

Validating genetic risk associations for ovarian cancer through the international Ovarian Cancer Association Consortium

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The search for genetic variants associated with ovarian cancer risk has focused on pathways including sex steroid hormones, DNA repair, and cell cycle control. The Ovarian Cancer Association Consortium (OCAC) identified 10 single-nucleotide polymorphisms (SNPs) in genes in these pathways, which had been genotyped by Consortium members and a pooled analysis of these data was conducted. Three of the 10 SNPs showed evidence of an association with ovarian cancer at $P \leq 0.10$ in a log-additive model: rs2740574 in CYP3A4 ($P = 0.011$), rs1805386 in LIG4 ($P = 0.007$), and rs3218536 in XRCC2 ($P = 0.095$). Additional genotyping in other OCAC studies was undertaken and only the variant in CYP3A4, rs2740574, continued to show an association in the replication data among homozygous carriers: $OR_{\text{homozygous(hom)}} = 2.50$ (95% CI 0.54–11.57, $P = 0.24$) with 1406 cases and 2827 controls. Overall, in the combined data the odds ratio was 2.81 among carriers of two copies of the minor allele (95% CI 1.20–6.56, $P = 0.017$, p_{het} across studies = 0.42) with 1969 cases and 3491 controls. There was no association among heterozygous carriers. CYP3A4 encodes a key enzyme in oestrogen metabolism and our finding between rs2740574 and risk of ovarian cancer suggests that this pathway may be involved in ovarian carcinogenesis. Additional follow-up is warranted.

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Ovarian cancer is the second most common gynaecologic cancer and the leading cause of gynaecologic cancer death; it is estimated that there were ~22 000 new diagnoses of ovarian cancer and ~15 000 deaths from the disease in the United States in 2007. In some families Mendelian inheritance of ovarian cancer is observed and high penetrance alleles have been identified in several genes including BRCA1, BRCA2, and DNA mismatch repair genes. However, disease-associated alleles of these genes account for less than 40% of the inherited variance in disease risk (Antoniou and Easton, 2006). Population-based case-control studies have described a two to three-fold increased risk in first-degree relatives of ovarian cancer patients (Godard *et al*, 1998; Stratton *et al*, 1998) and heritability is estimated to be approximately 22% (Lichtenstein *et al*, 2000). Ovarian cancer is probably a complex genetic disease with locus and allelic heterogeneity (Lander and Schork, 1994), and such complex traits are likely to be because of combinations of common, less penetrant alleles (Risch and Merikangas, 1996). However, the common alleles that might be responsible for susceptibility to ovarian cancer remain poorly understood.

The most powerful approach for identifying common, low-penetrance disease susceptibility alleles is the genetic association study. Until recently, most association studies have focused on the candidate gene approach in which common genetic variation in biologically relevant pathways is tested for association with disease. However, this approach has had limited success, and few initial findings of positive associations have been replicated in subsequent studies (Ioannidis *et al*, 2001; Lohmueller *et al*, 2003). One of the main reasons for these failures has been the limited power of small studies to detect associations at highly stringent levels of statistical significance. This is a particular problem in ovarian cancer where the largest individual studies have fewer than 2000 cases.

The Ovarian Cancer Association Consortium (OCAC) was formed in 2005 to provide a forum for testing candidate ovarian cancer susceptibility alleles in multiple studies with a large combined sample size (Gayther *et al*, 2007; Pearce *et al*, 2008; Ramus *et al*, 2008). Prior to the formation of the OCAC most groups had been carrying out candidate gene studies autonomously, although in many instances they had been studying the same candidate single nucleotide polymorphisms (SNPs) and genes. The purpose of the current study was to evaluate the evidence for association in SNPs, which had already been genotyped by multiple studies by combining the existing data. Where evidence for association emerged from these data, the associated SNPs were then genotyped in additional OCAC studies for replication.

MATERIALS AND METHODS

Study populations

The Ovarian Cancer Association Consortium is comprised of ovarian cancer case-control and cohort studies conducted around the world (Gayther *et al*, 2007; Pearce *et al*, 2008; Ramus *et al*, 2008). Included in this report are data from 16 OCAC studies. Ten of these are from the USA: the Diseases of the Ovary and their Evaluation (DOVE), the Genetic Epidemiology of Ovarian Cancer Study (GEOCS; previously FROCS) (Auranen *et al*, 2005; Song *et al*, 2006), the Hawaii Ovarian Cancer Study (HAWAII) (Goodman *et al*, 2001b), the Hormones and Ovarian Cancer Prediction Study (HOPE) (Pearce *et al*, 2008a), the Mayo Clinic Ovarian Cancer Case-Control Study (MAYO) (Sellers *et al*, 2005), the North Carolina Ovarian Cancer Study (NCOCS) (Berchuck *et al*, 2004), the New England-based Case-Control Study (Terry *et al*, 2005), the Ovarian Contraceptive and Reproductive Experiences study (Holt *et al*, 2007), the Orange and San Diego

Counties, California (UCI) study and the USC/Los Angeles County Case-Control Studies of Ovarian Cancer (USC) (Pearce *et al*, 2008b). There are data from three European studies: the Danish Malignant Ovarian Cancer Study (MALOVA) (Auranen *et al*, 2005; Song *et al*, 2006), the UK SEARCH Ovarian Cancer Study (SEARCH) (Auranen *et al*, 2005; Song *et al*, 2006), and the UK Ovarian Population Study (UKOPS) (Ramus *et al*, 2008). Finally, data were contributed by three studies from Australia: the Australian Cancer Study (ACS) (Merritt *et al*, 2008), the Australian Ovarian Cancer Study (AOCS) (Merritt *et al*, 2008), and Survey of Women's Health (SWH) (Spurdle *et al*, 2000). ACS and AOCS were combined for analysis purposes. Details of all but DOVE and UCI have been published earlier.

All studies have Institutional Review Board/Human Ethics Committee approval for the work presented. In addition, Duke University and the University of Southern California have Institutional Review Board approval as data coordinating centers.

SNP selection

At the inception of the OCAC and annually thereafter, members have provided a list of SNPs genotyped in their study population. By early 2007, there were 10 SNPs which had been genotyped by at least three groups: rs4680 in COMT, rs4646903 and rs1048943 in CYP1A1, rs1056836 in CYP1B1, rs2740574 in CYP3A4, rs743572 in CYP17, rs3020450 in ESR2, rs1805386 in LIG4, rs3218536 in XRCC2 and rs861539 in XRCC3. Some of these data have earlier been published by individual groups (Spurdle *et al*, 2000, 2002; Goodman *et al*, 2001a,b; Garner *et al*, 2002; Terry *et al*, 2003; Auranen *et al*, 2005; Sellers *et al*, 2005; Webb *et al*, 2005; Beesley *et al*, 2007; Holt *et al*, 2007; Pearce *et al*, 2008b). The original data on these 10 SNPs were then submitted to a central database for combined analysis. SNPs that showed some evidence for association in original data were also genotyped in additional OCAC studies for replication purposes.

Genotyping and quality control

The original data had been genotyped using a variety of methods described in the reports of these individual data (see Table 1 for references). For the replication genotyping, the 5' nuclease Taqman allelic discrimination assay (Taqman; Applied Biosystems, Foster City, CA, USA) was used by DOVE, HAWAII, HOPE, MALOVA, MAYO, SEARCH, UCI, UKOPS and USC using centrally supplied probes. ACS and AOCS used the Sequenom iPLEX gold genotyping platform (Sequenom Inc., San Diego, CA, USA).

For all genotype data, genotype frequencies by ethnic group and study in controls were tested for deviation from Hardy-Weinberg equilibrium (HWE). For the replication genotyping effort, we applied the OCAC quality control guidelines which stipulated intermixing of cases and controls on genotyping plates, including duplicate samples with no less than 98% concordance rate, overall call rate by each study of 95% or greater and call rate for each plate of at least 90%. In addition, consistency across labs was confirmed by genotyping a common set of 95 DNAs (90 CEPH trios and five duplicate samples; HAPMAPPT01 provided by Coriell, Camden, NJ, USA) with the requirement of >98% concordance in genotype calls.

Data analysis

Each group provided age and race/ethnicity for all participants and tumour histology for cases. Data analyses were restricted to invasive epithelial ovarian cancers and included White, Black and Latina individuals. Unconditional logistic regression stratified on study, age (five groups: <40, 40-49, 50-59, 60-69, 70+ years), and race/ethnicity, was used to analyze the data (SAS Version 9.1, Cary, NC, USA). Each SNP was evaluated under three genetic models: a co-dominant log additive model, a dominant model and

Table 1 Characteristics of the OCAC case-control studies included in this report

Study (Ref) ^a	Location	Years conducted	Control ascertainment	Case ascertainment	No. of controls/cases	SNPs genotyped
ACS	Australia	2002–2005	Randomly selected from Commonwealth electoral roll. Frequency matched for age and geographical region.	Cancer registries of New South Wales and Victoria.	364/166	rs2740574 (CYP3A4), rs1805386 (LIG4)
AOCS (Beesley et al, 2007)	Australia	2002–2006	Randomly selected from Commonwealth electoral roll. Frequency matched for age & geographical region.	Recruited through surgical treatment centres throughout Australia and cancer registries of Queensland, South Australia and West Australia.	698/558	rs2740574 CYP3A4), rs1805386 (LIG4), rs3218536 (XRCC2), rs861539 (XRCC3)
DOVE	Washington, USA	2002–2005	Random-digit dial identification from study area. Frequency matched to cases for race/ethnicity and 5-year age group.	Cases diagnosed with primary invasive ovarian cancer between 2002–2005 from a 13-county area of western Washington state.	744/548	rs3218536 (XRCC2)
GEOCS (Auranen et al, 2005)	Northern California, USA	1997–2002	Random-digit dial identification from study area. Frequency matched to cases for 5-year age group and race/ethnicity.	Greater Bay Area Cancer Registry, San Francisco.	419/317	rs1805386 (LIG4), rs3218536 (XRCC2), rs861539 (XRCC3)
HAWAII (Goodman et al, 2001a, b)	Hawaii, USA	1993 onwards	Randomly selected from Hawaii Department of Health Annual Survey of the representatives households.	Rapid case ascertainment through Hawaii Tumour Registry.	160/70	rs4680 (COMT), rs4646903 (CYP1A1), rs1048943 (CYP1A1), rs1056836 (CYP1B1), rs2740574 (CYP3A4), rs743572 (CYP17), rs3020450 (ESR2), rs3218536 (XRCC2)
HOPE	NY, OH and PA, USA	2003 onwards	Identified in same regions. Frequency matched for age and ethnicity.	Physician offices, cancer registries and pathology databases from counties of western PA, eastern OH and western NY.	662/297	RS3218536 (XRCC2)
MALOVA (Auranen et al, 2005)	Denmark	1994–1999	Random sample of general female population (35–79 years of age) in study area. Selected using computerised Central Population Register and matched to cases for age and geographical region.	Incident cases (35–79 years of age) from municipalities of Copenhagen and Frederiksberg and surrounding counties.	1197/42	rs2740574 (CYP3A4), rs1805386 (LIG4), rs3218536 (XRCC2), rs861539 (XRCC3)
MAYO (Sellers et al, 2005)	Mayo Clinic, USA	2000 onwards	Healthy women seeking general medical examination identified through Mayo Clinic. Frequency matched to cases for age, race, and state of residence.	Cases attending Mayo Clinic identified in a six-state surrounding region.	442/325	rs4680 (COMT), rs1048943 (CYP1A1), rs1056836 (CYP1B1), rs3218536 (XRCC2)
NCOCS	North Carolina, USA	1999 onwards	Controls identified from same region. Frequency matched to cases for age and race.	Identified from 48 counties within the region by rapid-case ascertainment.	941/702	rs2740574 (CYP3A4), rs743572 (CYP17), rs3020450 (ESR2), rs1805386 (LIG4), rs3218536 (XRCC2), rs861539 (XRCC3)
NECC (Garner et al, 2002; Terry et al, 2003)	New England, USA	1992–2003	Controls identified through random digit dialing, townbooks, and drivers' license lists. Frequency matched to cases on age and state of residence.	Identified through hospital tumour boards and state cancer registries in New Hampshire and Massachusetts.	484/268	rs4646903 (CYP1A1), rs1048943 (CYP1A1), rs743572 (CYP17), rs3020450 (ESR2)
OVCARE (Holt et al, 2007)	Washington, USA	1994–1998	Controls identified through random digit dialing in same three geographic regions as cases.	Incident cases (35–54 years of age) identified by SEER population-based cancer registries serving metropolitan Atlanta, Detroit, and Seattle areas.	577/188	rs4680 (COMT), rs4646903 (CYP1A1), rs1048943 (CYP1A1), rs1056836 (CYP1B1)
SEARCH (Auranen et al, 2005)	UK	1991 onwards	Selected from the EPIC-Norfolk cohort of 25,000 individuals aged 45–74, based in the same geographical regions as cases.	Caese < 70 years from East Anglian, West Midlands & Trent regions of England. Prevalent cases diagnosed 1991–1998; incident cases diagnosed 1998 onwards.	1221/851	rs1805386 (LIG4), rs3218536 (XRCC2), rs861539 (XRCC3)

Table 1 (Continued)

Study (Ref) ^a	Location	Years conducted	Control ascertainment	Case ascertainment	No. of controls/ cases	SNPs genotyped
SWH (Spurdle <i>et al</i> , 2002; Webb <i>et al</i> , 2005) UCI	Australia	1985–1996 (cases) 1992–1993 (controls) 1994–2004	From national twin study (one member of pairs of monozygotic twins). Controls identified through random digit dialing. Frequency matched to cases by age group and race/ethnicity.	Cancer registries of New South Wales and Queensland, Australia.	275/377	rs2740574 (CYP3A4), rs743572 (CYP17), rs3218536 (XRCC2), rs861539 (XRCC3)
UKOPS	UK	2006 onwards	Postmenopausal women from the general population participating in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKTOCS). All women followed up for cancers through the Office of National Statistics	Recruitment of cases was done by rapid case ascertainment through the Cancer Surveillance Program of Orange and San Diego Counties that resides at UCI and is part of the California Cancer Registry. Incident cases from ten gynaecological oncology National Health Service centres throughout the UK, from January 2006 onwards.	438/298	rs3218536 (XRCC2)
USC (Pearce <i>et al</i> , 2008b)	Los Angeles, USA	1993 onwards	Neighborhood recruited controls, frequency matched to cases for age and ethnicity.	Rapid case ascertainment through Los Angeles Cancer Surveillance Program.	584/262	rs2740574 (CYP3A4), rs3218536 (XRCC2)
					701/564	rs743572 (CYP17), rs3020450 (ESR2), rs1805386 (LIG4), rs3218536 (XRCC2)

^aSee Materials and Methods for full study name.

a recessive model. Results are given for the heterozygous and homozygous risk estimates.

Information on a first-degree family history of ovarian cancer was available on approximately 75% of cases and controls. Stratified analyses were conducted on this subset of subjects.

The original and replication data were analyzed separately and combined using the same methods. Heterogeneity across studies was tested using the likelihood ratio test by fitting models with and without interaction terms for study and SNP based on the final model presented in the results.

Published data from non-OCAC members were available on three SNPs: rs4680 (COMT) (Goodman *et al*, 2000), rs4646903 (CYP1A1, also known as CYP1A1 Msp1) (Sugawara *et al*, 2003) and rs1048943 (CYP1A1, also known as CYP1A1*3) (Aktas *et al*, 2002; Sugawara *et al*, 2003). The odds ratios and 95% confidence intervals from these published reports were abstracted and a meta-analysis was conducted utilizing these data as well as the OCAC data using Stata (Version 9, StataCorp, College Station, TX, USA). Both random and fixed-effects models were evaluated.

RESULTS

Details of the 16 case-control studies that provided data for these analyses are shown in Table 1. Genotype frequencies in White controls were consistent with HWE for all SNPs/studies except rs2740574 (CYP3A4) in HAW ($P=0.04$) (Supplementary Table 1). These data were retained in the analyses as the deviation was small, the clustering was unambiguous and given the number of SNP/study combinations evaluated it is likely to represent a chance finding.

Seven of the 10 SNPs showed no evidence of an association with invasive epithelial ovarian cancer (ovarian cancer; Table 2). These SNPs were not further evaluated in the OCAC, but three of them (COMT rs4680, CYP1A1 rs4646903, and CYP1A1 1048943) had been studied by groups outside of the OCAC and thus meta-analyses of the published literature and OCAC data were conducted. Neither the COMT variant nor the CYP1A1 rs4646903 variant were statistically significantly associated with ovarian cancer risk on meta-analysis (data not shown).

The CYP1A1 rs1048943 which showed a non-statistically significant 10% increased risk of ovarian cancer per copy of the minor allele carried in the OCAC dataset (95% CI 0.77–1.57) was statistically significantly associated with risk of ovarian cancer on meta-analysis with the published literature and the OCAC data ($OR_{\text{additive(Add)}} = 1.81$, 95% CI 1.36–2.40, $P < 0.001$) under a fixed effects model, but not a random-effects model ($OR_{\text{add}} = 1.61$, 95% CI 0.74–3.51, $P = 0.23$). The meta-analysis also revealed significant heterogeneity across studies ($P < 0.001$).

Three SNPs showed evidence of an association with ovarian cancer in the original OCAC data and were evaluated in additional case-control studies from OCAC members (Table 3; Figure 1). Based on original genotype data (three studies: 563 cases, 664 controls), CYP3A4 rs2740574 was associated with an increased risk of invasive ovarian cancer among women who carried two copies of the minor allele ($P = 0.015$). There was a 3.7-fold increased risk associated with carrying two copies of the minor allele. Similar results were found when this SNP was genotyped by three additional OCAC sites in an additional 1406 cases and 2827 controls, but the confidence interval was wide ($OR_{\text{homozygous(hom)}} = 2.50$, 95% CI 0.54–11.54, $P = 0.24$; Table 3) because the follow-up data consisted of White individuals in which the minor allele frequency was very low. In the combined dataset, women carrying two copies of this allele had a 2.8-fold increased risk of ovarian cancer ($OR_{\text{hom}} = 2.81$, 95% CI 1.20–6.56, $p_{\text{hom}} = 0.017$; Table 3; Figure 1). There was no evidence of heterogeneity across study sites ($p_{\text{het}} = 0.42$). This finding was

Table 2 Summary odds ratio (per allele) and 95% confidence interval for risk of invasive epithelial ovarian cancer among the indicated OCAC studies for SNPs that showed no association with ovarian cancer

Gene	SNP	Controls (N)	Cases (N)	OR _{het} ^a (95% CI)	P-value	OR _{hom} ^a (95% CI)	P-value	Studies
COMT	rs4680	874	381	1.01 (0.75–1.36)	0.96	1.00 (0.71–1.42)	0.98	HAWAII, MAYO OVCARE
CYP1A1	rs4646903	1182	490	1.15 (0.89–1.50)	0.29	0.77 (0.28–2.13)	0.61	HAWAII, NECC, OVCARE
CYP1A1	rs1048943	1308	611	1.13 (0.79–1.63)	0.50	—	0.97	HAWAII, MAYO, NECC, OVCARE
CYP1B1	rs1056836	875	384	0.91 (0.69–1.21)	0.52	0.83 (0.58–1.19)	0.31	HAWAII, MAYO OVCARE
CYP17	rs743572	1594	1078	1.09 (0.91–1.30)	0.36	1.19 (0.93–1.52)	0.17	HAWAII, NCOCS, NECC, SWH, USC
ESR2	rs3020450	2198	1523	0.95 (0.83–1.10)	0.52	1.09 (0.87–1.36)	0.44	HAWAII, NCOCS, NECC, USC
XRCC3	rs861539	5186	2352	0.92 (0.82–1.04)	0.17	1.01 (0.85–1.19)	0.95	AOCS, MALOVA, NCOCS, SEARCH, GEOCS, SWH

^aCI = confidence interval; het = heterozygous carriers; hom = homozygous carriers; OR = odds ratio. All ORs stratified on study site, race/ethnicity and age.

Table 3 Summary odds ratio and 95% confidence interval for risk of invasive epithelial ovarian cancer among OCAC studies for the three SNPs associated with risk of ovarian cancer in original data

	Controls (N)	Cases (N)	OR _{het} ^a	95% CI		P-value		95% CI	P-value
				CYP3A4	rs2740574 ^b	OR _{hom} ^a	P-value		
Original data	664	563	1.51	0.85–2.40	0.084	3.66	1.29–10.40	0.015	
Replication data	2827	1406	0.96	0.73–1.25	0.75	2.50	0.54–11.54	0.24	
Combined data	3491	1969	1.07	0.85–1.34	0.57	2.81	1.20–6.56	0.017	
LIG4 rs1805386^c									
Original data	2196	1630	1.21	1.04–1.40	0.013	1.34	0.90–1.99	0.15	
Replication data	2944	1691	0.87	0.75–1.00	0.046	0.67	0.45–1.01	0.056	
Combined data	5140	3321	1.01	0.91–1.12	0.82	0.94	0.71–1.25	0.68	
XRCC2 rs3218536^d									
Original data	3668	2763	0.92	0.79–1.06	0.24	0.60	0.31–1.17	0.13	
Replication data	4005	2551	1.05	0.91–1.21	0.50	0.79	0.40–1.57	0.50	
Combined data	7673	5314	0.97	0.88–1.08	0.61	0.68	0.42–1.09	0.11	

^ahet = heterozygous carriers; OR = odds ratio; hom = homozygous carriers. ^bStudies included in original data: HAWAII, NCOCS, SWH; studies included in follow-up data: ACS, AOCS, MALOVA, UKOPS. ^cStudies included in original data: GEOCS, NCOCS, SEARCH; studies included in follow-up data: ACS, AOCS, MALOVA, USC. ^dStudies included in original data: AOCS, GEOCS, MALOVA, NCOCS, SEARCH, SWH; studies included in follow-up data DOVE, HAWAII, HOPE, MAYO, SEARCH (additional accrued cases), UCI, UKOPS, USC.

consistent across histological subtypes (Table 4). There was no evidence of statistical interaction with family history ($P=0.52$).

The minor allele frequency for rs2740574 in White controls was 3.5%, compared with 59.7% in Blacks. The association between this CYP3A4 variant and risk of ovarian cancer was consistent across these two racial/ethnic groups in the combined existing and follow-up data: OR_{hom} in Blacks = 6.82 (95% CI 0.73–63.86, $P=0.093$) and OR_{hom} in Whites = 2.40 (95% CI 0.67–8.68, $P=0.18$).

There was a 21% increased risk of ovarian cancer associated with the rs1805386 variant in LIG4 among heterozygous carriers and a 34% increased risk among homozygous carriers ($P=0.013$ and $P=0.15$, respectively; Table 3) in the original data. When this SNP was genotyped by four additional OCAC sites (1691 cases and 2944 controls) a decreased risk of ovarian cancer was observed (OR_{heterozygous (het)} = 0.87, $P=0.046$ and OR_{hom} = 0.67, $P=0.056$; Table 3). After combining the original and replication data there was no association between rs1805386 and risk of ovarian cancer (OR_{het} = 0.97, $P=0.61$, OR_{hom} = 0.68, $P=0.11$; Table 3; Figure 1) in 3321 cases and 5140 controls. There was a significant heterogeneity across the study sites ($P=0.001$); the heterogeneity was not attributable to any single study. There was no evidence of statistical interaction with family history ($P=0.50$).

We found borderline evidence of a decrease in ovarian cancer risk associated with the XRCC2 variant rs3218536 using a log-additive model in the original data provided by six OCAC sites (OR = 0.89, 95% CI 0.78–1.02, $P=0.095$) with 2763 cases and 5479 controls. This SNP was genotyped by seven additional OCAC sites comprising 2551 cases and 4005 controls and no association was

observed with ovarian cancer risk (Table 3). In the combined data there was no association between rs3218536 and risk of ovarian cancer (Table 3; Figure 1). There was neither any evidence of heterogeneity across study sites ($P=0.30$), nor histological subtype-specific effects. There was also no evidence of statistical interaction with family history ($P=0.25$).

DISCUSSION

We evaluated the association between 10 SNPs from nine genes and ovarian cancer risk using existing data from 16 studies that participate in the OCAC. We found borderline evidence for association with ovarian cancer risk for three of these variants and replication genotyping was carried out to provide more definitive evidence of association. In the combined data, only rs2740574 in CYP3A4 was associated with disease among women who carried two copies of the minor allele ($P=0.017$). This finding was consistent across the original and replication data and also across White and Black racial/ethnic groups and histological subtypes (Table 4).

CYP3A4 encodes an enzyme critical for oxidation of oestrogens (Keshava *et al*, 2004) and its inhibition results in higher circulating oestrogen levels (Monroe *et al*, 2007). Given that exposure to oestrogen is associated with the risk of ovarian cancer (Beral *et al*, 2007) it is plausible that the CYP3A4 rs2740574 variant might influence ovarian cancer development through decreased expression of the gene and thus reduced metabolism of oestrogen. In addition to hormone metabolism, CYP3A4 is also involved in the

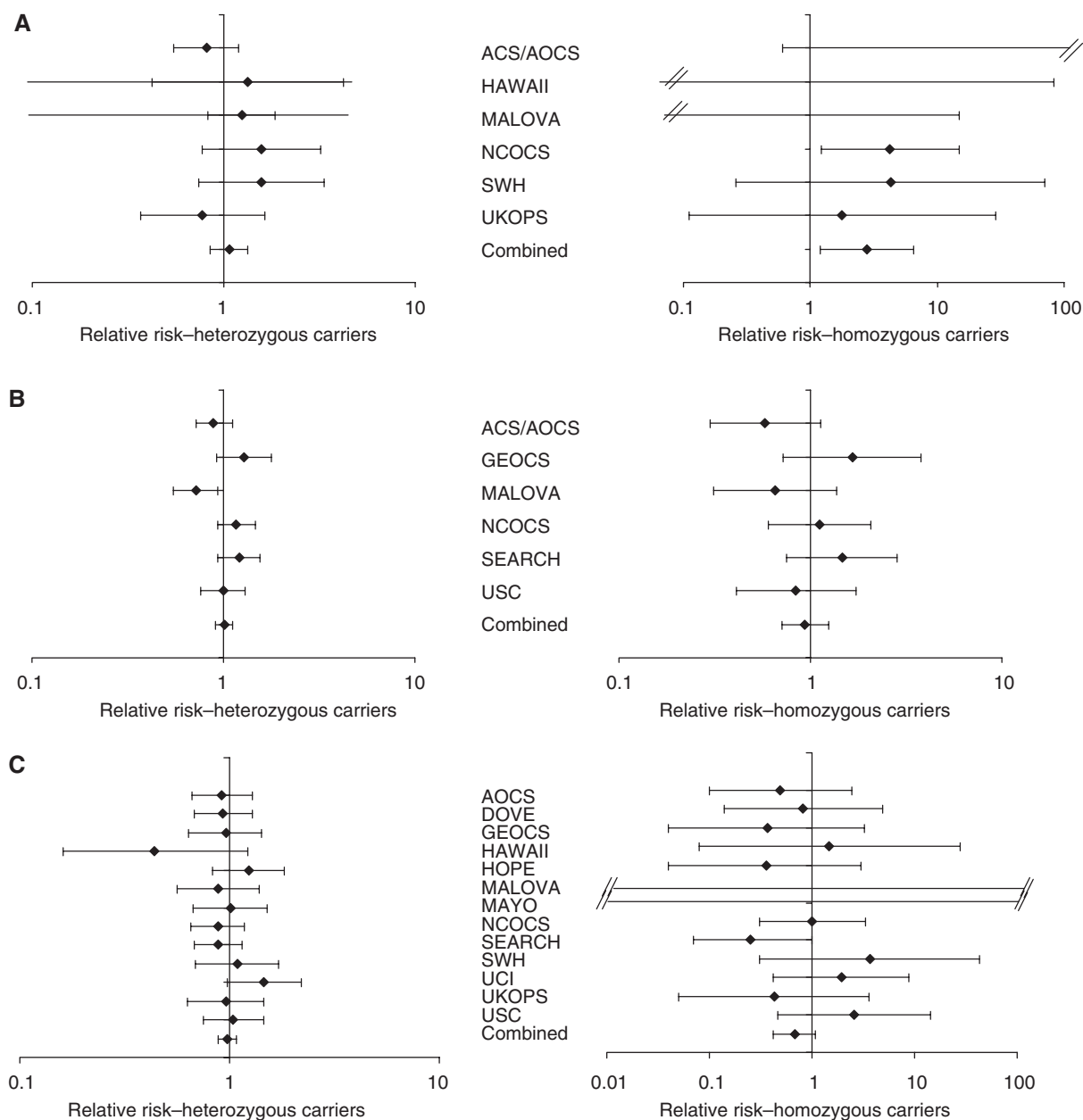


Figure 1 Forest plots of the study-specific and summary-relative risk and 95% confidence intervals for the association between ovarian cancer risk and three SNPs in the CYP3A4, LIG4 and XRCC2 genes. **(A)** rs2740574 in CYP3A4. The overall summary ovarian cancer risk among heterozygous carriers is 1.07 (0.85–1.34, $P=0.57$) and homozygous carriers is 2.81 (95% CI 1.20–6.56, $P=0.017$). **(B)** rs1805386 in LIG4. The overall summary ovarian cancer relative risk among heterozygous carriers is 1.01 (95% CI 0.91–1.12, $P=0.82$) and homozygous carriers is 0.94 (95% CI 0.71–1.25, $P=0.68$). **(C)** rs3218536 in XRCC2. The overall summary ovarian cancer relative risk among heterozygous carriers is 0.97 (95% CI 0.88–1.08, $P=0.61$) and homozygous carriers 0.68 (95% CI 0.42–1.09, $P=0.11$).

metabolism of approximately half of all marketed drugs, therefore individuals with differences in CYP3A4 expression might have different responses to any number of exogenous compounds, including oral contraceptives, an ovarian cancer protective factor.

The rs2740574 SNP is in the promoter region of the gene, but efforts to show a functional effect of this variant have proved difficult. Spurdle *et al* (2002) evaluated multiple reporter gene constructs, but found no differences in the transcription between the putative disease and wild-type allele; the results of other functional studies have been equivocal (Ball *et al*, 1999; Westlind *et al*, 1999; Amirimani *et al*, 2003; Rodriguez-Antona *et al*, 2005). Alternatively, it may be that rs2740574 is simply in linkage disequilibrium with the causal variant, which remains to be identified. Using data from the International Haplotype

Map Project (HapMap) to examine the region that includes CYP3A4, CYP3A5 and CYP3A7 genes and the 20 kb flanking this region, there are six variants in perfect linkage disequilibrium with rs2740574. Five of these variants are in the region immediately 5' of CYP3A4 and one is in intron 2 of the gene. Any of these SNPs, or an unidentified variant in linkage disequilibrium, could be the causal allele. At present, there are no data to support a functional role for any of these variants in ovarian cancer development. Additional follow-up is warranted to confirm the association between this CYP3A4 variant and risk of ovarian cancer, and ideally these studies should be performed in different racial groups.

Two additional variants, one in LIG4 and the other in XRCC2, evaluated as part of this project, showed association in the original

Table 4 Odds ratios and 95% CIs by race/ethnicity and histological sub-type^a for the CYP3A4 rs2740574 variant in the combined dataset

Characteristics	Cases	Controls	OR _{het} ^b	95% CI	P-value	OR _{hom} ^b	95% CI	P-value
Black	24	36	2.86	0.28–29.63	0.38	6.82	0.73–63.86	0.093
White	1944	3453	1.06	0.84–1.33	0.62	2.4	0.67–8.68	0.18
Endometrioid	229	3491	1.65	1.05–2.59	0.03	2.64	0.36–19.16	0.34
Mucinous	107	3491	0.54	0.19–1.51	0.24	4.75	0.47–47.84	0.19
Serous	1052	3491	0.93	0.70–1.24	0.63	2.8	1.00–7.83	0.050

^aClear cell histology not informative. ^bOR = odds ratio; het = heterozygous OR; hom = homozygous OR. Studies included: ACS, AOCS, HAW, MALOVA, NCO, SWH, UKOPS; all ORs stratified on study site, age and race/ethnicity (for histology analyses).

data provided by OCAC sites, but no association was observed after replication genotyping was carried out in additional OCAC studies. The LIG4 variant, rs1805386, showed significant heterogeneity across studies ($P=0.001$) for reasons that could not be elucidated. It is perplexing that the original data suggested a statistically significant positive association with risk, whereas the replication data suggested an inverse relationship. In the absence of any reasonable explanation it is likely that the heterogeneity was due to chance. The failure to replicate the association with the XRCC2 variant rs3218536 was not surprising as the evidence of association in the original data was weak under a co-dominant genetic model ($P=0.095$).

Seven additional variants did not show an association with the risk of ovarian cancer in the OCAC dataset. Three of these variants have been studied by groups outside the OCAC: rs4680 (COMT) (Goodman *et al*, 2000), rs4646903 (CYP1A1, also known as CYP1A1 Msp1) (Sugawara *et al*, 2003) and rs1048943 (CYP1A1, also known as CYP1A1*3) (Aktas *et al*, 2002; Sugawara *et al*, 2003). Neither the COMT variant nor the CYP1A1 rs4646903 variant were associated with the risk of ovarian cancer on meta-analyses of the published literature and the OCAC data.

The CYP1A1 rs1048943 variant was associated with a non-statistically significant increased risk of ovarian cancer per copy of the minor allele carried in the OCAC dataset and in a Japanese population (OR_{add} = 1.16, 95% CI 0.44–3.05) (Sugawara *et al*, 2003); in a Turkish population it was associated with a statistically significant increased risk of ovarian cancer (OR_{add} = 6.20, 95% CI 3.62–10.46) (Aktas *et al*, 2002). Overall, the meta-analysis of the published literature and the OCAC data showed a statistically significant increased risk of ovarian cancer (OR_{add} = 1.81, 95% CI 1.36–2.40, $P<0.001$) under a fixed-effects model, but not a random-effects model (OR_{add} = 1.61, 95% CI 0.74–3.51, $P=0.23$). The meta-analysis also revealed significant heterogeneity across studies ($P<0.001$) bringing this association into question. Further follow-up of this variant may be warranted.

There are several limitations to this study. The association with CYP3A4 rs2740574 was consistent in the original and replication

data and was consistent across racial/ethnic groups, but it was restricted to homozygous carriers of the minor allele. The risk allele is rare in Whites and the result is based on few cases and while the SNP is common in Blacks there are few included in this study. Also, four of the SNPs (rs4646903 and rs1048943 in CYP1A1, rs1056836 in CYP1B1, and rs743572 in CYP17), which were not statistically significantly associated with ovarian cancer and therefore not followed up by the OCAC, were associated with ~10% increased or decreased risk of ovarian cancer per copy of the allele carried. This size of effect is of the same magnitude as those observed in a recent breast cancer genome-wide association scan (Easton *et al*, 2007). Some of these results could be false negatives as we were only powered to detect odds ratios of ~1.18 and higher for these SNPs with 80% power and an α of 0.05. We also observed significant heterogeneity with the SNP in LIG4, which may have been a chance finding, but may have resulted from underlying differences in the study populations, an issue with pooled-analyses.

In conclusion, we have identified a possible association between an SNP (rs2740574) in the key oestrogen-metabolizing gene CYP3A4 and ovarian cancer risk. Follow-up of this association is warranted, especially in Blacks. Our study also underscores the importance of consortium-based replication of genetic epidemiological studies to achieve large sample sizes.

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Appendix

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