Association between invasive ovarian cancer susceptibility and 11 best candidate SNPs from breast cancer genome-wide association study


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Because both ovarian and breast cancer are hormone-related and are known to have some predisposition genes in common, we evaluated 11 of the most significant hits (six with confirmed associations with breast cancer) from the breast cancer genome-wide association study for association with invasive ovarian cancer. Eleven SNPs were initially genotyped in 2927 invasive ovarian cancer cases and 4143 controls from six ovarian cancer case–control studies. Genotype frequencies in cases and controls were compared using a likelihood ratio test in a logistic regression model stratified by study. Initially, three SNPs (rs2107425 in MRPL23, rs7313833 in PTHLH, rs3803662 in TNRC9) were weakly associated with ovarian cancer risk and one SNP (rs4954956 in NXPH2) was associated with serous ovarian cancer in non-Hispanic white subjects ($P$-trend < 0.1). These four SNPs were then genotyped in an additional 4060 cases and 6308 controls from eight independent studies. Only rs4954956 was significantly associated with ovarian cancer risk both in the replication study and in combined analyses. This association was stronger for the serous histological subtype [per minor allele odds ratio (OR) 1.07 95% CI 1.01–1.13, $P$-trend = 0.02 for all types of ovarian cancer and OR 1.14 95% CI 1.07–1.22, $P$-trend = 0.00017 for serous ovarian cancer]. In conclusion, we found that rs4954956 was associated with increased ovarian cancer risk, particularly for serous ovarian cancer. However, none of the six confirmed breast cancer susceptibility variants we tested was associated with ovarian cancer risk. Further work will be needed to identify the causal variant associated with rs4954956 or elucidate its function.

**INTRODUCTION**

Recent advances in high-throughput genotyping technologies have enabled rapid and efficient genotyping to be performed for hundreds of thousands of genetic variants without prior knowledge of gene function as part of genome-wide association studies (GWAS). Several GWAS have led to the identification of novel loci for many different common complex diseases, including diabetes, Crohn’s disease, rheumatoid arthritis and breast, prostate and colorectal cancers, confirming that susceptibility to these diseases has a polygenic component (1–4). The known ovarian cancer susceptibility genes, such as BRCA1 and BRCA2, appear to explain <40% of the excess familial risk of this disease (5). It is likely that a combination of multiple low or moderate penetrance genetic variants contribute to the remaining unexplained excess ovarian cancer risks. It is evident that some loci regulate carcinogenic pathways common to multiple cancers, for example, the variant rs6983267 in 8q24 is associated with colorectal, prostate and ovarian cancer risk (6). Also, BRCA1 and BRCA2 gene mutations are associated with the variation in the risks of both breast and ovarian cancers. The development of breast and ovarian cancers both have a hormonal basis of female cancers, therefore, it seems logical to hypothesize that these malignancies share some common genetic risks and that breast cancer susceptibility loci may also be associated with the risk of ovarian cancer.

The aim of this study is to evaluate whether the 11 SNPs that were most strongly associated with breast cancer risk in our breast cancer GWAS (7) were associated with epithelial ovarian cancer (EOC) risk in 14 case–control studies which comprised 6987 invasive EOC cases and 10451 controls. This represents the largest ovarian cancer case–control analysis conducted to date. These 11 SNPs included six breast cancer susceptibility variants that reach genome-wide significance ($P < 10^{-8}$) [i.e. rs2981582 (FGFR2), rs12443621 (TNRC9), rs13281615 (8q), rs3817198 (LSP1), rs3803662 (TNRC9) and rs889312 (MAP3K1)]. The remaining five top hits from breast cancer GWAS, namely rs4666451 (located on chromosome 2p), rs2107425 (MRPL23), rs7313833 (PTHLH), rs981782 (on chromosome 5p) and rs4954956 (NXPH2) are also strong candidate for breast cancer associations ($P < 10^{-5}$).

**RESULTS**

We have genotyped the 11 SNPs identified through our GWAS for breast cancer in a set of six ovarian cancer case–control studies. Genotype distributions in controls were consistent with Hardy–Weinberg equilibrium (HWE) except for rs4666451 in the USC ($P = 0.02$) and UKO study ($P = 0.01$) and rs7313833 in the AUS study ($P = 0.04$). These deviations are likely to be due to chance, rather than a reflection of poor genotyping, because inspection of the cluster plots indicated good discrimination between genotype; furthermore deviation from HWE was not observed in cases. In addition, the genotyping for rs981782 failed in the UKO study and rs7313833 failed in the GER study.

Genotype-specific odds ratios (ORs) and tests of association are presented in Table 1. The genotype-specific risks for serous ovarian cancer, estimated from the combined data, are also presented in Table 1. The observed genotype frequencies for each of the data sets are presented in Supplementary Material, Table S1. There was no association in controls between age and genotype frequency for any of the SNPs and age-adjusted genotype-specific risks were similar to the unadjusted ORs (data not shown). Two SNPs (rs7313833 and rs210742) showed some evidence of association with all types of invasive ovarian cancer, whereas rs4954956 and rs210742 showed some evidence of association with serous type ovarian. The association of rs3803662 with ovarian cancer risk was of borderline significance ($P = 0.07$) with ovarian cancer risks. There was no association for the remaining seven SNPs ($P > 0.1$).

Carriers of the minor allele of rs7313833 were at increased risk of ovarian cancer: per minor allele OR = 1.09, 95% CI 1.01–1.18, $P$-trend = 0.027. Carriers of the minor allele of rs2107425 were at decreased risk of ovarian cancer overall and serous type ovarian cancer: per minor allele OR = 0.91.
The combined data from the initial stage 1 studies of White non-Hispanic subjects. The following studies are included in the initial studies: AUS, SEA, MAL, STA, UKO and USC.

The effect of rs4954956 was slightly attenuated after adjusting for a first degree family history of breast cancer [per rare allele OR 1.06, 95% CI 0.97–1.16 (P = 0.17) for all types of ovarian cancer and 1.10, 95% CI 0.99–1.22 (P = 0.066) for serous type of ovarian cancer, respectively]. The remaining three SNPs were not validated. There was no evidence for between-study heterogeneity (P > 0.05) for all the SNPs tested except rs3817198 (P = 0.0002) in the initial set.

**DISCUSSION**

This is the largest ovarian cancer association study conducted to date involving 14 studies from Ovarian Cancer Association Consortium (OCAC) and comprising 5876 invasive EOC cases and 23,416 controls. This is the largest ovarian cancer association study conducted to date involving 14 studies from Ovarian Cancer Association Consortium (OCAC) and comprising 5876 invasive EOC cases and 23,416 controls.
cases and 9273 controls of non-Hispanic origin. We observed an association for the minor allele of SNP rs4954956 with increased risks of EOC both in the initial set and in the replication set with the strongest gene-dose effect for serous type EOC. We urge caution in the interpretation of these results as a number of reported positive associations in the literature have not been replicated by the subsequent studies. Indeed, the proportion of studies with false-positive findings can be as high as 95% in association studies between genetic variants and disease risks (8–10). To estimate the likelihood that our results represent a true association with ovarian cancer risks, we calculated the false-positive report probability (FPRP)

Figure 1. Genotype-specific risks of SNP rs4954956 for ovarian cancer by study in White non-Hispanic subjects. (A) All ovarian cancer subtypes included. (B) Analysis restricted to serous type ovarian cancers.
under different prior probability scenarios (11). The FPRP depends on the prior probability that a true association exists, the observed level of significance ($\alpha$) and the statistical power to detect the OR of the alternative hypothesis at the given $\alpha$. As there are a large number of common SNPs in the genome, the overall prior probability of association is very low ($< 1$ in $10^9$). However, the prior probability that rs4954956 is associated with ovarian cancer is more favourable as this is one of the best candidates from our breast cancer GWAS and therefore a good candidate for ovarian cancer susceptibility. The FPRPs for rs4954956 under various prior probabilities and the power to detect the association at our observed significance level $\alpha$ (assuming the true effect size is equal to that observed) are presented in Table 3. For example, assuming the prior probability to be 1 in 100 or 1 in 1000, the FPRP for association of rs4954956 with serous ovarian cancer would be 0.03 and 0.23, respectively. This, along with the fact that results were indeed independently replicated in the case-control validation studies (Table 2), suggests that this association is robust (Table 3). The evidence, however, is weaker for its association with all types of ovarian cancer under the same prior probabilities.

Underlying population stratification is another explanation for a spurious association. This occurs when allele frequencies differ between population subgroups and cases and controls are drawn differentially from those subgroups. To minimize the impact of population stratification, analyses were restricted to White subjects with non-Hispanic origin. If population stratification were present, it is unlikely that the same degree of stratification would be found in all 14 studies. We did not observe any heterogeneity between different studies in the initial or replication studies or the combined analysis for rs4954956, thus providing evidence against substantial population stratification or other study-specific biases.

If the observed association is confirmed, the SNP may be directly causal or an indirect marker in linkage disequilibrium with the real cause of malignancy. SNP rs4954956 is in an intergenic region situated $<7$ kb upstream of the gene NXPH2, which encodes the protein neurorexin 2. NXPH2 is expressed in kidney and brain and acts as a signalling molecule; it has also been shown to be expressed in the ovary (http://www.geneecards.org/). It is a signalling molecule that resembles neuropeptides and acts by binding to alpha-neurexins and possibly other receptors (12). However, it is not known whether rs4954956 directly affects NXPH2 gene expression: rs4954956 is not in a highly conserved region (http://genome.ucsc.edu/cgi-bin/hgGateway) and various bioinformatics tools such as SNAP (http://www.broad.mit.edu/mpg/snap) did not reveal any variants associated with this SNP ($r^2 > 0.8$) that have a putative function. It is possible that the functional effects of rs4954956 are due to other, as yet unidentified variants that are strongly correlated with this SNP.

Although breast cancer and ovarian cancer are both hormonally related female cancers and share some common genetic risk factors such as BRCA1/BRCA2 mutations, our data suggest that the overlap between ovarian and breast cancer susceptibility alleles is limited. We found no evidence of an association of ovarian cancer risk with the remaining 10 breast GWAS hits tested. Gates et al. (13) recently reported a null association for seven breast cancer susceptibility alleles in two ovarian cancer case-control populations, five of these alleles (i.e. rs2981582, rs3803662, rs889312, rs3817198 and rs1281615) were also genotyped in our study. Our meta-analysis pooling Gates et al.’s data together with ours for these five SNPs appears to confirm that they are not associated with ovarian cancer risks (data not shown). By combined data from 14 ovarian cancer case-control studies (5876 cases/9273 controls of non-Hispanic origin), we were able to provide at least 90% power to detect a co-dominant allele with a minor allele frequency of 0.27 that confers a relative risk of 1.1 at a Type I error of 0.05. However, our power to detect the alleles associated with smaller ovarian cancer risks is low, and we cannot exclude the possibility that the alleles investigated are associated with smaller risks for ovarian cancer.

In conclusion, we have found that rs4954956 is associated with an increased ovarian cancer risk, but none of the top six confirmed breast cancer susceptibility variants tested is associated with ovarian cancer. Further work will be needed to determine a functional rational for rs4954956 or any correlated variants in causing ovarian cancer.

**MATERIALS AND METHODS**

**Study subjects**

**Initial set.** Six case-control studies contributed data to the initial (stage 1) analysis, including three studies from Europe (SEA, MAL and UKO), two from the USA (STA and USC), and one from Australia (AUS). Table 4 provides details for each of the studies which followed a population-based case-control design. Participation rates for cases and controls were generally excellent, and included largely White non-Hispanic women. In total, stage 1 comprised 2927 invasive ovarian cases and 4143 controls.

**Validation set.** Eight case-control studies contributed data to the validation set (stage 2) which included six studies from the
USA (DOV, HOP, MAY, NCO, UCI, HAW) and two studies from Europe (GER, POL). Stage 2 also included additional samples from Australia (AUS) (413 cases/448 controls), UKO (180 cases/333 controls) and USC (323 cases/479 controls) studies described above. Thus, the total validation set comprised 4060 invasive ovarian cancer cases and 6308 controls (Table 4).

These 14 case–control studies from OCAC contained a total of 6987 invasive ovarian cancer cases and 10451 controls when combined. Details of all these case–control studies have been published (14,15).

To reduce the possibility of population stratification, the analyses were limited to the 5876 cases and 9273 controls who were of non-Hispanic White origin for whom genotype information was available. All studies were approved by the review boards and Ethics Committees of their parent institutions and written informed consent was obtained from all participants.

Genotyping

Genotyping was performed at 11 different centres in 384-well plate formats and all but one study (AUS) used Taqman™ 7900HT Sequence Detection System according to the manufacturer’s instructions. The AUS study used iPlex technology (Sequenom) for genotyping according to the manufacturer’s instructions. Genotypes were determined using Allelic Discrimination Sequence Detection Software (Applied Biosystems, Warrington, UK). Assays were carried out in 384-well plates and included at least 3% duplicate samples in each plate for quality control. The six studies in the initial set were genotyped either at the Department of Oncology, University of Cambridge or at the Gynaecological Oncology Unit, University College London. The validation studies were genotyped by the individual study centres. Each assay was carried out using 10 ng DNA in a 5 μl reaction using TaqMan universal PCR master mix, forward and reverse primers and FAM and VIC labelled probes designed by Applied Biosystems (ABI Assay-by-design). Details of primer and probe sequences and assay conditions used for each polymorphism analysed are available upon request.

Genotyping quality control. We compared genotype call rates and concordance by study and overall. We used the following criteria as a measure of acceptable genotyping: (1) >3% sample duplicates included; (2) concordance rate for

Table 4. Study description

<table>
<thead>
<tr>
<th>Study</th>
<th>Study name</th>
<th>No. controlsa</th>
<th>No. casesa</th>
<th>No. serous type casesa</th>
<th>Total subjectsa</th>
<th>% White non-His</th>
<th>Source</th>
<th>Participation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS</td>
<td>Australian Cancer Study (ovarian cancer) AOCOS</td>
<td>1163 (1082)</td>
<td>1130 (867)</td>
<td>731 (563)</td>
<td>2293 (1949)</td>
<td>85</td>
<td>Australia: population based</td>
<td>Case: 84%</td>
</tr>
<tr>
<td>DOV</td>
<td>DOVE, Seattle (16)</td>
<td>796 (724)</td>
<td>584 (533)</td>
<td>332 (303)</td>
<td>1380 (1257)</td>
<td>91</td>
<td>USA: population based</td>
<td>Control: 47%</td>
</tr>
<tr>
<td>GER</td>
<td>GOCS</td>
<td>433 (433)</td>
<td>229 (228)</td>
<td>107 (107)</td>
<td>662 (661)</td>
<td>100</td>
<td>Germany: population based</td>
<td>Case: 77%</td>
</tr>
<tr>
<td>HAW</td>
<td>Hawaii Ovarian Cancer Study</td>
<td>620 (158)</td>
<td>300 (70)</td>
<td>125 (36)</td>
<td>902 (228)</td>
<td>25</td>
<td>Hawaii USA: population based</td>
<td>Control: 69%</td>
</tr>
<tr>
<td>HOP</td>
<td>HOPE study, Pittsburgh</td>
<td>672 (643)</td>
<td>300 (285)</td>
<td>169 (162)</td>
<td>972 (928)</td>
<td>95</td>
<td>USA: population based</td>
<td>Case: 69%</td>
</tr>
<tr>
<td>MAL</td>
<td>MAOVA, Copenhagen</td>
<td>1221 (1221)</td>
<td>446 (446)</td>
<td>275 (275)</td>
<td>1667 (1667)</td>
<td>100</td>
<td>Denmark: population based</td>
<td>Control: 79%</td>
</tr>
<tr>
<td>MAY</td>
<td>Mayo Clinic Rochester Minnesota</td>
<td>467 (440)</td>
<td>337 (322)</td>
<td>206 (199)</td>
<td>804 (762)</td>
<td>95</td>
<td>USA: clinic-based</td>
<td>Case: 84%</td>
</tr>
<tr>
<td>NCO</td>
<td>NCOCS</td>
<td>917 (726)</td>
<td>791 (616)</td>
<td>478 (375)</td>
<td>1708 (1342)</td>
<td>79</td>
<td>USA: population based</td>
<td>Control: 65%</td>
</tr>
<tr>
<td>POL</td>
<td>POCS, Warsaw and Lodz Poland</td>
<td>625 (625)</td>
<td>264 (264)</td>
<td>118 (118)</td>
<td>889 (889)</td>
<td>100</td>
<td>Poland: population based</td>
<td>Case: 70%</td>
</tr>
<tr>
<td>SEA</td>
<td>SEARCH, Cambridge, UK</td>
<td>1235 (1229)</td>
<td>1013 (947)</td>
<td>391 (369)</td>
<td>2248 (2176)</td>
<td>97</td>
<td>England: population based</td>
<td>Control: 63%</td>
</tr>
<tr>
<td>STA</td>
<td>GEOCS, Stanford</td>
<td>429 (367)</td>
<td>325 (287)</td>
<td>176 (159)</td>
<td>754 (654)</td>
<td>87</td>
<td>USA: population based</td>
<td>Case: 67%</td>
</tr>
<tr>
<td>UCI</td>
<td>UC Irvine Ovarian Cancer Study, California</td>
<td>536 (431)</td>
<td>339 (284)</td>
<td>183 (148)</td>
<td>875 (715)</td>
<td>82</td>
<td>USA: population based</td>
<td>Case: 84%</td>
</tr>
<tr>
<td>UKO</td>
<td>UKOPS</td>
<td>601 (595)</td>
<td>298 (288)</td>
<td>137 (135)</td>
<td>899 (883)</td>
<td>98</td>
<td>England: population based</td>
<td>Case: 75%</td>
</tr>
<tr>
<td>USC</td>
<td>LAC-CCOC</td>
<td>754 (599)</td>
<td>631 (439)</td>
<td>380 (279)</td>
<td>1385 (1083)</td>
<td>75</td>
<td>USA: population based</td>
<td>Case: 75%</td>
</tr>
<tr>
<td>Total</td>
<td>10451 (9273)</td>
<td>6987 (5876)</td>
<td>3808 (3228)</td>
<td>17438 (15149)</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AOCS, Australian Ovarian Cancer Study; DOVE, Diseases of the Ovary and their Evaluation Study; GOCS, German Ovarian Cancer Study; HOPE, hormones and ovarian cancer prediction; MALOVA, Malignant Ovarian Cancer Study; NCOCS, North Carolina Ovarian Cancer Study; POCS, Polish Ovarian Cancer Study; GEOCS, genetic epidemiology of ovarian cancer; UKOPS, United Kingdom Ovarian Cancer Population Study; LAC-CCOC, Los Angeles County Case–Control Studies of Ovarian Cancer.

Numbers in parentheses are the number of women who are non-Hispanic White origin.
the duplicates ≥98%; (3) overall call rate (by study) >95% and (4) call rates >90% for each individual 384-well plate. The data for any SNP failing these criteria in any study were excluded from the final analyses. The HWE among White non-Hispanic controls was used to examine the quality of genotyping. For any SNP that was out of HWE (P < 0.05), the genotyping call rate was reviewed and the data excluded if the genotype clusters was found to be suboptimal. However, some studies with genotypes out of HWE were included if their genotypes, based on clusters, were of excellent quality. Genotyping consistency across labs was also evaluated by genotyping a common panel of CEPH-Utah trios including 90 individual DNA samples, five duplicate samples and one negative control (http://ccr.coriell.org/Sections/Search/Panel_Detail.aspx?Pgid=202&Ref=HAPMAPPT01). The concordance of genotyping results between the centres was required to be >98% in order for the genotype data to be included. No attempt was made to repeat genotyping in DNA samples that did not provide a clear genotype at the first attempt resulting in variations in the number of studies/samples that were successfully genotyped for each polymorphism.

Statistics

Deviation of genotype frequencies from those expected under HWE was assessed by χ² tests with one degree of freedom (1 df) for each study of controls as part of the genotyping quality control. The primary test of association was the comparison of genotype frequencies in cases and controls using a test for gene-dose effect for each SNP through an interval variable with three levels: 0, 1, 2; one assigned to each genotype. This was done using unconditional logistic regression stratified by study. OR for allele dosage and associated 95% CI were also estimated by unconditional logistic regression. We tested for heterogeneity between study strata by comparing logistic regression models with and without a genotype-stratum interaction term using likelihood ratio (1 df) for each study of controls as part of the genotyping quality control. The primary test of association was the comparison of genotype frequencies in cases and controls using a test for gene-dose effect for each SNP through an interval variable with three levels: 0, 1, 2; one assigned to each genotype. This was done using unconditional logistic regression stratified by study. OR for allele dosage and associated 95% CI were also estimated by unconditional logistic regression. We tested for heterogeneity between study strata by comparing logistic regression models with and without a genotype-stratum interaction term using likelihood ratio tests. A subgroup analysis was used to compare genotype-specific risks by disease subgroup with the controls. We limited subgroup analysis to the serious histology type as the number of cases diagnosed with other subtypes was low.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG online.

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Conflict of Interest statement. None declared.

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