Shared genetics underlying epidemiological association between endometriosis and ovarian cancer

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Supplementary Table 1. Description of individual OCAC studies and case-control sample size.

Study abbreviation	Study name	Study location	N_controls*	N_invasive cases (by histotypes)*				
				All invasive	Serous	Mucinous	Endometrioid	Clear cell
AUS	Australian Ovarian Cancer Study & Australian Cancer Study (Ovarian Cancer)	Australia	977	880	552	42	106	52
BAV	Bavarian Ovarian Cancer Cases and Controls	Germany	143	93	56	8	13	6
BEL	Belgium Ovarian Cancer Study	Belgium	1349	274	194	23	22	23
DOV	Diseases of the Ovary and their Evaluation	USA	1487	904	526	26	148	65
GER	Germany Ovarian Cancer Study	Germany	413	189	95	21	21	6
HAW	Hawaii Ovarian Cancer Study	USA	157	60	38	3	12	5
HJO	Hannover-Jena Ovarian Cancer Study	Germany	273	266	140	9	26	4
HMO	Hannover-Minsk Ovarian Cancer Study	Germany	138	142	50	7	12	1
HOC	Helsinki Ovarian Cancer Study	Finland	447	221	113	45	28	13
HOP	Hormones and Ovarian Cancer Prediction	USA	1464	654	377	30	84	42
MAL	Danish Malignant Ovarian Tumor Study	Denmark	828	440	272	42	54	33
MAY	Mayo Clinic Ovarian Cancer Case Control Study	USA	10	10	9	0	1	0
MCC	Melbourne Collaborative Cohort Study	Australia	66	63	34	7	7	6
MDA	MD Anderson Ovarian Cancer Study	USA	384	373	190	27	28	4
MSK	Memorial Sloan Kettering Cancer Center	USA	593	467	382		20	18
NCO	North Carolina Ovarian Cancer Study	USA	172	269	147	18	35	24
NEC	New England Case-Control Study	USA	980	634	371	41	140	33
NHS	Nurses' Health Study I and II	USA	425	127	68	7	14	6
NJO	New Jersey Ovarian Cancer Study	USA	181	169	100	7	27	20
NOR	University of Bergen, Haukeland University Hospital, Norway	Norway	371	237	135	15	27	11
NTH	Nijmegen Ovarian Cancer Study	Netherlands	323	255	116	33	64	20
OVA	Ovarian Cancer in Alberta and British Columbia	Canada	748	631	344	26	103	57

POC	Polish Ovarian Cancer Study	Poland	417	422	199	33	39	9
POL	Polish Ovarian cancer Case Control Study (NCI)	Poland	186	42	21	4	10	2
SEA	UK Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH) Ovarian Cancer Study	UK	6023	300	173	43	29	28
STA	Family Registry for Ovarian Cancer AND Genetic Epidemiology of Ovarian Cancer	USA	313	251	154	16	32	20
TOR	Familial Ovarian Tumor Study	Canada	74	21	8	1	7	2
UCI	UC Irvine Ovarian Cancer Study	USA	367	277	166	19	48	23
UKO	UK Ovarian Cancer Population Study	UK	1103	503	219	57	94	36
SOC	Southampton Ovarian Cancer Study	UK						
USC	Los Angeles County Case-Control Studies of Ovarian Cancer	USA	1047	689	447	44	79	35
WOC	Warsaw Ovarian Cancer Study	Poland	204	202	132	8	20	17
TOTAL			**21663**	**10065**	**5828**	**662**	**1350**	**621**

*: All the subjects are of European Ancestry.

Supplementary Table 2. Control-control contrast study using iCOGS controls.

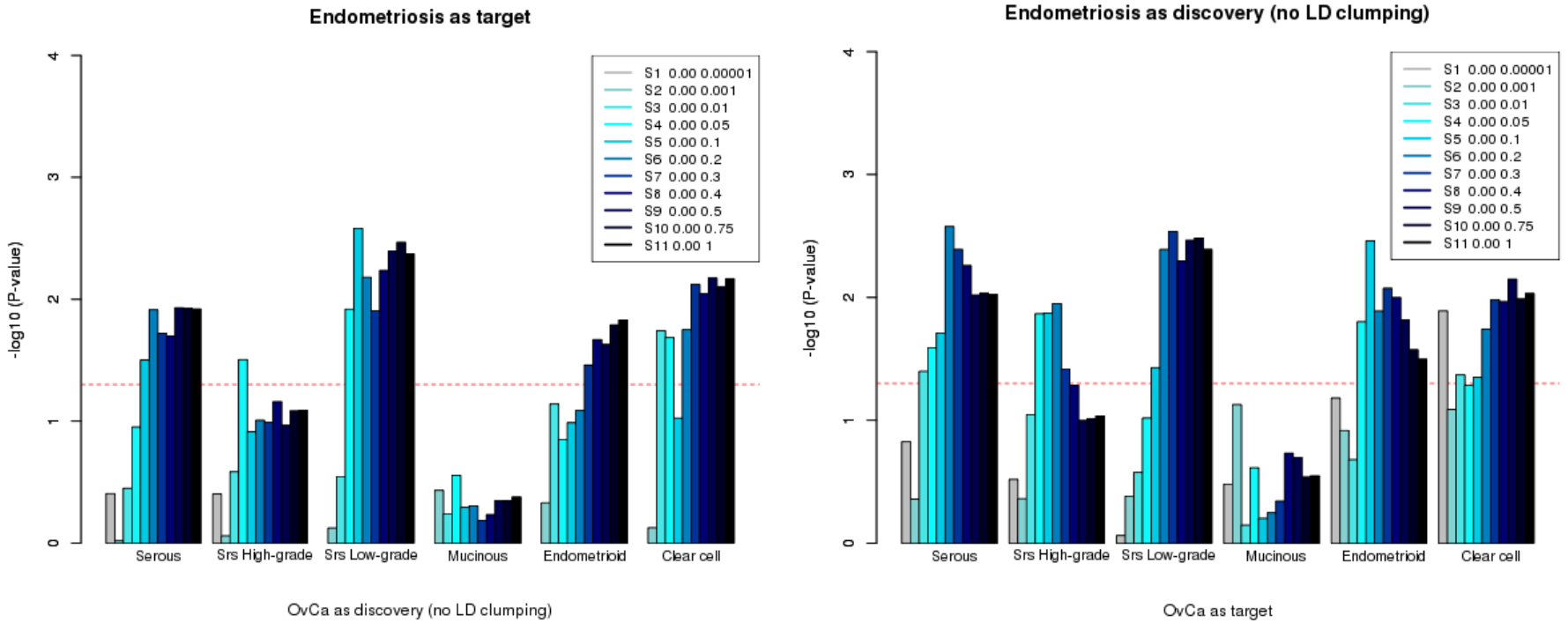
	Sample size		**array heritability**	
	Ncase	**Ncont**	**h^2_g (%)**	**se (%)**
Pseudo case-cont set 1	2694	2694	2.1	2.3
Pseudo case-cont set 2	2694	2694	0.4	2.4
Pseudo case-cont set 3	2694	2694	0.6	2.3
Pseudo case-cont set 4	2694	2805	2.8	2.4

Supplementary Table 3. Sensitivity checks using different genetic relatedness threshold and disease prevalence for ovarian cancer.

	relatedness threshold	N_Case	N_Control	Excluded N	K	h^2_g (%)	s.e.(%)
all EOC		11738	21663				
	relatedness < 0.1	11677	21242	482	0.01	**4.93**	**0.53**
	relatedness < 0.05	10868	19931	2602	**0.01**	**4.98**	**0.56**
all invasive EOC		10065	21663				
	relatedness < 0.1	10014	21242	472	0.01	**5.72**	**0.59**
	relatedness < 0.05	9316	19931	2481	0.01	**5.83**	**0.63**
	relatedness < 0.05	9316	19931	2009	**0.009**	**5.58**	**0.58**

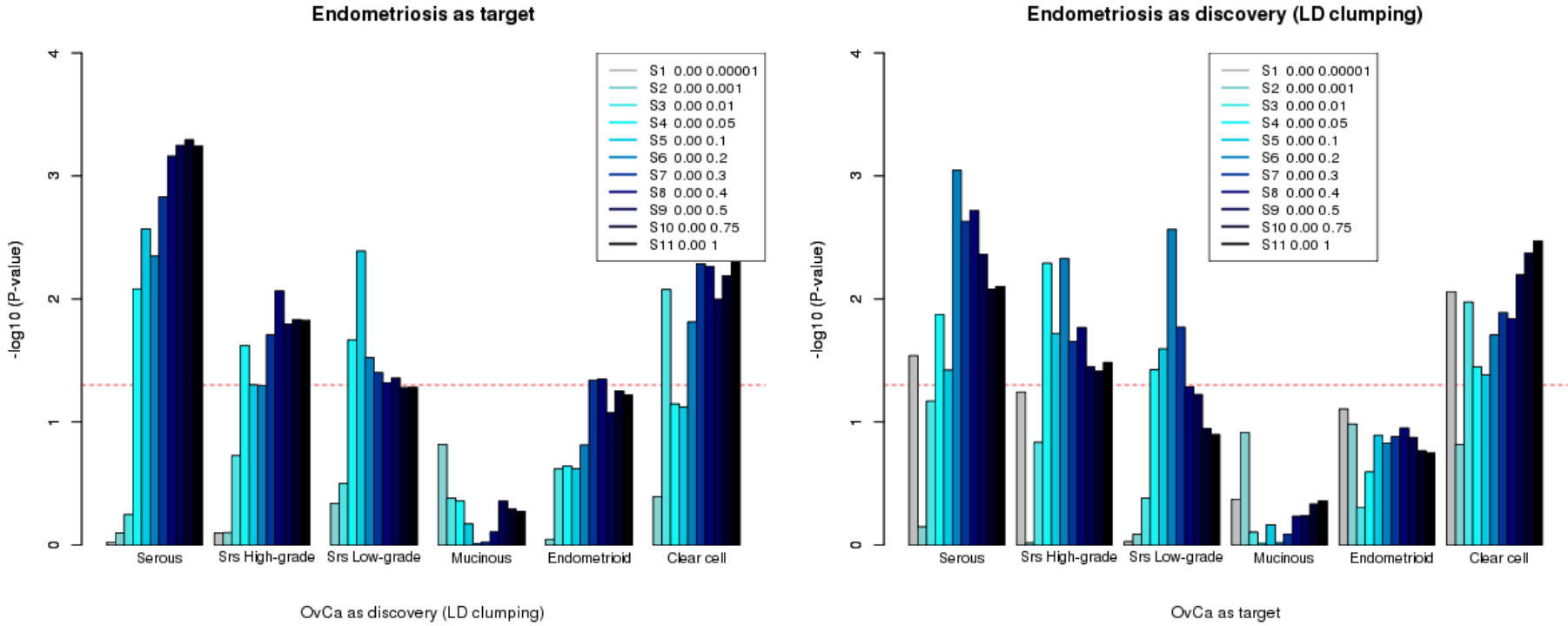
Relatedness threshold: cutoffs that were applied to select individuals with pair-wise genetic relatedness below certain values (here compare the results of 0.1 and 0.05); N_Case, N_Control, Excluded N: the case and control sample size in the analysis, and the numbers of samples that were excluded due to the corresponding relatedness threshold; K: disease prevalence of ovarian cancer (we used lifetime risk of 0.1 and 0.009 for disease prevalence of all EOC and all invasive EOC respectively). h^2_g: array heritability estimated using ovarian cancer iCOGS data, while adjusting for ten principal components and study sites (the estimates with P<0.05 are in bold).

Supplementary Figure 1. Restricting the relatedness threshold at 0.1 between discovery and replication set using genetic risk prediction approach (no LD clumping).



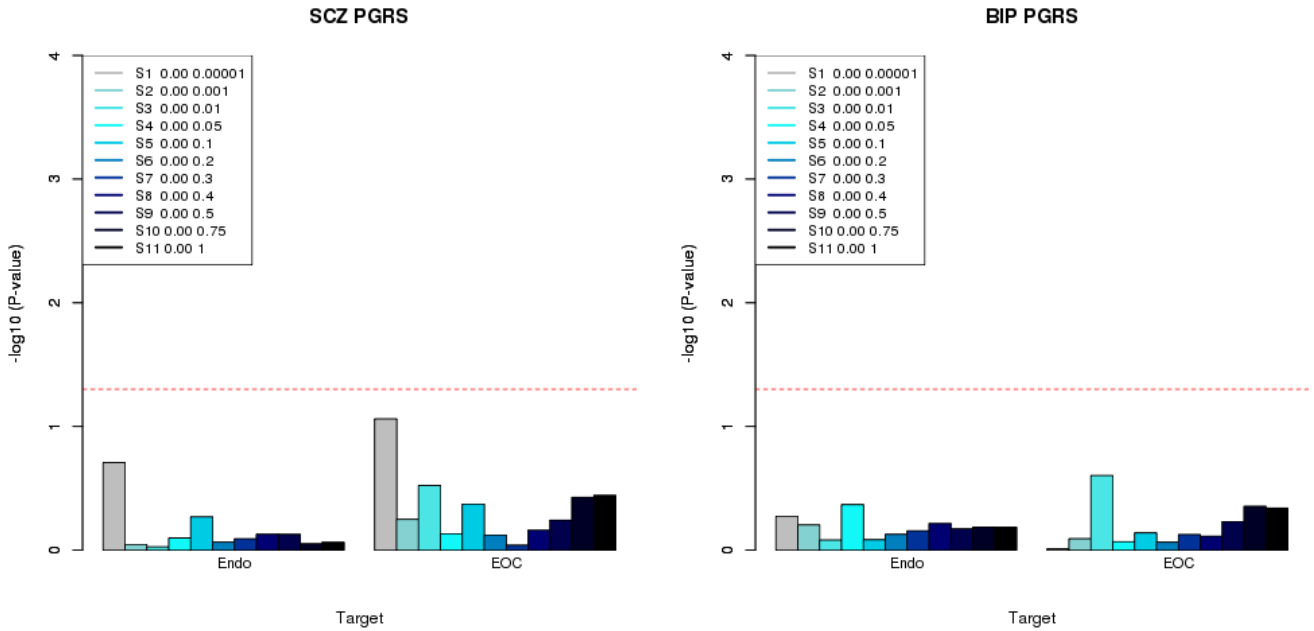
The left figure showed the association (y-axis: $-\log_{10}P$) of endometriosis (target) with genetic risk scores that were calculated from ovarian cancer histotypes (discovery), while the right figure showed the association of ovarian cancer histotypes (target) with genetic risk scores calculated from endometriosis (discovery). The colour coding denotes the P-value bins used to select SNPs from the discovery set. The dashed red line marks the significance threshold (P=0.05). The genetic risk scores were calculated from all overlapping SNPs without LD clumping.

Supplementary Figure 2. Restricting genetic risk scores calculated from SNPs with low LD (genetic relatedness threshold of 0.85 between discovery and target sets)



The left figure showed the association (y-axis: $-\log_{10}P$) of endometriosis (target) with genetic risk scores that were calculated from ovarian cancer histotypes (discovery), while the right figure showed the association of ovarian cancer subtypes (target) with genetic risk scores calculated from endometriosis (discovery). The colour coding denotes the P-value bins used to select SNPs from the discovery set. The dashed red line marks the significance threshold (P=0.05). The genetic risk scores were calculated from all overlapping SNPs after LD clumping (clumping threshold: LD r^2=0.2 and distance of 1Mb with the index SNP).

Supplementary Figure 3. Negative control experiments using PGC data



The left figure showed the association (y-axis: $-\log_{10}P$) of endometriosis ('Endo', Australian set only) and invasive EOC with genetic risk scores that were calculated from the PGC schizophrenia set ('SCZ'), while the right figure showed the association of endometriosis (Australian set only) and invasive EOC with genetic risk scores calculated from PGC bipolar disorder set ('BIP'). The colour coding denotes the P-value bins used to select SNPs from the discovery set. The dashed red line marks the significance threshold (P=0.05). The genetic risk scores were calculated from all overlapping SNPs without LD clumping.