ORIGINAL ARTICLE: GENETICS

Evidence of a genetic link between endometriosis and ovarian cancer

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Objective: To evaluate whether endometriosis-associated genetic variation affects risk of ovarian cancer.
Design: Pooled genetic analysis.
Setting: University hospital.
Patient(s): Genetic data from 46,176 participants (15,361 ovarian cancer cases and 30,815 controls) from 41 ovarian cancer studies.
Intervention(s): None.
Main Outcome Measure(s): Endometriosis-associated genetic variation and ovarian cancer.
Result(s): There was significant evidence of an association between endometriosis-related genetic variation and ovarian cancer risk, especially for the high-grade serous and clear cell histotypes. Overall we observed 15 significant burden statistics, which was three times more than expected.

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Conclusion(s): By focusing on candidate regions from a phenotype associated with ovarian cancer, we have shown a clear genetic link between endometriosis and ovarian cancer that warrants further follow-up. The functional significance of the identified regions and SNPs is presently uncertain, though future fine mapping and histotype-specific functional analyses may shed light on the etiologies of both gynecologic conditions. (Fertil Steril® 2015;■:--■. ©2015 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, ovarian cancer, genetic variation, SNPs

Ovarian carcinoma (ovarian cancer) is the most fatal malignancy in the female reproductive system, accounting for more than 140,000 deaths annually worldwide (1). Endometriosis, the presence of ectopic endometrial glands and tissue in the peritoneum, is a common gynecologic condition, occurring in 6%–10% of the general female population (2). Studies that have controlled for parity have shown that endometriosis is a well-established ovarian cancer risk factor, especially for the endometrioid and clear cell histotypes (3). Although the etiology of endometriosis remains enigmatic, it is influenced by genetic factors, with an estimated heritability of 51% and an incidence that is approximately seven times higher in relatives of women with endometriosis than in women without such family history (4, 5). To date, seven variants reaching genome-wide significance have been identified in association with risk of endometriosis (6–8). In addition, the most recent meta-analysis by Nyholt et al. (9) has identified multiple additional variants associated with risk, albeit some at a sub-genome-wide significance level ($P \leq 1 \times 10^{-5}$).

Genetics also plays a role in the etiology of ovarian cancer: women with first-degree family histories of the disease have more than a twofold increased risk (10). High-penetrance susceptibility genes, such as *BRCA1* and *BRCA2*, as well as 18 published common variants identified through genome-wide association studies (GWASs) account for a substantial portion of ovarian cancer's familial risk, but at least 60% remains unexplained (6–8,11–16). Lee et al. (17) have previously shown that the cumulative effect of many risk variants contributes to disease heritability, and hence it is likely that the germline genetic contributions to ovarian cancer are not limited to GWAS-identified variants.

Given the important role genetics plays in the etiologies of both endometriosis and ovarian cancer and the consistent epidemiologic evidence of their association with one another, the two gynecologic conditions may also have a similar genetic profile. Hence, on the basis of the results presented by Nyholt et al. of their endometriosis GWAS meta-analysis, we present the first report that evaluates whether variation in the 18 regions harboring the top 38 endometriosis-associated single-nucleotide polymorphisms (SNPs) is associated with risk of ovarian cancer.

MATERIALS AND METHODS

All studies included in this report obtained institutional ethics committee approval, and all participating subjects provided written, informed consent.

Study Populations

Our analysis included 41 studies participating in the Ovarian Cancer Association Consortium (OCAC), an international collaboration of ovarian cancer studies founded in 2005. In total, 20 studies were conducted in Europe, 19 in North America, and 2 in Australia. Only participants of European ancestry were included, as was determined from the program LAMP (Local Ancestry in Admixed Populations) (see "Statistical Analysis," below). We used a combined total of 46,176 participants (15,361 ovarian cancer cases and 30,815 controls) in our analyses; borderline tumors were excluded. Details regarding sample quality control have been previously published (15). Supplemental Table 1 (available online) provides an overview of each study's characteristics and the numbers of subjects included.

Genotyping and Imputation Analyses

The genetic data for our analyses came from three population-based ovarian cancer GWASs, which comprised 2,162 cases and 2,564 controls from a GWAS in North America ("US GWAS") (18), 1,763 cases and 6,118 controls from a GWAS in the United Kingdom ("UK GWAS") (11), and 443 cases and 441 controls from a second GWAS in North America. In addition, 11,030 cases and 21,693 controls were genotyped using the iCOGS array, which was a large-scale genotyping project by the Collaborative Oncological Gene-environment Study (COGS) (15). The US and UK GWASs included several independent case–control studies, and samples from these studies were also genotyped using the iCOGS array. All duplicates were removed from the analyses, resulting in genetic data for 15,361 women diagnosed with ovarian cancer and 30,815 controls. Study sets were created on the basis of the scope of genotyping information (GWAS vs. COGS) available for imputation. These sets are indicated in Supplemental Table 1. Details regarding the genotyping platform for each dataset have been published previously (15).

Imputation of the entire scope of genetic variation in the genome was carried out separately for iCOGS samples and