Short Communication

Polymorphism in the IL18 Gene and Epithelial Ovarian Cancer in Non-Hispanic White Women


On behalf of the Ovarian Cancer Association Consortium; Australian Cancer Study (Ovarian Cancer Group); Australian Ovarian Cancer Study Group

1Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; 2Department of Statistical Science, Duke University; 3Comprehensive Cancer Center, 4Department of Community and Family Medicine, and 5Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina; 6Keck School of Medicine, University of Southern California; 7Department of Urology University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California; 8Departments of Health Sciences and Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota; 9Department of Epidemiology, School of Medicine, University of California, Irvine, Irvine, California; 10Queensland Institute of Medical Research, Brisbane, Queensland, Australia; 11Queensland Institute of Medical Research, Brisbane, Queensland, Australia; 12Department of Virus, Hormones and Cancer, Institute of Cancer Epidemiology, Danish Cancer Society; 13The Gynaecologic Clinic, The Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 14Cancer Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii; 15Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany; Departments of 16Cancer Genetics and 17Cancer Prevention and Population Sciences, Roswell Park Cancer Institute, Buffalo, New York; 18Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, Washington; 19Genetic Epidemiology Unit and 20Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Cambridge, United Kingdom; 21Gynaecological Cancer Research Centre, University College London, EGA Institute for Women’s Health, London, United Kingdom; 22Department of Obstetrics and Gynecology, Aultman Hospital, Canton, Ohio; 23Women’s Center, Akron General Medical Center, Akron, Ohio; 24Department of Gynecology and Obstetrics, Aarhus University Hospital, Aarhus, Skejby, Denmark; 25Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California; 26Department of Epidemiology and University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, Pennsylvania; and 27Department of Obstetrics and Gynecology, University of Ulm, Ulm, Germany

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D.F. Easton is a principal research fellow of Cancer Research UK. P.D.P. Pharoah is a Cancer Research UK senior clinical research fellow.

Requests for reprints: Joellen M. Schildkraut, Department of Community and Family Medicine, Duke University Medical Center, Box 2499, Durham, NC 27710. Phone: 919-681-4761; Fax: 919-681-4766. E-mail: schil001@mc.duke.edu

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interleukin-18 (IL18) showed the strongest evidence for association with epithelial ovarian cancer in a gene-by-gene analysis (P = 0.002) with a <25% chance of being a false-positive finding (q value = 0.240). Using a multivariate model search algorithm over 11 IL18 tagging SNPs, we found that the association was best modeled by rs1834481. Further, this SNP uniquely tagged a significantly associated IL18 haplotype and there was an increased risk of epithelial ovarian cancer per rs1834481 allele (odds ratio, 1.24; 95% confidence interval, 1.06-1.45). In a replication stage, 12 independent studies from the Ovarian Cancer Association Consortium (OCAC) genotyped rs1834481 in an additional 5,877 cases and 7,791 controls. The fixed effects estimate per rs1834481 allele was null (odds ratio, 0.99; 95% confidence interval, 0.94-1.05) when data from the 12 OCAC studies were combined. The effect estimate remained unchanged with the addition of the initial North Carolina Ovarian Cancer Study data. This analysis shows the importance of consortia, like the OCAC, in either confirming or refuting the validity of putative findings in studies with smaller sample sizes. (Cancer Epidemiol Biomarkers Prev 2008;17(12):3567–72)

Introduction

Ovarian cancer is the leading cause of death among cancers of the female reproductive tract and is the fifth leading cause of cancer death in women in the United States (1). The most commonly reported factors that increase ovarian cancer risk are germ-line mutations in the BRCA1 or BRCA2 genes, family history of ovarian cancer, and endometriosis and characteristics such as increasing parity, oral contraceptive use, and tubal ligation reduce risk (2-4). Although the mechanisms underlying these reproductive risk factors have yet to be fully elucidated, it has been hypothesized that they may relate to inflammation and DNA damage (5-7). Ovulation involves disruption of the ovarian surface and is associated with an inflammatory response that involves prostaglandins (8), cytokines (9), and reactive oxygen species (10, 11), all of which have been implicated in carcinogenesis (11-14). The inflammation hypothesis is further supported by the observations that endometriosis may cause inflammation, whereas tubal ligation may reduce inflammation by blocking external agents from coming in contact with the ovary (5). Repair of the ovary after ovulation involves cellular replication that may be prone to DNA damage; thus, errors in DNA repair could also contribute to ovarian cancer. In view of the potential importance of inflammation and DNA repair pathways in ovarian carcinogenesis, inherited variation in genes in these pathways could affect ovarian cancer susceptibility.

To address this hypothesis, we used a candidate gene approach to examine the associations between genes involved in inflammation and DNA repair in a population-based, case-control study of ovarian cancer. When examining numerous single nucleotide polymorphisms (SNP) in multiple genes, the risk of identifying false-positives is present even when statistically adjusting for multiple comparisons. Replication of significant findings using additional independent studies is critical to establish whether true associations exist. In this article, we describe our evaluation of candidate genes related to DNA repair and inflammation followed by replication of putative significant findings within a large international consortium of ovarian cancer case-control studies.

Materials and Methods

Hypothesis Generating Study. The North Carolina Ovarian Cancer Study (NCO) is a population-based case-control study of epithelial ovarian cancer (borderline and invasive) among women in 48 North Carolina counties. Eligible cases, ages 20 to 74 years, were diagnosed between January 1, 1999 and March 31, 2007 and were identified via rapid case ascertainment through the North Carolina Central Cancer Registry. Population-based controls were identified using list-assisted random-digit dialing and were frequency-matched to the cases by age and race. DNA was obtained from >98% of participants. Further details of the study have been described elsewhere (15). All participants signed informed consent forms and approval for the study was obtained from the Duke University Medical Center Institutional Review Board, participating hospitals, and the Human Subjects Committee at the North Carolina Central Cancer Registry.

Replication Studies. The Ovarian Cancer Association Consortium (OCAC) was formed to provide a forum for researchers to evaluate genetic associations with ovarian cancer with increased power. A major aim of the OCAC is to follow up on promising genetic associations while addressing the problem of multiple comparisons and false discoveries that are inherent to studies using high-throughput genotyping technologies. Twelve OCAC studies from the United States (DOV, HAW, HOP, MAY, STA, UCI, and USC), Europe (GER, MAL, SEA, and UKO), and Australia (AUS) contributed data to the current analysis for a total of 5,877 cases and 7,791 controls of self-reported Caucasian ancestry. These studies have been described in detail previously and are summarized in Table 1 (6, 16-26). All studies obtained approval from their respective human subjects ethics committees and all participants provided signed informed consent.

SNP Selection, Genotyping, and Quality Control. The NCO genotyped a total of 1,536 SNPs using the Illumina Golden Gate Assay (Supplementary Table S1). SNPs tagging 120 candidate genes and nonsynonymous SNPs from an additional 50 candidate genes were included on the Illumina OPA. Genes were chosen based on previous literature and were defined at 10 kb upstream and downstream of the gene. Although the DNA repair, inflammation, and hormone candidate gene pathways were predominantly represented, a limited number of genes from the cell cycle, metabolism, methylation, and signal transduction pathways were also included on the Illumina OPA. Tagging SNPs were selected using HapMap version 28 www.hapmap.org and IdSelect (27); a
minor allele frequency > 0.05 and pairwise linkage disequilibrium threshold of $r^2 > 0.8$ were used for selection. Cases and controls were randomly mixed within each plate and six CEPH-Utah trios-standard by Coriell were distributed across six plates. Only five samples (<1%) failed genotyping. There was one within-plate and one across-plate duplicate sample on each 96-well DNA plate; the concordance rate for these samples was 99.5%.

Eleven of the 12 OCAC studies used the 5′ nuclease TaqMan allelic discrimination assay (TaqMan; Applied Biosystems) to genotype interleukin-18 ($IL18$) rs1834481 in seven laboratories using a common batch of reagents. One study (AUS) used the iPLEX Sequenom MassArray system (Sequenom). To ensure consistency of genotype calls across laboratories, each site also genotyped a common set of samples from Coriell29 consisting of 90 unique DNA samples (30 CEPH-Utah trios), 5 duplicate samples, and a negative template control. Genotype concordance on these plates was >98%.

Statistical Analyses: NCO. We restricted our analysis to White, non-Hispanic NCO participants for whom genotyping data were available. We performed tests for Hardy-Weinberg equilibrium among the controls for all SNPs using $m^2$ goodness-of-fit tests and carried out a two-stage analysis. First, for each gene, we fitted an unconditional logistic regression model for disease given

### Table 1. Description of the NCO and 12 OCAC replication studies with $IL18$ rs1834481 genotype frequencies (G>C) by case status (listed alphabetically)

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Case ascertainment</th>
<th>Cases (n)</th>
<th>Control ascertainment*</th>
<th>Controls (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS (16)</td>
<td>Multiregional, Australia</td>
<td>Cancer registries, surgical treatment centers</td>
<td>475 359 85</td>
<td>P: Electoral roll</td>
<td>573 410 71</td>
</tr>
<tr>
<td>DOV (17)</td>
<td>Washington, USA</td>
<td>Cancer Surveillance System, SEER Hospital admissions</td>
<td>411 272 55</td>
<td>P: RDD</td>
<td>422 271 46</td>
</tr>
<tr>
<td>GER (18)</td>
<td>Multiregional, Germany</td>
<td>Hawaii, USA</td>
<td>143 89 13</td>
<td>P: Population registries</td>
<td>172 81 13</td>
</tr>
<tr>
<td>HAW (19)</td>
<td>Hawaii, USA</td>
<td>Hawaii Tumor Registry, SEER Registries, physician offices, pathology databases</td>
<td>56 30 2</td>
<td>P: Annual Hawaii Health Survey</td>
<td>91 57 8</td>
</tr>
<tr>
<td>HOP (20)</td>
<td>Ohio, Pennsylvania, and New York, USA</td>
<td></td>
<td>174 124 20</td>
<td>P: RDD</td>
<td>367 233 36</td>
</tr>
<tr>
<td>MAL (21)</td>
<td>Multiregional, Denmark</td>
<td>Danish Cancer Registry, 16 gynecologic departments</td>
<td>232 154 29</td>
<td>P: Danish Central Population Register</td>
<td>643 442 89</td>
</tr>
<tr>
<td>MAY (22)</td>
<td>Multiregional, USA</td>
<td>Mayo Clinic</td>
<td>221 142 13</td>
<td>C: Women seeking general examinations at Mayo Clinic</td>
<td>245 186 22</td>
</tr>
<tr>
<td>NCO (15)</td>
<td>North Carolina, USA</td>
<td>North Carolina Central Cancer Registry</td>
<td>450 334 64</td>
<td>P: RDD</td>
<td>470 285 43</td>
</tr>
<tr>
<td>SEA (6)</td>
<td>Cambridge, UK</td>
<td>East Anglia and West Midlands cancer registries</td>
<td>625 395 71</td>
<td>P: European Prospective Investigation into Cancer and Nutrition-Norfolk cohort</td>
<td>672 456 82</td>
</tr>
<tr>
<td>STA (23)</td>
<td>California, USA</td>
<td>Greater Bay Area Cancer Registry, SEER</td>
<td>201 102 16</td>
<td>P: RDD</td>
<td>244 141 28</td>
</tr>
<tr>
<td>UCI (24)</td>
<td>California, USA</td>
<td>Cancer Surveillance Program of Orange County, Tumor Registry</td>
<td>268 159 24</td>
<td>P: RDD</td>
<td>264 172 29</td>
</tr>
<tr>
<td>UKO (25)</td>
<td>Multiregional, UK</td>
<td>10 Gynecologic oncology National Health Service Centers</td>
<td>148 291 17</td>
<td>P: UK Collaborative Trial of Ovarian Cancer Screening and all women followed up for cancers by Office of National Statistics</td>
<td>302 231 43</td>
</tr>
<tr>
<td>USC (26)</td>
<td>California, USA</td>
<td>Los Angeles Cancer Surveillance Program</td>
<td>413 211 37</td>
<td>P: Neighborhood recruits</td>
<td>408 205 36</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td>3,817 2,462 446</td>
<td></td>
<td>4,873 3,170 546</td>
</tr>
</tbody>
</table>

Abbreviations: SEER, Surveillance Epidemiology and End Results; RDD, random-digit dialing.

*P, population-based; C, clinic-based.

29 http://ccr.coriell.org/Sections/Search/Panel_Detail.aspx?PgId=202&Ref=HAPMAPP (T01).
age and indicator variables for both the dominant and the recessive genotypes of each SNP in the gene. We used a likelihood ratio test of this model against the model containing only age to assess the degree of association of the gene. We prioritized genes according to the P values of these tests and calculated a q value for each gene to provide estimates of false discovery rates (28). Second, within the top genes, we carried out a Bayesian model selection analysis of the SNP genotype variables using the bic.glm algorithm in the BMA package (29) for the R statistical language to determine the combination(s) giving the best fit. The two-stage analysis was completed using the statistical software package R (30). A haplotype analysis for the gene with the strongest evidence for an association with epithelial ovarian cancer was conducted using Haploview version 3.32 (31).

We completed a full analysis of known and suspected risk factors for epithelial ovarian cancer to determine the extent of confounding; covariates that changed the estimate of effect by ≥10% were considered to be confounders (there were none).

Statistical Analyses: OCAC. IL18 rs1834481 was evaluated by 12 OCAC studies. Among controls, Hardy-Weinberg equilibrium was tested and minor allele frequencies were compared to ensure that there were no important population differences with respect to the allele frequencies of the SNPs. For each OCAC study, we fitted unconditional logistic regression models, adjusting for age, to estimate odds ratios (OR) and 95% confidence intervals (95% CI). Using the same approach to confounding described above, we evaluated the final models for confounding (there was none).

Fixed- and random-effects models accounting for study site were fitted using inverse variance weighting and the DerSimonian-Laird (32) methods, respectively, to study site were fitted using inverse variance weighting for confounding (there was none).

founding described above, we evaluated the final models for age, to estimate odds ratios (OR) and 95% confidence intervals (95% CI). Using the same approach to confounding described above, we evaluated the final models for confounding (there was none).

Table 2. Site-specific and fixed-effects summary ORs (per allele), 95% CIs, and heterogeneity statistics for IL18 rs1834481 among 12 OCAC studies, excluding NCO

<table>
<thead>
<tr>
<th>Site</th>
<th>All cases, OR (95% CI)</th>
<th>Invasive cases, OR (95% CI)</th>
<th>Serous invasive cases, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS</td>
<td>1.14 (0.99-1.31)</td>
<td>1.08 (0.93-1.26)</td>
<td>1.17 (0.98-1.39)</td>
</tr>
<tr>
<td>DOV</td>
<td>1.07 (0.91-1.26)</td>
<td>1.04 (0.87-1.25)</td>
<td>1.06 (0.86-1.32)</td>
</tr>
<tr>
<td>GER</td>
<td>1.22 (0.91-1.63)</td>
<td>1.17 (0.86-1.58)</td>
<td>0.93 (0.62-1.39)</td>
</tr>
<tr>
<td>HAW</td>
<td>0.77 (0.48-1.23)</td>
<td>0.80 (0.48-1.33)</td>
<td>0.68 (0.34-1.33)</td>
</tr>
<tr>
<td>HOP</td>
<td>1.10 (0.89-1.38)</td>
<td>1.16 (0.92-1.45)</td>
<td>1.19 (0.89-1.58)</td>
</tr>
<tr>
<td>MAL</td>
<td>0.96 (0.80-1.15)</td>
<td>0.96 (0.80-1.15)</td>
<td>0.99 (0.80-1.23)</td>
</tr>
<tr>
<td>MAY</td>
<td>0.83 (0.66-1.06)</td>
<td>0.85 (0.66-1.10)</td>
<td>0.91 (0.68-1.24)</td>
</tr>
<tr>
<td>SEA</td>
<td>0.95 (0.83-1.08)</td>
<td>0.94 (0.82-1.08)</td>
<td>0.88 (0.72-1.08)</td>
</tr>
<tr>
<td>STA</td>
<td>0.84 (0.66-1.07)</td>
<td>0.84 (0.63-1.07)</td>
<td>0.92 (0.68-1.24)</td>
</tr>
<tr>
<td>UCI</td>
<td>0.91 (0.73-1.12)</td>
<td>0.86 (0.67-1.11)</td>
<td>0.93 (0.68-1.26)</td>
</tr>
<tr>
<td>UKO</td>
<td>0.86 (0.67-1.09)</td>
<td>0.86 (0.68-1.10)</td>
<td>0.85 (0.62-1.18)</td>
</tr>
<tr>
<td>USC</td>
<td>1.01 (0.85-1.22)</td>
<td>1.08 (0.89-1.31)</td>
<td>1.10 (0.88-1.38)</td>
</tr>
<tr>
<td>Combined 1</td>
<td>0.99 (0.94-1.05)</td>
<td>0.99 (0.93-1.05)</td>
<td>1.01 (0.94-1.09)</td>
</tr>
</tbody>
</table>

*Total cases = 5,877, total invasive cases = 4,774 and total serous invasive cases = 2,583 among 12 OCAC studies, excluding NCO.
1ORs are age-adjusted.
2For all cases, Cochran’s Q = 15.147, P = 0.18, and I² = 27. For invasive cases, Cochran’s Q = 12.173, P = 0.35, and I² = 10. For serous invasive cases, Cochran’s Q = 10.053, P = 0.53, and I² = 0. Low, moderate, and high levels of heterogeneity correspond to I² values of 25, 50, and 75, respectively (36).

The unconditional logistic regression models for the OCAC studies were fitted using SAS (version 9.1.3) and the fixed- and random-effects analyses were fitted using STATA (version 9; StataCorp).

Results

Hypothesis Generating Study: NCO. The initial NCO analysis included 848 epithelial ovarian cancer cases, with a mean age at diagnosis of 55 years, and 798 controls; all participants were White, non-Hispanic. The majority of cases (79%) were invasive and >65% of invasive cases were International Federation of Gynecology and Obstetrics stage III or IV. Serous histology was the most common subtype (61%).

The gene-by-gene analysis identified IL18 as the gene with the strongest evidence for association (that is, smallest P value) with epithelial ovarian cancer (P = 0.002; q = 0.240) compared with all other genes. Eleven SNPs tagging IL18 had been genotyped in the NCO: rs243908, rs1293344, rs1834481, rs1946519, rs2043055, rs549908, rs5744247, rs5744258, rs5744280, rs4937113, and rs11214109. The Bayesian model selection analysis of the IL18 SNPs identified models that included only rs1834481 genotypes as being the most likely, a posteriori. In a subsequent haplotype analysis of IL18 (Supplementary Table S2), four haplotypes had estimated frequencies of >5%. Only one was significantly associated with epithelial ovarian cancer (P = 0.0007) and was uniquely tagged by rs1834481, which was in Hardy-Weinberg equilibrium (P = 0.981) and had a minor allele frequency of 0.23 in NCO controls.

Using Akaike’s Information Criterion, we determined that a log-additive genetic model for rs1834481 best fit the data. There was an increased risk of epithelial ovarian cancer (per allele) for all cases (OR, 1.24; 95% CI, 1.06, 1.45), invasive cases (OR, 1.25; 95% CI, 1.06, 1.28), and serous invasive cases (OR, 1.31; 95% CI, 1.08, 1.60).

Replication Studies: OCAC. Twelve OCAC studies genotyped IL18 rs1834481 in an additional 5,877 cases and 7,791 controls. The SNP was in Hardy-Weinberg equilibrium in all studies (x = 0.10). The minor allele
Table 2. Studies investigated the association between rs1834481 and ovarian cancer and the sample size and power needed to detect modest associations with epithelial ovarian cancer. Consortia such as the OCAC fill an important role for achieving the sample size and power needed to detect modest associations with common SNPs and aid in confirmation of initial findings from smaller studies.

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**References**


30 See http://www.aocstudy.org/.
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