytochrome P450. Mol Pharmacol 2001;59:386–92.
67. Downie D, McFadyen MCE, Rooney PH, Cruickshank ME, Parkin DE, Miller ID, et al. Profiling cytochrome P450 expression in ovarian cancer: identification of prognostic markers. Clin Cancer Res 2005;11:7369–75.
68. Prossnitz ER, Barton M. The G-protein-coupled estrogen receptor GPER in health and disease. Nat Rev Endocrinol 2011;7:715–26.
69. Clark BJ, Prough RA, Klinge CM. Mechanisms of action of dehydroepiandrosterone. Vitam Horm 2018;108:29–73.
70. Kuchenbaecker KB, Ramus SJ, Tyrer J, Lee A, Shen HC, Beesley J, et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet 2015;47:164–71.