Polymorphisms in Inflammation Pathway Genes and Endometrial Cancer Risk


Abstract

Background: Experimental and epidemiologic 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 (SNP) in inflammatory pathway genes in association with endometrial cancer risk. In stage I, 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 I 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 II, which consisted of 10 additional studies including 6,604 endometrial cancer cases and 8,511 controls.

Results: Five of the 21 SNPs had significant allelic odds ratios (ORs) and 95% confidence intervals (CI) 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.

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Introduction

Endometrial cancer is the most common gynecologic 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 2 decades to 7.62 per 100,000 in 2007 (3), although it is still substantially lower than the incidence seen in developed countries (United States: 22.0 per 100,000; Europe: 11.8–12.5 per 100,000; ref. 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 epidemiologic 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; ref. 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 2-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 (SECGS) and 10 additional studies of endometrial cancer conducted among women in the United States, Australia, Europe, and China.

Materials and Methods

This study involved 2 stages, as shown in Table 1. Study populations are described below, and the overall study design and single-nucleotide polymorphisms (SNP) selection procedure are depicted in Fig. 1.

Study population

Stage I was conducted among the participants of the 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 with the Affymetrix 6.0 array were included in the stage I study. Genomewide scan data from 2,049 women from the SBCS served as controls. The mean age of cases was 54.7 years and for controls was 51.7 years; 45% of cases and 30% of controls were post-menopausal. Data for stage II included 6,604 cases and 8,511 controls from a total of 10 studies (Table 1).

Candidate SNP selection

The SNP selection scheme is shown in Fig. 1. Sixty-four candidate genes involved in inflammatory pathways were identified on the basis of literature review and bioinformatics searches. 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 S1). A total of 4,542 SNPs with minor allele frequencies of 0.05 or greater and located in or near (±20 kb) ReSeq transcripts of these genes were identified for the stage I 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) or that could be imputed were eligible for selection. SNPs for stage II 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 Fig. S1 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 II 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 I genotyping and QC procedures have been described in detail in previous publications (18, 21). Briefly, genotyping was conducted 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 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 II, 21 of the 24 SNPs selected for replication genotyping as described above were successfully genotyped. Some stage II studies (e.g., HAECs and HJECs) screened fewer than 21 SNPs. Only SNPs which met QC criteria similar to that applied for stage I were included in the stage II 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 ORs and 95% confidence intervals (CI) for associations between genotypes and endometrial cancer risk in stage I. 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 II. 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 to derive summary statistics (25). An overall z-statistic and P value based on the weighted average of the individual statistics were calculated. The resulting ORs and 95% CIs 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 2-tailed tests.

### SNP functional annotation

The relationship between P values and LD measures relating to 2 sample SNPs selected for stage II genotyping are shown in Supplementary Fig. S1 and were done using LocusZoom plotting P values for stage I 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 I, II, and combined results for the 21 SNPs promoted to stage II study along with the number of studies and samples contributing to the analysis are presented in Table 2. In total, 5 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 5 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 5 SNPs.

Table 3 presents the heterozygous, homozygous, and per-allele associations with type 1 endometrial (endome-
Table 3. Association with endometrial cancer risk for selected variants by ethnicity and histologic type

<table>
<thead>
<tr>
<th>Population</th>
<th>SNP</th>
<th>N Cases</th>
<th>N Controls</th>
<th>Allele frequency</th>
<th>OR (95% CI)</th>
<th>P</th>
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<tr>
<td>All women, endometrial cancer cases vs. controls</td>
<td>rs2970924</td>
<td>5,832</td>
<td>7,037</td>
<td>0.15</td>
<td>0.90 (0.82–0.98)</td>
<td>0.024</td>
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<td>5,784</td>
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<td>rs10503574</td>
<td>3,026</td>
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<td>0.87 (0.70–1.08)</td>
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<td>0.91 (0.73–1.13)</td>
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<td>0.206</td>
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<td>4,111</td>
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<td>1.16 (0.87–1.54)</td>
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<td></td>
<td>rs2069852</td>
<td>3,889</td>
<td>2,850</td>
<td>0.03</td>
<td>1.00 (0.80–1.26)</td>
<td>0.997</td>
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<td>1.10 (0.82–1.48)</td>
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<td>0.97 (0.87–1.06)</td>
<td>0.126</td>
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<td>4,098</td>
<td>0.35</td>
<td>0.97 (0.87–1.06)</td>
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<td>Asian ancestry women, type I endometrial cancer cases vs. controls</td>
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<td>3,783</td>
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<td>0.90 (0.78–1.04)</td>
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<td>1,453</td>
<td>3,654</td>
<td>0.70</td>
<td>0.93 (0.74–1.18)</td>
<td>0.015</td>
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<td>European ancestry women, type I endometrial cancer cases vs. controls</td>
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<td>3,037</td>
<td>2,856</td>
<td>0.15</td>
<td>0.86 (0.76–0.98)</td>
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<td>0.98 (0.88–1.10)</td>
<td>0.017</td>
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*P values less than 0.05 are boldfaced.

Random-effects model used.

Discussion

The link between inflammation and endometrial cancer is supported by a great deal of experimental and epidemiologic evidence; conditions related to chronic inflammation, such as prolonged menstruation, obesity, unopposed menopausal estrogen use, and other factors, have all been linked to an 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 promote the growth of endometrial tissue.
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 2-stage study, including samples from both Asian and European-ancestry populations, we found that genetic variants in 5 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 II 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 hepatocyte growth factor (HGF), in endometrial cancer cell lines, which, in turn, increases cancer cell invasiveness (31). Expression of MMP9 is known to be upregulated through pro-inflammatory cytokines, including NF-kB, interleukin (IL)8, and TNF-α, 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 splicing enhancers. Furthermore, it is in LD with 2 nonsynonymous coding SNPs, rs17576 and rs2250889, in MMP9 (Supplementary Table S2). Further investigation of the role of this gene in endometrial carcinogenesis is warranted as is fine mapping of this locus and for other possible causal alleles.

SNP rs352038 near the CXCL3 gene was one of the 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 CXCL 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 been shown to be upregulated 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), although this gene is more than 300 kb distant from rs352038 (42). This SNP is in LD with 2 other SNPs predicted to be potential transcription factor binding sites (Supplementary Table S2).

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

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 I 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’ 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 3 of the 5 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 nongenetic risk factors for stage II data, which limited our ability to evaluate the potential confounding effects of these factors. However, within stage I data, adjusting for known nongenetic factors, including age, body mass index (BMI), age at menarche, age at menopause, nulliparity, and hormone replacement therapy, use did not materially alter point estimates for SNPs selected for stage II replication genotyping. Last, this analysis was restricted to SNPs in or near (within 20 kb) 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.

Disclosure of Potential Conflicts of Interest
The authors take sole responsibility for the content of this article. D. Kaydarova has employment (other than primary affiliation; e.g., consulting) with Alimta Oncology Centre as the Director. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Development of methodology: W. Lu, X.-O. Shu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y.-B. Xiang, A. Spurde, F. Aman, X.-O. Shu

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References
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