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Analysis of Over 10,000 Cases Finds No Association between Previously-Reported Candidate Polymorphisms and Ovarian Cancer Outcome

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Abstract

Background—Ovarian cancer is a leading cause of cancer-related death among women. In an effort to understand contributors to disease outcome, we evaluated single-nucleotide polymorphisms (SNPs) previously associated with ovarian cancer recurrence or survival, specifically in angiogenesis, inflammation, mitosis, and drug disposition genes.

Methods—Twenty-seven SNPs in *VHL*, *HGF*, *IL18*, *PRKACB*, *ABCB1*, *CYP2C8*, *ERCC2*, and *ERCC1* previously associated with ovarian cancer outcome were genotyped in 10,084 invasive cases from 28 studies from the Ovarian Cancer Association Consortium with over 37,000 observed person-years and 4,478 deaths. Cox proportional hazards models were used to examine the association between candidate SNPs and ovarian cancer recurrence or survival with and without adjustment for key covariates.

Results—We observed no association between genotype and ovarian cancer recurrence or survival for any of the SNPs examined.

Conclusions—These results refute prior associations between these SNPs and ovarian cancer outcome and underscore the importance of maximally powered genetic association studies.

Impact—These variants should not be used in prognostic models. Alternate approaches to uncovering inherited prognostic factors, if they exist, are needed.

INTRODUCTION

In 2012, ovarian cancer was estimated to be the seventh leading cause of female cancer-related deaths worldwide (1). Despite standardized treatment approaches, inter-individual variation in outcomes exists; understanding the source of this variation, including potential inherited factors, is of high importance (2). Our prior studies of over 400 candidate genes in biological pathways that are relevant to ovarian cancer suggested association between ovarian cancer outcome and inherited variation in certain genes (3–5). These include the angiogenesis genes *VHL* (3) and *HGF* (4), taxol efflux and metabolism genes *ABCB1* and *CYP2C8* (5), DNA repair genes *ERCC2* and *ERCC1* (5), the inflammation gene *IL18* (3), and the mitosis gene *PRKACB* (4). Here, we sought to confirm prior associations ($p < 0.05$) between ovarian cancer outcome and 27 single-nucleotide polymorphisms (SNPs) in these genes using a much larger sample size than the discovery studies.

MATERIALS AND METHODS

A total of 10,084 women with invasive epithelial ovarian cancer (over 37,000 person-years follow-up) including 5,248 high-grade serous cases were examined. Participants from 28 studies (Table 1) in the Ovarian Cancer Association Consortium (OCAC) were genotyped on a custom Illumina iSelect BeadArray using centralized genotype calling and quality control procedures, as previously described (6). In brief, we excluded SNPs and samples with call rate $< 95\%$; we restricted to women with $> 90\%$ predicted European ancestry and estimated principal components (PCs) representing European substructure (6).

Cox proportional hazards regression modeling accounting for left truncation and censoring at 10 years following diagnosis was used to estimate per-allele hazard ratios (HRs) and 95% confidence intervals (CIs) for associations with death from any cause for all cases and for high-grade serous cases. Two models were assessed: a minimally adjusted model including covariates for age at diagnosis, five population substructure PCs, and study site, and a fully adjusted model which additionally included histology (for analyses of all cases only), tumor stage, tumor grade, and oral contraceptive use as these covariates were associated with survival in these data ($p < 0.05$). Analyses were also conducted with a recurrence endpoint

defined by time to disease recurrence or death (377 additional events, including 273 among women with high-grade serous disease).

RESULTS

Overall, there were no associations between SNPs and ovarian cancer survival in either the minimally or fully adjusted models; Table 2 shows HRs, 95% CIs, and p-values for all cases and high-grade serous cases. No heterogeneity across studies was observed (p -values >0.05). SNP rs2214825 in *HGF* was significantly associated with survival in the minimally adjusted model ($p=0.03$), although not in the fully adjusted model (Table 2). After excluding 2,015 women who contributed to the original report (4), no association was seen at $p<0.05$ (minimally adjusted HR=1.04, 95% CI=0.98–1.10, $p=0.19$). Additionally, in *ERCC2*, SNP rs50872 conferred a slightly increased risk of death among women with high-grade serous disease ($p=0.03$) in the fully adjusted model, but this association was not statistically significant at $\alpha=0.05$ in the minimally adjusted model, and, after excluding 497 women in the original report (5), no statistically significant association was seen (fully adjusted HR=1.06, 95% CI=1.00–1.14, $p=0.06$). Near identical results were seen for these SNPs in analysis of time to recurrence. On the whole, while these candidates showed promise with large effect sizes (i.e., HRs >1.23 or <0.82) in earlier reports (3–5), our very large scale study refutes association at these loci with 95% CIs excluding prior risk estimates.

DISCUSSION

Here, we aimed to confirm the relationship between previously-associated SNPs and ovarian cancer outcome using a sample of over 10,000 women from 28 studies participating in the OCAC. Results of this analysis did not confirm the associations originally observed (3–5). While associations with other SNPs may exist, we report no consistent associations between these 27 SNPs and ovarian cancer outcome and believe it critical to disseminate results to reduce the possibility of publication bias. These null results highlight the necessity of large-scale replication of initial SNP associations, as the most likely explanation for non-replication is that initial false positive findings resulted from chance in smaller studies.

Studies of SNPs and cancer outcome have been less fruitful than cancer susceptibility studies (7). This may be due to several challenges: lack of a large collection of homogeneous cases due to missing baseline clinical data, inability to verify chemotherapeutic or surgical data to evaluate whether SNP effects arise only in certain clinical contexts, and inconsistent follow-up methods leading to variable completeness of endpoints (8). Although ovarian cancer has high mortality rate and a generally uniform treatment compared to other cancers, there is a trade-off in expected power between the larger sample sizes of observational studies and the detailed data available from clinical trials. We propose that utilization of both study designs, including detailed tumor characteristics and coordination with animal and mechanistic studies, is the best path forward for the identification of predictive and prognostic factors in ovarian cancer outcomes.

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Table 1

Participating Invasive Epithelial Ovarian Cancer Studies

Abbreviation	Name	Location	Case source	All Histologies			High-Grade Serous		
				N	N Deaths (%)	Person-years	N	N Deaths (%)	Person-years
SEA	Study of Epidemiology and Risk Factors in Cancer Heredity	UK: East Anglia and West Midlands	Population	1,341	426 (32%)	5,010	518	229 (44%)	1,595
AUS	Australian Ovarian Cancer Study/Australian Cancer Study (Ovarian Cancer)	Australia	Population	848	432 (51%)	2,796	498	313 (63%)	1,547
DOV	Diseases of the Ovary and their Evaluation	USA: 13 counties in western Washington state	Population	761	296 (39%)	2,280	435	193 (44%)	1,224
MAY	Mayo Clinic Ovarian Cancer Case-Control Study	USA: North Central (MN, SD, ND, IL, IA, WI)	Clinic	695	364 (52%)	1,858	497	297 (60%)	1,233
NEC	New England Case Control Study	USA: New Hampshire and Eastern Massachusetts	Population	671	334 (50%)	3,948	343	236 (69%)	1,573
USC	Los Angeles County Case-control studies of Ovarian Cancer-1	Los Angeles County	Population	638	273 (43%)	2,323	363	189 (52%)	1,263
NCO	North Carolina Ovarian Cancer Study	USA: Central and eastern North Carolina (48 counties)	Population	636	327 (51%)	2,708	366	240 (66%)	1,382
UKO	United Kingdom Ovarian Cancer Population Study	United Kingdom (England, Wales and Northern Ireland)	Population	620	200 (32%)	2,180	269	110 (41%)	941
MAL	MALignant OVARIAN Cancer	Denmark	Population	440	322 (73%)	2,046	183	158 (86%)	666
MSK	Memorial Sloan-Kettering Cancer Center	USA: New York City	Hospital	391	108 (28%)	1,070	302	84 (28%)	749
POC	Polish Ovarian Cancer Study	Poland: Szczecin, Poznan, Opole, Rzeszow	Population	355	203 (57%)	1,288	0	0	0
UCI	University of California Irvine Ovarian Study	USA: Southern California (Orange and San-Diego, Imperial Counties)	Population	275	90 (33%)	968	144	63 (44%)	456
STA	Genetic Epidemiology of Ovarian Cancer	USA: Six counties in the San Francisco Bay area	Population	257	142 (55%)	1,300	135	95 (70%)	581
LAX	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	USA: Southern California	Hospital	256	148 (58%)	1,050	201	127 (63%)	831
BEL	Belgian Ovarian Cancer Study	Belgium, University Hospital Leuven	Hospital	245	53 (22%)	307	173	46 (27%)	220
POL	Polish Ovarian Cancer Case Control Study	Poland, Warsaw and Lodz	Population	211	113 (54%)	746	60	40 (67%)	187
WOC	Warsaw Ovarian Cancer Study	Poland: Warsaw and central Poland	Clinic	201	85 (42%)	724	143	74 (52%)	498
GER	German Ovarian Cancer Study	Germany: two geographical regions in the states of Baden-Württemberg and Rhineland-Palatinate	Population	183	118 (65%)	907	75	59 (79%)	312

Abbreviation	Name	Location	Case source	All Histologies			High-Grade Serous		
				N	N Deaths (%)	Person-years	N	N Deaths (%)	Person-years
NJO	New Jersey Ovarian Cancer Study	USA: New Jersey (six counties)	Population	169	33 (20%)	316	80	24 (30%)	135
PVD	Danish Pelvic Mass Study	Denmark	Population	162	69 (43%)	438	121	58 (48%)	310
HSK	Dr. Horst Schmidt Klimiken	Germany	Clinic	141	84 (60%)	634	109	71 (65%)	463
RMH	Royal Marsden Hospital Ovarian Cancer Study	UK: London	Hospital	138	59 (43%)	1,000	0	0	0
SRO	Scottish Randomised Trial in Ovarian Cancer	Coordinated through clinical trials unit, Glasgow UK from patients recruited world-wide	Clinical trial	132	67 (51%)	231	94	47 (50%)	169
BAV	Bavarian Ovarian Cancer Cases and Controls	Southeast Germany	Population	85	34 (40%)	245	44	18 (41%)	119
SOC	Southampton Ovarian Cancer Study	United Kingdom, Wessex region	Hospital	74	33 (45%)	157	25	10 (40%)	47
HAW	Hawaii Ovarian Cancer Case-Control Study	USA: Hawaii	Population	60	27 (45%)	266	36	18 (50%)	145
ORE	Oregon Ovarian Cancer Registry	Portland, Oregon	Clinic	52	9 (17%)	123	34	6 (18%)	71
UKR	UK Familial Ovarian Cancer Registry	UK: National	Familial register	47	29 (62%)	254	0	0	0
TOTAL				10,084	4,478 (44%)	37,171	5,248	2,805 (53%)	16,717

All cases are of European ancestry; grade is missing for UCI, RMH, and UKR, thus excluded from high grade serous analysis; person-years indicates person-years at risk accounting for left truncation and right censoring at 10 years.

Table 2

Association between SNPs and Ovarian Cancer Survival

Gene	SNP	Min/Maj	MAF	All Histologies (n=10,084)				High-Grade Serous (n=5,248)			
				Minimally Adjusted		Fully Adjusted		Minimally Adjusted		Fully Adjusted	
				HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
<i>PRKACB</i>	rs12031680	A/C	0.34	1.02 (0.97-1.07)	0.41	1.02 (0.97-1.06)	0.42	1.00 (0.94-1.06)	1.00	1.01 (0.96-1.07)	0.62
	rs12405120	G/A	0.49	1.00 (0.96-1.05)	0.86	1.01 (0.96-1.05)	0.79	1.01 (0.96-1.06)	0.73	1.00 (0.95-1.06)	0.95
	rs1402694	G/A	0.44	0.99 (0.95-1.03)	0.65	0.98 (0.94-1.02)	0.39	0.98 (0.93-1.03)	0.40	1.00 (0.94-1.05)	0.87
	rs12129768	G/A	0.11	0.99 (0.93-1.06)	0.85	1.02 (0.95-1.09)	0.57	0.99 (0.91-1.08)	0.85	1.03 (0.94-1.12)	0.56
<i>VHL</i>	rs265318	C/A	0.11	1.02 (0.96-1.09)	0.55	1.05 (0.99-1.12)	0.12	1.04 (0.96-1.13)	0.31	1.06 (0.98-1.15)	0.18
	rs1678607	A/C	0.12	1.01 (0.95-1.07)	0.79	1.02 (0.96-1.08)	0.57	1.00 (0.92-1.08)	0.99	1.00 (0.92-1.08)	0.95
<i>HGF</i>	rs1800793	A/G	0.20	1.05 (0.99-1.10)	0.09	1.03 (0.98-1.08)	0.26	1.05 (0.99-1.12)	0.10	1.05 (0.98-1.12)	0.17
	rs2214825	A/G	0.23	1.06 (1.01-1.11)	0.03	1.04 (0.99-1.09)	0.10	1.06 (1.00-1.13)	0.05	1.06 (1.00-1.12)	0.07
<i>ABCB1</i>	rs2235023	A/G	0.07	0.98 (0.90-1.06)	0.54	0.98 (0.90-1.06)	0.59	0.98 (0.89-1.08)	0.72	1.00 (0.90-1.10)	0.96
	rs13237132	G/C	0.32	1.01 (0.96-1.05)	0.78	1.01 (0.97-1.06)	0.54	1.02 (0.97-1.08)	0.44	1.01 (0.96-1.07)	0.61
	rs12334183	G/A	0.20	0.99 (0.94-1.04)	0.58	0.98 (0.93-1.03)	0.37	0.96 (0.90-1.02)	0.21	0.95 (0.89-1.01)	0.12
	rs10264990	G/A	0.34	1.00 (0.96-1.04)	0.90	1.00 (0.96-1.05)	0.84	1.02 (0.96-1.08)	0.54	1.01 (0.96-1.07)	0.72
	rs4148732	G/A	0.14	1.01 (0.96-1.08)	0.63	1.01 (0.95-1.07)	0.73	1.03 (0.95-1.11)	0.47	0.99 (0.92-1.08)	0.89
<i>CYP2C8</i>	rs1934954	G/A	0.08	0.97 (0.90-1.05)	0.50	1.00 (0.93-1.08)	0.99	0.97 (0.88-1.07)	0.55	0.98 (0.89-1.08)	0.71
	rs11188148	G/A	0.12	0.99 (0.93-1.06)	0.81	1.00 (0.94-1.07)	0.98	0.97 (0.89-1.06)	0.52	0.98 (0.90-1.07)	0.68
	rs1934983	G/A	0.29	0.99 (0.95-1.04)	0.79	0.99 (0.95-1.04)	0.78	1.00 (0.94-1.06)	0.92	1.00 (0.94-1.06)	0.89
	rs2185571	A/G	0.29	0.99 (0.95-1.04)	0.71	0.99 (0.95-1.04)	0.67	0.99 (0.94-1.06)	0.86	0.99 (0.94-1.05)	0.82
<i>IL18</i>	rs549908	C/A	0.31	1.02 (0.98-1.07)	0.38	1.03 (0.98-1.08)	0.20	0.99 (0.94-1.05)	0.84	1.00 (0.94-1.05)	0.88
	rs744247	C/G	0.10	0.95 (0.89-1.02)	0.17	0.96 (0.89-1.03)	0.23	0.98 (0.90-1.07)	0.68	0.99 (0.91-1.08)	0.88
	rs11214108	A/G	0.12	0.95 (0.89-1.02)	0.15	0.96 (0.90-1.03)	0.23	0.98 (0.90-1.06)	0.62	0.99 (0.92-1.08)	0.90
<i>ERCC2</i>	rs13181	C/A	0.38	0.99 (0.95-1.03)	0.64	0.99 (0.95-1.04)	0.71	0.98 (0.93-1.04)	0.52	0.98 (0.93-1.03)	0.43
	rs1799787	A/G	0.31	1.00 (0.95-1.04)	0.87	0.99 (0.95-1.04)	0.67	0.98 (0.92-1.04)	0.48	0.97 (0.92-1.03)	0.33
	rs238417	C/G	0.42	1.00 (0.96-1.04)	0.99	1.01 (0.97-1.06)	0.49	1.02 (0.97-1.08)	0.43	1.02 (0.96-1.07)	0.54
	rs238416	A/G	0.36	1.01 (0.97-1.05)	0.71	1.02 (0.97-1.06)	0.45	1.02 (0.97-1.08)	0.44	1.02 (0.96-1.07)	0.58

Gene	SNP	Min/Maj	MAF	All Histologies (n=10,084)			High-Grade Serous (n=5,248)				
				Minimally Adjusted HR (95% CI)	p	Fully Adjusted HR (95% CI)	p	Minimally Adjusted HR (95% CI)	p	Fully Adjusted HR (95% CI)	p
	rs238415	C/G	0.40	1.00 (0.96–1.05)	0.86	1.02 (0.97–1.06)	0.46	1.02 (0.97–1.08)	0.43	1.02 (0.96–1.07)	0.56
	rs50872	A/G	0.24	1.01 (0.97–1.07)	0.56	1.02 (0.97–1.07)	0.50	1.06 (1.00–1.13)	0.05	1.07 (1.01–1.14)	0.03
<i>ERCC1</i>	rs735482	C/A	0.14	0.97 (0.91–1.03)	0.32	1.00 (0.94–1.06)	0.91	0.97 (0.90–1.05)	0.42	0.98 (0.91–1.06)	0.56

SNPs are listed by rsid in chromosomal order; Min/Maj, minor/major allele; MAF, minor allele frequency; HR, hazard ratio represent the relative risk of death per-allele (0, 1, 2 copies of the minor allele); 95% CI, 95% confidence interval; P, P-values < 0.05 are bold; fully adjusted Cox model adjusted for age at diagnosis, population substructure principal components, study site, histology (for analyses of all cases only), tumor stage (I, II, III, unknown), tumor grade (grade 1, grade 2, grade 3, grade 4, unknown), and oral contraceptive use (yes, no, unknown); minimally adjusted Cox model adjusted for age at diagnosis, population substructure principal components, and study site.