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Cancer Epidemiology, Biomarkers & Prevention

Null Results in Brief

Prostate Cancer Susceptibility Polymorphism rs2660753 Is Not Associated with Invasive Ovarian Cancer

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Abstract

Background: We previously reported an association between rs2660753, a prostate cancer susceptibility polymorphism, and invasive epithelial ovarian cancer (EOC; OR = 1.2, 95% CI= 1.0–1.4, $P_{\text{trend}} = 0.01$) that showed a stronger association with the serous histological subtype (OR = 1.3, 95% CI = 1.1–1.5, $P_{\text{trend}} = 0.003$).

Methods: We sought to replicate this association in 12 other studies comprising 4,482 cases and 6,894 controls of white non-Hispanic ancestry in the Ovarian Cancer Association Consortium.

Results: No evidence for an association with all cancers or serous cancers was observed in a combined analysis of data from the replication studies (all: OR = 1.0, 95% CI = 0.9–1.1, $P_{\text{trend}} = 0.61$; serous: OR = 1.0, 95% CI = 0.9–1.1, $P_{\text{trend}} = 0.85$) or from the combined analysis of discovery and replication studies (all: OR = 1.0, 95% CI = 1.0–1.1, $P_{\text{trend}} = 0.28$; serous: OR = 1.1, 95% CI = 1.0–1.2, $P_{\text{trend}} = 0.11$). There was no evidence for statistical heterogeneity in ORs across the studies.

Conclusions: Although rs2660753 is a strong prostate cancer susceptibility polymorphism, the association with another hormonally related cancer, invasive EOC, is not supported by this replication study.

Impact: Our findings, based on a larger sample size, emphasize the importance of replicating potentially promising genetic risk associations. *Cancer Epidemiol Biomarkers Prev; 20(5); 1028–31. ©2011 AACR.*

Introduction

Invasive epithelial ovarian cancer (EOC) has a recognized genetic component, but known high penetrance genes, such as *BRCA1* and *BRCA2*, explain less than 10% of EOC risk (1). The remaining unexplained risk is probably caused by a combination of multiple low to moderate penetrance genetic variants (2).

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Table 1. Genotype counts and statistics for rs2667053 among white non-Hispanic ovarian cancer cases (all histologies) and controls in OCAC studies.

Study[a]	Controls[b]			Cases[b]			MAF[b]	P_{HWE}[b]	OR (95% CI)[c]	P_{trend}
	AA	Aa	aa	AA	Aa	aa				
Discovery set										
STA	141	39	1	197	67	3	0.11	0.48	1.3 (0.8–2.0)	0.24
UKO	467	89	5	366	95	5	0.09	0.79	1.3 (1.0–1.8)	0.10
MAL	677	115	2	368	66	4	0.07	0.30	1.2 (0.8–1.6)	0.37
SEA	1020	187	6	645	142	10	0.08	0.57	1.3 (1.0–1.6)	0.03
Summary, discovery	2,305	430	14	1,576	370	22	0.08	0.26	1.2 (1.1–1.4)	0.004
Replication set										
HAW	123	33	2	53	16	0	0.12	1.0	0.9 (0.5–1.7)	0.71
NHS	271	80	6	84	21	3	0.13	0.97	1.0 (0.6–1.5)	0.90
MAY	306	58	5	221	54	0	0.09	0.22	1.1 (0.7–1.6)	0.68
GER	341	83	6	174	31	1	0.11	0.63	0.7 (0.5–1.1)	0.09
UCI	350	93	8	225	44	7	0.12	0.51	0.9 (0.6–1.2)	0.46
USC	376	108	11	297	73	5	0.13	0.32	0.8 (0.6–1.1)	0.24
POL	435	142	18	187	68	2	0.15	0.14	0.9 (0.7–1.2)	0.60
HOP	453	131	10	227	57	7	0.13	0.85	0.9 (0.7–1.3)	0.69
DOV	572	141	6	419	105	7	0.11	0.56	1.1 (0.8–1.4)	0.66
NCO	575	153	9	491	112	2	0.12	0.86	0.8 (0.6–1.0)	0.09
NEC	692	179	18	450	150	13	0.12	0.11	1.2 (1.0–1.5)	0.12
AUS	884	202	14	685	182	9	0.11	0.52	1.1 (0.9–1.4)	0.34
Summary, replication	5,378	1,403	113	3,513	913	56	0.12	0.06	1.0 (0.9–1.1)	0.61
Summary, combined	7,683	1,833	127	5,089	1,283	78	0.11	0.14	1.0 (1.0–1.1)	0.28

[a]STA, GEOCS (Genetic Epidemiology of Ovarian Cancer Study), California; UKO, UKOPS (United Kingdom Ovarian Cancer Population Study), United Kingdom; MAL, MALOVA (Malignant Ovarian Cancer Study), Denmark; SEA, SEARCH (Studies of Epidemiology and Risk Factors in Cancer Heredity Ovarian Cancer Study), England; HAW, HAWAII (Hawaii Ovarian Cancer Study), Hawaii; NHS (Nurses' Health Study); MAY, MAYO (Mayo Clinic Ovarian Cancer Case Control Study), Mid-west; GER, GOCS (German Ovarian Cancer Study), Germany; UCI (the Orange and San Diego Counties California Study), California; USC, LAC-CCOC (Los Angeles County Case-Control Studies of Ovarian Cancer), California; POL (Polish Ovarian Cancer Study), Poland; HOP, HOPE (Hormones and Ovarian Cancer Prediction Study), Pittsburg; DOV, DOVE (Diseases of the Ovary and their Evaluation), Washington; NCO, NCOCS (North Carolina Ovarian Cancer Study), North Carolina; NEC, NECC (New England based Case-Control Study), New England; AUS, AOCS (Australian Ovarian Cancer Study) and ACS (Australian Cancer Study-Ovarian cancer), Australia.
[b]AA, homozygous major allele; Aa, heterozygous; aa, homozygous minor allele; MAF, minor allele frequency in controls; P_{HWE}, P values from the chi-square test assessing deviation of genotype frequencies among controls from those expected under HWE.
[c]OR and 95% CI adjusted for age (<40, 40–49, 50–59, 60–69, and $\geq$70 years) in study-specific analyses and for age and study in summary analyses.

We previously reported an association between rs2660753 on chromosome 3p12 and invasive EOC (OR = 1.2, 95% CI = 1.0–1.4, P_{trend} = 0.01, 1,973 cases/3,419 controls) that showed a stronger association with the serous histological subtype (OR = 1.3, 95% CI = 1.1–1.5, P_{trend} = 0.003, 901 cases/3,303 controls; ref. 3). rs2660753 is a prostate cancer susceptibility polymorphism identified from a genome-wide association study of Europeans (4) and replicated in independent populations of European (5) and non-European (6) ancestry. The nearest genes (70–198 kb away) to rs2660753, *VGLL3*, *CHMP2B*, and *Pit-1/POU1F1*, encode proteins with potential roles in tumorigenesis (3) and the 3p12.3-pcen region has been identified as a candidate tumor suppressor gene locus (7).

In this investigation, we sought to replicate the association between rs2660753 and invasive EOC in a larger sample of 12 additional studies from the international Ovarian Cancer Association Consortium (OCAC) comprising 4,482 cases and 6,894 controls.

Materials and Methods

Study population

Sixteen ovarian cancer case-control studies contributed data to this analysis. Four of the studies were included in

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our initial report (discovery set; ref. 3) and 12 were included in follow up genotyping (replication set). Details of each of the studies have been published previously (8). Each study received ethics committee approval and all study subjects provided informed written consent. Pathologic and questionnaire data included tumor behavior, histology, age at diagnosis (or comparable date for controls), family history of breast or ovarian cancer and ethnicity/race.

Genotyping

Genotyping was carried out by using the 5′ nuclease Taqman allelic discrimination assay (Applied Biosystems), except the Australian Ovarian Cancer Study and the Australian Cancer Study-Ovarian Cancer that used the Sequenom iPLEX protocol (Sequenom Inc.), and by using similar conditions as the original study (3). Consistency across laboratories was assessed by genotyping a common set of 95 DNAs (90 CEPH trios and 5 duplicate samples) with 98% or more concordance in genotype calls. Details of OCAC's criteria for acceptable genotyping have been described previously (8).

Statistical analysis

Analyses were restricted to white non-Hispanic subjects. We excluded cases with non-EOC and borderline tumors. Genotypes of participants were used to estimate allele frequencies and departure from Hardy–Weinberg equilibrium (HWE) was assessed in controls by by using a chi-squared test. Single nucleotide polymorphism associations were evaluated by using unconditional logistic regression under ordinal and codominant genetic models to estimate ORs and 95% CIs. Statistical models were adjusted for age (<40, 40–49, 50–59, 60—69, and ≥70 years) in study-specific analyses and for age and study in combined analyses. Prior to pooling, tests of heterogeneity in ORs across studies were conducted by using the likelihood ratio test comparing models with and without a product term for genotype and study. Statistical tests were implemented with SAS software (SAS Institute).

Results

Genotype distributions for controls in all the studies were consistent with HWE (Table 1). No evidence for an association was observed at rs2667053 in the replication set (OR = 1.0, 95% CI = 0.9–1.1, $P_{\text{trend}} = 0.61$ for all 4,482 cancers and OR = 1.0, 95% CI = 0.9–1.1, $P_{\text{trend}} = 0.85$ for 2,515 serous cancers) or in the combined discovery and replication sets (OR = 1.0, 95% CI = 1.0–1.1, $P_{\text{trend}} = 0.28$ for all 6,450 cancers and OR = 1.1, 95% CI = 1.0–1.2, P_{trend} = 0.11 for 3,563 serous cancers) under the ordinal model (Fig. 1). No statistically significant associations were observed under the codominant model (data not shown). There was no statistical heterogeneity in ORs for all ovarian cancers or serous cancers when the discovery and replication sets were combined ($P_{\text{heterogeneity}} > 0.10$).

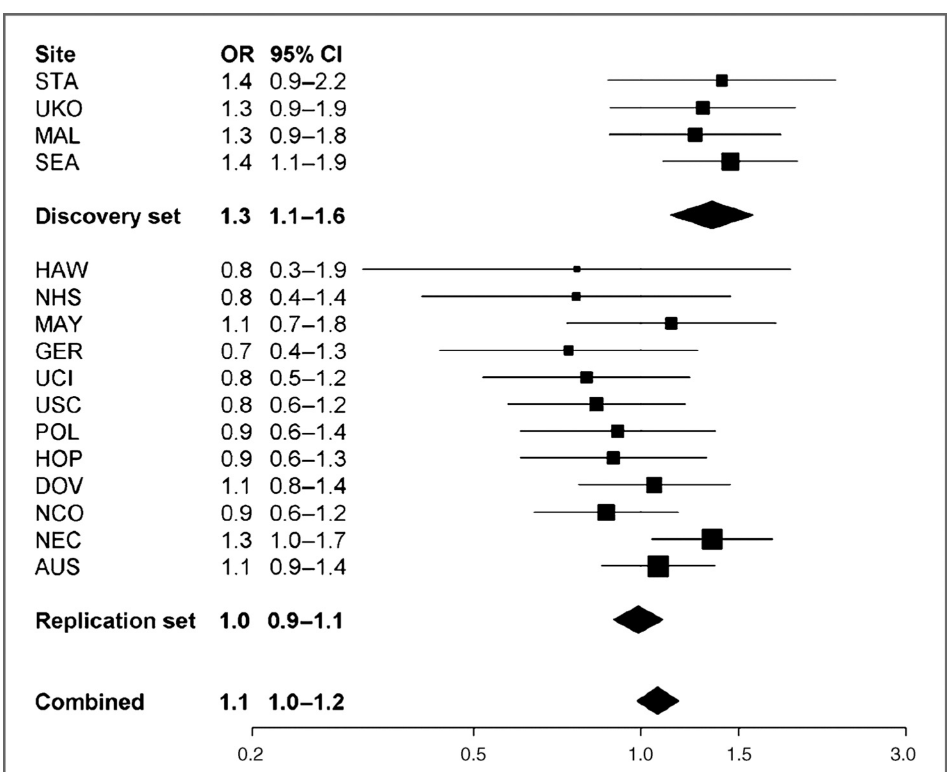

Figure 1. Funnel plot of study-specific and summary OR and 95% CI for the association between rs2660753 and serous ovarian cancer among white non-Hispanic subjects in OCAC studies by using the ordinal genetic risk model. Squares (■) indicate study-specific OR; the size of squares is proportional to study-specific sample size; the width of lines (–) indicate the study-specific 95% CI; diamonds (♦) indicate summary OR; and the width of diamonds indicate summary 95% CI. Refer to footnote of Table 1 for study nomenclature.

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Analyses stratified by family history of breast or ovarian cancer in first-degree relatives did not show statistically significant associations for all cancers (OR = 0.9, P = 0.67, 481 cases with family history and OR = 1.0, P = 0.81, 1,576 cases without family history) or for serous cancers (OR = 1.1, P = 0.70, 297 cases with family history and OR = 1.0, P = 0.93, 928 cases without family history).

Discussion

Our findings, based on 12 studies participating in the international OCAC, do not support an association between rs2667053 and invasive EOC overall or for the serous histological type. We used a larger sample size and applied similar assays and stringent quality control criteria to genotype data as in the original study. In the current study, the power to detect an OR of 1.2, as previously reported (3), with minor allele frequency of 0.12 and Type 1 error of 0.01 was 87%. To detect smaller effects, as observed for serous cancers in the current study, a much larger sample is required. There was no evidence of statistical heterogeneity in ORs across studies or of effect modification by family history. Although variant rs2667053 is a strong candidate for prostate cancer susceptibility, it does not seem to be a candidate risk factor for ovarian cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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