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Polymorphisms in inflammation pathway genes and endometrial cancer risk

Ryan J. Delahanty[1], **Yong-Bing Xiang**[2], **Amanda Spurdle**[3], **Alicia Beeghly-Fadiel**[1], **Jirong Long**[1], **Deborah Thompson**[4], **Ian Tomlinson**[5], **Herbert Yu**[6], **Diether Lambrechts**[7], **Thilo Dörk**[8], **Marc T. Goodman**[9], **Ying Zheng**[10], **Helga B. Salvesen**[11,12], **Ping-Ping Bao**[10], **Frederic Amant**[7], **Matthias W. Beckmann**[13], **Lieve Coenegrachts**[7], **An Coosemans**[7], **Natalia Dubrowinskaja**[8], **Alison Dunning**[5], **Ingo B. Runnebaum**[14], **Douglas Easton**[4], **Arif B. Ekici**[15], **Peter A. Fasching**[13,16], **Mari K. Halle**[11,12], **Alexander Hein**[13], **Kimberly Howarth**[5], **Maggie Gorman**[5], **Dylyara Kaydarova**[17], **Camilla Krakstad**[11,12], **Felicity Lose**[3], **Lingeng Lu**[6], **Galina Lurie**[9], **Tracy O'Mara**[3,18], **Rayna K. Matsuno**[9], **Paul Pharoah**[4], **Harvey Risch**[6], **Madeleine Corssen**[8], **Jone Trovik**[11,12], **Nurzhan Turmanov**[8], **Wanqing Wen**[1], **Wei Lu**[10], **Qiuyin Cai**[1], **Wei Zheng**[1], and **Xiao-Ou Shu**[1]

[1]Division of Epidemiology, Department of Medicine and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA

[2]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

[3]Division of Genetics and Population Health, Queensland Institute of Medical Research, Brisbane Queensland, Australia

[4]Department of Oncology, Strangeways Research Laboratory, University of Cambridge, Worts Causeway, Cambridge, UK

[5]Wellcome Trust Centre for Human Genetics and NIHR Comprehensive Biomedical Research Centre, University of Oxford, Oxford, UK

[6]Department of Epidemiology and Public Health, Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA

[7]Division Gynaecological Oncology, Katholieke Universiteit Leuven, Leuven, Belgium

[8]Gynaecology Research Unit, Hannover Medical School, Hannover, Germany

[9]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA

[10]Shanghai Institute of Preventive Medicine, Shanghai, China

[11]Department of Obstetrics and Gynecology, Haukeland University Hospital, 5021 Bergen, Norway

[12]Department of Clinical Medicine, University of Bergen, 5020 Bergen, Norway

[13]Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich Alexander University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-Nuremberg, Nuremberg, Erlangen, Germany

[14]Department of Gynecology, Jena University Hospital, Jena, Germany

Corresponding Author: Xiao-Ou Shu, M.D., Ph.D. Professor of Medicine Vanderbilt Epidemiology Center 2525 West End Avenue, Suite 600 (IMPH) Nashville, TN 37203-1738 Tel: 615-936-0713 Fax: 615-936-8291 xiao-ou.shu@vanderbilt.edu.

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[15]Institute of Human Genetics, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany

[16]Division of Hematology and Oncology, Department of Medicine, University of California at Los Angeles, Los Angeles, CA, USA

[17]Almaty Oncology Center, State Oncology Institute, Almaty, Kazakhstan

[18]Cancer Program, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane Queensland, Australia

Abstract

Background—Experimental and epidemiological evidence have suggested that chronic inflammation may play a critical role in endometrial carcinogenesis.

Methods—To investigate this hypothesis, a two-stage study was carried out to evaluate single nucleotide polymorphisms (SNPs) in inflammatory pathway genes in association with endometrial cancer risk. In stage 1, 64 candidate pathway genes were identified and 4,542 directly genotyped or imputed SNPs were analyzed among 832 endometrial cancer cases and 2,049 controls, using data from the Shanghai Endometrial Cancer Genetics Study. Linkage disequilibrium of stage 1 SNPs significantly associated with endometrial cancer ($P<0.05$) indicated that the majority of associations could be linked to one of 24 distinct loci. One SNP from each of the 24 loci was then selected for follow-up genotyping. Of these, 21 SNPs were successfully designed and genotyped in stage 2, which consisted of ten additional studies including 6,604 endometrial cancer cases and 8,511 controls.

Results—Five of the 21 SNPs had significant allelic odds ratios and 95% confidence intervals as follows: *FABP1*, 0.92 (0.85-0.99); *CXCL3*, 1.16 (1.05-1.29); *IL6*, 1.08 (1.00-1.17); *MSR1*, 0.90 (0.82-0.98); and *MMP9*, 0.91 (0.87-0.97). Two of these polymorphisms were independently significant in the replication sample (rs352038 in *CXCL3* and rs3918249 in *MMP9*). The association for the *MMP9* polymorphism remained significant after Bonferroni correction and showed a significant association with endometrial cancer in both Asian- and European-ancestry samples.

Conclusions—These findings lend support to the hypothesis that genetic polymorphisms in genes involved in the inflammatory pathway may contribute to genetic susceptibility to endometrial cancer.

Impact Statement—This study adds to the growing evidence that inflammation plays an important role in endometrial carcinogenesis.

Keywords

endometrial cancer; inflammation; genetic risk variants; meta-analysis

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in developed countries and the second most common in the world (1, 2). In China, the incidence of endometrial cancer has increased 90% over the past two decades to 7.62/100,000 in 2007 (3), although it is still substantially lower than the incidence seen in developed countries (US 22.0/100,000; Europe 11.8-12.5/100,000) (2). Obesity, early age at menarche, late age at menopause, nulliparity, and use of estrogen hormone replacement therapy are established risk factors for endometrial cancer (4).

Although the genetics of endometrial cancer are poorly understood, its heritability of approximately 0.5 indicates that there is a strong genetic component for disease risk (5, 6). A number of lines of experimental and epidemiological evidence have indicated that inflammation may play an important role in the transition from normal endometrium to malignancy. Of the many risk factors associated with endometrial cancer, several -- including use of unopposed estrogen (7), anovulation (8), endometriosis (9), early age at menarche (10), late age at menopause (11), nulliparity (12, 13), polycystic ovary syndrome (PCOS) (14), and obesity (15) -- may contribute to a state of prolonged exposure to inflammation (16). Chronic inflammation can result in derangement of cellular processes, leading to excessive mitosis, decreased apoptosis, the accumulation of DNA damage, and thus initiate and promote neoplastic transformation (12, 17). Given that inflammatory process are influenced by inflammation-related genes, we hypothesized that common genetic polymorphisms in inflammatory pathway genes may also influence the risk of endometrial cancer.

To investigate this hypothesis, a two-stage study was carried out to determine whether common variants in genes involved in the inflammatory response were associated with endometrial cancer risk using the resources of the Shanghai Endometrial Cancer Genetics Study and ten additional studies of endometrial cancer conducted among women in the US, Australia, Europe, and China.

MATERIALS AND METHODS

This study involved two stages, as shown in Table 1. Study populations are described below and the overall study design and SNP selection procedure are depicted in Figure 1.

Study population

Stage 1 was conducted among the participants of the Shanghai Endometrial Cancer Genetics Study (SECGS), which included 832 cases from the Shanghai Endometrial Cancer Study (SECS) and 2,049 controls from the Shanghai Breast Cancer Study (SBCS) and the Shanghai Women's Health Study (SWHS). Details of these studies have been described previously (18). Briefly, among 1,199 endometrial cancer cases included in the SECS, 832 women who donated a blood sample to the study and were successfully genotyped by Affymetrix 6.0 array were included in the stage 1 study. Genome-wide scan data from 2,049 women from the SBCS served as controls. The mean age of cases was 54.7 and for controls was 51.7; 45% of cases and 30% of controls were post-menopausal. Data for stage 2 included 6,604 cases and 8,511 controls from a total of 10 studies (Table 1). IRB approval was obtained for all of the parent studies from all contributing institutions, and informed consent was obtained from all participants.

Candidate SNP selection

The SNP selection scheme is shown in Figure 1. Sixty-four candidate genes involved in inflammatory pathways were identified based on literature review and bioinformatics searches. In order to cast a comprehensive net, we did literature review of genes involved in inflammatory pathways, searched Vanderbilt's Gene List Automatically Derived for You (19), and String-DB (20) for related inflammatory network genes (Supplementary Table 1). A total of 4,542 SNPs with minor allele frequencies of 0.05 or greater were located in or near (± 20kb) RefSeq transcripts of these genes were identified for the stage 1 study. Genotyping of these SNPs was carried out as part of a larger genome-wide association study previously described (18). Only SNPs that passed quality control (QC) from the Affymetrix 6.0 array (Affymetrix, Santa Clara, CA, USA) or that could be imputed were eligible for selection. SNPs for stage 2 were selected, using data from HapMap, release 28, after

evaluation of linkage disequilibrium (LD) between the associated SNPs. From this, it was determined that the majority of associations could be linked to one of 24 distinct loci as determined by LD to other SNPs (see Supplementary Figure 1 for an example in *MMP9* and *CXCL3*). The SNP with the lowest *P* value from each of the 24 loci was selected for follow-up genotyping in stage 2 unless assay design parameters indicated it would fail genotyping. In the latter case, the next most significant SNP was chosen for validation.

Genotyping, quality control, and imputation

Stage 1 genotyping and QC procedures have been described in detail in previous publications (18, 21). Briefly, genotyping was performed using the Affymetrix 6.0 array, which includes 906,602 SNPs. The Birdseed v2 algorithm was used to call genotypes (22). QC samples from Coriell Cell Repositories (Camden, NJ) were included on each 96-well plate, and the average concordance percentage among QC samples was 99.85%. Female sex was confirmed for all samples. Multidimensional scaling analysis of the genotypes with 210 unrelated HapMap samples indicated that all participants clustered with HapMap Asian samples (CHB+JPT). All potential relatives with pairwise identity by descent (IBD) of PI_HAT>0.25 were removed. SNPs that failed the Hardy-Weinberg equilibrium test ($P<0.0001$) and SNPs that had significantly different missing genotyping rates for cases and controls ($P<0.0001$) were excluded. After QC was completed, the Hidden Markov Model as implemented in Mach 1.0 was used to impute the genotype for variants of interest that were not directly genotyped using Asian genotyping data from HapMap phase 2 for reference genotypes (23).

In stage 2, 21 of the 24 SNPs selected for replication genotyping as described above, were successfully genotyped. Some stage 2 studies (e.g. HAECS and HJECS) genotyped fewer than 21 SNPs. Only SNPs which met QC criteria similar to that applied for stage 1 were included in the stage 2 analysis. Imputed genotypes were used for some SNPs in ANECS/NECS, NSECG, and control samples derived from the WTCCC when direct genotyping data were not available (24).

Statistical analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between genotypes and endometrial cancer risk in stage 1. Covariates adjusted for included age, income, and education. Directly genotyped or imputed information for 4,542 SNPs was evaluated for associations with endometrial cancer and 614 SNPs showed a nominal association with endometrial cancer ($P<0.05$).

Unconditional logistic regression was used to analyze the 21 SNPs selected for stage 2. These analyses were adjusted for age only, because a unifying set of common demographic or anthropometric covariates was not available across all studies. Using the ORs derived from individual studies, a meta-analysis was conducted derive summary statistics (25). An overall Z-statistic and *P* value based on the weighted average of the individual statistics was calculated. The resulting ORs and 95CIs are based on the fixed effect model, unless heterogeneity across studies was evident ($P<0.05$ for homogeneity test). In the latter case, ORs, 95 CIs, and *P* values derived from the random effect model are presented. All *P* values presented are based on two-tailed tests.

SNP functional annotation

The relationship between *P* values LD measures relative to two sample SNPs selected for stage 2 genotyping are shown in Supplementary Figure 1 and was done using LocusZoom plotting *P* values for stage 1 data (26). Functional annotation of the SNPs of interest was carried out using the NIEHS SNP Info Webserver's SNP function prediction module (27).

RESULTS

Stage 1, Stage 2, and combined results for the 21 SNPs promoted to Stage 2 study along with the number of studies and samples contributing to the analysis are presented in Table 2. In total, five of the 21 SNPs had significant allelic ORs (95%CIs) in the overall dataset: *FABP1*, 0.92 (0.85-0.99); *CXCL3*, 1.16 (1.05-1.29); *IL6*, 1.08 (1.00-1.17); *MSR1*, 0.90 (0.82-0.98); and *MMP9*, 0.91 (0.87-0.97). The directions of association in the discovery and replication samples were consistent for all five SNPs. Of these SNPs, only the polymorphisms near *CXCL3* and in *MMP9* were significantly associated with endometrial cancer risk in the replication stage. No heterogeneity across studies was found for these five SNPs.

Table 3 presents the heterozygous, homozygous, and per allele associations with type 1 endometrial (endometroid) cancer for the five significant SNPs among all women combined, among women of Asian ancestry, and among women of European ancestry. SNP rs3918249 in *MMP9* was associated with endometrial cancer risk in women of both Asian and European ancestry. Other SNPs were not significantly associated with endometrial cancer in European-ancestry women. SNP rs10503574 in *MSR1* was more significant in Asian-ancestry women than in the overall sample. When restricting analyses to women with type 1 endometrial cancer, the results were largely unchanged.

DISCUSSION

The link between inflammation and endometrial cancer is supported by a great deal of experimental and epidemiological evidence; conditions related to chronic inflammation, such as prolonged menstruation, obesity, unopposed menopausal estrogen use, and other factors, have all been linked to and increased risk of endometrial cancer (28, 29). Menstruation itself, during which the endometrium goes through proliferative, secretory, and menstrual phases, mimics an inflammatory process and is associated with the activation of inflammatory cytokines that results in the shedding of the endometrium (29). Estrogen directly regulates the production of a number of inflammatory cytokines, growth factors, and corresponding receptors (30). Inflammation increases mitotic activity in endometrial epithelial cells, which in turn results in increased DNA replication and repair errors, subsequently leading to somatic mutations that may ultimately give rise to hyperplasia and endometrial cancer (12).

In this large two-stage study, including samples from both Asian- and European-ancestry populations, we found that genetic variants in five candidate genes, *FABP1, CXCL3, IL6, MSR1*, and *MMP9*, were associated with endometrial cancer in combined analyses. Of these, the *CXCL3* and *MMP9* polymorphisms had significant associations in the stage 2 analysis. Only rs3918249, the *MMP9* variant, was associated with endometrial cancer in both Asian- and European-ancestry samples and remained statistically significant after adjustment for multiple comparisons.

MMP9 encodes a matrix metalloproteinase, involved in the breakdown of the extracellular matrix, a process which has been well studied for its relationship with cancer. MMP9 is secreted from endometrial stromal cells in response to induction by growth factors, such as HGF, in endometrial cancer cell lines, which, in turn, increases cancer cell invasiveness (31). Expression of *MMP9* is known to be up-regulated through pro-inflammatory cytokines, including nuclear factor kappa B, IL8, and TNF-alpha, leading to increased tumor cell proliferation (32-34). *MMP9* expression level has been correlated to the grade and stage of endometrial cancer (35). The MMP9 protein has been shown to be frequently expressed in endometriosis, a benign disease, in which MMP9 expression level is higher in aggressive

lesions than in normal endometrium (36, 37). *MMP9* transgenic mice show significantly increased susceptibility to chemically induced cancer (38). The significant SNP we found, rs3918249, resides in a promoter region of *MMP9*, and is predicted to be in a transcription factor binding site and has modestly strong LD with some sites predicted to act as miRNA binding sites or splice enhancers. Further, it is in LD with two non-synonymous coding SNPs, rs17576 and rs2250889, in *MMP9* (Supplementary Table 2). Further investigation of the role of this gene in endometrial carcinogenesis is warranted as is fine-mapping of this locus for other possible causal alleles.

SNP rs352038 near the *CXCL3* gene was our second most significant finding overall and, like *MMP9*, independently significant in the replication sample. *CXCL3* is an attractive candidate gene, although rs352038 is not located in the *CXCL3* gene, but 14.2kb downstream. However, it is in LD with SNPs in other CXC chemokine genes in the 4q21 region, including *CXCL2* and *CXCL5*. *CXCL3* is upregulated in breast cancer, is present at higher levels in metastases, and is associated with shorter relapse-free survival in patients treated with tamoxifen (39). Consistent with the hormonal etiology of endometrial cancer, gonadotropin releasing hormone (GnRH) I and II may regulate the expression of *CXCL3* (40). *CXCL3* has shown to be up-regulated in uterine smooth muscle. Inhibition of *CXCL3* and *IL6* has been shown in cancer cell lines to reduce Stat3 activation (41). It is worth noting that the genotyped SNP rs352038 is predicted to act as an eQTL for another inflammatory gene, *IL8* ($P = 0.007$), though this gene is over 300kb distant from rs352038 (42). This SNP is in LD with two other SNPs predicted to be potential transcription factor binding sites (Supplementary Table 2).

Three other SNPs in or near *FABP1* (rs2970294), *IL6* (rs2069852), and *MSR1* (rs10503574) with significant associations in stage 1 data were also significant in the overall dataset, although they were not replicated in stage 2.

The present study has a number of strengths and weaknesses. The study benefits from its collection of a relatively large number of case and control samples from a number of study sites. The increased sample size and consistent directions of association across a number of study sites strengthens the evidence that these findings — particularly for the *CXCL3* and *MMP9* SNPs — are much more likely to represent true associations. Limitations include that stage 1 was carried out in an Asian population, and only one SNP per region was selected for the replication study. Some association findings may not extend to non-Asian populations, because of LD structure differences resulting in false negative results, as may be the case for rs10503574 in *MSR1*, where LD blocks as defined by D-prime are quite different between HapMap samples for CEU and CHB+JPT. False positive findings resulting from multiple testing is another concern. Minor allele frequencies in European populations were quite low for three of the five SNPs significant in stage I (in *CXCL3*, *IL6*, and *MSR1)*, suggesting low statistical power for validating these associations. Furthermore, we did not have information on most of the non-genetic risk factors for stage 2 data, which limited our ability to evaluate the potential confounding effects of these factors. However, within stage 1 data, adjusting for known non-genetic factors, including age BMI, age at menarche, age at menopause, nulliparity, and HRT use did not materially alter point estimates for SNPs selected for stage 2 replication genotyping, Last, this analysis was restricted to SNPs in or near (within 20kb) the 64 candidate inflammation genes. Future studies may wish to expand investigations to SNPs known to be eQTLs for inflammatory genes, some of which may be more distant or even in trans to the genes they regulate. Such variations may offer more potent explanations of the expression levels of inflammatory genes. As new resources such as The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression project (GTEx) are developed, the tools to determine the SNPs controlling the

expression of these genes in relevant tissue types will allow more specific tests to be carried out.

In summary, this study found evidence for the involvement of *MMP9* and *CXCL3* in endometrial carcinogenesis in both Asian- and European-ancestry populations. These findings may warrant additional and functional studies to determine the mechanisms by which these common variants increase disease risk. Future studies may focus on specific eQTL SNPs in the tissues of interest and seek to better explore the link between these inflammatory pathway genes and endometrial carcinogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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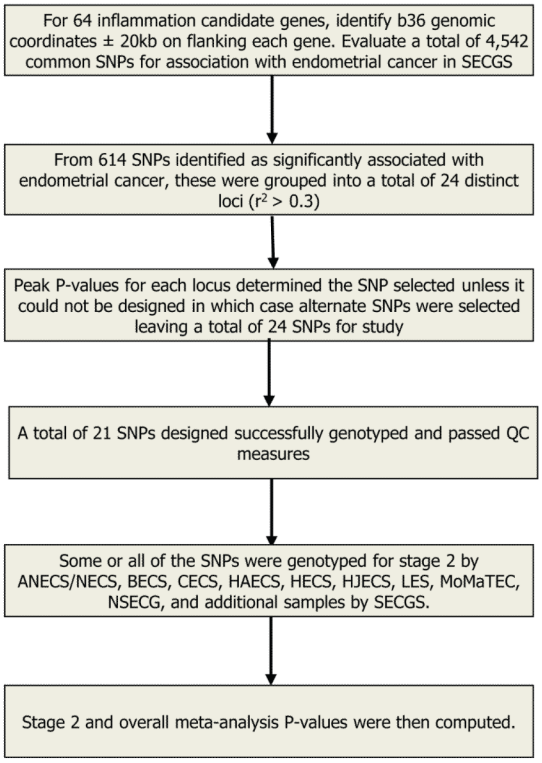

Figure 1.
Selection and prioritization of inflammation-related SNPs for meta-analysis.

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Table 1

Study populations included.

Study	Abbreviation	General Setting	Cases	Controls	Genotyping platform
Stage 1 Sample Sets	**Stage 1**				
Shanghai Endometrial Cancer Genetic Study	SECGS-I	Shanghai, China; Population-based, case-control studies	832	2,682	Affymetrix 6.0
Stage2 Sample Sets	**Stage 2**				
Australian National Endometrial Cancer Study/Newcastle Endometrial Cancer Study	ANECS/NECS	Australia; Population-based, case-control study/Hospital-based study	1,436	1,175	Sequenom
Bavarian Endometrial Cancer Study	BECS	Germany; Population-based, case-control study	202	387	Sequenom
Connecticut Endometrial Cancer Study	CECS	Connecticut, USA; Population-based, case-control study	534	621	Sequenom
Hannover-Almaty Endometrial Cancer Study	HAECS	Kazakhstan; Hospital-based, case-control study	218	232	Taqman
Hawaii Endometrial Cancer Study	HECS	Hawaii, USA; Population-based, case-control study	168	574	Sequenom
Hannover-Jena Endometrial Cancer Study	HJECS	Germany; Hospital-based, case-control study	229	554	Taqman
Leuven Endometrial Cancer Study	LES	Belgium; Hospital-based, case-control study	264	591	Sequenom
Molecular Markers in Treatment of Endometrial Cancer	MoMaTEC	Norway; Population-based, case-control study	411	210	Sequenom
National Study of the Genetics of Endometrial Cancer	NSECG	United Kingdom; Population-based, case-control study	1,514	507	Illumina 550K / Sequenom
Shanghai Endometrial Cancer Genetic Study	SECGS-II	Shanghai, China; Population-based, case-control studies	796	978	Sequenom

Study	Abbreviation	General Setting	Cases	Controls	Genotyping platform
Total			**6,604**	**8,511**	

Table 2

Associations with endometrial cancer for the 21 SNPs included in each stage and overall.

rsID	Reference allele[a]	Adjacent Genes	Discovery		Replication			Overall			
			OR (95% CI)[b]	*P* [c]	Studies[d]	OR (95%CI)[e]	*P* [f]	OR meta (95%CI)[g]	*P* [h]	*P*j	Heterogeneity *P*-value
rs3918249	C	MMP9	0.81 (0.70-0.92)	0.002	10	0.94(0.88-1.00)	**0.042**	0.91(0.87-0.97)	**0.001**	**0.021**	0.153
rs352038	G	CXCL3	1.26 (1.06-1.50)	0.008	10	1.14(1.00-1.29)	**0.050**	1.16(1.05-1.29)	**0.003**	0.063	0.498
rs10503574	C	MSR1	0.81 (0.70-0.94)	0.006	6	0.97(0.86-1.08)	0.547	0.90(0.82-0.98)	**0.016**	0.336	0.088
rs2970924	T	FABP1	0.80 (0.68-0.96)	0.013	7	0.95(0.87-1.03)	0.214	0.92(0.85-0.99)	**0.024**	0.504	0.244
rs2069852	A	IL6	1.19 (1.04-1.36)	0.013	7	1.05(0.96-1.16)	0.284	1.08(1.00-1.17)	**0.049**	1.000	0.154
rs1472095	T	PPARGC1A	1.41 (1.13-1.77)	0.003	8	1.09(0.97-1.24) [i]	0.152	1.13(1.00-1.28) [i]	0.054	1.000	0.006
rs4149319	A	ABCA1	0.76 (0.63-0.91)	0.003	8	0.99(0.87-1.13)	0.937	0.91(0.82-1.01)	0.074	1.000	0.194
rs7709864	C	LOC729123	1.25 (1.07-1.46)	0.006	8	1.20(0.94-1.52) [i]	0.137	1.17(0.98-1.41) [i]	0.084	1.000	0.001
rs12368672	G	STAT6	1.32 (1.15-1.53)	1.05E-04	8	1.00(0.94-1.06)	0.987	1.04(0.99-1.10)	0.139	1.000	0.096
rs2239349	A	IL4R	1.17 (1.00-1.36)	0.046	8	1.14(0.92-1.40) [i]	0.235	1.13(0.96-1.34) [i]	0.15	1.000	0.001
rs2780815	G	JAK1	0.74 (0.63-0.88)	3.72E-04	8	0.98(0.92-1.04)	0.471	0.94(0.86-1.03) [i]	0.193	1.000	0.032
rs6914211	A	ESR1	1.40 (1.15-1.70)	0.001	8	0.99(0.90-1.09)	0.905	1.05(0.97-1.15)	0.237	1.000	0.341
rs9839934	G	THRB	0.80 (0.69-0.94)	0.006	8	1.00(0.94-1.07)	0.951	0.97(0.91-1.02)	0.253	1.000	0.282
rs933360	C	GRB10	0.75 (0.65-0.87)	8.40E-05	8	1.02(0.96-1.09)	0.542	0.97(0.91-1.03)	0.269	1.000	0.067
rs12757165	G	ESRRG	0.78 (0.68-0.89)	2.49E-04	8	0.99(0.93-1.05)	0.638	0.95(0.87-1.04) [i]	0.299	1.000	0.023
rs2735188	C	HDAC3	1.38 (1.09-1.75)	0.007	8	1.00(0.90-1.10)	0.939	1.05(0.96-1.14)	0.311	1.000	0.099
rs310247	A	JAK1	0.81 (0.71-0.91)	0.001	8	0.99(0.90-1.08) [i]	0.769	0.96(0.88-1.06) [i]	0.412	1.000	0.006
rs3781619	A	DDB2	1.18 (1.04-1.35)	0.013	8	0.93(0.87-1.00)	0.062	0.96(0.87-1.06) [i]	0.457	1.000	0.041
rs17627111	G	ESRRG	0.72 (0.62-0.85)	0.0000493	8	0.99(0.93-1.05)	0.782	0.98(0.89-1.08) [i]	0.681	1.000	0.01
rs1421894	T	CENTD3	0.86 (0.75-0.98)	0.028	8	1.04(0.97-1.12)	0.225	0.98(0.89-1.09) [i]	0.767	1.000	0.021
rs9896401	C	SAMD14	1.43 (1.14-1.80)	0.002	8	0.96(0.90-1.03)	0.286	1.00(0.93-1.07)	0.944	1.000	0.061

[a] Allele associated with the ORs specified in the table.

[b] OR in discovery stage of inflammation study.

[c] *P*-value for discovery stage (SECGS-I data)

[d] Number of studies contributing data to replication stage.

[e] OR meta based on some or all of the following studies ANECS, BECS, CECS, HAECS, HECS, HJECS, LES, MoMaTEC, NSECG, and SECGS-II.

[f] Meta-analysis *P*-value for replication stage including ANECS, BECS, CECS, HAECS, HECS, HJECS, LES, MoMaTEC, NSECG, and SECGS-II

[g] OR for all studies combined.

[h] *P*-value for overall meta-analysis including replication and discovery stages.

[i] Random effects model used

[j] *P*-value Bonferroni corrected

Table 3

A ssociation with endometrial cancer risk for selected variants by ethnicity and histological type.

		N		Allele Freq		OR (95% CI)			
Population	**SNP**	**Cases**	**Controls**	**Cases**	**Controls**	**Heterozygous**	**Homozygous**	**Allelic**	***P***
All women, endometrial cancer cases vs. controls									
	rs2970924	5832	7037	0.15	0.16	**0.90(0.82-0.98)**	**0.93(0.72-1.20)**	**0.92(0.85-0.99)**	**0.024**
	rs352038	6568	8405	0.06	0.08	**1.16(1.03-1.30)**	1.30(0.90-1.86)	**1.16(1.05-1.29)**	**0.003**
	rs2069852	5784	6922	0.21	0.38	0.98(0.86-1.13)	1.08(0.90-1.29)	**1.08(1.00-1.17)**	**0.049**
	rs10503574	3026	6685	0.16	0.17	0.93(0.84-1.04)	**0.76(0.59-0.98)**	**0.90(0.82-0.98)**	**0.016**
	rs3918249	6561	8273	0.44	0.53	0.95(0.87-1.04)	**0.83(0.73-0.93)**	**0.91(0.87-0.97)**	**0.001**
All Asian-ancestry endometrial cancer cases vs. controls									
	rs2970924	1714	3783	0.15	0.16	0.87(0.70-1.08)	0.77(0.48-1.25)	0.82(0.63-1.07)	**0.140** [a]
	rs352038	1693	3773	0.17	0.16	1.11(0.98-1.27)	1.28(0.88-1.88)	**1.12(1.00-1.26)**	**0.047**
	rs2069852	1635	3675	0.66	0.65	0.91(0.75-1.11)	1.07(0.88-1.30)	1.08(0.99-1.18)	**0.101**
	rs10503574	1685	3823	0.24	0.26	0.89(0.79-1.01)	**0.70(0.54-0.91)**	**0.86(0.78-0.95)**	**0.003**
	rs3918249	1700	3654	0.70	0.72	0.91(0.73-1.13)	**0.78(0.63-0.98)**	**0.88(0.80-0.97)**	**0.008**
All European-ancestry endometrial cancer cases vs. controls									
	rs2970924	3856	2856	0.16	0.15	**0.89(0.79-1.00)**	1.07(0.77-1.50)	0.94(0.84-1.04)	0.206
	rs352038	4553	4111	0.02	0.01	1.16(0.87-1.54)	1.23(0.99-1.54)	1.18(0.89-1.57)	0.250
	rs2069852	3889	2850	0.03	0.03	1.00(0.80-1.26)	0.31(0.06-1.49)	1.00(0.80-1.25)	0.997
	rs10503574	1214	2450	0.05	0.04	1.10(0.82-1.49)	0.31(0.06-1.49)	1.07(0.80-1.43)	0.653
	rs3918249	4539	4098	0.35	0.36	0.97(0.87-1.08)	**0.82(0.70-0.96)**	0.92(0.86-0.99)	**0.024**
All women, type I endometrial cancer cases vs. controls									
	rs2970924	4703	7037	0.15	0.16	**0.89(0.81-0.98)**	0.94(0.72-1.22)	**0.91(0.84-0.99)**	**0.027**
	rs352038	5285	8405	0.06	0.08	1.17(1.03-1.32)	1.28(0.87-1.88)	**1.17(1.05-1.30)**	**0.004**
	rs2069852	4653	6922	0.22	0.38	0.98(0.85-1.13)	1.08(0.89-1.31)	**1.10(1.01-1.19)**	**0.030**
	rs10503574	2605	6685	0.16	0.17	0.93(0.83-1.04)	**0.70(0.53-0.92)**	**0.88(0.80-0.96)**	**0.007**
	rs3918249	5484	8273	0.45	0.53	0.97(0.88-1.07)	**0.82(0.72-0.93)**	**0.91(0.86-0.97)**	**0.002**
Asian-ancestry women, type I endometrial cancer cases vs. controls									
	rs2970924	1464	3783	0.15	0.16	0.90(0.78-1.04)	0.79(0.52-1.20)	0.89(0.79-1.00)	0.055

		N		Allele Freq		OR (95% CI)			
Population	**SNP**	**Cases**	**Controls**	**Cases**	**Controls**	**Heterozygous**	**Homozygous**	**Allelic**	***P***
	rs352038	1448	3773	0.17	0.16	1.14(0.99-1.31)	1.24(0.83-1.87)	**1.13(1.00-1.28)**	**0.041**
	rs2069852	1393	3675	0.67	0.65	0.88(0.71-1.07)	1.07(0.88-1.32)	1.09(0.99-1.20)	0.075
	rs10503574	1439	3823	0.23	0.26	0.88(0.78-1.01)	**0.68(0.51-0.90)**	**0.85(0.77-0.94)**	**0.002**
	rs3918249	1453	3654	0.70	0.72	0.93(0.74-1.18)	0.80(0.63-1.01)	**0.89(0.80-0.98)**	**0.015**
European-ancestry women, type I endometrial cancer cases vs. controls									
	rs2970924	3037	2856	0.15	0.15	**0.86(0.76-0.98)**	1.05(0.74-1.49)	0.91(0.82-1.02)	0.099
	rs352038	3580	4111	**0.02**	**0.01**	1.16(0.86-1.57)	1.26(1.00-1.59)	1.19(0.88-1.60)	0.255
	rs2069852	3060	2850	**0.03**	**0.03**	1.07(0.72-1.60)	0.54(0.05-5.40)	1.08(0.72-1.62)	0.703 [a]
	rs10503574	1061	2450	**0.05**	**0.04**	1.12(0.82-1.53)	0.54(0.05-5.40)	1.07(0.80-1.45)	0.644
	rs3918249	3574	4098	0.35	0.36	0.98(0.88-1.10)	**0.79(0.67-0.93)**	**0.91(0.84-0.98)**	**0.017**

[a]Random effects model used

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