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ORIGINAL RESEARCH

Genetic association between HER2 and ESR2 polymorphisms and ovarian cancer: a meta-analysis

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Objective: The estrogen receptor (ER) and the human epidermal growth factor receptor 2 (HER2) each play an important role in female cancers. This study aimed to investigate the genetic association between three common single nucleotide polymorphisms (SNPs) and the risk of ovarian cancer. The SNPs investigated in this study were ESR2 rs1271572 and rs3020450 and HER2 rs1801200.

Methods: In this study, databases were electronically searched in a meta-analysis. Databases used were PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang and Cochrane library. Case–control studies on the association between ESR2 and HER2 polymorphisms were selected according to inclusion and exclusion standard. Articles were evaluated for quality, and data were extracted.

Results: A total of 13 articles with 5,461 cases and 7,603 controls were included in this meta-analysis. The recessive model of ESR2 rs1271572 was shown to be significantly associated with the risk of ovarian cancer ($p = 0.008$, odds ratio [OR] [95% confidence interval {CI}] = 1.13 [1.03, 1.24]), and this significant association still existed in a subgroup analysis stratified by ethnicity (Asian: $p = 0.04$, OR [95% CI] = 1.92 [1.04, 3.56]; Caucasian: $p = 0.02$, OR [95% CI] = 1.12 [1.02, 1.23]). In addition, the distribution of the dominant model of ESR2 rs3020450 was significantly different in the total group ($p = 0.02$, OR [95% CI] = 0.71 [0.53, 0.95]) and the Caucasian subgroup ($p = 0.02$, OR [95% CI] = 0.67 [0.48, 0.94]). Furthermore, no significant association between allelic, dominant, codominant and recessive models of HER2 rs1801200 (V655I) and ovarian cancer was found ($p > 0.05$).

Conclusion: The recessive model of ESR2 rs1271572 and the dominant model of ESR2 rs3020450 might be susceptible factors for ovarian cancer.

Keywords: ESR2, ovarian cancer, HER2, meta-analysis

Introduction

Ovarian cancer is one of the most lethal female cancers in women with 15%–25% 5-year overall survival rates.[1] Family and twin studies suggested that genetic factors are one of the important causes of ovarian cancer.[2] The most well-documented inherited factors are the BRCA1 and BRCA12 genes.[3,4] However, these two genes account for <40% of the established ovarian cancer risk, indicating that there are other yet unexplained genetic factors contributing to ovarian cancer. It is widely accepted that tumor formation is a multistep process accompanied by an accumulation of multiple genetic alterations. Recently, a number of genes referring to DNA repair (BRCA1-interacting protein 1 [BRIP1][5] and FANCJ[6]), etinoblastoma-1 (RB1),[7] estrogen receptor (ER) genes (ESR1 and ESR2[8,9]) and vitamin D receptor (VDR) genes[10] have been reported to be associated with the susceptibility of ovarian cancer.

Research has shown that increasing levels of estrogen may increase the risk of ovarian cancer by binding to the ER-α, encoded by ESR1. The target of action enhances

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cell proliferation, apoptosis and migration.[11,12] However, the specific functions of the ER-β, encoded by ESR2 in cancer, are not yet clear. There is evidence that ESR2 mRNA was highly expressed in normal ovarian tissue when compared to tumor tissue,[13,14] which indicated a tumor suppressive role of ER-β in ovary. Human epidermal growth factor receptor 2 (HER2), a member of the HER receptor tyrosine kinase family, is a well-known susceptible factor in breast cancer.[15,16] HER2 was reported to interact with the ER and regulate tumor cell proliferation and survival.[17] Overexpression of HER2 was observed in up to 20%–30% of breast and ovarian cancers.[18] These data suggest an important role of ESR2 and HER2 in the susceptibility of ovarian cancer.

In recent years, a multitude of single nucleotide polymorphisms (SNPs) both in HER2 and ESR2 genes have been reported to be associated with the risk of ovarian cancer. In the human HER2 gene, a common SNP called rs1801200 (V655I) was identified in the transmembrane coding region at codon 655 that encodes either isoleucine (ATC) or valine (GTC).[19] Four studies investigated the genetic association between this SNP and the risk of ovarian cancer.[20–23] In addition, only two studies reported that Val/Val homozygosity was significantly associated with ovarian cancer.[21,23] For ESR2, rs1271572 was suggested to be an ovarian cancer susceptibility marker in Japanese,[24] Australian,[9] and Caucasian (Hawaii) patients.[24] However, these results cannot be replicated in German, American, Polish, Danish and British patients.[9,26,27]

Owing to the inconsistent and inconclusive results found in the literature, it is the aim of this study to get a more precise and comprehensive understanding of the association between polymorphisms in the ESR2 and HER2 genes and ovarian cancer using a meta-analysis.

Methods

Literature search strategy

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[28] Two authors searched the databases PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang and Cochrane Library using the following terms: "Estrogen receptor 2", "ESR2", "Human epidermal growth factor receptor 2", "HER2", "polymorphism", "single nucleotide polymorphism", "SNP", "ovarian cancer" and "ovarian carcinoma" up to July 1, 2017. There was no limitation in language. All the results from the databases were screened. All available results from the database were screened starting with the title. Then, the abstracts were screened in the articles where the title fulfilled the criteria. Other potentially relevant articles were identified by cross-references within eligible studies.

Inclusion/exclusion criteria

The inclusion criteria were as follows: 1) case–control design; 2) regarding ESR2 or HER2 polymorphisms and ovarian cancer risk and 3) included allelic or genotype frequencies in cases and controls.

The exclusion criteria were as follows: 1) not regarding ESR2 or HER2 polymorphisms and ovarian cancer risk; 2) duplicate publications; 3) case reports, letters, commentaries, meeting records or review articles and 4) insufficient published data for calculating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

The following information from each study was summarized: first author, year of publication, ethnicity, number of cases and controls, mean age of cases and controls, gender component in cases and controls, genotyping method, sample source, SNPs and evidence of Hardy–Weinberg equilibrium (HWE) in the control group by L. T. and Y. W. Any disagreements were resolved by the third author (J. X.).

Quality assessment

The quality of the research found in the articles was accessed independently according to the Newcastle–Ottawa Scale (NOS) by J. L. and M. B.[28] A quality score was calculated from group selection and comparability and assessment of outcome or exposure. Any discrepancies in the assessment were resolved by the third author (L. T.).

Statistical analysis

Crude OR and 95% CI were calculated to test the strength of associations between the allelic, dominant, codominant and recessive models of ESR2 or HER2 polymorphisms and ovarian cancer susceptibility. The significance of the pooled OR was determined by the *Z*-test. Heterogeneity was conducted using Cochran's Q test and I^2 statistics. I^2 values of >50% indicated heterogeneity among studies. A random effects model was applied if heterogeneity was observed ($I^2 > 50\%$). Otherwise, the fixed effects model was used. Sensitivity analysis was performed to assess the effects of individual studies on pooled results and the stability of the results. Publication bias was accessed using funnel plots by the methods of Begg's test

and Egger's test. A value of $p < 0.05$ was considered to be statistically significant. The statistical tests were performed using the Stata software (version 12.0; StataCorp LP, College Station, TX, USA) and RevMan software (version 5.1; The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Study characteristics

A total of 333 articles for HER2 and 1,152 articles for ESR2 were identified through the literature search. After reviewing the titles, abstracts and full-texts, finally four eligible articles for HER2[20–23] and three studies with nine populations for ESR2[9,24,26,27] were included in the present study. Each population was treated as an individual study. Thus, nine studies were collected for ESR2 in this meta-analysis. The detailed steps of our literature search are shown in Figure 1. The information for the selected studies is summarized in Table 1. Four studies with 348 cases and 540 controls confirmed the association between HER2 rs1801200 (V655I) and ovarian cancer. Nine studies with 5,109 cases and 6,893 controls confirmed the association between ESR rs1271572 and rs3020450 and ovarian cancer.

Meta-analysis results

Significant association was detected between ESR2 rs1271572 and ovarian cancer in the recessive model. The genetic association between the recessive model rs1271572 and ovarian cancer was found in both Asian and Caucasian subgroups (Asian: $p = 0.04$, OR [95% CI] = 1.92 [1.04, 3.56]; Caucasian: $p = 0.02$, OR [95% CI] = 1.12 [1.02, 1.23]) but not in the total group ($p > 0.05$). No significant association was detected between allelic, codominant and dominant models of ESR2 rs1271572 and ovarian cancer ($p > 0.05$; Table 2 and Figure 2).

For rs3020450, a significant difference was observed between the frequency of the dominant model ($p = 0.02$, OR [95% CI] = 0.71 [0.53, 0.95]) and ovarian cancer. However, the significant difference was only found in Caucasian but not in Asian (Asian: $p = 0.52$, OR [95% CI] = 0.84 [0.49, 1.44]; Caucasian: $p = 0.02$, OR [95% CI] = 0.67 [0.48, 0.94]). No significant association was detected between rs3020450 and ovarian cancer in allelic, codominant and recessive models ($p > 0.05$; Table 2 and Figure 3). Furthermore, no association was detected between allelic, codominant, recessive and dominant models of HER2 rs1801200 (V655I) and the risk of ovarian cancer ($p > 0.05$; Table 2 and Figure 4).

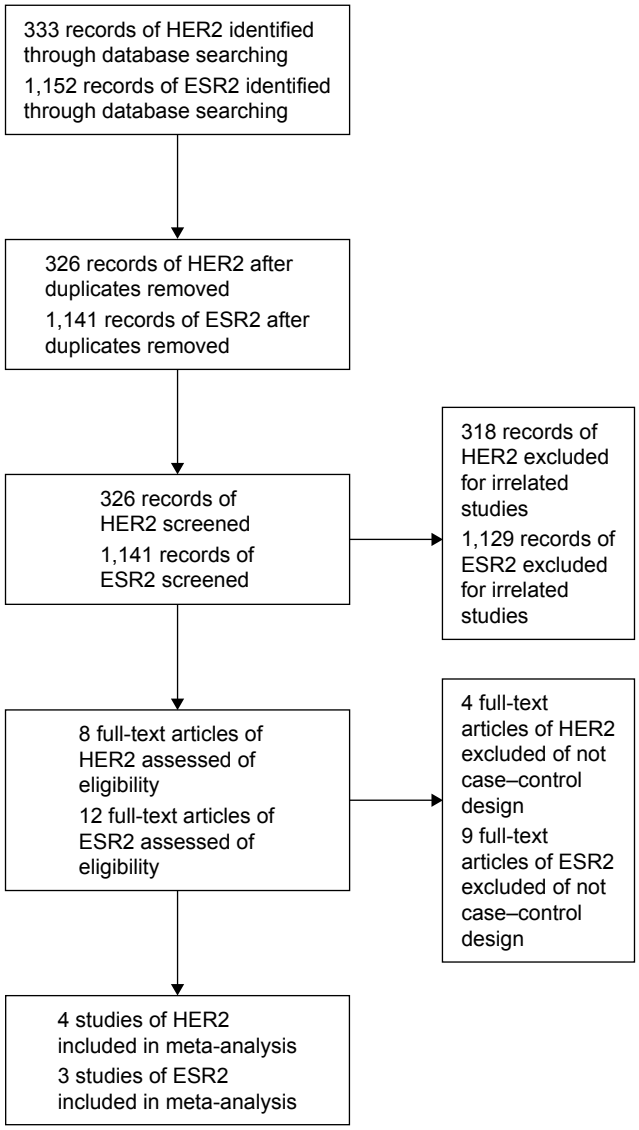


Figure 1 PRISMA flow chart regarding inclusion and exclusion criteria of studies.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Sources of heterogeneity

Significant heterogeneities were detected in the allelic model of rs1271572 in the total group and the Caucasian subgroup (total group: $I^2 = 89\%$; Caucasian subgroup: $I^2 = 89\%$). The heterogeneity in this SNP was contributed primarily by an American population.[9] Removal of this study from the meta-analysis gave 0% ($p = 0.63$) heterogeneity and showed that it had the highest effect on the association between the allelic model of rs1271572 and ovarian cancer. In addition, significant heterogeneities were also found in the allelic, dominant, codominant and recessive models of HER rs1801200 (V655I) in the total group (allelic: $I^2 = 93\%$, dominant: $I^2 = 69\%$, codominant: $I^2 = 66$,

Table 1 Main characteristic of the studies for polymorphisms included in meta-analysis

Gene	Study	Year	Ethnicity	Case	Control	Age (case/control)	Genotype method	Sample source	SNPs	HWE in controls	Results	QA
HER2	Mojtahedi et al[20]	2013	Iranish	107	130	45.9 ± 16.1/ 46.6 ± 15.5	PCR-RFLP	Blood	rs1801200 (Ile655Val)	$p > 0.05$	$p > 0.05$	9
	Puputti et al[21]	2006	Finnish	27	22	NA	PCR sequencing	Tissue	rs1801200 (Ile655Val)	$p > 0.05$	$p < 0.05$	7
	Shanmughapriya et al[23]	2013	Indian	72	288	48.31 ± 2.28/ 48.03 ± 2.38	PCR-RFLP	Blood	rs1801200 (Ile655Val)	$p > 0.05$	$p < 0.001$	9
	Watrowski et al[22]	2016	Austrian	142	100	54.2 ± 13.5/NA	Pyrosequencing	Blood	rs1801200 (Ile655Val)	$p > 0.05$	$p > 0.05$	8
ESR2	Lurie et al[24]	2009	Caucasian	70	143	NA	TaqMan	Blood	rs1271572; rs3020450; rs1256030; rs1256031	$p > 0.05$	$p < 0.05$	7
	Lurie et al[10]	2009	Japanese	93	168	NA	TaqMan	Blood	rs1271572; rs3020450; rs1256030; rs1256031	$p > 0.05$	$p < 0.05$	7
	Schüler et al[25]	2014	Caucasian	184	170	NA	Allele-specific PCR	Blood	rs3020450; rs3020449; rs2987983	$p > 0.05$	$p > 0.05$	7
	Lurie et al[9]	2011	Australian	1,051	1,148	NA	TaqMan	Blood	rs1271572	$p < 0.05$	$p < 0.05$	7
	Lurie et al[9]	2011	Germany	204	229	NA	TaqMan	Blood	rs1271572	$p > 0.05$	$p > 0.05$	7
	Lurie et al[9]	2011	American	1,228	1,591	NA	TaqMan	Blood	rs1271572	$p > 0.05$	$p > 0.05$	7
	Lurie et al[9]	2011	Denmark	348	893	NA	TaqMan	Blood	rs1271572	$p > 0.05$	$p > 0.05$	7
	Lurie et al[9]	2011	Poznan	545	525	NA	TaqMan	Blood	rs1271572	$p > 0.05$	$p > 0.05$	7
	Lurie et al[9]	2011	British	1,570	2,196	NA	TaqMan	Blood	rs1271572	$p > 0.05$	$p > 0.05$	7

Abbreviations: SNP, single nucleotide polymorphism; HWE, Hardy–Weinberg equilibrium; QA, quality assessment; HER2, human epidermal growth factor receptor 2; PCR-RFLP, restriction fragment length polymorphism polymerase chain reaction; NA, not available; PCR, polymerase chain reaction; ESR2, estrogen receptor 2.

Table 2 The results of meta-analysis for ESR2 rs1271572, rs3020450 and HER2 rs1801200 (Val655Ile) and risk of ovarian cancer

Gene	SNPs (minor allele)	Genetic model	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
				Case	Control	OR (95% CI)	*p*-value		*p*-value	I^2 (%)
ESR2	rs1271572 (T)	Allelic (T)								
		Total	8	10,218	13,786	1.02 (0.86, 1.21)	0.79	R	< 0.00001	89
		Asian	1	186	336	1.41 (0.98, 2.03)	0.06	–	–	–
		Caucasian	7	10,032	13,450	0.99 (0.83, 1.18)	0.91	R	< 0.00001	89
		Dominant (TT + GT/GG)								
		Total	8	5,109	6,893	1.01 (0.93, 1.09)	0.79	F	0.93	0
		Asian	1	93	168	1.32 (0.77, 2.28)	0.31	–	–	–
		Caucasian	7	5,016	6,725	1.00 (0.93, 1.09)	0.91	F	0.96	0
		Recessive (TT/GT + TT)								
		Total	8	5,109	6,893	1.13 (1.03, 1.24)	0.008	F	0.24	24
		Asian	1	93	168	1.92 (1.04, 3.56)	0.04	–	–	–
		Caucasian	7	5,016	6,725	1.12 (1.02, 1.23)	0.02	F	0.39	4
		Codominant (TT/GG)								
		Total	8	2,610	3,380	1.10 (0.99, 1.23)	0.06	F	0.83	0
		Asian	1	63	88	1.49 (0.75, 2.93)	0.25	–	–	–
		Caucasian	7	2,547	3,292	1.10 (0.99, 1.22)	0.09	F	0.84	0
	rs3020450 (A)	Allelic (A)								
		Total	3	694	962	0.87 (0.70, 1.09)	0.23	F	0.29	19
		Asian	1	186	336	1.06 (0.67, 1.66)	0.81	–	–	–
		Caucasian	2	508	626	0.83 (0.64, 1.06)	0.14	F	0.21	37
		Dominant (AA + AG/GG)								
		Total	3	347	481	0.71 (0.53, 0.95)	0.02	F	0.34	8
		Asian	1	93	168	0.84 (0.49, 1.44)	0.52	–	–	–
		Caucasian	2	254	313	0.67 (0.48, 0.94)	0.02	F	0.19	41
		Recessive (AA/AG + GG)								
		Total	3	347	481	1.32 (0.84, 2.08)	0.23	F	0.23	32
		Asian	1	93	168	3.07 (0.97, 9.67)	0.06	–	–	–
		Caucasian	2	254	313	1.12 (0.68, 1.85)	0.65	F	0.48	0
		Codominant (AA/GG)								
		Total	3	235	298	1.21 (0.75, 1.95)	0.43	F	0.25	29
		Asian	1	73	118	2.78 (0.87, 8.86)	0.08	–	–	–
		Caucasian	2	162	180	1.02 (0.60, 1.72)	0.94	F	0.52	0
HER2	rs1801200 (V655I) (V)	Allelic (V)								
		Total	4	696	1,080	1.03 (0.37, 2.83)	0.96	R	< 0.00001	93
		Asian	2	358	836	1.70 (0.49, 5.87)	0.40	R	0.0005	92
		Caucasian	2	338	244	0.58 (0.22, 1.50)	0.26	R	0.05	73
		Dominant (VV + VI/II)								
		Total	4	348	540	1.15 (0.64, 2.07)	0.64	R	0.02	69
		Asian	2	179	418	1.55 (0.59, 4.09)	0.38	R	0.02	82
		Caucasian	2	169	122	0.83 (0.51, 1.34)	0.45	F	0.68	0
		Recessive (VV/VI + II)								
		Total	4	348	540	3.67 (0.83, 16.36)	0.09	R	0.04	63
		Asian	2	179	418	2.79 (0.07, 105.02)	0.58	R	0.006	87
		Caucasian	2	169	122	3.36 (1.02, 11.03)	0.05	F	0.65	0
		Codominant (VV/II)								
		Total	4	263	417	3.44 (0.72, 16.50)	0.12	R	0.03	66
		Asian	2	139	341	2.91 (0.07, 122.22)	0.58	R	0.005	88
		Caucasian	2	124	76	2.93 (0.88, 9.72)	0.08	F	0.74	0

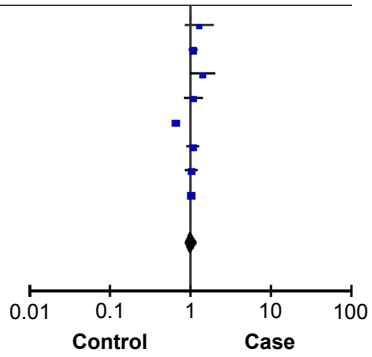
Abbreviations: ESR2, estrogen receptor 2; HER2, human epidermal growth factor receptor 2; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; R, random model; F, fixed model; V, val; I, ile.

recessive: $I^2 = 63\%$), Asian subgroup (allelic: $I^2 = 92\%$, dominant: $I^2 = 82\%$, codominant: $I^2 = 88$, recessive: $I^2 = 87\%$) and Caucasian subgroup (allelic: $I^2 = 73\%$), with the exception of the dominant, codominant and recessive models in the Caucasian subgroup. The heterogeneity in this variant was contributed primarily by two studies.[22,23] Removal of these two studies from the meta-analysis gave 0% ($p = 0.80$) heterogeneity and showed that they had the highest effect

A

Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Lurie et al[24] (2009)	68	140	121	286	8.3	1.29 (0.86, 1.93)
Lurie et al[9] (2011)	964	2,102	1,015	2,296	14.6	1.07 (0.95, 1.20)
Lurie et al[24] (2009)	90	186	134	336	9.2	1.41 (0.98, 2.03)
Lurie et al[9] (2011)	177	408	190	458	11.3	1.08 (0.83, 1.42)
Lurie et al[9] (2011)	847	2,456	1,418	3,182	14.7	0.65 (0.59, 0.73)
Lurie et al[9] (2011)	327	696	809	1,786	13.4	1.07 (0.90, 1.28)
Lurie et al[9] (2011)	470	1,090	448	1,050	13.5	1.02 (0.86, 1.21)
Lurie et al[9] (2011)	1,437	3,140	1,992	4,392	15.0	1.02 (0.93, 1.11)
Total (95% CI)		**10,218**		**13,786**	**100**	**1.02 (0.86, 1.21)**
Total events	4,380		6,127			

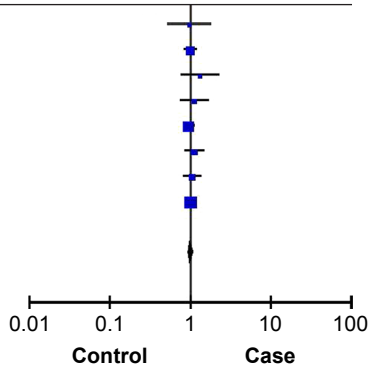
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 60.94$, $df = 7$ ($p < 0.00001$); I^2=89%
Test for overall effect: $Z = 0.26$ ($p = 0.79$)



B

Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Lurie et al[24] (2009)	49	70	101	143	1.6	0.97 (0.52, 1.81)
Lurie et al[9] (2011)	739	1,051	809	1,148	19.0	0.99 (0.83, 1.19)
Lurie et al[24] (2009)	65	93	107	168	1.9	1.32 (0.77, 2.28)
Lurie et al[9] (2011)	142	204	154	229	3.7	1.12 (0.74, 1.67)
Lurie et al[9] (2011)	847	1,228	1,115	1,591	25.0	0.95 (0.81, 1.12)
Lurie et al[9] (2011)	256	348	636	893	7.8	1.12 (0.85, 1.49)
Lurie et al[9] (2011)	368	545	349	525	9.6	1.05 (0.81, 1.35)
Lurie et al[9] (2011)	1,108	1,570	1,549	2,196	31.5	1.00 (0.87, 1.15)
Total (95% CI)		**5,109**		**6,893**	**100**	**1.01 (0.93, 1.09)**
Total events	3,574		4,820			

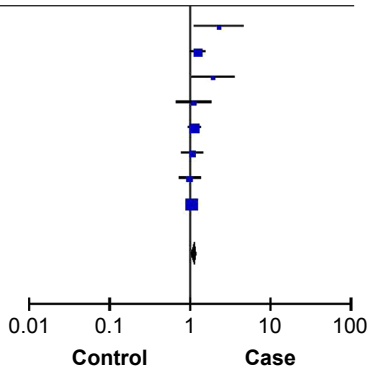
Heterogeneity: $\chi^2 = 2.46$, $df = 7$ ($p = 0.93$); $I^2 = 0\%$
Test for overall effect: $Z = 0.26$ ($p = 0.79$)



C

Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Lurie et al[24] (2009)	19	70	20	143	1.1	2.29 (1.13, 4.65)
Lurie et al[9] (2011)	225	1,051	206	1,148	17.9	1.25 (1.01, 1.54)
Lurie et al[24] (2009)	25	93	27	168	1.6	1.92 (1.04, 3.56)
Lurie et al[9] (2011)	35	204	36	229	3.2	1.11 (0.67, 1.85)
Lurie et al[9] (2011)	259	1,228	303	1,591	24.1	1.14 (0.94, 1.37)
Lurie et al[9] (2011)	71	348	173	893	8.9	1.07 (0.78, 1.45)
Lurie et al[9] (2011)	102	545	99	525	9.5	0.99 (0.73, 1.35)
Lurie et al[9] (2011)	329	1,570	443	2,196	33.7	1.05 (0.89, 1.23)
Total (95% CI)		**5,109**		**6,893**	**100**	**1.13 (1.03, 1.24)**
Total events	1,065		1,307			

Heterogeneity: $\chi^2 = 9.17$, $df = 7$ ($p = 0.24$); $I^2 = 24\%$
Test for overall effect: $Z = 2.65$ ($p = 0.008$)



D

Study or subgroup	Case Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Lurie et al[24] (2009)	19	40	20	62	1.2	1.90 (0.84, 4.30)
Lurie et al[9] (2011)	225	537	206	545	18.0	1.19 (0.93, 1.51)
Lurie et al[24] (2009)	25	63	27	88	2.1	1.49 (0.75, 2.93)
Lurie et al[9] (2011)	35	97	36	111	3.3	1.18 (0.66, 2.09)
Lurie et al[9] (2011)	259	640	303	779	24.7	1.07 (0.86, 1.32)
Lurie et al[9] (2011)	71	163	173	430	8.1	1.15 (0.80, 1.65)
Lurie et al[9] (2011)	102	279	99	275	9.6	1.02 (0.72, 1.45)
Lurie et al[9] (2011)	329	791	443	1,090	33.0	1.04 (0.86, 1.25)
Total (95% CI)		**2,610**		**3,380**	**100**	**1.10 (0.99, 1.23)**
Total events	1,065		1,307			

Heterogeneity: $\chi^2 = 3.52$, $df = 7$ ($p = 0.83$); $I^2 = 0\%$
Test for overall effect: $Z = 1.86$ ($p = 0.06$)

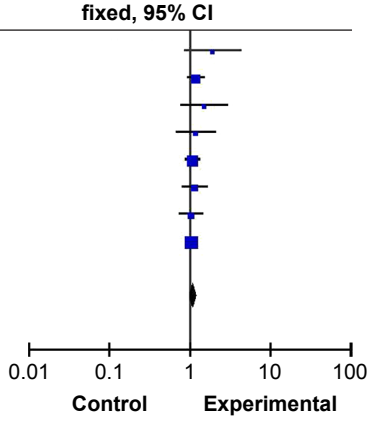


Figure 2 Forest plots of ORs for the association between ESR2 rs1271572 and ovarian cancer.
Note: (**A**) Allelic model, (**B**) dominant model, (**C**) recessive model and (**D**) codominant model.
Abbreviations: OR, odds ratio; M–H, Mantel–Haenszel; CI, confidence interval.

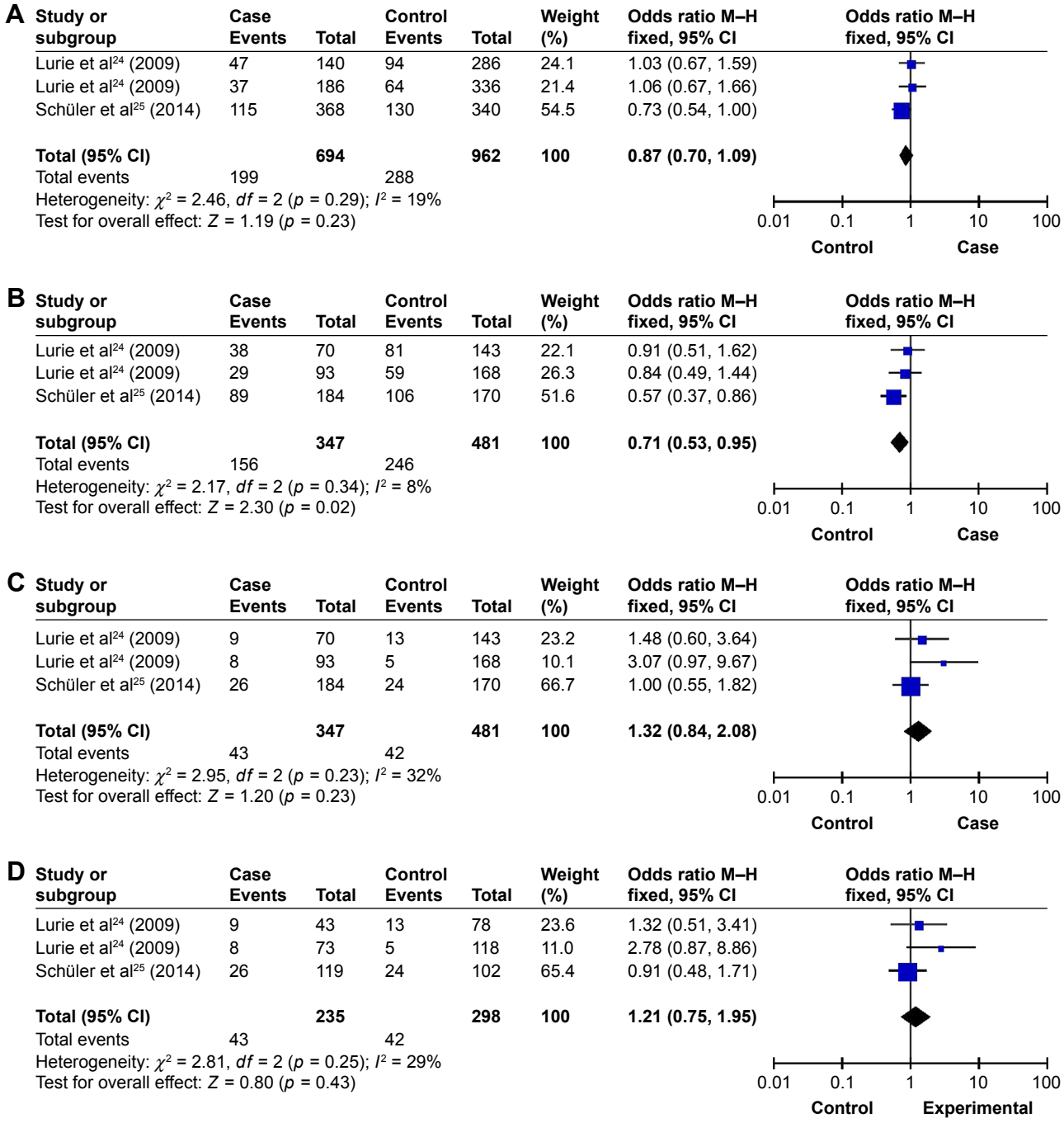


Figure 3 Forest plots of ORs for the association between ESR2 rs3020450 and ovarian cancer.
Note: (**A**) Allelic model, (**B**) dominant model, (**C**) recessive model and (**D**) codominant model.
Abbreviations: OR, odds ratio; M–H, Mantel–Haenszel; CI, confidence interval.

on the association between allelic, dominant, codominant and recessive models of HER rs1801200 (V655I) and ovarian cancer.

Sensitivity analysis

Sensitivity analysis that excluded the influence of a single study on the overall risk estimate by excluding one study at a time was confirmed. The ORs were not significantly altered in each SNP (Figure 5).

Publication bias

Begg's and Egger's tests were carried out to evaluate the publication bias. The shape of the funnel plot did not reveal any obvious asymmetry (Figure 6). The *p*-values for the Egger's test and Begg's test are shown in Table 3 separately.

Discussion

The meta-analysis presented here demonstrates that the recessive model ESR2 rs1271572 and the dominant model

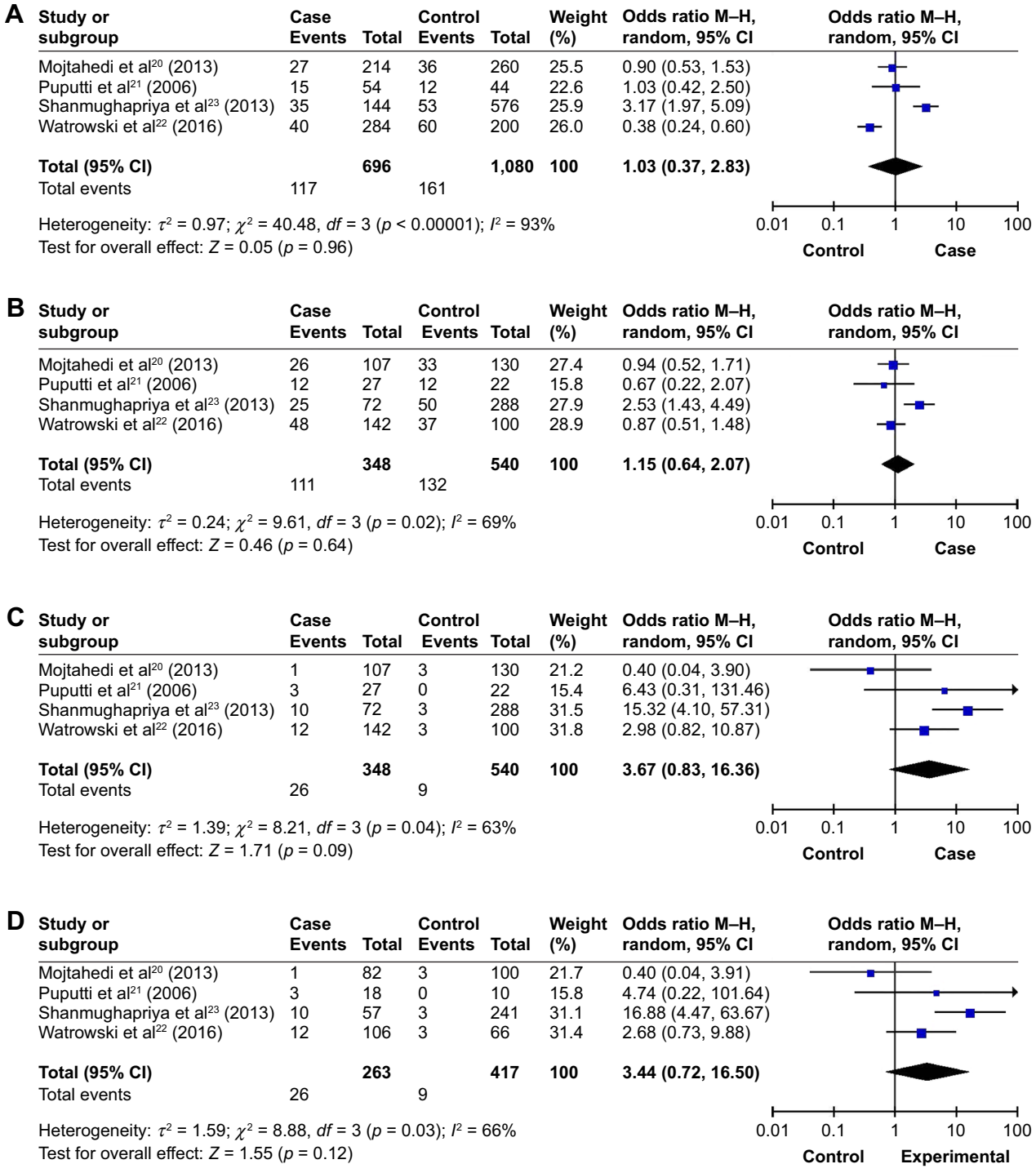


Figure 4 Forest plots of ORs for the association between HER2 rs1801200 (V655I) and ovarian cancer.
Note: (**A**) Allelic model, (**B**) dominant model, (**C**) recessive model and (**D**) codominant model.
Abbreviations: OR, odds ratio; M–H, Mantel–Haenszel; CI, confidence interval.

ESR2 rs3020450 are significantly associated with the risk of ovarian cancer.

A significant association was detected between the recessive model ESR2 rs1271572 and ovarian cancer. This SNP was previously associated with the risk of breast, prostate and ovarian cancers.[27,29,30] The rs1271572 gene is located in the *ESR2* promoter region (−53 bp upstream), close to the AP-4/MyoD binding site. This has been identified as a region of predicted intense transcription factor binding that might influence gene expression.[31] The variation in rs1271572 might interfere with some of the ER-β-proposed antiproliferative effects by altering ESR2 responsiveness to transcription

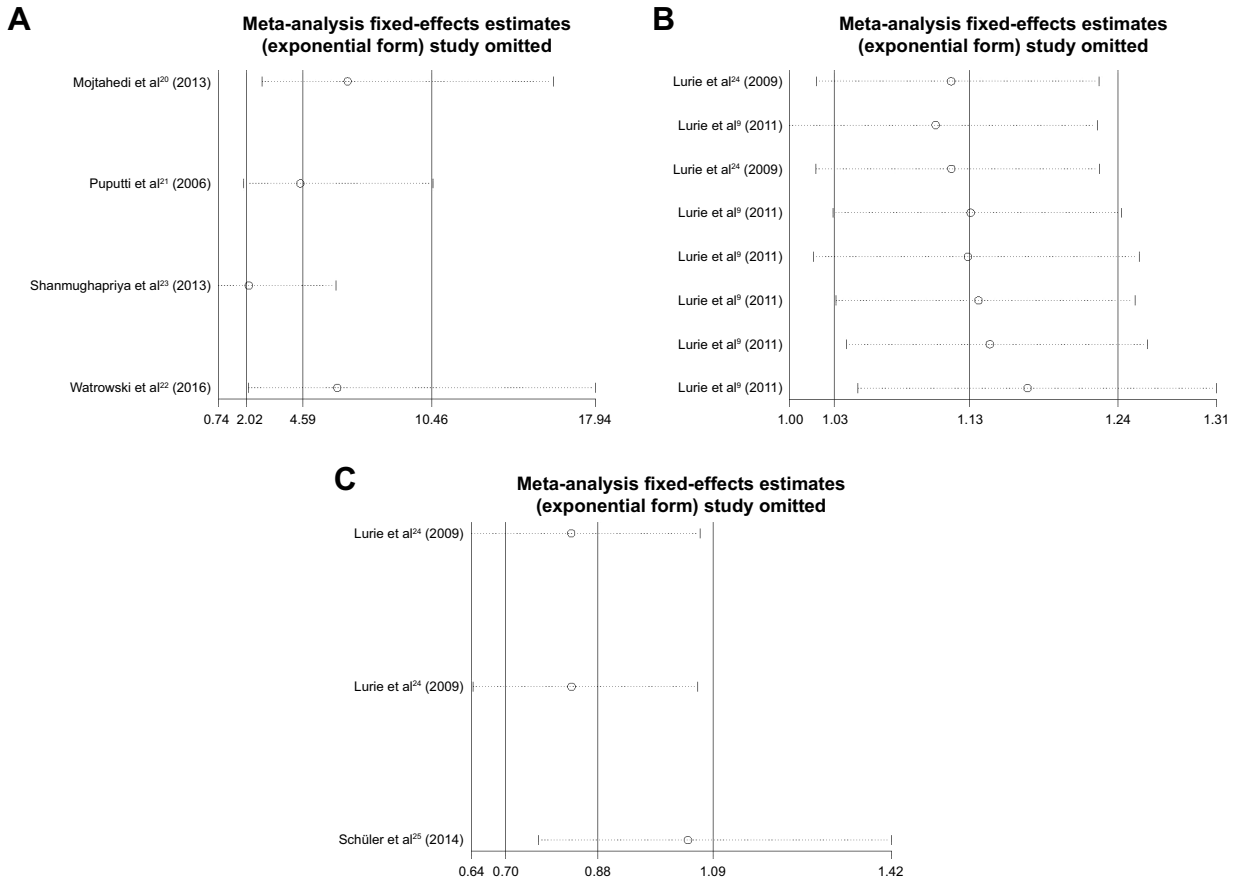


Figure 5 Sensitivity analyses between allelic models of ESR2 rs1271572, rs3020450 and HER2 rs1801200 (V655I).
Note: (**A**) HER2 rs1801200 (V655I), (**B**) ESR2 rs1271572 and (**C**) ESR2 rs3020450.

regulators.[14] Previously, Leigh et al evaluated[26] ESR2 variations in relation to ovarian cancer risk using a haplotype approach. No statistically significant associations were found. Additionally, another large study of the Ovarian Cancer Association Consortium examined ESR2 rs1271572 and found it to be weakly associated with susceptibility to ovarian cancer.[9] Notably, a significant association was detected between rs1271572 and epithelial ovarian cancer in Americans.[24] The inconsistent results for this SNP in different populations may be due to the limited number of subjects included in case–control studies and complex genetic background in these populations. In the present meta-analysis, we observed a significant correlation of rs1271572TT, but not rs1271572T, and ovarian cancer in Asian and Caucasian subgroups, which indicated that the homozygote of rs1271572 may be the risk factor of ovarian cancer susceptibility.

Our combined analysis on the association between ESR2 rs3020450 and ovarian cancer was not in line with recent individual studies analyzing this polymorphism. None of the three studies[24–26] showed positive results on the correlation of rs3020450 and ovarian cancer risk, which may be due to the relatively small sample size in the combined studies. However, our meta-analysis indicated that the dominant model rs3020450 might be associated with the risk of ovarian cancer in Caucasians, but not in Asians. The different ethnic background in each group may lead to this inconsistency. The results of the present meta-analysis should be interpreted carefully due to the relatively small sample size in the Caucasian and Asian groups. To confirm these results, studies with larger sample sizes are necessary.

Given that in the ESR2 gene no non-synonymous exon SNPs exist (which would lead to an altered amino acid sequence of the ER-β protein), the function of SNPs in the promoter region of the ESR2 genes such as rs3020450, rs2987983 and rs3020449 has been taken into account. The hypothesis was that SNPs located in this region could be able to affect binding of enhancer or repressor proteins regulating the transcription of the ESR2 gene. Altered ER-β protein levels could then modulate estrogen effects on cancer development.[32]

The recessive model HER2 rs1801200 (V655I) was not associated with the risk of ovarian cancer. We initially

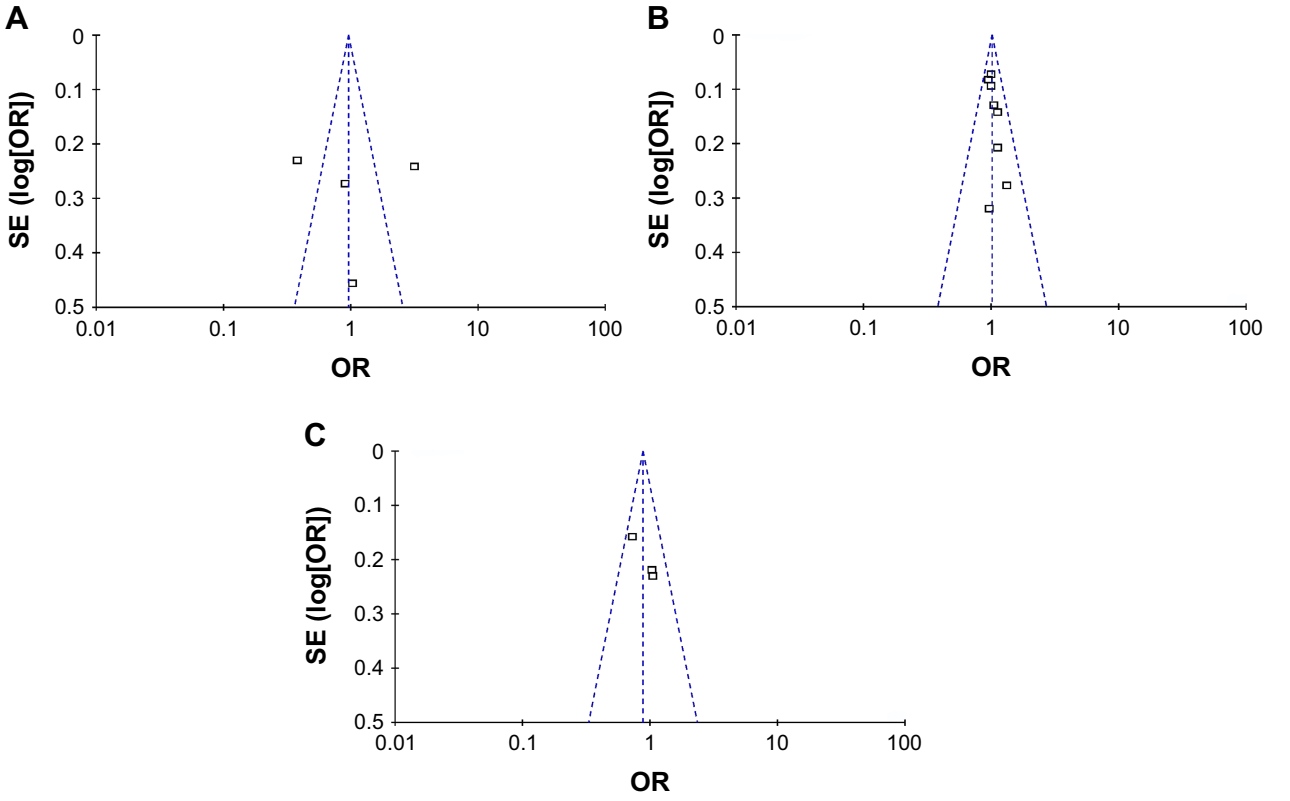


Figure 6 Funnel plots of ESR2 rs1271572 and rs3020450 and HER2 rs1801200 (V655I).
Note: (**A**) HER2 rs1801200 (V655I), (**B**) ESR2 rs1271572 and (**C**) ESR2 rs3020450.
Abbreviations: SE, standard error; OR, odds ratio.

detected the relationship of HER2 rs1801200 (V655I) with the risk of ovarian cancer using a meta-analysis with 888 subjects. The HER2 gene belongs to the family of tyrosine kinase type I receptors, which was reported to be strongly involved in female cancers.[33] Importantly, both preclinical and clinical studies indicated that HER2 overexpression is involved in oncogenic transformation and tumorigenesis, accounting for 20%–30% of breast and ovarian cancers.[34] The mechanism related to the association between the HER2 gene and ovarian cancer is complex and is still inadequately understood. The homo- or heterozygous Val genotype is associated with an increased risk of breast cancer,[35] while the results were inconsistent in ovarian cancer. This may be due to the heterogeneity of disease in breast and ovarian cancers. Although a negative result was reported by combined analysis, we could not draw out the genetic association between HER2 rs1801200 (V655I) and ovarian cancer risk. This suggests that more research with larger sample sizes is needed in the future.

Limitations in this study should be mentioned. First, the number of patients was relatively small and may influence the outcome. Only a total of four studies with 348 cases and 540 controls were included for the association between HER2 rs1801200 (V655I) and ovarian cancer in the present meta-analysis. Second, there were only two populations in the subgroup analysis for the HER2 gene and only one

Table 3 Begg's test and Egger's test for funnel plot asymmetries of rs1801200 (V655I), rs1271572 and rs3020450

Models of test	rs1801200 (V655I)				rs1271572				rs3020450			
	V	VV	VV + VI	VV/II	T	TT	TT + TG	TT/GG	A	AA	AA + AG	AA/GG
Begg's test	0.734	1.000	1.000	1.000	0.711	0.063	0.108	0.062	0.296	0.296	0.296	0.117
Egger'test	0.934	0.589	0.706	0.561	0.305	0.099	0.065	0.031	0.050	0.150	0.059	0.184
95% CI	−41.4157, 43.2700	−14.1688, 10.5101	−20.3479, 16.6089	−14.6508, 10.5964	−3.15666, 8.49750	−0.384899, 3.43546	−0.075108, 1.82562	0.201067, 2.16302	0.023507, 10.5435	−7.43968, 14.7046	2.70019, 9.89699	−10.184, 17.53889

Abbreviations: V, val; I, ile; CI, confidence interval.

population in the subgroup analysis for SNPs of the ESR2 gene. Third, all the patients in the present study were either Asian or Caucasian, which may limit the general application of the results to other populations. Since genetic variations might be different among different ethnicities, future studies on various ethnicities are needed. Fourth, multiple factors such as reproductive factors, food intake, smoking status and physical activity were reported to contribute to the risk of ovarian cancer. The gene–environmental interaction or gene–gene interaction may also play a role in ovarian cancer risk.

Conclusion

We found that the allelic and recessive models of ESR2 rs1271572 and the dominant model of ESR2 rs3020450 might be susceptible factors in ovarian cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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