

Cross-cancer genome-wide association study of endometrial cancer and epithelial ovarian cancer identifies genetic risk regions associated with risk of both cancers.

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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 LD Score 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, co-localization, 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 sub-genome 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 (eQTL) data highlighted candidate target genes for further investigation.

Conclusion: 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 endometrioid¹. Herein, “ovarian cancer” refers to epithelial types of this disease. On both histological 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 gynecological cancer, although it ranks fifth for cancer incidence in women globally². 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 epidemiological studies showing concordant direction of effect in relation to exposure to estrogen and progesterone (reviewed by Cramer³). 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^{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 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, et al. ¹⁶). Methylation profiling has found endometrioid endometrial and endometrioid ovarian tumors cluster together¹⁷, and similar gene expression patterns have been observed for clear cell endometrial and clear cell ovarian tumors¹⁸. Further, there is increasing evidence that clear cell and endometrioid ovarian tumors arise in part from endometriosis (reviewed by King, et al. 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 40-60% and 8-15% lifetime risks of endometrial cancer and ovarian cancer, respectively²⁰. 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 datasets 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 datasets 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.

Methods

GWAS Datasets

GWAS summary statistics were obtained from the latest meta-analyses performed by the Endometrial Cancer Association Consortium (ECAC)²¹ and the Ovarian Cancer Association Consortium (OCAC)²². Because of the low number of non-endometrioid endometrial cancer available in ECAC, summary statistics were provided for all endometrial cancer risk (including all endometrial cancer cases) and analyses restricted to endometrioid cases only. OCAC summary statistics were available for all ovarian cancer risk (including all ovarian cancer cases), as well analyses restricted to eight different subtypes: endometrioid histology, serous (including borderline, high- 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 Regression²⁵. 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 MTAG²⁶. Because of the significant heterogeneity in risk estimates observed for genetic variants across ovarian cancer subtypes²², 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 two cancers ($P_{\text{het}} > 0.05$); 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-values²⁷ were generated for variants reaching suggestive evidence of association ($P < 5 \times 10^{-7}$) using METASOFT²⁸. 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 co-localization by GWAS-PW²⁹, using all genetic variants at the query locus. Query loci were defined using LD from the European 1000 Genomes Phase I reference panel³⁰ 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)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 $\mu\text{g/ml}$ 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 min, the reaction was quenched by washing with 125 mM 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 previously³². Sequencing libraries were generated using HiChIP libraries and the Nextera DNA preparation kit (Illumina). Size selection was performed using Ampure XP beads to capture 300-700 bp fragments. Two independent sequencing libraries were pooled to provide 25 µl of library at ≥ 10 nM for Illumina HiSeq4000 (AGRF, Brisbane, QLD, Australia) 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 v2.9.0³³ and default settings used to filter for valid interactions as previously³². 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 hicchipper pipeline v0.7.0³⁴ as previously³². 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 Mango³⁵ 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 was also available from our previous analysis of a normal immortalized endometrial cell line (E6E7hTERT)³².

Credible candidate risk variants

Using 100:1 log likelihood ratios, “credible variants” (CVs) 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/)³⁶, and from 101 non-cancerous uterus samples and 122 ovarian tissue samples from GTEx (data release v7; <http://gtexportal.org>)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>)³⁸. Genes were considered potential targets if their expression associated with CVs that had a p-values within two orders of magnitude of the best eQTL variant in any of these eQTL datasets.

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 = 2.9×10^{-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 study³⁹. 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, **Figure 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 line³², we intersected CVs coincident with putative enhancers (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. **Figure 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 datasets: blood, non-cancerous 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 since 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 multi-cancer 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 risk⁴¹. 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 significance³⁹, 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, et al. ⁴²) and has oncogenic interactions with *MYC* (reviewed in Pestana, et al. ⁴³).

Our results suggest, at a sub-genome 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 gene⁴⁴. Cyclin D1 is considered an oncogene due to its central role in cell cycle regulation, and ability to promote cell proliferation⁴⁵. *CCND1* has been found to be significantly mutated in gynecological (including endometrial and ovarian cancers) and breast cancers⁴⁶. 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 cancer⁴⁷⁻⁵⁰. 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)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* promoter⁴⁷, which may lead to increased secretion of insulin, a risk factor for endometrial cancer⁵¹.

The 17q21.32 region is a known shared endometrial²¹ and ovarian cancer²² 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 endometriosis⁵². Epidemiological and molecular data provide strong evidence that clear cell and endometrioid ovarian cancer arise in part from endometriosis (reviewed by King, et al. 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 endometriosis⁵³, and subsequently found to be associated with endometriosis risk independently⁵⁴. 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 studies³².

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 endometriosis risk locus⁵³. 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 cancer⁵³. 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 cancer⁵⁵ and ovarian cancer⁵⁶.

The 2p16.1 region is a known endometrial cancer risk locus and was found to associate 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 non-endometrioid 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)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 cells³². 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 anti-cancer effects⁵⁹. 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 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 leukaemia⁶³. 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 apoptosis⁶⁴.

Two of the sub-genome 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 levels⁶⁵. The sole candidate target gene at this locus, *CYP3A43*, encodes a cytochrome P450 enzyme that may be involved in androgen metabolism⁶⁶ and is upregulated in ovarian tumors⁶⁷. 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 ⁶⁸). Further, it appears that androgen can also bind to GPER1 to stimulate cancer cell growth⁶⁹.

Despite these findings, the present study does have some limitations. The low numbers of non-endometrioid 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 impacted 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 cancer⁷⁰ 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 epidemiological and histopathological 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.

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

Phenotype	ECAC (N)	OCAC (N)
All Cases*	12906	23342
Endometrioid cases	8578	2810
Serous cases	NA	16003
Serous high grade cases	NA	13037
Serous low grade cases	NA	1012
Serous borderline cases	NA	1954
Serous low grade and borderline cases	NA	2966
Clear cell cases	NA	1366
Mucinous cases	NA	2566
Controls	108979	40941

Abbreviations – ECAC: Endometrial Cancer Association Consortium; OCAC: Ovarian Cancer Association Consortium; N: sample counts

*All cases also includes those with unknown or mixed histology

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 & 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

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

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		Model 3 PPA
								OR (95% CI)	P-value	M-value	OR (95% CI)	P-value	M-value	OR (95% CI)	P-value	
<i>Known endometrial and ovarian cancer risk regions</i>																
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 & 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
<i>Known endometrial cancer risk regions</i>																
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
<i>Known ovarian cancer risk regions</i>																
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

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		Model 3 PPA
								OR (95% CI)	P-value	M-value	OR (95% CI)	P-value	M-value	OR (95% CI)	P-value	
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
<i>5p15.33</i>	<i>all</i>	<i>serous LG & borderline</i>	<i>rs2853672</i>	<i>5:1292983</i>	<i>A/C</i>	<i>0.48/0.49</i>	<i>1.00/1.00</i>	<i>0.94 (0.91-0.96)</i>	<i>1.30E-05</i>	<i>1.00</i>	<i>0.88 (0.83-0.93)</i>	<i>5.72E-06</i>	<i>1.00</i>	<i>0.92 (0.90-0.95)</i>	<i>1.03E-08</i>	<i>1.00</i>
<i>5p15.33</i>	<i>endometrioid</i>	<i>serous LG & borderline</i>	<i>rs2853672</i>	<i>5:1292983</i>	<i>A/C</i>	<i>0.48/0.49</i>	<i>1.00/1.00</i>	<i>0.93 (0.89-0.96)</i>	<i>2.27E-05</i>	<i>1.00</i>	<i>0.88 (0.83-0.93)</i>	<i>5.72E-06</i>	<i>1.00</i>	<i>0.91 (0.88-0.94)</i>	<i>7.20E-09</i>	<i>1.00</i>
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
<i>10p12.31</i>	<i>all</i>	<i>serous HG</i>	<i>rs7090708</i>	<i>10:21929179</i>	<i>G/A</i>	<i>0.33/0.33</i>	<i>1.00/0.99</i>	<i>1.05 (1.02-1.08)</i>	<i>2.6E-03</i>	<i>0.92</i>	<i>1.10 (1.07-1.14)</i>	<i>5.02E-08</i>	<i>1.00</i>	<i>1.07 (1.05-1.10)</i>	<i>7.63E-09</i>	<i>0.99</i>
<i>Novel regions</i>																
7p22.2	<i>all</i>	<i>all</i>	<i>rs13221982</i>	<i>7:3865621</i>	<i>C/T</i>	<i>0.06/0.06</i>	<i>0.98/0.98</i>	<i>1.13 (1.06-1.21)</i>	<i>1.32E-04</i>	<i>1.00</i>	<i>1.12 (1.06-1.18)</i>	<i>6.85E-05</i>	<i>1.00</i>	<i>1.13 (1.08-1.18)</i>	<i>1.57E-07</i>	<i>0.90</i>
9p12	<i>endometrioid</i>	<i>serous LG & borderline</i>	<i>rs2475339</i>	<i>9:10262484</i>	<i>T/C</i>	<i>0.83/0.83</i>	<i>0.99/0.99</i>	<i>0.89 (0.85-0.93)</i>	<i>8.64E-07</i>	<i>1.00</i>	<i>0.90 (0.84-0.97)</i>	<i>4.50E-03</i>	<i>0.99</i>	<i>0.89 (0.86-0.93)</i>	<i>4.36E-08</i>	<i>0.94</i>
7q22.1	<i>all</i>	<i>serous borderline</i>	<i>rs139380031</i>	<i>7:98911827</i>	<i>A/C</i>	<i>0.03/0.03</i>	<i>0.97/0.95</i>	<i>0.77 (0.70-0.85)</i>	<i>5.98E-07</i>	<i>1.00</i>	<i>0.77 (0.61-0.97)</i>	<i>0.03</i>	<i>0.95</i>	<i>0.77 (0.70-0.85)</i>	<i>1.28E-07</i>	<i>0.57</i>
11q13.3	<i>endometrioid</i>	<i>all</i>	<i>rs7118966</i>	<i>11:69019272</i>	<i>C/T</i>	<i>0.24/0.25</i>	<i>1.00/1.00</i>	<i>0.93 (0.89-0.97)</i>	<i>4.30E-04</i>	<i>0.99</i>	<i>0.94 (0.91-0.97)</i>	<i>1.96E-05</i>	<i>1.00</i>	<i>0.93 (0.91-0.96)</i>	<i>1.25E-07</i>	<i>0.82</i>

Abbreviations – EA: Effect Allele; OA: Other Allele; EAF: Effect Allele Frequency; OR: Odds Ratio; CI: Confidence Interval; PPA: Posterior Probability of Association; HG: High grade; LG: Low grade
 Italicized results meet suggestive association ($P < 5 \times 10^{-7}$)

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

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

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).