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Original Article

Association between CYP19 polymorphisms and endometriosis risk: a meta-analysis

Cheng-Lei Gu[1,2*], Lu-Yang Zhao[1*], Ke Huang[1], Wen-Sheng Fan[1], Li-An Li[1], Ming-Xia Ye[1] , Wei-Dong Han[3], Yuan-Guang Meng[1]

[1]Department of Gynecology and Obstetrics, PLA Medical School, Chinese People's Liberation Army General Hospital, Beijing, China; [2]Department of Gynecology and Obstetrics, The 309th Hospital of Chinese People's Liberation Army, Beijing, China; [3]Department of Molecular Biology, Institute of Basic Medicine, PLA Medical School, Chinese People's Liberation Army General Hospital, Beijing, China. [*]Equal contributors.

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Abstract: Purpose: Studies have come to conflicting conclusions about whether CYP19 polymorphisms are associated with endometriosis risk. To help resolve this question, we carried out a meta-analysis of case-control studies in the literature. Methods: All eligible case-control studies published up to Dec. 16, 2015 were identified by searching PubMed, Embase, the Chinese Biological Medical Database and the Chinese National Knowledge Infrastructure Database, without language restrictions. Pooled odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Results: A total of nine eligible articles with sixteen studies were included. Overall, no evidence indicated that the rs10046 polymorphism was associated with endometriosis risk. However, after stratification by ethnicity, a lower risk of endometriosis was found with rs10046 among Caucasians under the allele model. For the rs700519 polymorphism, a lower risk of endometriosis was found among Asians using the recessive and heterozygous models. No significant association was observed between the rs2236722 and rs700518 polymorphisms and endometriosis risk among Asians. Conclusions: Our meta-analysis detected that the CYP19 rs10046 polymorphism might be associated with endometriosis risk among Caucasians and the rs700519 polymorphism might be associated with endometriosis risk among Asians, while the rs700518 and rs2236722 polymorphisms might not be associated with endometriosis risk among Asians.

Keywords: CYP19, aromatase, endometriosis, polymorphism, meta-analysis

Introduction

Endometriosis is a common gynecologic disorder defined as the presence of endometrial tissue outside the uterine cavity. It is reported to occur in around 10% of women of reproductive age and in 30-50% of infertile women [1]. Although the exact etiology and pathogenesis of endometriosis remain unknown, its phenotype is believed to be influenced by multiple genetic and environmental factors. It is well known that endometriosis is an estrogen-dependent chronic inflammatory disease. Women of reproductive age and postmenopausal women undergoing estrogen replacement therapy are most susceptible to endometriosis [2]. Therefore, it is considered that discrepancies in the process of estrogen production and metabolism should play a role in the development of endometriosis. It is logical to think that changes in genes that control levels of estrogen, as in the case of CYP19, are potential candidates that predispose women to this illness.

The human CYP19 gene is located on chromosome 15q21.2 and comprises a 30 kb coding region and a 93 kb regulatory unit [3]. This gene encodes aromatase, an enzyme whose function is to catalyze the conversion of androgens into estrogens, a reaction known as aromatization [4]. Reports have indicated that increased expression of CYP19 aromatase occurs in ectopically located endometriotic lesions, especially ovarian endometriosis [5], whereas endometrial tissue from uterine-disease-free women does not exhibit aromatase activity. In contrast, aromatase enzyme activity and increased mRNA levels are readily detectable in endometriosis [6-8].

Although a number of studies have focused on CYP19 genetic variation with respect to endometriosis, they have yielded contradictory results [9-17]. The reasons for this disparity may be explained by potential limitations of these studies, such as sample size and the source of the controls. Therefore, we performed a meta-analysis on published papers to clarify the association of CYP19 polymorphisms with endometriosis, including rs10046: C>T (1531C>T), rs700518: G>A (240A>G, Val80), rs2236722: T>C (115T>C), and rs700519: C>T (Arg264Cys).

Materials and methods

Literature sources and search strategy

The PubMed, Embase, Chinese Biomedical Literature database (CBM) and China National Knowledge Infrastructure (CNKI) were searched by two reviewers to retrieve all papers available. The latest searches were undertaken on Dec. 16, 2015. The combination of the terms "CYP19" or "aromatase"; "polymorphism", "variant", "SNP" or "mutation"; and "endometriosis" was used without restrictions on language restriction or publication date. In addition, references cited in the retrieved articles were reviewed to trace additional relevant studies missed by the search. Authors were contacted to obtain related data not revealed in original articles.

Inclusion and exclusion criteria

The inclusion criteria were: (1) evaluation of the association between CYP19 polymorphisms (rs10046, rs700518, rs2236722, rs700519) and endometriosis; (2) case-control or cohort design; (3) human study; (4) the number or frequency of genotypes was provided in the study or could be obtained by contacting the authors. The exclusion criteria were: (1) studies with insufficient information, such as genotype number not reported; (2) absence of control subjects; (3) non-clinical studies; (4) review, comment or conference papers. For studies with overlapping samples, only the one with the largest sample size was included.

Data extraction and quality assessment

Two investigators (Chenglei Gu and Luyang Zhao) independently selected the article and extracted data with a consensus on all of the terms. If the data were not identical, the two investigators would recheck the data to come to an agreement. The following items were collected from the eligible articles: first author's name, year of publication, country of origin, ethnicity, source of control, source of sample, genotype method, number of cases and controls, genotype or allele distribution in cases and controls, and probability (*P*) value for the test of Hardy-Weinberg equilibrium (HWE) in the controls.

The quality of all eligible studies was independently evaluated on the basis of the Newcastle-Ottawa Scale (NOS). The NOS provides a quality rating based on criteria covering three study dimensions: study group selection, comparability of cases and controls, and exposure of cases and controls. If all criteria are met, nine stars were rewarded. Seven stars were considered the cut-off for distinguishing "high-quality studies" from "low-quality studies".

Statistical analysis

We tested whether the genotype frequencies of the controls were in Hardy-Weinberg equilibrium (HWE) using a χ^2 test ($P>0.05$). The strength of the association between the CYP19 polymorphisms and the risk of endometriosis was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The pooled ORs were calculated for the allele model (T vs. C for rs10046, A vs. G for rs700518, C vs. T for rs2236722, and T vs. C for rs700519), dominant model (TT+CT vs. CC for rs10046, AA+GA vs. GG for rs700518, CC+TC vs. TT for rs2236722, and TT+CT vs. CC for rs700519), recessive model (TT vs. CT+CC for rs10046, AA vs. GA+GG for rs700518, CC vs. TC+TT for rs2236722, and TT vs. CT+CC for rs700519), homozygous model (TT vs. CC for rs10046, AA vs. GG for rs700518, CC vs. TT for rs2236722, and TT vs. CC for rs700519), and heterozygous model (TT vs. CT for rs10046, AA vs. GA for rs700518, CC vs. TC for rs2236722, and TT vs. CT for rs700519). The statistical significance of the pooled ORs was determined by the Z test, with $P < 0.05$ indicating statistical significance. Heterogeneity was evaluated using a χ^2-based Cochan's Q statistic, and inconsistency was tested by the I^2 metric. Heterogeneity was considered statistically significant at $P < 0.10$ for the Q statistic or $I^2>50\%$ for the I^2 metric statistic [18, 19]. When the heterogeneity was indicated to be non-significant

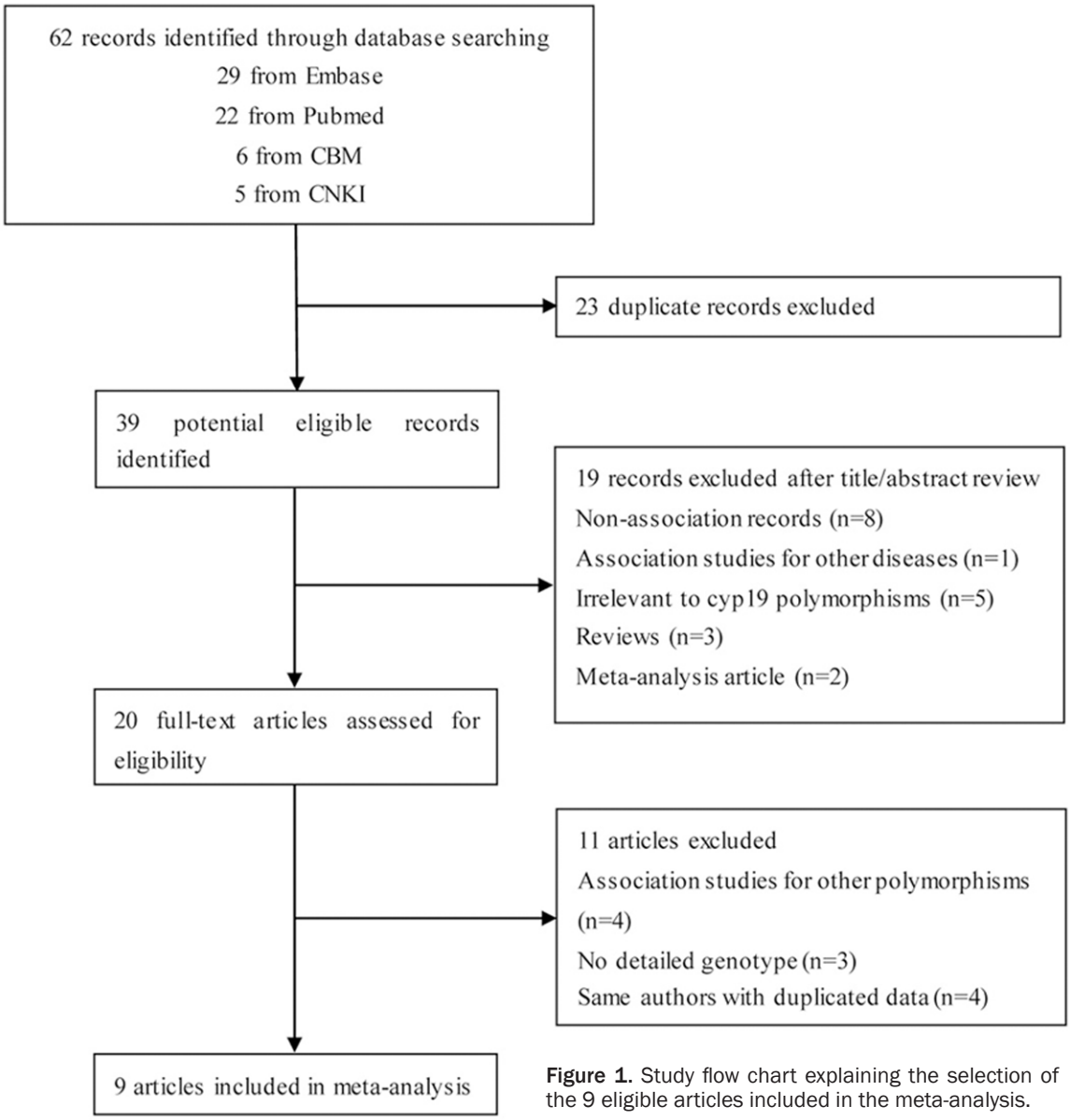

Figure 1. Study flow chart explaining the selection of the 9 eligible articles included in the meta-analysis.

(P>0.10), the fixed-effects model (Mantel-Haenszel method) [20] was applied; otherwise the random-effects model (DerSimonian and Laird method) [21] was performed. Considering that the frequency of the CYP19 polymorphisms varied across different populations, gene-disease associations for the different inheritance models were also analyzed. All statistical analyses were performed using Stata 12.0 software (Stata Corp, College Station, TX, USA).

Results

Literature selection and study characteristics

The selection process of this literature review is summarized in the flow diagram (**Figure 1**). A total of nine eligible articles with sixteen studies fully met the inclusion criteria and were incorporated into this meta-analysis. The main characteristics of the sixteen case-control studies are presented in **Table 1**. These articles were published between 2005 and 2014. The studies were carried out in China, Japan, Korea, Italy, Estonia and Poland. Of these studies, twelve were performed on an Asian population, and four on a Caucasian population. There were six case-control studies with 788 endometriosis cases and 955 controls concerning the rs10046 polymorphism, five case-control studies with 553 cases and 637 controls concerning rs700518, three case-control studies with 419 cases and 513 controls concerning

Table 1. Characteristics of studies included in the meta-analysis

Author (year)	Country	Ethnicity	Control source	Genotyping method	Genotype distribution						No. of case/ control	HWE in control	NOS score
					Cases			Controls					
rs10046 (C>T)					CC	CT	TT	CC	CT	TT			
Hur (2007)	Korea	Asian	HB	PCR-RFLP	43	111	69	37	92	59	223/188	Yes	8
Vietri (2009)	Italy	Caucasian	HB	PCR-RFLP	50	36	18	26	36	24	104/86	Yes	6
Yang (2010)	China	Asian	HB	PCR-RFLP	42	48	12	38	42	20	102/100	Yes	8
Lamp (2011)	Estonia	Caucasian	PB	PCR-RFLP	27	81	42	36	88	75	150/199	Yes	9
Szczepańska (2013)	Poland	Caucasian	HB	Other methods	19	55	41	31	93	73	115/197	Yes	7
Wang (2014)	China	Asian	PB	PCR-RFLP	14	50	30	40	116	69	94/225	Yes	7
rs700518 (G>A)					GG	GA	AA	GG	GA	AA			
Hur (2007)	Korea	Asian	HB	PCR-RFLP	50	112	61	39	95	54	223/188	Yes	8
Vietri (2009)	Italy	Caucasian	HB	PCR-RFLP	21	31	52	21	37	28	104/86	Yes	6
Yang (2010)	China	Asian	HB	PCR-RFLP	24	50	28	14	41	45	102/100	Yes	8
Li (2013)	China	Asian	HB	PCR-RFLP	7	17	6	5	13	20	30/38	Yes	8
Wang (2014)	China	Asian	PB	PCR-RFLP	20	45	29	43	125	57	94/225	Yes	7
rs2236722 (T>C)					TT	TC	CC	TT	TC	CC			
Hur (2007)	Korea	Asian	HB	PCR-RFLP	213	10	0	172	15	1	223/188	Yes	8
Yang (2010)	China	Asian	HB	PCR-RFLP	93	9	0	88	11	1	102/100	Yes	8
Wang (2014)	China	Asian	PB	PCR-RFLP	86	8	0	202	21	2	94/225	Yes	7
rs700519 (C>T)					CC	CT	TT	CC	CT	TT			
Tsuchiya (2005)	Japan	Asian	HB	PCR-RFLP	35	37	4	29	23	6	76/58	Yes	8
Wang (2012)	China	Asian	PB	Other methods	222	36	42	242	28	67	300/337	No	6

PB, population-based; HB, hospital-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

rs2236722, and two case-control studies with 376 cases and 395 controls concerning rs700519. Blood samples were used to determine genetic polymorphisms in all of the included studies.

Quantitative data synthesis

Table 2 lists the main results of the meta-analysis of CYP19 polymorphisms and endometriosis risk. For the rs10046 polymorphism, six case-control studies with 788 cases and 995 controls were identified. Overall, there was no significant difference in the rs10046 genotype distribution between endometriosis and control subjects (allele model: OR = 0.88, 95% CI: 0.77-1.01, P = 0.068; dominant model: OR = 0.89, 95% CI: 0.71-1.12, P = 0.332; recessive model: OR = 0.81, 95% CI: 0.6-1.00, P = 0.053; homozygous model: OR = 0.79, 95% CI: 0.60-1.05, P = 0.101; heterozygous model: OR = 0.82, 95% CI: 0.66-1.03, P = 0.084 Figure S1). However, after stratification by ethnicity, an association was found among Caucasians under allele model (OR = 0.79, 95% CI: 0.65-0.96, P = 0.02); this association was not observed among Asians under any genetic model (**Figure 2**).

For the rs700518 polymorphism, five case-control studies with 553 cases and 637 controls were identified. Meta-analysis revealed no remarkable association between the rs700518 polymorphism and endometriosis in the selected samples (allele model: OR = 0.86, 95% CI 0.59-1.25, P = 0.438; dominant model: OR = 0.85, 95% CI 0.64-1.14, P = 0.270; recessive model: OR = 0.84, 95% CI 0.46-1.54, P = 0.572; homozygous model: OR = 0.77, 95% CI 0.42-1.43, P = 0.409; heterozygous model: OR = 0.90, 95% CI 0.49-1.63, P = 0.718, Figure S2). However, after stratification by different ethnicities, an association was found among Caucasians under three genetic models (allele model: OR = 1.57, 95% CI: 1.04-2.38, P = 0.032; recessive model: OR = 2.07, 95% CI: 1.15-3.75, P = 0.016; heterozygous model: OR = 2.22, 95% CI: 1.14-4.30, P = 0.019); this association was not observed among Asians under any genetic model (**Figure 3**).

For the rs2236722 polymorphism, three case-control studies with 419 cases and 513 controls were identified. No significant association between the rs223722 polymorphism and endometriosis risk was observed under any of the genetic models (allele model: OR = 0.62, 95% CI 0.39-1.00, P = 0.050; dominant model:

Table 2. Summary of ORs of the CYP19 polymorphisms and endometriosis risk

	Allele model		Dominant model		Recessive model		Homozygous model		Heterozygous model		n
rs10046 (C>T)	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	
Overall	0.88 [0.77, 1.01]	0.068	0.89 [0.71, 1.12]	0.332	0.81 [0.66, 1.00]	0.053	0.79 [0.60, 1.05]	0.101	0.82 [0.66, 1.03]	0.084	6
Control source											
HB	0.85 [0.72, 1.01]	0.071	0.81 [0.62, 1.08]	0.148	0.82 [0.63, 1.07]	0.150	0.73 [0.52, 1.03]	0.074	0.86 [0.65, 1.15]	0.307	4
PB	0.93 [0.74, 1.17]	0.526	1.10 [0.72, 1.67]	0.671	0.80 [0.57, 1.13]	0.198	0.93 [0.58, 1.49]	0.748	0.76 [0.53, 1.90]	0.136	2
Ethnicity											
Asian	0.97 [0.80, 1.18]	0.766	1.02 [0.74, 1.41]	0.907	0.92 [0.68, 1.24]	0.564	0.93 [0.63, 1.38]	0.716	0.90 [0.65, 1.23]	0.496	3
Caucasian	0.79 [0.65, 0.96]	0.020	0.77 [0.55, 1.08]	0.125	0.72 [0.54, 0.97]	0.032	0.67 [0.45, 1.00]	0.051	0.75 [0.55, 1.03]	0.077	3
NOS											
High	0.93 [0.81, 1.08]	0.342	1.00 [0.78, 1.29]	0.997	0.85 [0.68, 1.06]	0.141	0.88 [0.66, 1.19]	0.411	0.83 [0.66, 1.05]	0.113	5
Low	0.56 [0.37, 0.84]	0.005	0.47 [0.26, 0.85]	0.013	0.54 [0.27, 1.08]	0.082	0.39 [0.18, 0.85]	0.017	0.75 [0.35, 1.61]	0.462	1
Method											
PCR-RFLP	0.87 [0.75, 1.01]	0.060	0.88 [0.69, 1.13]	0.331	0.78 [0.62, 0.99]	0.042	0.77 [0.57, 1.04]	0.092	0.79 [0.62, 1.02]	0.067	5
Other methods	0.96 [0.69, .33]	0.787	0.94 [0.51, 1.76]	0.855	0.94 [0.58, 1.52]	0.804	0.92 [0.46, 1.82]	0.803	0.95 [0.57, 1.58]	0.842	1
rs700518 (G>A)											
Overall	0.86 [0.59, 1.25]	0.438	0.85 [0.64, 1.14]	0.270	0.84 [0.46, 1.54]	0.572	0.77 [0.42, 1.43]	0.409	0.90 [0.49, 1.63]	0.718	5
Control source											
HB	0.80 [0.49, 1.31]	0.379	0.83 [0.56, 1.22]	0.341	0.73[0.34, 1.58]	0.424	0.68 [0.30, 1.52]	0.346	0.77 [0.36, 1.66]	0.512	4
PB	1.07 [0.59, 1.25]	0.699	0.87 [0.48, 1.59]	0.658	1.32 [0.77, 2.24]	0.312	1.09 [0.55, 2.19]	0.800	1.41 [0.81, 2.48]	0.228	1
Ethinity											
Asian	0.75 [0.52, 1.08]	0.126	0.78 [0.57, 1.07]	0.123	0.68 [0.37, 1.25]	0.209	0.62 [0.34, 1.16]	0.138	0.72 [0.39, 1.33]	0.297	4
Caucasian	1.57 [1.04, 2.38]	0.032	1.28 [0.64, 2.54]	0.485	2.07 [1.15, 3.75]	0.016	1.86 [0.42, 1.43]	0.110	2.22 [1.14, 4.30]	0.019	1
NOS											
High	0.75 [0.52, 1.08]	0.126	0.78 [0.57, 1.07]	0.123	0.68 [0.37, 1.25]	0.209	0.62 [0.34, 1.16]	0.138	0.72 [0.39, 1.33]	0.297	4
Low	1.57 [1.04, 2.38]	0.032	1.28 [0.64, 2.54]	0.485	2.07 [1.15, 3.75]	0.016	1.86 [0.42, 1.43]	0.110	2.22 [1.14, 4.30]	0.019	1
rs2236722 (T>C)											
Overall	0.62 [0.39, 1.00]	0.050	0.68 [0.40, 1.08]	0.710	0.36 [0.06, 2.22]	0.269	0.35 [0.06, 2.17]	0.258	0.47 [0.07, 3.05]	0.426	3
rs700519 (C>T)											
Overall	0.82 [0.65, 1.05]	0.111	0.95 [0.69, 1.29]	0.729	0.64 [0.43, 0.95]	0.028	0.67 [0.24, 1.01]	0.054	0.47 [0.27, 0.84]	0.010	2

P, *P* value of pooled effect; n, number of studies.

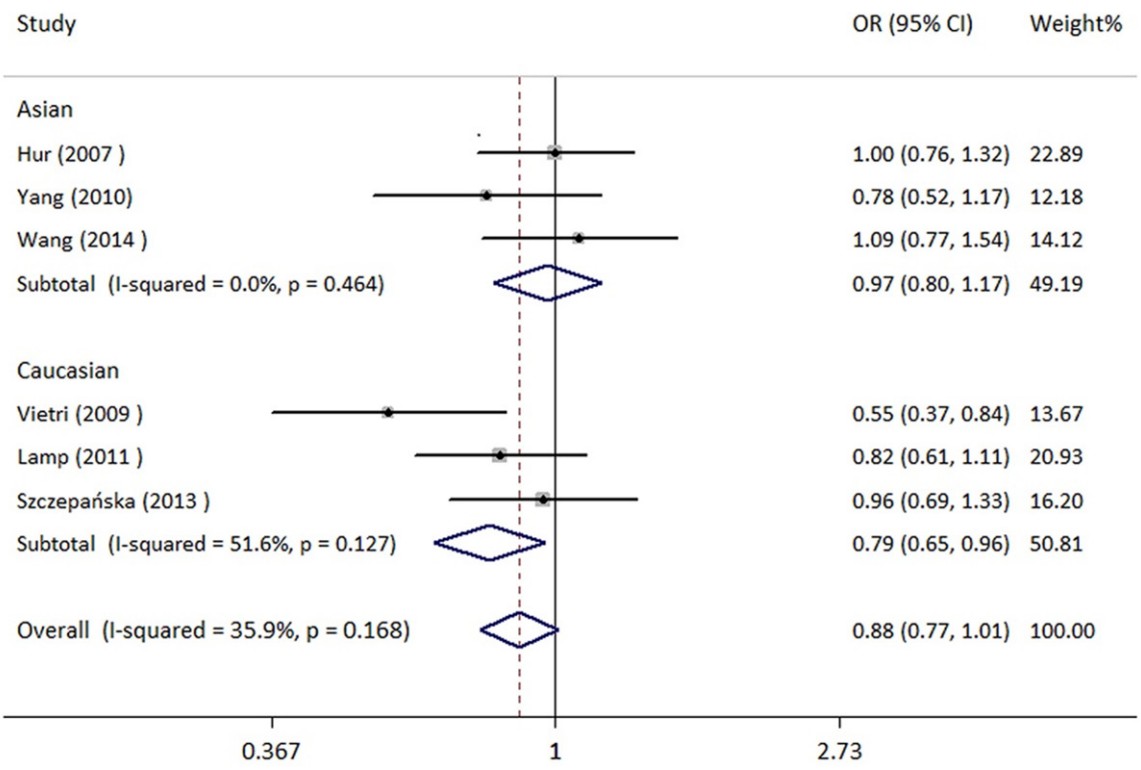

Figure 2. Forest plot of rs10046 (C>T) polymorphism and endometriosis risk under allele model (Subgroup analysis by ethnicity).

OR = 0.68, 95% CI 0.40-1.08, P = 0.710; recessive model: OR = 0.36, 95% CI 0.06-2.22, P = 0.269; homozygous model: OR = 0.35, 95% CI 0.06-2.17, P = 0.258; heterozygous model: OR = 0.47, 95% CI 0.07-3.05, P = 0.426, Figure S3).

For the rs700519 polymorphism, two case-control studies with 376 cases and 395 controls were identified. Overall, we found an association under two genetic models (recessive model: OR = 0.64, 95% CI: 0.43-0.95, P = 0.028; heterozygous model: OR = 0.47, 95% CI: 0.27-0.84, P = 0.01), but no significant association was found using the other three models (allele model: OR = 0.82, 95% CI 0.65-1.05, P = 0.111; dominant model: OR = 0.95, 95% CI 0.69-1.29, P = 0.729; homozygous model: OR = 0.67, 95% CI 0.24-1.01, P = 0.054, Figure S4).

Heterogeneity and sensitivity analysis

There was no obvious heterogeneity for the rs10046, rs2236722 and rs700519 polymorphisms. However, for the rs700518 polymorphism, significant heterogeneity between the studies was found in overall comparisons under the allele, recessive, homozygous and heterozygous models (I^2 = 77.8%, P = 0.001; I^2 = 80.5%, P < 0.001; I^2 = 67.3%, P = 0.016; I^2 = 77.3%, P = 0.001, respectively). A random effects model was performed in these analyses. For the rs700518 polymorphism, we performed subgroup analyses based on control source, ethnicity and quality score, but the heterogeneity did not decrease.

Sensitivity analysis was performed to evaluate the stability of the results by sequentially excluding individual studies. For analyses pooling more than three individual studies, the observed significant result was not materially altered after excluding any single study (**Figure 4**), indicating that our results were statistically stable.

Discussion

Endometriosis is an estrogen-dependent disease. Polymorphisms of genes encoding key proteins involved in sex-steroid hormone biosynthesis have primarily been chosen as functional candidate susceptibility genes for endo-

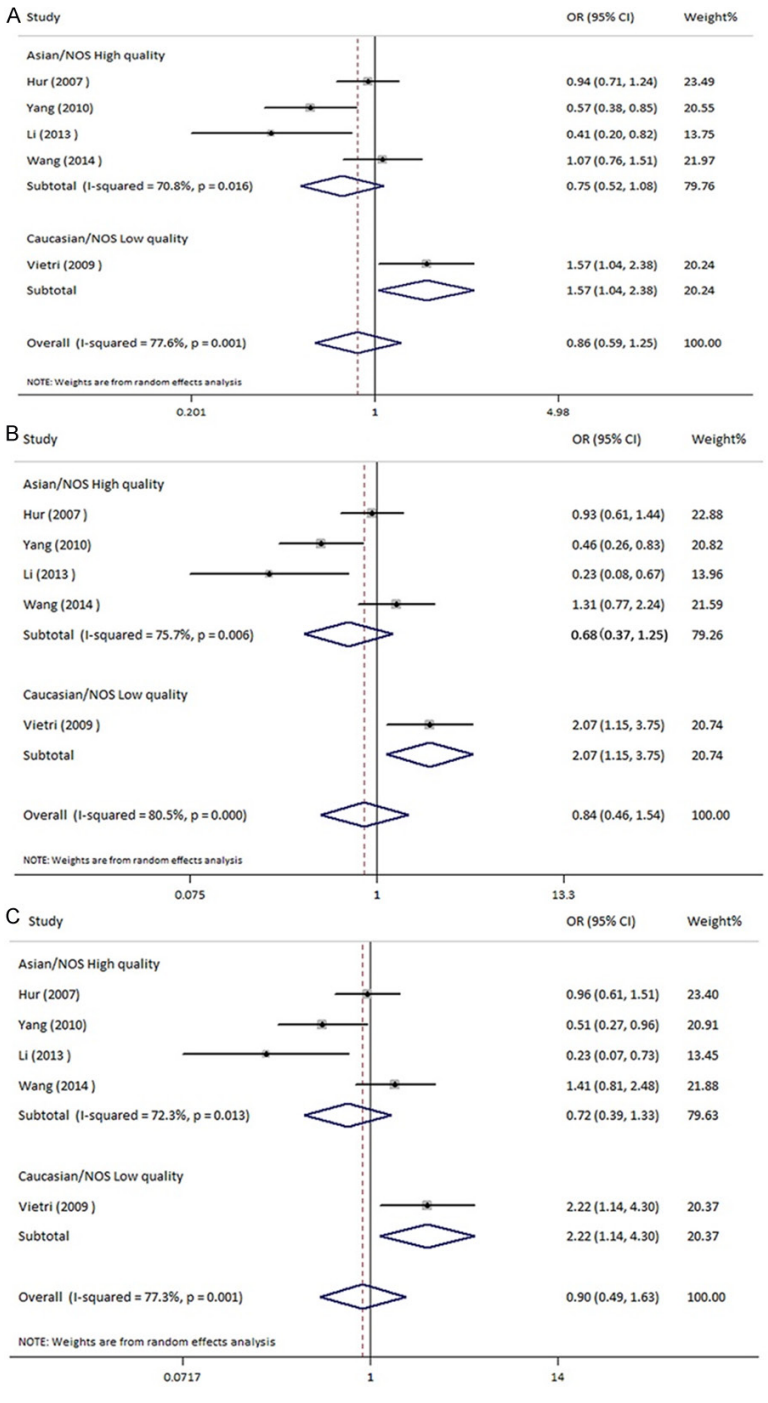

Figure 3. Forest plot of 700518 (G>A) polymorphism and endometriosis risk (Subgroup analysis by ethnicity or quality score). A: Allele model; B: Recessive model; C: Heterozygous model.

metriosis. The CYP19 gene encodes aromatase, the key enzyme for the terminal step of estrogen biosynthesis that converts 19-carbon steroids (testosterone and androstenedione) to 18-carbon estrogen (testosterone and androstenedione). Polymorphisms in CYP19 have been associated with sex-steroid hormone levels and other estrogen-dependent diseases, including endometrial cancer and breast cancer [22-25].

We noticed that a previous meta-analysis had been performed by Hu et al. [26], which reported on the endometriosis risk with genetic polymorphisms involving the biosynthesis of sex steroids (CYP17, ER, PR, HSD17B1, and CYP-19). The pooled analysis suggested that no significant association was found between CYP19 polymorphisms (rs10046, rs700518, rs2236-722, 3 bp I/D) and the risk of endometriosis. However, only two articles with six studies for the rs10046, rs700518 and rs2236722 polymorphisms were included in that meta-analysis. Some differences exist between our study and Hu's report. First, our work is more recent than the work of other groups, which allowed for the inclusion of some new studies. Second, five genetic models were used in our meta-analysis. More importantly, we performed subgroup analyses, thus we believe our results for CYP19 polymorphisms are more convincing.

The CYP19 rs10046 polymorphism is a C-to-T variation located in the 3' untranslated region (3'-UTR), 19 bp downstream of the amber stop codon in exon 10. Seven previous studies on this polymorphism in endometriosis have been published [9, 10, 12-15, 27]. Vietri et al. [13] found a higher percentage of C homozygosis for the rs10046 polymorphism in patients with endometriosis, whereas other studies found no association. Our meta-analysis showed the rs10046 polymorphism was not associ-

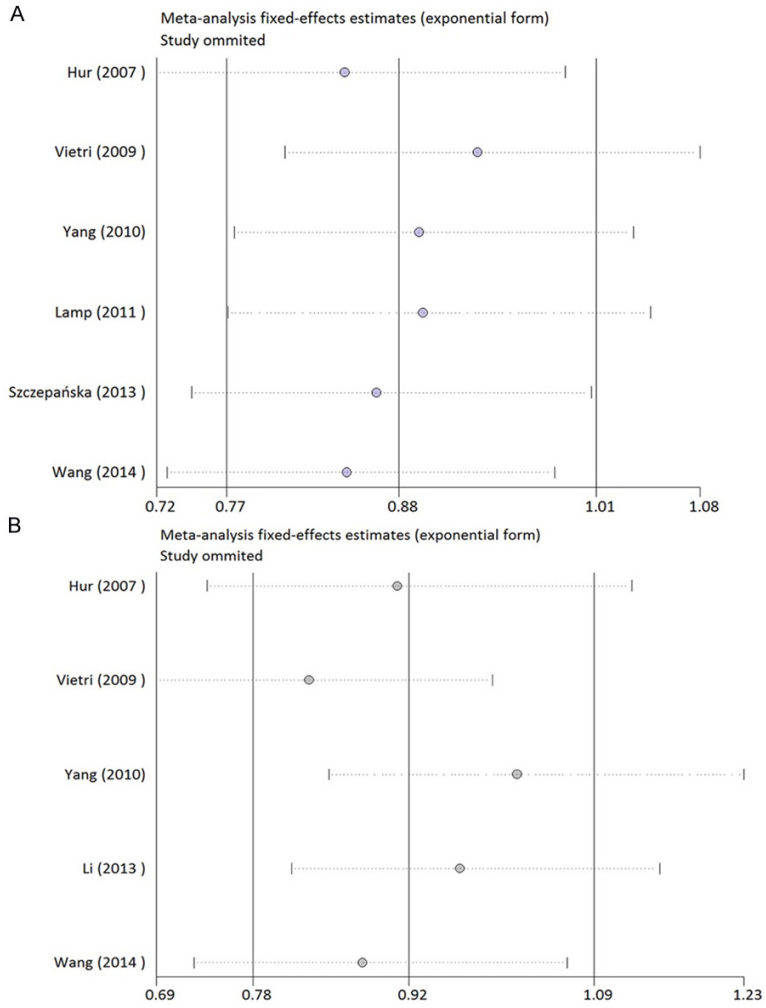

Figure 4. Sensitivity analysis of the summary ORs on the association for rs10046 and rs700518 polymorphisms with endometriosis risk. A: rs10046 polymorphism under allele model; B: rs700518 polymorphism under allele model.

ated with the overall risk of endometriosis. However, subgroup analyses showed that the rs10046 polymorphism might be a lower risk factor for endometriosis among Caucasians under the allele model. This subgroup analyses suggested that the T allele variant might decrease the risk of endometriosis among Caucasians, but this association was not observed among Asians. There was no obvious heterogeneity for the rs10046 polymorphism, and the result was confirmed as in HWE among the studies.

The CYP19 rs700518 polymorphism is an anonymous variation in exon 3, but it may affect posttranscriptional modification, resulting in changes in gene expression and aromatase levels, and further affecting estrogen production [28]. In our meta-analysis, the overall result did not indicate any associations between this polymorphism and endometriosis risk. After further stratification analysis by ethnicity, the results showed that the rs700518 polymorphism might be a risk factor for endometriosis among Caucasians under three genetic models, but this association was not observed in Asians. There was only one study included for Caucasians, and the score of this study was low. This result should therefore be interpreted with caution, as this article might be a small sample bias. However, the association among Caucasians may indeed be related, although further studies are required. This analysis suggested that there was no association between this polymorphism and endometriosis risk among Asians, and more articles are needed to confirm this association among Caucasians. Specifically, there was significant heterogeneity found for the rs700518 polymorphism under the allele, recessive, homozygous and heterozygous models. Heterogeneity plays an important role when performing meta-analysis, and so finding the source of heterogeneity is very important for the final result. In the current study, an obvious heterogeneity between the studies was found in the overall population. This heterogeneity cannot be explained by several possible sources of heterogeneity, including the source of the control, the ethnicity and the quality score. It is possible that other limitations of the recruited studies may partially contribute to the observed heterogeneity. For this reason, we conducted these analyses using the random effects model.

The CYP19 rs2236722 polymorphism is a T-to-C variation resulting in a Trp39Arg amino-acid exchange in exon 2. In our meta-analysis, no significant association was identified bet-

ween this polymorphism and endometriosis under all five genetic models. It is noteworthy that all the studies were carried out among Asians. This suggests that there is no association among Asians.

The CYP19 rs70019 polymorphism is a C-to-T variation resulting in an Arg264Cys amino-acid exchange in exon 7. It was suggested that the rs700519 polymorphism is located in a near recognition site of CYP19 aromatase, and so it might enhance estrogen synthesis and the exposure to endogenous estrogen. The studies both came from Asian populations and the results suggested that the TT genotype could increase the risk of endometriosis when compared with the CT+CC and CT genotypes among Asians. However, the distribution of the genotypes in the control population of the study by Wang et al. was not consistent with HWE, although we did not exclude this article because of the limited number of studies. This result should be interpreted with caution.

Although comprehensive analysis was performed to show the association between CYP19 polymorphisms and endometriosis risk, there are still some limitations that should be pointed out. First, the number of studies and the number of samples included in the meta-analysis were relatively small. Second, for the rs700518 polymorphism, the heterogeneity was large, and the comprehensive analysis should be explained with caution. Third, the distribution of the genotypes in the control population of the study by Wang et al. was not consistent with HWE. Finally, our results were based on unadjusted estimates. A more precise analysis should be conducted if individual data were available, which would allow for the adjustment for other covariants including age, endometriosis stages, and environmental factors.

Conclusions

This meta-analysis shows a relationship between CYP19 polymorphisms (rs10046, rs700518, rs2236722, rs700519) and endometriosis. We found that the T allele variant of the rs10046 polymorphism might decrease the risk of endometriosis among Caucasians. Meanwhile, the dominant recessive model and the heterozygous model of the rs700519 polymorphism suggested that the TT genotype could increase the risk of endometriosis when compared with the CT+CC and CT genotypes among Asians. However, the rs700518 and rs2236722 polymorphisms might not be associated with the risk of endometriosis among Asians. Considering the limited sample size included in the meta-analysis, further large-scale and well-designed studies are needed to confirm our results. Moreover, as many factors have been associated with endometriosis risk, additional factors (such as age, pregnancy times and environmental factors) should be taken into consideration in future studies on this topic.

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Disclosure of conflict of interest

None.

Address correspondence to: Yuan-Guang Meng, Department of Gynecology and Obstetrics, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China. Tel: +86 1066938244; E-mail: meng6512@vip.sina.com

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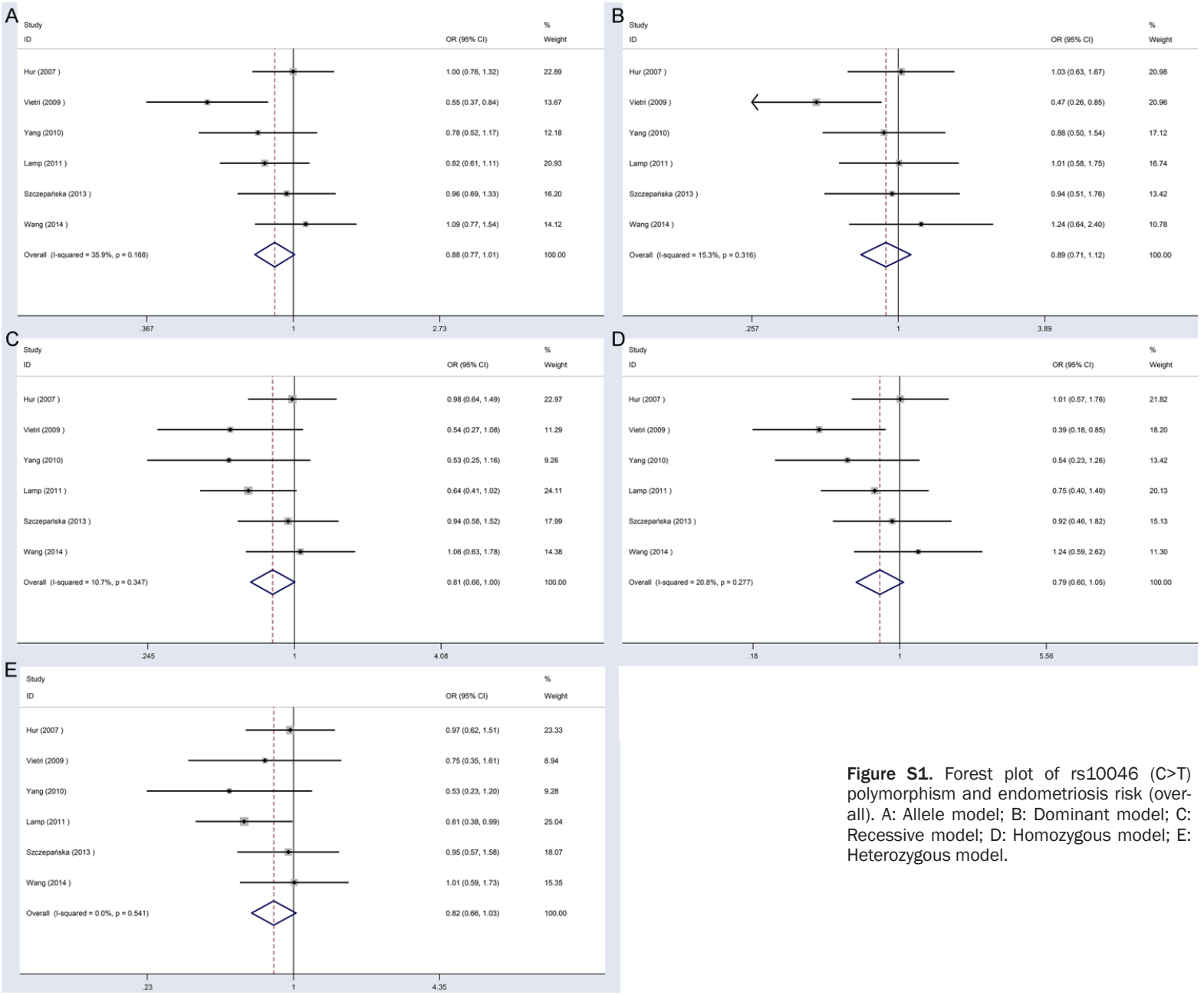

Figure S1. Forest plot of rs10046 (C>T) polymorphism and endometriosis risk (overall). A: Allele model; B: Dominant model; C: Recessive model; D: Homozygous model; E: Heterozygous model.

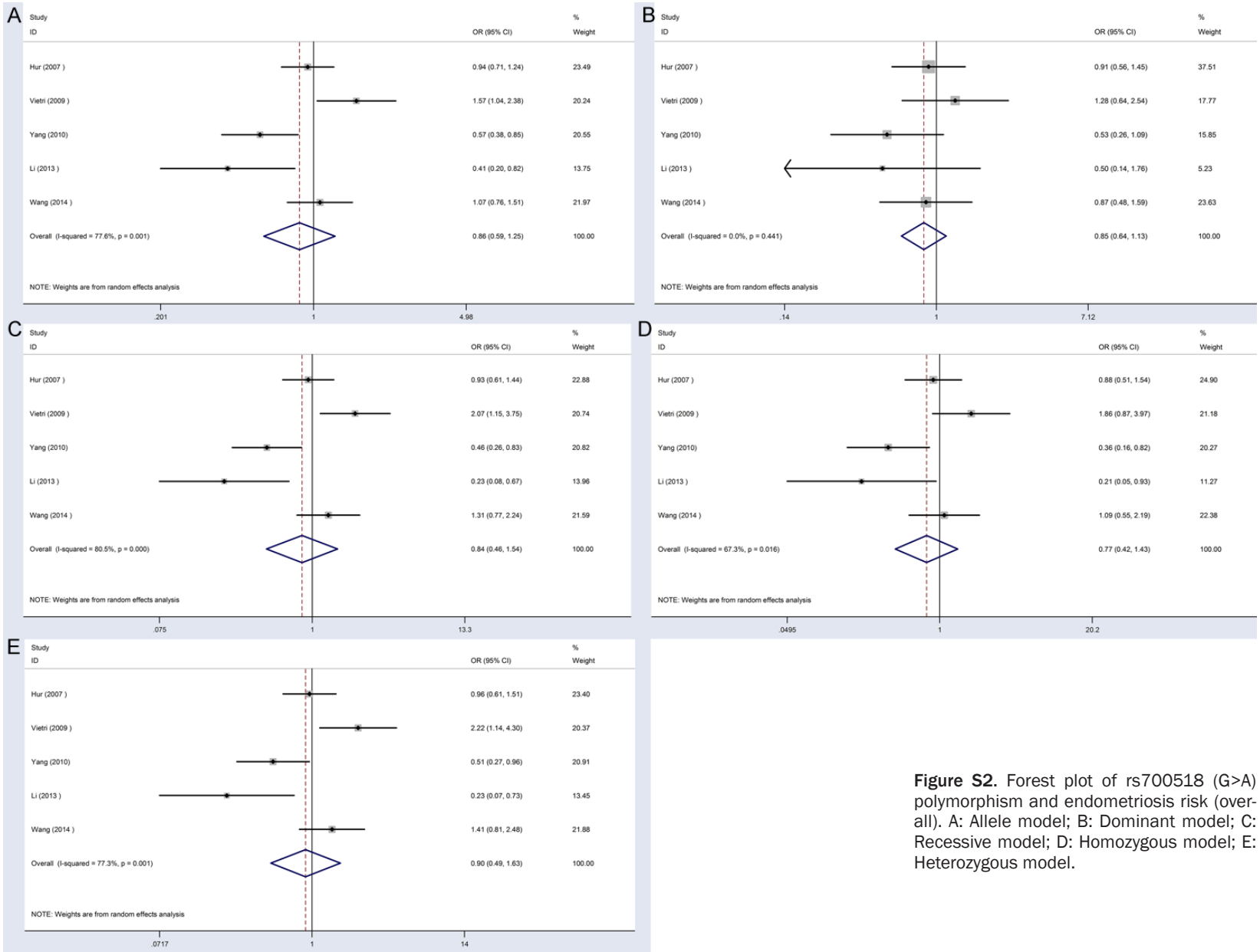

Figure S2. Forest plot of rs700518 (G>A) polymorphism and endometriosis risk (overall). A: Allele model; B: Dominant model; C: Recessive model; D: Homozygous model; E: Heterozygous model.

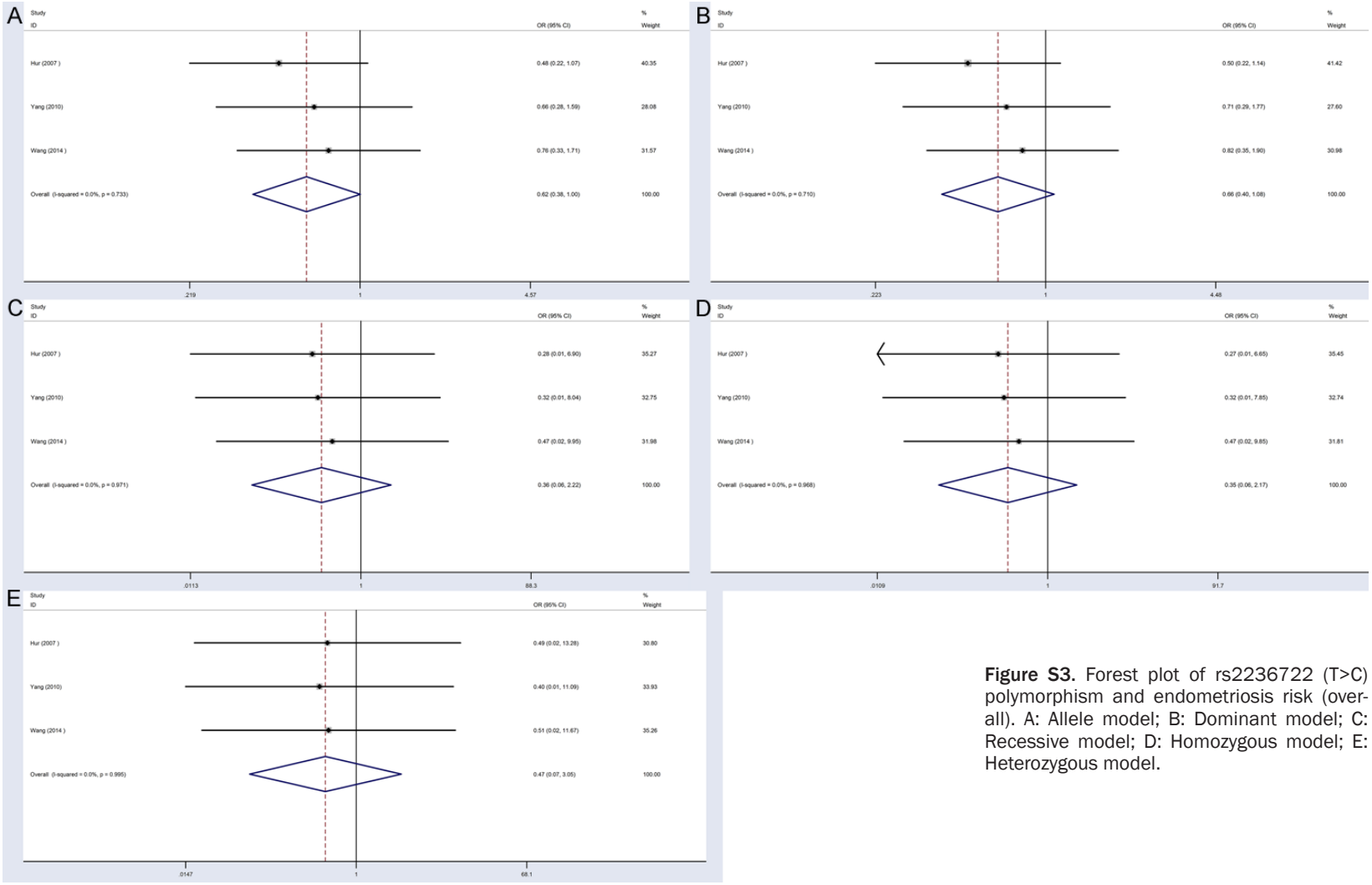

Figure S3. Forest plot of rs2236722 (T>C) polymorphism and endometriosis risk (overall). A: Allele model; B: Dominant model; C: Recessive model; D: Homozygous model; E: Heterozygous model.

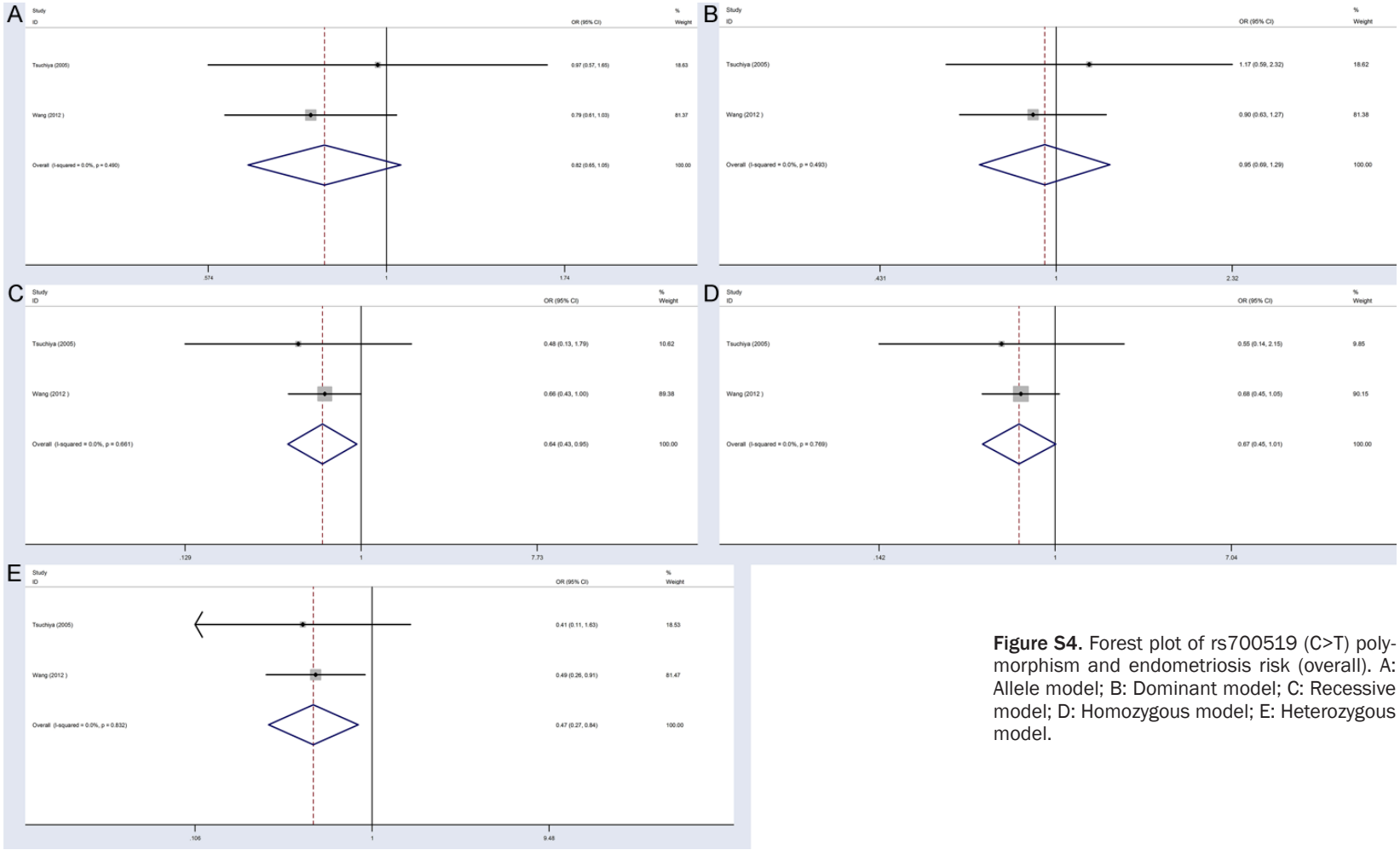

Figure S4. Forest plot of rs700519 (C>T) polymorphism and endometriosis risk (overall). A: Allele model; B: Dominant model; C: Recessive model; D: Homozygous model; E: Heterozygous model.