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REVIEW

Association between oestrogen receptor alpha (ESR1) gene polymorphisms and endometriosis: a meta-analysis of 24 case-control studies

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Abstract The PvuII (C > T), XbaI (A > G) and $(TA)_n$ polymorphisms of ESR1 gene are potentially associated with susceptibility to endometriosis. A meta-analysis was conducted to evaluate comprehensively the associations between endometriosis and ESR1 polymorphisms. Twenty-four studies, including 2740 cases and 3208 controls, were retrieved through searches of PubMed, EMBASE, Web of Science, CBM and CNKI. Meta-analyses showed that PvuII was associated with endometriosis only for stage I–III, only under a recessive model (OR = 1.53, 95% CI 1.05 to 2.21; P = 0.025). The short allele and TA_{13} of $(TA)_n$ were associated with a higher risk of endometriosis (OR_S = 1.71, 95% CI 1.01 to 2.81, P = 0.046; OR_{TA13} = 1.45, 95% CI 1.06 to 1.97, P_{TA13} = 0.019); TA_{20} repeats was associated with a lower risk (OR = 0.36, 95% CI 0.16 to 0.80; P = 0.012). No statistically significant association was found in the XbaI polymorphism. This meta-analysis indicated that the PvuII and XbaI polymorphisms were not associated with the risk of endometriosis, whereas stage classification of endometriosis was likely to influence the association of PvuII polymorphism. The $(TA)_n$ polymorphisms might play roles in the susceptibility to, or protection against, the pathogenesis of endometriosis.

KEYWORDS: endometriosis, estrogen receptor α, meta-analysis

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Introduction

Endometriosis is a common and highly investigated gynaecologic disease affecting 6–10% women of reproductive age. It is characterized by the presence of endometrial tissue, including endometrial glandular and stromal cells, outside the uterine cavity, mainly on the pelvic peritoneum, ovaries and in the rectovaginal septum (Giudice and Kao, 2004). Despite the high prevalence of this disease, its cause and pathophysiology remain obscure. Previous evidence has shown that endometriosis is a complex hormone-dependent disorder influenced by multiple environmental and genetic factors (Falconer et al., 2007; Rizner, 2009). Oestrogen receptor alpha, as the predominant form of oestrogen receptors in the normal endometrium, is encoded by the oestrogen receptor 1 (ESR1) gene. Therefore, genetic mutations in ESR1 may lead to aberrant gene expression and may be involved in pathogenesis and development of endometriosis.

A number of ESR1 polymorphisms, such as rs2234693, rs9340799, rs3138774, rs1884052, rs3020348, and rs1159327, have been investigated for their potential associations with endometriosis. Among these variants, two of the most studied are defined by the restriction enzymes PvuII (rs2234693, C > T) and XbaI (rs9340799, A > G) in intron 1 of ESR1, which have been evaluated in 25 studies (Chen et al., 2011; Ding et al., 2005; Dong et al., 2005; Fu et al., 2001, 2002; Georgiou et al., 1999; Govindan et al., 2009; Gu et al., 2012; Hsieh et al., 2007; Huang et al., 2005; Kim et al., 2005; Kitawaki et al., 2001; Lamp et al., 2011; Luisi et al., 2006; Matsuzaka et al., 2012; Paskulin et al., 2013; Renner et al., 2006; Shan et al., 2006; Song et al., 2005; Sun et al., 2010; Trabert et al., 2011; Wang et al., 2004; Xie et al., 2009; Zhang et al., 2007; Zhao et al., 2011) and 17 studies (Chen et al., 2011; Ding et al., 2005; Dong et al., 2005; Fu et al., 2002; Gu et al., 2012; Hsieh et al., 2007; Huang et al., 2005; Kim et al., 2005; Matsuzaka et al., 2012; Paskulin et al., 2013; Renner et al., 2006; Shan et al., 2006; Song et al., 2005; Sun et al., 2010; Trabert et al., 2011; Wang et al., 2004; Xie et al., 2009), respectively. The third most investigated polymorphism is the $(TA)_n$ dinucleotide repeat in the promoter region of ESR1, which has been evaluated in six studies (Georgiou et al., 1999; Hsieh et al., 2005; Kim et al., 2005; Lamp et al., 2011; Matsuzaka et al., 2012; Shan et al., 2006).

So far, the roles of these three variants in the pathogenesis of endometriosis remain controversial; the outcomes of the previously reported articles were inconsistent, and the three published meta-analyses (Guo, 2006; Hu et al., 2012; Li et al., 2012) have some limitations. The previous meta-analyses considered a relatively small sample size because some qualified studies were not included owing to limitations of search criteria and publication date. Meanwhile, the subgroup analyses were insufficient. Many factors that can cause heterogeneity were not fully considered. These limitations are likely to affect the accuracy of their results.

Moreover, it is also worth mentioning that several genome-wide association studies focusing on patients with endometriosis have been published to date. A number of susceptible polymorphisms in several related genes, such as CDKN2BAS, NFE2L3, WNT4, ID4 and GREB1, have been revealed (Adachi et al., 2010; Albertsen et al., 2013; Nyholt et al., 2012; Painter et al., 2011; Uno et al., 2010). To the best of our knowledge, no polymorphism in or near ESR1 gene associated with endometriosis has been detected. Most genome-wide association studies, however, were conducted in white people, whereas limited studies were conducted in other populations till now. In addition, genome-wide association studies of endometriosis are still ongoing, which indicates that endometriosis has not been adequately studied and many candidate genes have not yet been revealed.

On the basis of the above reasons, an updated meta-analysis of 24 detailed studies was conducted to further evaluate the association between ESR1 polymorphisms and endometriosis susceptibility.

Materials and methods

Literature search

Relevant papers published before October 2015 were searched in several electronic databases, particularly, PubMed, EMBASE, Web of Science, CBM (Chinese Biomedical Literature Database), and CNKI (China National Knowledge Infrastructure). No restrictions on language, population, or sample size were set in this meta-analysis. The search strategies were based on the combinations of the following keywords: ("estradiol receptor alpha" or "ER alpha" or "estrogen receptor 1" or "ESR1") and ("polymorphism" or "variant" or "mutation") and "endometriosis". Additional relevant literatures were obtained from the reference lists of the prospective articles.

Inclusion and exclusion criteria

Studies were included on the basis of the following criteria: full-text articles; original case-control or cohort study evaluating at least one of the three ESR1 polymorphisms linked with the risk of endometriosis; sufficient data to estimate an odds ratio (OR) and 95% confidence interval (CI); Chinese articles published in Chinese core periodicals; and no overlapping data. For the studies with the same authors, only those with the largest sample sizes or the most recent publication dates were selected to avoid overlapping patients and controls. Studies were excluded on the basis of the following criteria: meta-analyses, letters, reviews, or editorial articles; studies with no control cases; studies based on incomplete or sufficient data, such as deficiency of specific genotype distribution in cases and controls.

Data extraction

Two investigators (LZ and CG) independently extracted useful data from each study. Discrepancies were resolved through discussion. The following information was collected from each included study: name of the first author, year of publication, country of origin, ethnicity of descent, number of participants, source of control, detected sample, genotype method, genotype distribution in cases and controls, minor allele frequency, disease stage, outcomes, and probability

value for the test of Hardy–Weinberg equilibrium (HWE) in controls. According to the revised American Fertility Society classification (Brosens et al., 1985) of endometriosis, the severity of disease was classified as stages I–III (minimal to moderate) and stage IV (severe). Authorship and sample sources were also checked to identify the existence of multiple publications from the same study.

Quality evaluation of the included studies

The Newcastle–Ottawa Scale (NOS) (Wells et al., 2011) was used to assess the quality of the included studies by two investigators. The NOS quality score system ranges from zero to nine stars. The study with scores of seven stars or greater was categorized as "high quality"; otherwise, the study was categorized as "low quality". Discrepancies were resolved as described above.

Statistical analysis

Hardy–Weinberg equilibrium was assessed in the control group using chhi-squared test for goodness of fit, with $P < 0.05$ considered as a deviation. Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the strengths of the associations between the ESR1 polymorphisms and the risk of endometriosis. For PvuII (C > T) polymorphism, the risks of the allele model (T versus C), dominant model (TT + CT versus CC), recessive model (TT versus CT + CC), homozygous model (TT versus CC), and heterozygous model (CT versus CC) were evaluated. For the XbaI (A > G) polymorphism, the risks of the allele model (G versus A), dominant model (GG + AG versus AA), recessive model (GG versus AG + AA), homozygous model (GG versus AA), and heterozygous model (AG versus AA) were evaluated. For the $(TA)_n$ dinucleotide repeat polymorphism, the alleles with repeat numbers 10–29 were simplified as TA_{10}–TA_{29}, respectively. A cut-off point was set between TA_{19} and TA_{20}. Alleles ≤ 19 repeats were defined as short alleles (S), whereas alleles 20 repeats or more were regarded as long alleles (L). Allelic frequencies (S versus L, TA_{14} versus TA_{23} and TA_n vs. TA_{other}) were compared. The statistical significance of the pooled OR was determined by the Z test, with $P < 0.05$ indicating statistical significance. Heterogeneity was assessed by the Q-test and quantified by the I^2 test. When heterogeneity existed ($P < 0.05$ or $I^2 > 50\%$), the random-effects model (DerSimonian Laird method) was used; otherwise, the fixed-effects model (Mantel–Haenszel method) was used. In addition, subgroup analyses stratified by ethnicity (Asian or white), source of control (population-based or hospital-based), detected sample (blood or tissue), genotype method (polymerase chain reaction [PCR]-restriction fragment length polymorphism [RFLP] or other methods), HWE in controls (yes or no), NOS quality score (high or low), and disease stage (stage I–III or stage IV) were evaluated. Sensitivity analysis was used to assess the quality and stability of the results. Begg's test and Egger's test were used to evaluate potential publication bias, with $P < 0.05$ considered as statistically significant. All analyses were conducted by Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the included studies

A detailed flow chart of the inclusion and exclusion process is presented in **Figure 1**. A total of 302 citations were identified in the initial search. After removed duplicates, 225 articles were excluded. After title and abstract screened, the remaining 34 articles were screened in full texts. Three articles were excluded for only being related to the other polymorphisms of ESR1 (Sato et al., 2008; Wang et al., 2013; Wu et al., 2013) and three for meta-analyses (Guo, 2006; Hu et al., 2012; Li et al., 2012). One investigation was excluded for not providing detail information of genotype or allele frequency (Matsuzaka et al., 2012) and one for duplicate data (Li and Xie, 2010). One study was excluded because it did not use healthy controls (Luisi et al., 2006), and one study was excluded because it focused on gene polymorphism (Huang et al., 2014). Finally, 24 studies (Chen et al., 2011; Ding et al., 2005; Dong et al., 2005; Fu et al., 2001, 2002; Georgiou et al., 1999; Govindan et al., 2009; Gu et al., 2012; Hsieh et al., 2005, 2007; Huang et al., 2005; Kim et al., 2005; Kitawaki et al., 2001; Lamp et al., 2011; Paskulin et al., 2013; Renner et al., 2006; Shan et al., 2006; Song et al., 2005; Sun et al., 2010; Trabert et al., 2011; Wang et al., 2004; Xie et al., 2009; Zhang et al., 2007; Zhao et al., 2011), including 2740 cases and 3208 controls were retrieved in this meta-analysis based on the inclusion and exclusion criteria. The publication year of the included studies ranged from 1999 to 2013. Studies were carried out in China, Japan, Korea, India, Greece, Germany, Estonia America and Brazil. The participants of the 19 studies were Asian and in the remaining five studies they were white. Thirteen studies used hospital-based controls, whereas 11 studies used population-based controls. A total of 21 studies extracted DNA samples from peripheral blood and three studies from tissue. The genotype assays included PCR, PCR–RFLP, autoradiography PCR, fluorescent PCR, DNA sequencing, high-resolution melt, and TaqMan assay. In all studies, HWE test was conducted on the genotype of controls. The NOS scores of eligible studies were five to nine stars. Among them, 17 studies were considered as high quality, and seven studies were considered a low quality. The main characteristics and genotype distributions of PvuII and XbaI polymorphisms of ESR1 gene in all included studies are presented in **Table 1**. The main characteristics and genotype distributions of $(TA)_n$ polymorphism of ESR1 gene are shown in **Table 2**.

Quantitative data synthesis

A total of 23 studies, which included 2621 cases and 3100 controls, discussed the association of the PvuII polymorphism with endometriosis, and the main results are presented in **Table 3**. The random-effects model was selected because the heterogeneity was significant in all models. The results indicate that the ESR1 PvuII (C > T) polymorphism is not associated with endometriosis risk under all genetic models (allele model: OR = 0.95, 95% CI 0.79 to 1.14) (Supplementary Figure S1A); dominant model: OR = 0.89, 95% CI 0.69 to 1.15 (Supplementary Figure S1B); recessive model: OR = 0.82, 95% CI 0.63 to 1.07 (Supplementary Figure S1C); homozygous model: OR = 0.75,

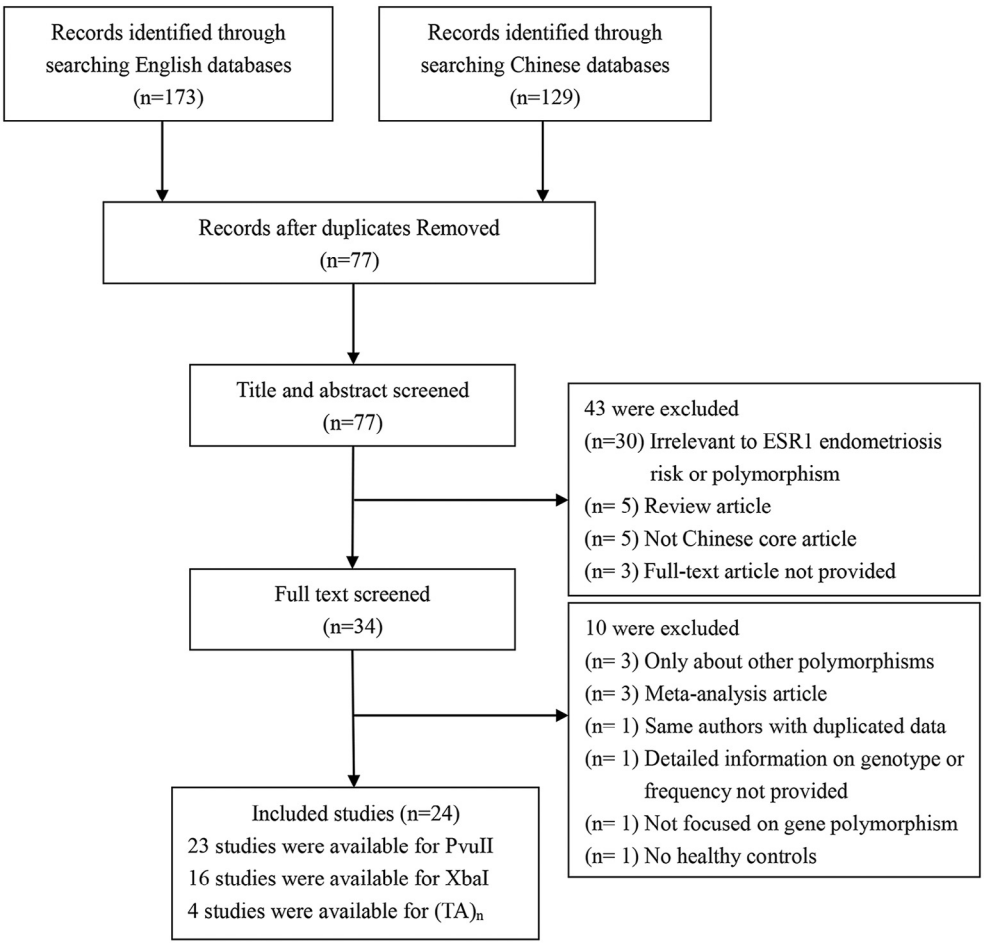

Figure 1 Study search and selection process.

95% CI 0.53 to 1.08 (Supplementary Figure S1D); and heterozygous model: OR = 0.95, 95% CI 0.77 to 1.18 (Supplementary Figure S1E). In the subgroup analyses by ethnicity, control source, detected sample, genotype method, and quality score, associations were still not found. When stratifying by HWE in control, however, an association was observed among studies with controls that deviated from the HWE (dominant model: OR = 0.54, 95% CI 0.37 to 0.81; P = 0.002). Four studies that focused on women with endometriosis stage I–III cases and five studies that focused on women with endometriosis stage IV according to the revised American Fertility Society grade were also identified. The result showed that the recessive model (OR = 1.53, 95% CI 1.05 to 2.21; $P = 0.025$) was associated with increased risk of stage I–III endometriosis (**Figure 2**).

A total of 16 studies, which included 1640 cases and 2081controls, reported the potential association between the XbaI (A > G) polymorphism and the pathogenesis of endometriosis. Heterogeneity was observed under the allele, dominant, homozygous and heterozygous models; therefore, the random-effects model was used. No associations were observed in all models (allele model: OR = 1.11, 95% CI 0.94 to 1.32) (Supplementary Figure S2A); dominant model: OR = 1.12, 95% CI 0.90 to 1.38 (Supplementary Figure S2B); recessive model: OR = 1.24, 95% CI 0.96 to 1.59 (Supplementary Figure S2C); homozygous model: OR = 1.32, 95% CI 0.88 to 1.98 (Supplementary Figure S2D) and heterozygous model: OR = 1.09, 95% CI 0.88 to 1.35 (Supplementary Figure S2E). Upon stratifying by genotype method, a slight association was observed among studies that did not apply the PCR–RFLP method (recessive model: OR = 2.47, 95% CI 1.09 to 5.60; $P = 0.031$) (**Table 4**).

Furthermore, the associations between the $(TA)_n$ dinucleotide repeat polymorphism and endometriosis in four related studies were evaluated. The number of tandem repeats (TA) varied between 10 and 27 in the endometriosis group and between 10 and 29 in the control group. Among these reported articles, no consensus on the optimal cut-off point was reached to classify the alleles. Therefore, the median number, between TA_{19} and TA_{20}, was set as the cut-off point in this meta-analysis. The S versus L comparison between cases and controls showed an association of the S allele to the risk of endometriosis (OR = 1.71, 95% CI 1.01 to 2.81; $P = 0.046$), especially in one single study that recruited a white population and population-based controls and showed a high NOS score (OR = 1.92, 95% CI 1.13 to 3.26; $P = 0.017$ in **Figure 3**). TA_{14} and TA_{23} were the two most common alleles found in the S and L groups; therefore, these two alleles were compared to identify the exact susceptible allele. No associations were observed between TA_{14} and TA_{23} (OR = 1.56, 95% CI 0.76 to 3.2) (Supplementary Figure S3 and **Table 5**). In addition, each specific length of TA repeats (TA_n) was compared with all other

Table 1 The main characteristics and genotype distributions of PvuII and XbaI polymorphisms of ESR1 gene in all eligible studies.

Number	First author	Year	Country	Ethnicity	SNP	Control source	Genotype method	Detected sample	Case group					Control group					NOS
									Total	M/M	M/W	W/W	MAF	Total	M/M	M/W	W/W	MAF	
1	Georgiou	1999	Greece	White	PvuII	PB	PCR	Blood	57	2	28	27	0.28	57	16	26	15	0.49	8
2	Fu	2001	China	Asian	PvuII	PB	PCR-RFLP	Blood	50	22	22	6	0.34	50	17	23	10	0.43	7
3	Kitawaki	2001	Japan	Asian	PvuII	PB	PCR-RFLP	Blood	109	36	59	14	0.4	27	3	12	12	0.33	7
4	Fu	2002	China	Asian	PvuII	HB	PCR-RFLP	Blood	63	25	26	12	0.4	41	27	11	3	0.21	8
4	Fu	2002	China	Asian	XbaI	HB	PCR-RFLP	Blood	63	9	24	30	0.33	41	3	14	24	0.24	8
5	Wang	2004	Japan	Asian	PvuII	PB	PCR-RFLP	Blood	121	48	49	24	0.40	172	47	88	37	0.47	5
5	Wang	2004	Japan	Asian	XbaI	PB	PCR-RFLP	Blood	122	6	38	78	0.20	171	12	56	103	0.23	5
6	Ding	2005	China	Asian	PvuII	HB	PCR-RFLP	Blood	85	29	49	7	0.37	105	40	53	12	0.37	8
6	Ding	2005	China	Asian	XbaI	HB	PCR-RFLP	Blood	85	3	31	51	0.22	105	8	44	53	0.29	8
7	Dong	2005	China	Asian	PvuII	HB	PCR-RFLP	Blood	65	42	16	7	0.23	107	46	49	12	0.34	8
7	Dong	2005	China	Asian	XbaI	HB	PCR-RFLP	Blood	65	5	19	41	0.22	107	5	26	76	0.17	5
9	Huang	2005	China	Asian	PvuII	PB	PCR-RFLP	Blood	85	23	49	13	0.44	90	42	39	9	0.32	6
9	Huang	2005	China	Asian	XbaI	PB	PCR-RFLP	Blood	85	5	38	42	0.28	90	4	36	50	0.24	6
10	Kim	2005	Korea	Asian	PvuII	HB	PCR-RFLP	Blood	180	73	84	23	0.36	165	66	67	32	0.40	6
10	Kim	2005	Korea	Asian	XbaI	HB	PCR-RFLP	Blood	180	5	50	125	0.17	165	8	45	112	0.18	6
11	Song	2005	China	Asian	PvuII	HB	PCR-RFLP	Blood	49	19	21	9	0.40	50	16	22	12	0.46	8
11	Song	2005	China	Asian	XbaI	HB	PCR-RFLP	Blood	49	5	17	27	0.28	50	4	25	21	0.33	8
12	Renner	2006	Germany	White	PvuII	PB	PCR-RFLP	Blood	98	58	20	20	0.31	98	53	29	16	0.31	8
12	Renner	2006	Germany	White	XbaI	PB	PCR-RFLP	Blood	98	11	25	62	0.24	98	12	26	60	0.26	8
13	Shan	2006	China	Asian	PvuII	HB	PCR-RFLP	Blood	40	16	15	9	0.41	52	19	24	9	0.37	5
13	Shan	2006	China	Asian	XbaI	HB	PCR-RFLP	Blood	40	3	18	19	0.30	52	5	18	29	0.27	5
14	Hsieh	2007	China	Asian	PvuII	PB	PCR-RFLP	Blood	112	27	68	17	0.46	110	60	44	6	0.25	7
14	Hsieh	2007	China	Asian	XbaI	PB	PCR-RFLP	Blood	112	18	64	30	0.45	110	2	71	37	0.34	7
15	Zhang	2007	China	Asian	PvuII	HB	PCR-RFLP	Blood	78	31	32	15	0.40	81	48	29	4	0.23	7
16	Govindan	2009	India	Asian	PvuII	PB	PCR-RFLP	Blood	110	5	32	73	0.19	115	29	32	54	0.30	7
17	Xie	2009	China	Asian	PvuII	PB	PCR-RFLP	Tissue	214	62	122	30	0.43	160	64	76	20	0.36	7
17	Xie	2009	China	Asian	XbaI	PB	PCR-RFLP	Tissue	214	10	92	112	0.26	160	10	40	110	0.19	7
18	Sun	2010	China	Asian	PvuII	HB	DNA-Seq	Tissue	60	18	33	9	0.43	56	22	23	11	0.40	6
18	Sun	2010	China	Asian	XbaI	HB	DNA-Seq	Tissue	60	1	18	41	0.17	56	1	21	34	0.21	6
19	Chen	2011	China	Asian	PvuII	HB	PCR-RFLP	Blood	56	25	21	10	0.37	78	31	38	9	0.36	7
19	Chen	2011	China	Asian	XbaI	HB	PCR-RFLP	Blood	56	2	18	36	0.20	78	2	32	44	0.23	7
20	Lamp	2011	Estonia	White	PvuII	PB	PCR-RFLP	Blood	150	35	76	39	0.45	199	59	102	38	0.47	6
21	Trabert	2011	USA	White	PvuII	PB	PCR-RFLP	Blood	255	81	129	45	0.43	558	173	280	105	0.44	7
21	Trabert	2011	USA	White	XbaI	PB	PCR-RFLP	Blood	256	28	105	123	0.31	558	60	244	254	0.33	7
22	Zhao	2011	China	Asian	PvuII	HB	HRM	Blood	429	1	29	399	0.04	489	0	19	470	0.02	7
23	Gu	2012	China	Asian	PvuII	HB	PCR-RFLP	Tissue	57	20	28	9	0.40	106	33	63	10	0.39	7
23	Gu	2012	China	Asian	XbaI	HB	PCR-RFLP	Tissue	57	5	19	33	0.25	106	2	40	64	0.20	7
24	Paskulin	2013	Brazil	White	PvuII	HB	TaqMan	Blood	98	26	54	18	0.46	134	38	69	27	0.46	7
24	Paskulin	2013	Brazil	White	XbaI	HB	TaqMan	Blood	98	16	55	27	0.44	134	9	54	71	0.27	7

ESR1, oestrogen receptor alpha; HB, hospital-based; HRM, high resolution melt; M, mutant allele; MAF, minor allele frequency; NOS, Newcastle–Ottawa Scale; PB, population-based; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SNP, single nucleotide polymorphism; W, wild allele; W/M, heterozygote; W/W, wild homozygote.

Table 2 The main characteristics and genotype distributions of $(TA)_n$ of ESR1 gene in all eligible studies.

Number	First author	Year	Country	Ethnicity	Control Source	Genotype method	Detected sample	Case group						Control group						NOS
								Total	Short	Long	TA — 13	TA — 14	TA — 20	Total	Short	Long	TA — 13	TA — 14	TA — 20	TA — 23	
1	Georgiou	1999	Greece	Caucasian	PB	PCR	Blood	57	74	40	12	19	4	11	57	56	58	7	15	9	14	8
8	Hsieh	2005	China	Asian	HB	Autoradiography PCR	Blood	119	192	46	25	70	4	9	108	161	55	17	36	10	14	5
10	Kim	2005	Korea	Asian	HB	Fluorescent PCR	Blood	180	272	88	71	66	13	20	165	250	80	46	62	16	15	6
13	Shan	2006	China	Asian	HB	DNA-seq	Blood	36	64	8	8	4	4	0	34	42	26	8	6	22	2	5

ESR1, ostrogen receptor alpha; HB, hospital-based; PB, population-based; PCR, polymerase chain reaction; NOS, Newcastle–Ottawa Scale.

TA repeats ($TA_{10-29\ without\ n}$). The results showed that associations were observed between the TA_{13} repeats and the risk of endometriosis (OR = 1.45, 95% CI 1.06 to 1.97; $P = 0.019$) and between the TA_{20} repeats and the risk of endometriosis (OR = 0.36, 95% CI 0.16 to 0.80; $P = 0.012$) (**Table 5**, Supplementary Table S1 and Figure S3).

Heterogeneity and sensitivity analysis

For the ESR1 PvuII (C > T) polymorphism, the heterogeneity was observed in overall comparisons as well as subgroup analyses. For the XbaI (A > G) polymorphism, the heterogeneity was observed under the allele, dominant, homozygous and heterozygous models. In addition, the heterogeneity was also observed in S versus L, TA_{14} versus TA_{23}, and TA_{20} versus TA_{others}. To explore the sources of heterogeneity, we assessed all of the comparison models by ethnicity, control source, detected sample, genotype method, HWE in controls, quality score, and disease stage. None of these variables, however, could explain the heterogeneity.

In the sensitivity analysis, eligible studies were sequentially removed to assess the influence of each individual study on the pooled ORs. The results showed that the pooled ORs were not qualitatively changed when any single study was omitted under PuvII, XbaI, and $(TA)_n$ polymorphisms (**Figure 4**), suggesting that the analysis was reliable and robust.

Publication bias

To identify potential publication bias, the Begger's funnel plot and Egger's linear regression test was carried out on all models of the PvuII and XbaI polymorphisms in the ESR1 gene. Neither of the studies tested indicated publication bias. Using the PvuII (C > T) polymorphism as an example, the shapes of the Begger's funnel plot did not show obvious asymmetry (**Figure 5**), and the Egger's test did not reveal any evidence of publication bias (allele model: t = 0.29; dominant model: t = –0.64; recessive model: t = –0.56; homozygous model: t = –0.95; and heterozygous model: t = –0.38).

Discussion

The PvuII (C > T), XbaI (A > G), and $(TA)_n$ polymorphisms of ESR1 gene are hot loci that have been reported to be correlated with many diseases, such as endometrial cancer (Ashton et al., 2010), systemic lupus erythematous (Cai et al., 2014), and hip fractures (Zhou et al., 2013). Guo (2006) first conducted a meta-analysis on the association of the PvuII and $(TA)_n$ repeat polymorphisms with endometriosis. Because of the publication date restriction, he only enrolled two studies that investigated PuvII (C > T) polymorphism and two studies that investigated $(TA)_n$ polymorphism. Hu et al. (2012) conducted a meta-analysis, in which eight studies focused on PuvII (C > T) and four studies focused on XbaI (A > G) were enrolled with a restriction of including only studies reported in English. Considering that only a few eligible studies were included with considerable unexplainable heterogeneity, we should view these two meta-analyses as preliminary. A recent

Table 3 Main results of the pooled data in the meta-analysis of PvuII (C > T) polymorphism.

Groups	*Number of studies*	*Allele model* (T versus C) OR[95%CI]	*Dominant model* (TT + CT versus CC) OR[95%CI]	*Recessive model* (TT versus CT + CC) OR[95%CI]	*Homozygous model* (TT versus CC) OR[95%CI]	*Heterozygous model* (CT versus CC) OR[95%CI]
Overall ethnicity	23	0.95 [0.79 to 1.14]	0.89 [0.69 to 1.15]	0.82 [0.63 to 1.07]	0.75 [0.53 to 1.08]	0.95 [0.77 to 1.18]
Caucasian	5	0.83 [0.63 to 1.10]	0.81 [0.58 to 1.13]	0.83 [0.54 to 1.26]	0.69 [0.39 to 1.23]	0.88 [0.67 to 1.14]
Asian	18	1.00 [0.79 to 1.27]	0.93 [0.66 to 1.30]	0.84 [0.59 to 1.18]	0.79 [0.50 to 1.26]	1.00 [0.76 to 1.33]
Control source						
PB	11	0.86 [0.66 to 1.13]	0.83 [0.58 to 1.20]	0.69 [0.44 to 1.09]	0.65 [0.36 to 1.17]	0.91 [0.70 to 1.19]
HB	12	1.05 [0.18 to 1.35]	0.89 [0.69 to 1.15]	0.95 [0.71 to 1.28]	0.90 [0.61 to 1.32]	0.99 [0.70 to 1.40]
Detected sample						
Blood	20	0.97 [0.78 to 1.20]	0.89 [0.67 to 1.19]	0.83 [0.61 to 1.12]	0.75 [0.50 to 1.14]	0.95 [0.75 to 1.20]
Tissue	3	0.83[0.67 to 1.05]	0.88 [0.57 to 1.38]	0.75 [0.50 to 1.12]	0.72 [0.44 to 1.18]	0.99 [0.53 to 1.84]
Genotype method						
PCR-RFLP	19	0.96 [0.79 to 1.18]	0.86 [0.65 to 1.13]	0.86 [0.64 to 1.15]	0.78 [0.53, 1.14]	0.90 [0.71 to 1.14]
Other methods	4	0.90 [0.50 to 1.60]	1.05 [0.54 to 2.04]	0.56 [0.22 to 1.44]	0.61 [0.17, 2.19]	1.24 [0.76 to 2.02]
HWE in control						
Yes	20	0.96 [0.78 to 1.19]	0.96 [0.73 to 1.26]	0.84 [0.64 to 1.14]	0.82 [0.57, 1.20]	1.02 [0.83 to 1.29]
No	3	0.89 [0.69 to 1.15]	0.54 [0.37 to 0.81][a]	0.63 [0.20 to 2.04]	0.43 [0.13, 1.41]	0.63 [0.41, 0.99][a]
Quality score						
High	17	0.92 [0.73 to 1.15]	0.86 [0.61 to 1.20]	0.80 [0.56 to 1.13]	0.70 [0.43, 1.13]	0.93 [0.71, 1.22]
Low	6	1.05 [0.75 to 1.46]	0.98 [0.69 to 1.38]	0.88 [0.59 to 1.32]	0.92 [0.57, 1.47]	1.00 [0.71, 1.42]
Disease stage						
I–III	4	1.30[1.00 to 1.71]	1.15[0.69 to 1.89]	1.53[1.05 to 2.21][a]	1.40[0.82, 2.39]	0.91[0.55, 1.58]
IV	5	0.83 [0.50 to 1.36]	0.66[0.40 to 1.07]	0.87[0.38 to 1.97]	0.65[0.27, 1.55]	0.99[0.41, 2.43]

[a] $P < 0.05$.

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

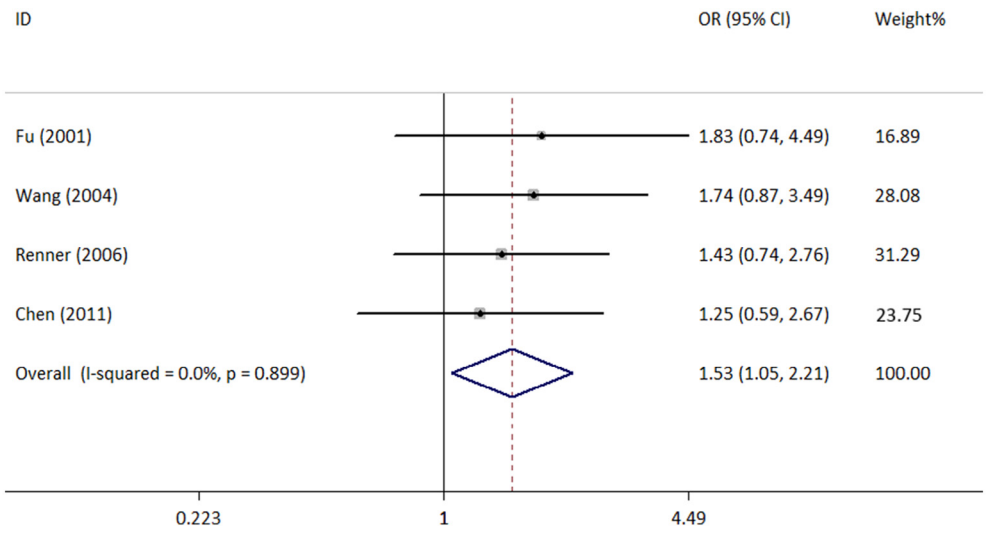

Figure 2 Odds ratios for the association between PvuII (C > T) polymorphism and susceptibility to stage I–III endometriosis.

meta-analysis conducted by Li et al. (2012) retrieved 20 studies focusing on PuvII (C > T) and 15 studies focusing on XbaI (A > G), and indicated that the PuvII (C > T) polymorphism is associated with endometriosis risk in white populations. Their inclusion criteria, however, were not strict. For example, their meta-analysis included Luisi et al. (2006)'s study, which chose recurrent endometriosis patients as cases and first-time endometriosis patients as controls. Clearly, this study should not have been included in the meta-analysis. After this article was eliminated, and four new published studies included in our meta-analysis, no positive finding was identified in white people. In addition, the subgroup analyses were insufficient. Many factors that can cause heterogeneity, such as sources of control, genotype method, and disease stage, were not fully considered. In addition, wild-type (C) and mutant-type (T) alleles of the PvuII polymorphism apparently were confused, contributing to analytical errors and relatively unconvincing results. Therefore, based on the above factors, an updated meta-analysis was conducted of all eligible case–control studies that investigated the risk of endometriosis to explore more precise relationships of the PvuII, XbaI, and $(TA)_n$ polymorphisms of the ESR1 gene to the risk of endometriosis.

Sequentially, the present meta-analysis consisted of 24 studies, including 2740 endometriosis cases and 3208 controls. When all the eligible studies were pooled into the meta-analysis, the result indicated that the PvuII (C > T) polymorphism is not a risk factor of endometriosis under all models, although many studies have indicated that this polymorphism is related to the pathogenesis of endometriosis (Dong et al., 2005; Fu et al., 2002; Georgiou et al., 1999; Govindan et al., 2009; Hsieh et al., 2005; Huang et al., 2005; Kitawaki et al., 2001). These contradictory findings might have been caused by the considerable heterogeneity that resulted from ethnicity, control source, detected sample, and genotype methods in the different studies. Therefore, we conducted subgroup analyses based on the above-mentioned factors. When using non-HWE women as controls, women carrying T allele presented an increased risk of endometriosis compared with women carrying CC genotype. Given that non-HWE may result from many causes, especially a small sample size, this result is most likely attributed to small-study bias and has no clinical significance. In the subgroup analysis stratified by the revised American Fertility Society stage, women carrying TT genotype might present an increased risk of stage I–III endometriosis compared with those carrying CT or CC genotype. Surprisingly, the same result was not observed in the stage IV group. To better interpret the result, some hypotheses were drawn. First, the revised American Fertility Society disease stage depends on the location, type, size, and depth of invasion of the lesions and is correlated with the progression of endometriosis to some extent (Fauconnier et al., 2009; Gentilini et al., 2008; Vercellini et al., 2007). Hence, the TT genotype of PvuII polymorphism may represent a risk factor for the implantation of endometrial debris refluxed into pelvic cavity but not for the development and invasion process. Second, because the data of the revised American Fertiliy Society stage were extracted from studies whose primary aims were to analyse gene polymorphism with and without endometriosis in general, the sample size may be relatively insufficient to provide reliable subgroup analyses and produce firm conclusions. In the analyses of the XbaI (A > G) polymorphism, no associations were found in all models. When using non-PCR–RFLP method to identify XbaI polymorphism, women with GG genotype presented a higher risk of endometriosis compared with women with A allele. As only two published articles were included, a small-study bias may have arisen from the results in this regard. For the $(TA)_n$ repeat polymorphism, the S allele portended a higher risk of endometriosis compared with the L allele, especially in one study with a high NOS score that involved a white population and population-based controls. This finding showed that the S allele of $(TA)_n$ polymorphism may be associated with susceptibility to endometriosis. Furthermore, the results also suggested that TA_{13} repeats may be a pathogenic site while TA_{20} repeats may be a protective factor of endometriosis.

In addition, two special issues should be considered when interpreting the results. The first one is the selection of controls. In case-control studies, it is common to recruit controls from the hospital population or the healthy public population. Normally, population-based controls are ideal choices

Table 4 Main results of the pooled data in the meta-analysis of XbaI (A > G) polymorphism.

Groups	*Number of studies*	*Allele model* (G versus A) OR [95% CI]	*Dominant model* (GG + AG versus AA) OR [95%CI]	*Recessive model* (GG versus AG + AA) OR [95% CI]	*Homozygous model* (GG versus AA) OR [95% CI]	*Heterozygous model* (AG versus AA) OR [95% CI]
Overall ethnicity	16	1.11 [0.94 to 1.32]	1.12 [0.90 to 1.38]	1.24 [0.96 to 1.59]	1.32 [0.88 to 1.98]	1.09 [0.88 to 1.35]
Asian	13	1.09 [0.91 to 1.29]	1.08 [0.87 to 1.34]	1.26 [0.90 to 1.78]	1.25 [0.78 to 2.02]	1.06 [0.84 to 1.33]
Caucasian	3	1.23 [0.72 to 2.10]	1.32 [0.64 to 2.73]	1.21 [0.84 to 1.75]	1.52 [0.59 to 3.94]	1.28 [0.64 to 2.55]
Control source						
HB	10	1.09 [0.84 to 1.43]	1.08 [0.78 to 1.50]	1.39 [0.92 to 2.08]	1.42 [0.78 to 2.60]	1.04 [0.77 to 1.42]
PB	6	1.13 [0.90 to 1.41]	1.16 [0.86 to 1.55]	1.16 [0.84 to 1.59]	1.19 [0.88 to 1.98]	1.15 [0.84 to 1.59]
Detected sample						
Blood	13	1.09 [0.90 to 1.32]	1.08 [0.86 to 1.35]	1.25 [0.96 to 1.63]	1.29 [0.82 to 2.04]	1.24 [0.93 to 1.64]
Tissue	3	1.26 [0.872 to 1.81]	1.24 [0.67 to 2.29]	1.16 [0.56 to 2.43]	1.52 [0.53 to 4.36]	0.87 [0.41 to 1.87]
Genotype method						
PCR-RFLP	14	1.07 [0.92 to 1.24]	1.06 [0.88 to 1.28]	1.15 [0.88 to 1.50]	1.15 [0.79 to 1.67]	1.05 [0.86 to 1.27]
Other methods	2	1.35 [0.49 to 3.69]	1.49 [0.37 to 6.00]	2.47[1.09 to 5.60][a]	3.34 [0.87 to 12.79]	1.41 [0.39 to 5.19]
HWE in control						
Yes	13	1.06 [0.88 to 1.28]	1.05 [0.83 to 1.32]	1.16 [0.87 to 1.55]	1.24 [0.81 to 1.92]	1.02 [0.82 to 1.27]
No	3	1.34 [0.94 to 1.32]	1.41 [0.90 to 1.38]	1.51 [0.90 to 2.57]	0.34 [0.88 to 1.98]	1.38 [0.88 to 2.43]
Quality score						
High	10	1.16 [0.92 to 1.47]	1.02 [0.80 to 1.30]	1.36 [1.02 to 1.81]	1.56 [0.89 to 2.74]	1.04 [0.81 to 1.34]
Low	6	1.00 [0.81 to 1.22]	1.15 [0.90 to 1.38]	0.90 [0.53 to 1.53]	0.93 [0.53 to 1.61]	1.10 [0.80 to 1.51]
Disease stage						
I–III	3	0.81 [0.55 to 1.19]	0.78 [0.49 to 1.25]	0.70 [0.29 to 1.67]	0.70 [0.29 to 1.71]	0.83 [0.51 to 1.34]
IV	4	1.09 [0.76 to 1.56]	1.04 [0.74 to 1.45]	2.05 [0.63 to 1.67]	1.95 [0.58 to 6.57]	0.95 [0.17 to 1.37]

[a] $P < 0.05$.

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

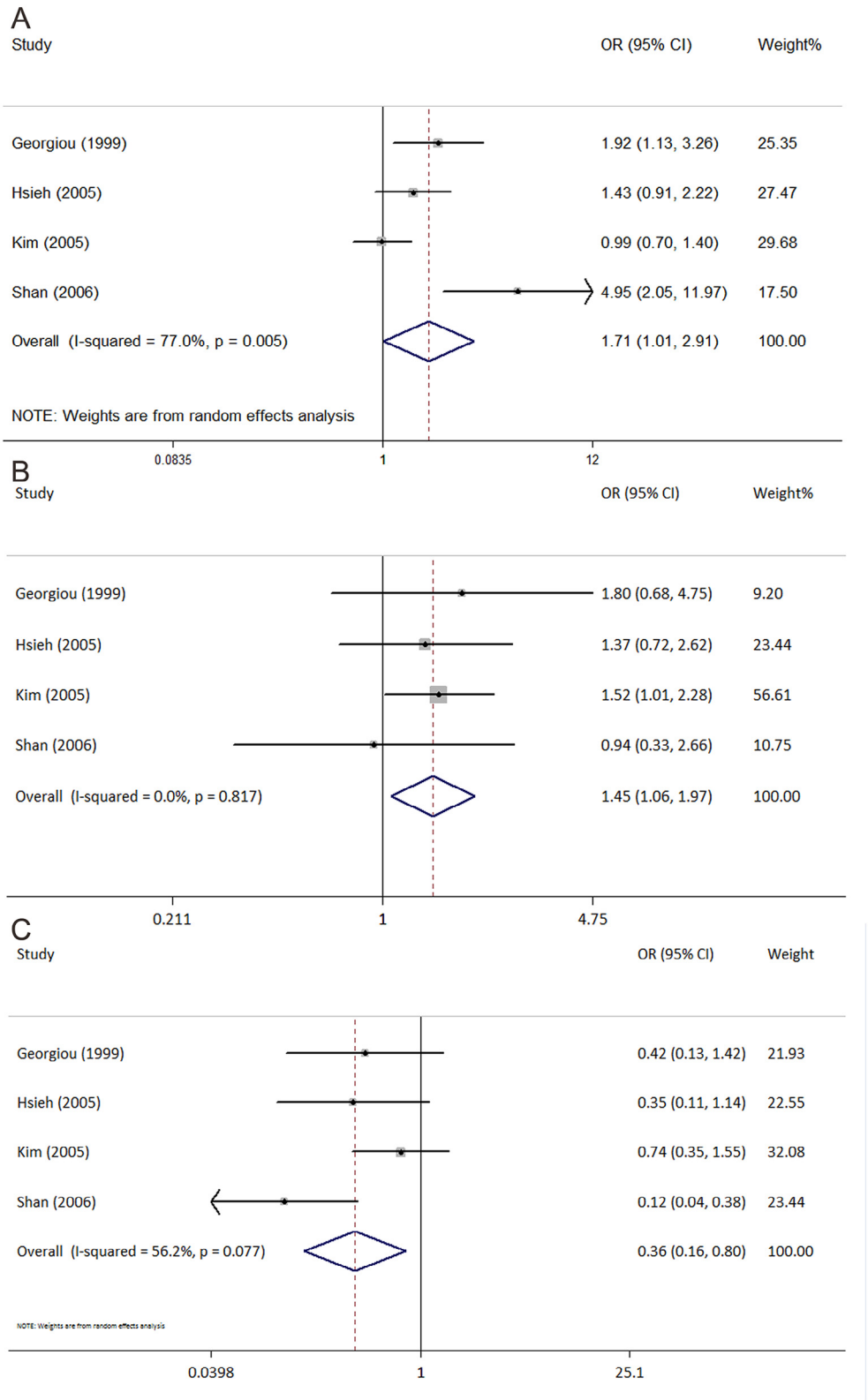

Figure 3 Odds ratios for subgroup analysis of the association between $(TA)_n$ and endometriosis. "A" represents S versus L; "B" represents TA_{13} versus TA_{others}; "C" represents TA_{20} vs. TA_{others}.

because hopsital-based controls suffering from other disorders could carry the same pathogenic sites of endometriosis. The population-based control group, however, might contain some asymptomatic endometriosis patients, which could confound the "purity" of the healthy controls and influence the heterogeneity and final result. The second issue is the ethnicity of research subjects. The "ethnicity" issue has a strong effect on genetic association studies. In the

Table 5 Main results of the pooled data in the meta-analysis of $(TA)_n$ polymorphism.

Groups	Number of studies	S versus L	TA_{14} versus TA_{23}	TA_{13} versus TA_{others}	TA_{20} versus TA_{others}
		OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95%CI]
Overall ethnicity	4	1.71 [1.01 to 2.91][a]	1.56 [0.76 to 3.20]	1.45 [1.06 to 1.97][a]	0.36 [0.17 to 0.80][a]
Caucasian	1	1.92 [1.13 to 3.26][a]	1.61[0.57 to 4.56]	1.80 [0.68 to 4.75]	0.42 [0.12 to 1.42]
Asian	3	1.70 [0.84 to 3.43]	1.63 [0.54 to 4.91]	1.41 [1.02 to 1.95][a]	0.34 [0.12 to 0.99][a]
Source of control					
PB	1	1.92 [1.13 to 3.26][a]	1.61[0.57 to 4.56]	1.80 [0.68 to 4.75]	0.42 [0.12 to 1.42]
HB	3	1.70 [0.84 to 3.43]	1.63 [0.54 to 4.91]	1.41 [1.02 to 1.95][a]	0.34 [0.12 to 0.99][a]
NOS score					
High	1	1.92 [1.13 to 3.26][a]	1.61[0.57 to 4.56]	1.80 [0.68 to 4.75]	0.42 [0.12 to 1.42]
Low	3	1.70 [0.84 to 3.43]	1.63 [0.54 to 4.91]	1.41 [1.02 to 1.95][a]	0.34 [0.12 to 0.99][a]

[a] $P < 0.05$.
HB, hospital-based, PB, population-based.

present study, only Asian and white participants have been analysed because no studies focusing on Hispanics and African Americans have been reported. Therefore, associations derived from specific racial and ethnic groups might occur in future studies.

The present meta-analysis also involved some limitations that should be mentioned. First, two studies (Lamp et al., 2011; Matsuzaka et al., 2012) focused on the $(TA)_n$ dinucleotide repeat polymorphism, and one study (Matsuzaka et al., 2012) focused on the other two analysed polymorphisms, but insufficient genotype details were provided for analysis. This limitation may influence the accuracy of the meta-analysis results and cause a misinterpretation of the association between the TA repeat polymorphism and endometriosis risk. Second, this meta-analysis has a significant heterogeneity between studies in nearly all models. Although the potential sources have been evaluated separately, these sources cannot completely explain the heterogeneity. Another explanation may be that endometriosis is a complex disease influenced by the environment and heredity. Therefore, some impact factors, such as lifestyle, toxic-exposure history and menstrual cycle, might influence the pathogenesis of this disease (Vigano et al., 2007). Moreover, endometriosis consists of many different types, such as the peritoneal, ovarian, and deeply infiltrating types; each of these types should be considered a separate entity to consider the possibility of different pathogenesis (Nisolle and Donnez, 1997). All of these differences, which lack detailed information or cannot be quantified, can partially contribute to the heterogeneity. Third, our meta-analysis did not pay attention to the genetic linkages and haplotypes of endometriosis. Fourth, some selection bias may have been caused by the inclusion of only English and Chinese articles, as well as only Asian and white individuals. Fifth, not all published endometriosis-related polymorphisms of the ESR1 gene were analysed. Some variants have been identified by two studies, particularly, rs1884052 (Matsuzaka et al., 2012; Trabert et al., 2011), rs1884053 (Matsuzaka et al., 2012; Trabert et al., 2011), rs2207396 (Matsuzaka et al., 2012; Trabert et al., 2011), rs712221 (Matsuzaka et al., 2012; Trabert et al., 2011), rs1801132 (Matsuzaka et al., 2012; Wu et al., 2013), and rs2228480 (Matsuzaka et al., 2012; Wu et al., 2013) but were not included in the meta-analysis. Finally, not all of the included studies provided adjusted OR; hence, we only pooled the data using unadjusted information. Despite these shortcomings, our meta-analysis included the largest cases and controls as well as the most comprehensively investigated polymorphic sites to date.

In conclusion, this present meta-analysis reported that PvuII (C > T) polymorphism was not related to the susceptibility to endometriosis except for a slight association of stage I–III endometriosis under recessive model. In addition, the S allele and TA_{13} of $(TA)_n$ polymorphism could increase slightly the risk of endometriosis, whereas TA_{20} repeats could decrease the endometriosis risk. No statistically significant associations were found in the XbaI (A > G) polymorphism and other comparisons of the PvuII and $(TA)_n$ repeat polymorphisms. Such results might be able to offer more detailed interpretations of how ESR1 gene mutations influence the pathogenesis of endometriosis. Even so, future large-scale and well-designed studies are needed to validate our results and further analyse the associations of the combined effects of PvuII and XbaI and other

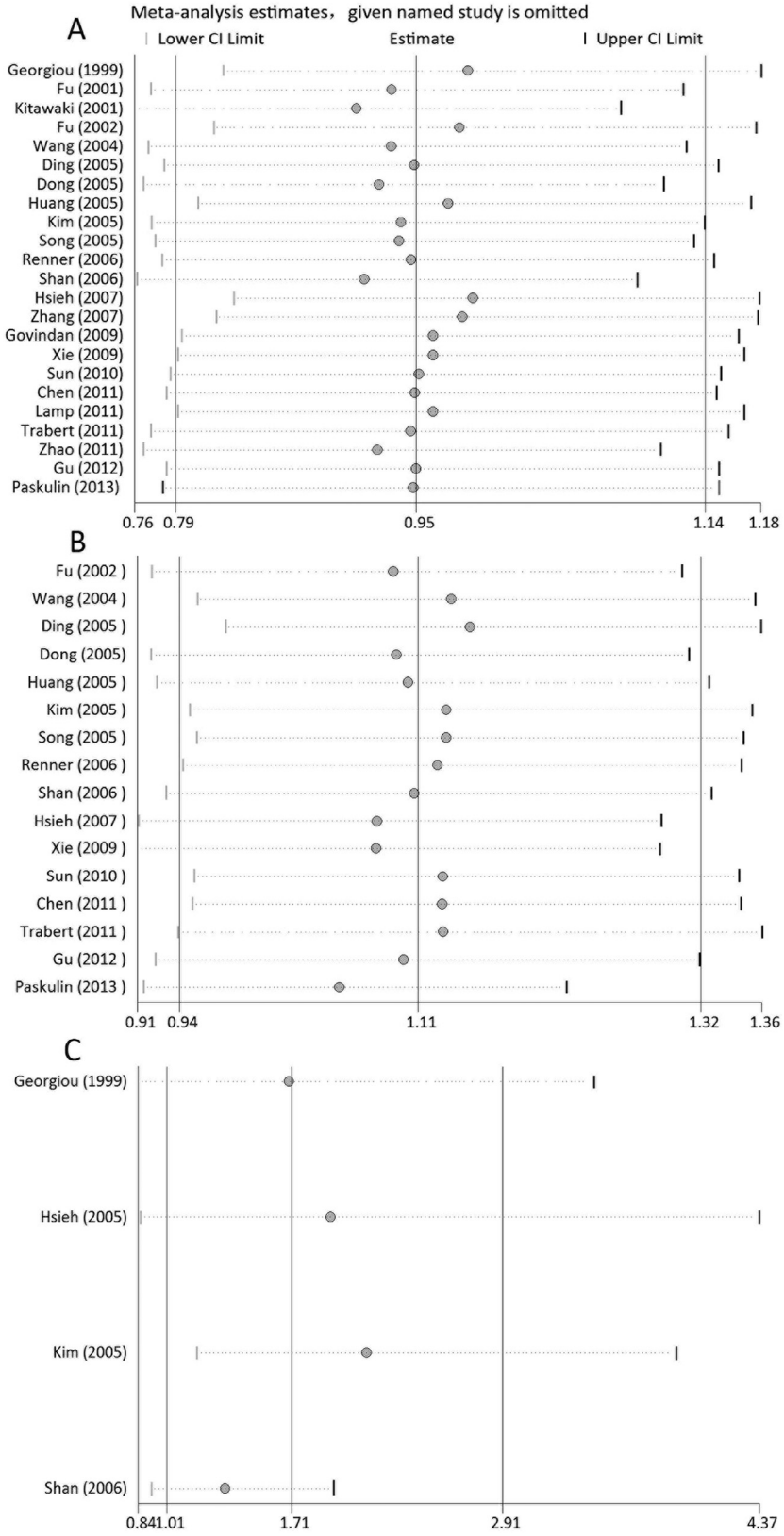

Figure 4 Sensitivity analysis of the summary odds ratios on the association between ESR1 PvuII (C > T), XbaI (A > G) and $(TA)_n$ polymorphisms with endometriosis risk. "A" represents sensitivity analysis of allele model of PvuII (C > T) polymorphism; "B" represents sensitivity analysis of allele model of XbaI (A > G) polymorphism; "C" represents sensitivity analysis of S versus L of $(TA)_n$ polymorphism.

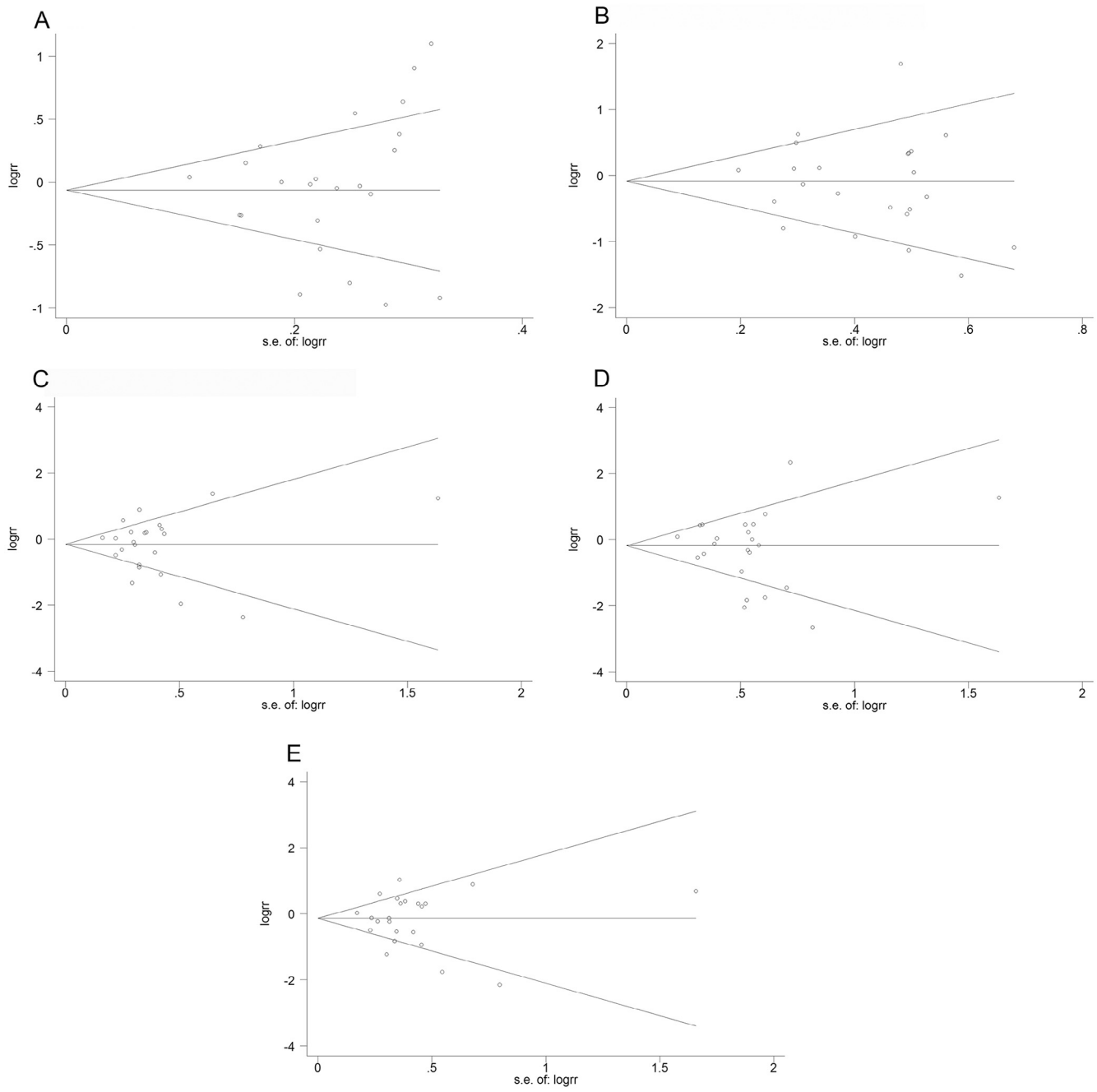

Figure 5 PvuII (C > T) and endometriosis (Begg's funnel plot with pseudo 95% confidence limits). "A" represents allele model; "B" represents dominant model; "C" represents recessive model; "D" represents homozygous model; "E" represents heterozygous model.

polymorphisms in the ESR1 gene with endometriosis risk. Such investigations may finally lead to a more comprehensive understanding of their possible roles in the development of endometriosis.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2016.06.003.

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