

## Review Article

# The association between XRCC1 Arg399Gln polymorphism and endometrial cancer risk: a system review and meta-analysis

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**Abstract:** Background: The results of the association between XRCC1 Arg399Gln polymorphism and endometrial cancer are inconsistent. The aim of this study is to quantitatively evaluate the relationship between XRCC1 polymorphism and endometrial cancer risk. Methods: Medline, Embase, China National Knowledge Infrastructure and Chinese Biomedicine Databases were searched to identify eligible studies. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for XRCC1 Arg399Gln polymorphism and endometrial cancer were calculated in a fixed-effects model and a random effects model when appropriate. Results: A total of 6 studies (1113 cases and 1226 controls) were enrolled in this meta-analysis. Overall, no significant association was found in pooled analysis. When excluding low-quality studies, significant associations were found among Caucasian population in all model: allele contrast (Arg vs. Gln), OR = 1.58, 95% CI = 1.25-2.00; homozygote (Arg/Arg vs. Gln/Gln), OR = 2.54, 95% CI = 1.56-4.14; heterozygote (Arg/Gln vs. Gln/Gln), OR = 1.46, 95% CI = 1.03-2.07; dominant model (Arg/Arg + Arg/Gln vs. Gln/Gln), OR = 1.69, 95% CI = 1.22-2.35; recessive model (Arg/Arg vs. Arg/Gln + Gln/Gln), OR = 1.91, 95% CI = 1.24-2.96. Conclusion: The XRCC1 Arg399Gln polymorphism may be a risk factor for endometrial cancer in Caucasians.

**Keywords:** XRCC1, endometrial cancer, genetic polymorphism, meta-analysis

## Introduction

Endometrial cancer is the most common gynecologic malignant tumor. Environmental factors including obesity, nulliparity, unopposed estrogen exposure, early menarche, late menopause and unovulation were reported to be correlated with endometrial cancer risk [1, 2]. However, a large number of subjects without such risk factors were diagnosed with endometrial cancer, so environmental factors alone cannot be entirely blamed. Apparently, the interaction between genetic and environmental factors plays an important role in the pathogenesis and development of endometrial cancer [3, 4].

X-ray repair cross-complementing group 1 gene (XRCC1) is located in chromosome 19q13.2 with 17 exons, and encodes an enzyme involved

in base excision repair pathway [5, 6]. The most common functional polymorphism in the XRCC1 gene is a glutamine-to-arginine transition that affects functions of the XRCC1 protein, resulting in the development of cancer [7].

In the past two decades, numerous studies have explored the potential association between XRCC1 Arg399Gln polymorphism and endometrial cancer risk in different ethnicities; however, the results are inconsistent and inconclusive [8-13]. No meta-analysis had been performed to assess the relationship between XRCC1 Arg399Gln polymorphism and endometrial cancer risk. Hence, we conducted a meta-analysis of published case-control studies to evaluate the association between XRCC1 Arg399Gln polymorphism and endometrial cancer risk.

## Materials and methods

### Publication search

Embase, PubMed, CNKI (China National Knowledge Infrastructure) and Chinese Biomedicine databases were searched for all case-control studies on the relationship between XRCC1 polymorphism and endometrial cancer risk (last search update 20<sup>th</sup> was on June 2015). The following keywords were used in the literature search: “XRCC1” or “Arg399Gln” and “polymorphism” or “variant” and “endometrial cancer”. Review studies were hand-searched to derive additional eligible articles and no language restrictions were applied.

### Inclusion and exclusion criteria

Studies were included if the publications met all of the following criteria: (i) evaluated the potential association between XRCC1 Arg399Gln polymorphism and endometriosis risk, (ii) studies were based on case-control design and (iii) studies presented sufficient data on all genotype frequencies. The exclusion criteria included: (i) duplicate publications, as well as (ii) comments, abstracts and review articles.

### Data extraction

Extraction of information from all available articles was independently conducted by two investigators (K. Yi and LY. Yang). Disagreements were resolved by consulting with an arbitrator (MR. Xi). The following information were extracted from all eligible publications: first author's surname, publication time, country of origin, ethnicity, source of control groups (population-based or hospital-based controls), matching variables, sample size of cases and controls, minor allele frequency (MAF), and Hardy-Weinberg equilibrium (HWE). Ethnicities were categorized as Asian, African, Caucasian or Mixed (composed of different descents). Specifically, the term “Asian” essentially included Chinese, Korean, Japanese and Thai studies, whereas the term “Caucasian” pertained to Indo-European and Berber populations.

Fisher's exact test was used to evaluate the HWE of the control group in each study and a *P* value < 0.05 was considered as significant disequilibrium. The pooled odds ratio (OR) and corresponding 95% confidence interval (95% CI) was utilized to evaluate the strength of the

association between XRCC1 Arg399Gln polymorphism and endometriosis risk. Five different ORs were calculated: (i) allele contrast (Arg vs. Gln), (ii) homozygote (Arg/Arg vs. Gln/Gln), (iii) heterozygote (Arg/Gln vs. Gln/Gln), (iv) dominant model (Arg/Arg + Arg/Gln vs. Gln/Gln) and (v) recessive model (Arg/Arg vs. Arg/Gln + Gln/Gln).

Heterogeneity analysis was checked and confirmed by the Cochran Q statistic and the *I*<sup>2</sup> [14]. A *P* value > 0.10 for the Q statistic indicated a lack of heterogeneity among studies. Thus fixed-effects model (Mantel-Haenszel method) was selected to calculate the ORs [15]; otherwise, random-effects model (DerSimonian and Laird method) was selected to pool the ORs [16].

Begg's rank correlation method and Egger's weighted regression method were employed to explore publication bias through visual inspection of the funnel plot (*P* value < 0.05 was considered statistically significant) [17, 18]. All statistical analyses were performed using STATA software, version 13.0 (STATA Corp., College Station, TX, United States).

## Result

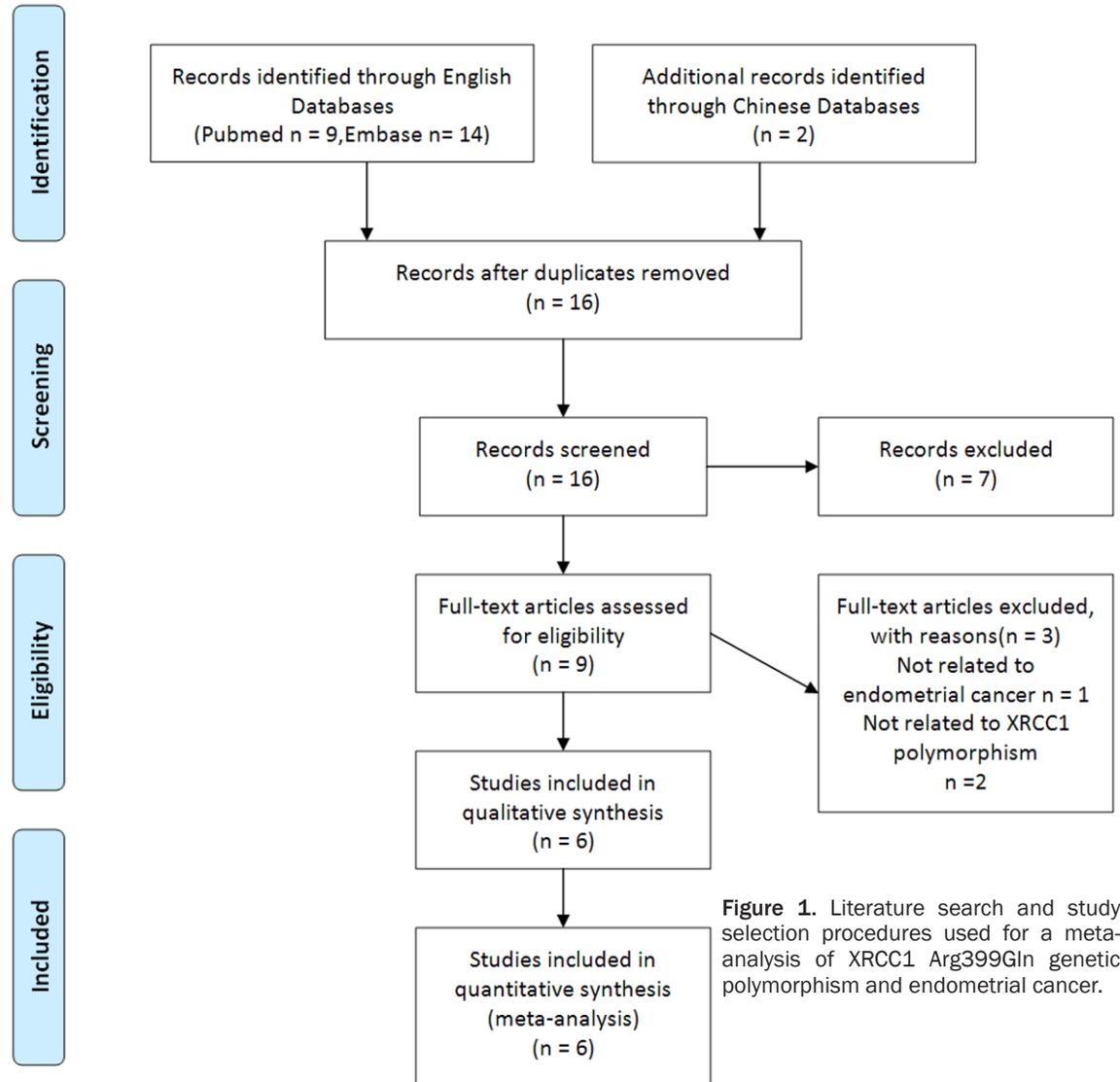
### Characteristics of studies

**Figure 1** presents the flowchart of the study selection and reasons for exclusion. Through literature search and selection, 16 articles were identified as potentially relevant studies, of these, 7 were excluded after screening the titles and abstracts. Then, 9 studies were retrieved for full-text articles assessed, of which 3 articles were excluded (one study was not related to endometrial cancer [19], two studies were not related to XRCC1 polymorphism [20, 21]). Finally, a total of 6 case control studies were found to examine the XRCC1 polymorphism and endometrial cancer susceptibility [9-13, 22], and identified based on MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines [23]. **Table 1** presents the characteristics of selected studies. **Table 2** lists the quality of studies included in the metaanalysis.

### Quantitative analysis

The main results of this pooled analysis were presented in **Table 3**. Overall, no significant

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**Figure 1.** Literature search and study selection procedures used for a meta-analysis of XRCC1 Arg399Gln genetic polymorphism and endometrial cancer.

**Table 1.** Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Source of Controls	Simple size (case/control)	Genotyping Methods	Matching criteria	MAF in Controls	HWE
Samulak	2011	Poland	Caucasian	HCC	456/300	PCR-RFLP	Status of menopause	0.48	0.51
Romanowicz	2011	Poland	Caucasian	HCC	150/150	PCR-RFLP	Geographic region	0.35	0.99
Cincin	2012	Turkey	Caucasian	HCC	104/158	PCR-RFLP	Age	0.06	0.40
Sobczuk	2012	Poland	Caucasian	HCC	94/114	PCR-RFLP	Age	0.41	0.16
Hosono	2013	Japan	Asian	HCC	91/261	Taqman	Status of menopause	0.27	0.68
Wang	2015	China	Asian	HCC	218/243	PCR-RFLP	Age	0.33	0.06

Abbreviations: HCC, hospital-based case-control; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

association was found between endometrial cancer and XRCC1 polymorphism in all models: allele contrast (Arg vs. Gln), OR = 1.04, 95% CI = 0.57-1.88; homozygote (Arg/Arg vs. Gln/Gln),

OR = 1.24, 95% CI = 0.39-3.93; heterozygote (Arg/Gln vs. Gln/Gln), OR = 0.83, 95% CI = 0.38-1.81; dominant model (Arg/Arg + Arg/Gln vs. Gln/Gln), OR = 0.94, 95% CI = 0.43-2.06;

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**Table 2.** Quality assessment of case-control studies included in this meta-analysis<sup>a</sup>

Study	Adequate definition of cases	Representativeness of cases	Selection of control	Definition of control	Control for important factor or additional factor <sup>b</sup>	Exposure assessment	Same method of ascertainment for cases and controls	Non-response rate <sup>c</sup>	Total quality scores
Samulak	★	-	-	-	★	-	★	-	3
Romanowicz	★	★	★	★	★	-	★	-	6
Cincin	★	★	★	★	★	-	★	-	6
Sobczuk	★	★	★	★	★★	-	★	-	7
Hosono	★	-	-	★	★	-	★	-	4
Wang	★	★	★	★	★★	-	★	-	7

<sup>a</sup>A study can be awarded a maximum of one star for each numbered item except for the item Control for most important factor or second important factor. <sup>b</sup>A maximum of two stars can be awarded for Control for most important factor or second important factor. Studies that controlled for tobacco smoking received one star, whereas studies that controlled for high risk factor (diabetes or hypertension or obesity) received one additional star. <sup>c</sup>One star was awarded if there was no significant difference in the response rate between control subjects and cases in the chi-square test ( $P > 0.05$ ).

recessive model (Arg/Arg vs. Arg/Gln + Gln/Gln), OR = 1.30, 95% CI = 0.61-2.76).

### Heterogeneity analysis

A substantial heterogeneity of XRCC1 polymorphism and endometrial cancer was observed among studies in overall comparisons: allele contrast (Arg vs. Gln),  $P_{\text{heterogeneity}} < 0.01$ ; homozygote comparison (Arg/Arg vs. Gln/Gln),  $P_{\text{heterogeneity}} < 0.01$ ; heterozygote comparison (Arg/Gln vs. Gln/Gln),  $P_{\text{heterogeneity}} < 0.01$ ; dominant model (Arg/Arg + Arg/Gln vs. Gln/Gln),  $P_{\text{heterogeneity}} < 0.01$ ; recessive model (Arg/Arg vs. Arg/Gln + Gln/Gln),  $P_{\text{heterogeneity}} < 0.01$ .

To explore sources of heterogeneity across studies, stratified analyses were performed by ethnicity. In stratified analyses, heterogeneity still existed in both subgroups and no significant associations were found in the allele contrast, homozygote, heterozygous, dominant model and recessive model in any subgroup (Table 3).

The scores of two included studies were lower than 6 stars in quality assessment [10, 12]. They were considered to be low-quality studies. When excluding the low-quality studies, the heterogeneity decreased significantly: allele contrast (Arg vs. Gln),  $P_{\text{heterogeneity}} = 0.413$ ; homozygote comparison (Arg/Arg vs. Gln/Gln),  $P_{\text{heterogeneity}} = 0.286$ ; heterozygote comparison (Arg/Gln vs. Gln/Gln),  $P_{\text{heterogeneity}} = 0.403$ ; dominant model (Arg/Arg + Arg/Gln vs. Gln/Gln),  $P_{\text{heterogeneity}} = 0.460$ ; recessive model (Arg/Arg vs. Arg/Gln + Gln/Gln),  $P_{\text{heterogeneity}} = 0.177$ ). We re-evaluated the association after excluding

these two outlier studies and found significant associations between XRCC1 polymorphism and endometrial cancer among Caucasian descent in all models (Table 4). The forest plot evaluating the association of XRCC1 polymorphism with endometrial cancer risk was presented in Figure 2.

### Publication bias

Begg's and Egger's tests were conducted to assess publication bias of the literatures (Figure 3). No potential publication bias were observed in the statistical results: allele contrast (Arg vs. Gln), Begg's test  $P = 0.85$ , Egger's test  $P = 0.25$ ; homozygote (Arg/Arg vs. Gln/Gln), Begg's test  $P = 1.00$ , Egger's test  $P = 0.61$ ; heterozygote (Arg/Gln vs. Gln/Gln), Begg's test  $P = 0.45$ , Egger's test  $P = 0.18$ ; dominant model (Arg/Arg + Arg/Gln vs. Gln/Gln), Begg's test  $P = 0.85$ , Egger's test  $P = 0.18$ ; recessive model (Arg/Arg vs. Arg/Gln + Gln/Gln), Begg's test  $P = 0.82$ , Egger's test  $P = 0.62$ .

### Discussion

This meta-analysis is based on 6 case-control studies with 1113 endometriosis cases and 1226 control cases, and is the first time to focus on the association between XRCC1 polymorphism and endometrial cancer risk. No significant associations were found between the XRCC1 polymorphism and endometrial cancer risk in all pooled analysis. Subgroup analysis stratified by ethnicity was performed and the results revealed that no significant associations were found for the XRCC1 genotype and endometrial cancer in neither Caucasian groups nor Asian groups.

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**Table 3.** Quantitative analyses of the XRCC1 polymorphism on the endometrial cancer risk

Genetic model	Sample size		Allele contrast		Homozygote		Heterozygote		Dominant Model		Recessive Model	
			Arg vs. Gln		Arg/Arg vs. Gln /Gln		Arg/Gln vs. Gln /Gln		Arg/Arg + Arg/Gln vs. Gln/Gln		Arg/Arg vs. Arg/Gln + Gln/Gln	
			N <sup>a</sup>	Case/control	OR (95% CI)	P <sub>value</sub> <sup>b</sup>	OR (95% CI)	P <sub>value</sub> <sup>b</sup>	OR (95% CI)	P <sub>value</sub> <sup>b</sup>	OR (95% CI)	P <sub>value</sub> <sup>b</sup>
Total	6	1113/1226	1.04 (0.57, 1.88)	< 0.01	1.24 (0.39, 3.93)	< 0.01	0.83 (0.38, 1.81)	< 0.01	0.94 (0.43, 2.06)	< 0.01	1.30 (0.61, 2.76)	< 0.01
Ethnicity												
Caucasian	4	804/722	1.10 (0.45, 2.71)	< 0.01	1.62 (0.36, 7.36)	< 0.01	0.82 (0.23, 2.92)	< 0.01	0.97 (0.28, 3.41)	< 0.01	1.41 (0.58, 3.43)	< 0.01
Asian	2	309/504	0.94 (0.45, 1.95)	< 0.01	0.66 (0.04, 13.4)	< 0.01	0.90 (0.66, 1.22)	0.359	0.91 (0.51, 1.63)	0.057	0.70 (0.04, 11.5)	< 0.01

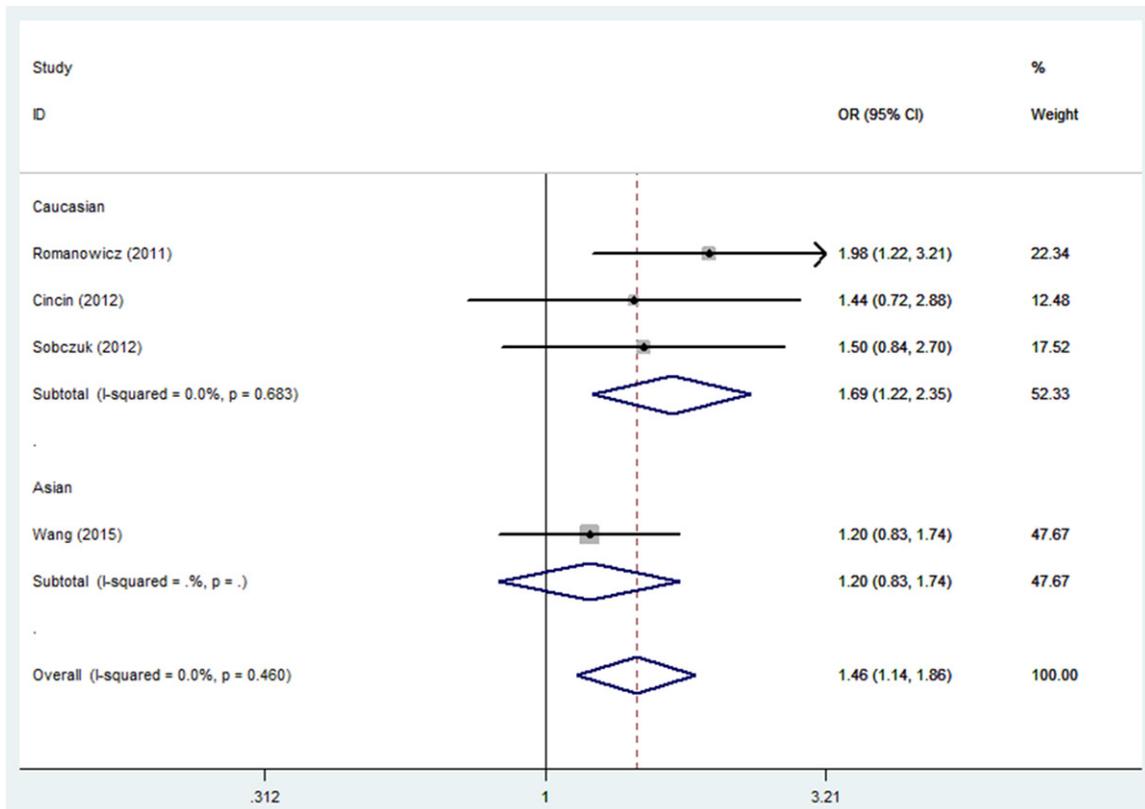
<sup>a</sup>Number of comparisons. <sup>b</sup>P value of Q-test for heterogeneity test. Random-effects model was used when P value for heterogeneity test < 0.10; otherwise, fixed-effects model was used.

**Table 4.** Reevaluation of the association after excluding the studies of low quality studies

Genetic model	Sample size		Allele contrast		Homozygote		Heterozygote		Dominant Model		Recessive Model	
			Arg vs. Gln		Arg/Arg vs. Gln /Gln		Arg/Gln vs. Gln /Gln		Arg/Arg + Arg/Gln vs. Gln/Gln		Arg/Arg vs. Arg/Gln + Gln/Gln	
			N <sup>a</sup>	Case/control	OR (95% CI)	P <sub>value</sub> <sup>b</sup>	OR (95% CI)	P <sub>value</sub> <sup>b</sup>	OR (95% CI)	P <sub>value</sub> <sup>b</sup>	OR (95% CI)	P <sub>value</sub> <sup>b</sup>
Total	4	566/665	1.47 (1.24, 1.78)	0.413	2.47 (1.69, 3.62)	0.286	1.24 (0.95, 1.61)	0.403	1.45 (1.14, 1.86)	0.460	2.07 (1.46, 2.93)	0.177
Ethnicity												
Caucasian	3	348/422	1.58 (1.25, 2.00)	0.458	2.54 (1.56, 4.14)	0.149	1.46 (1.03, 2.07)	0.589	1.69 (1.22, 2.35)	0.683	1.91 (1.24, 2.96)	0.108
Asian	1	218/243	1.34 (1.02, 1.76)	NA <sup>e</sup>	2.36 (1.28, 4.37)	NA <sup>e</sup>	1.01 (0.68, 1.49)	NA <sup>e</sup>	1.20 (0.83, 1.74)	NA <sup>e</sup>	2.35 (1.32, 4.19)	NA <sup>e</sup>

<sup>a</sup>Number of comparisons. <sup>b</sup>P value of Q-test for heterogeneity test. Random-effects model was used when P value for heterogeneity test < 0.10; otherwise, fixed-effects model was used. <sup>e</sup>NA, Not available.

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**Figure 2.** Forest plots of ORs with 95% CIs for XRCC1 Arg399Gln polymorphism and risk for endometrial cancer.

In the quality assessment, the low-quality studies were considered as those with scores lower than six stars. Two included studies were identified as low-quality studies [10, 12].

Interestingly, when the aforementioned studies were excluded, the heterogeneity decreased significantly and a significant association was found between XRCC1 polymorphism and endometrial cancer among the Caucasian populations in all models (**Table 4**). The reason for this diversity remains undetermined, and selection biases of low-quality studies may explain the difference. In the two low-quality studies, the subjects of case and control groups comprised menopausal women, which may not represent the general female population. Fluctuations in the balance of two main female hormones, namely, estrogen and progesterone, cause periodic changes in the endometrium. However, the changes in the balance of female hormones are considered to be a major risk factor for endometrial cancer. Compared with women in their reproductive age, the subjects with declined ovarian functions are more likely to

experience female hormonal imbalance of. Thus, the morbidity of endometrial cancer in menopausal women is higher than that in the general female population. Endometrial cancer patients are more likely to include in the menopausal women. Nevertheless, the subjects based on the general population may be more efficiently to reduce bias in these genetic association studies.

In addition, when excluding the low-quality studies, a significant association was found between XRCC1 polymorphism and endometrial cancer in all models except in the heterozygote comparison. Although fewer studies are enrolled in the re-evaluation of high-quality studies, 95% confidence intervals are narrower than those in overall pooled analysis. This indicates that the pooled results of high-quality studies are more likely to reveal the true effect of the association.

The pooled results of high-quality studies reveal an analogy with the results of a previous meta-analysis of cervical cancer, which found a sig-

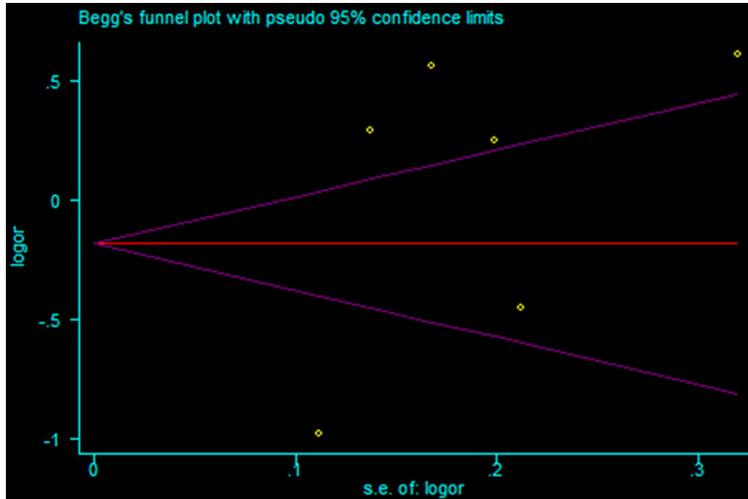


Figure 3. Begg's funnel plot for publication bias test.

nificant association between XRCC1 polymorphism and cervical cancer in both Caucasian and Asian populations [24]. Another meta-analysis also found a significant association between XRCC1 polymorphism and breast cancer among Asians, except Chinese population [25]. This epidemiological analogy may be explained by a potential underlying physiological mechanism: these three tumors are correlated to DNA damage and repair; and the XRCC1 gene plays a key role in the process of DNA repair.

One important issue for any meta-analysis is publication bias because of the potential selective publication of reports. In the present meta-analysis, Begg's funnel plot and Egger's test were conducted to explore the publication bias. Both statistical results and the shape of funnel plots exhibited no signs of publication bias.

The present study have several limitations: (i) the number of subjects in the studies and the number of studies included in the meta-analysis of XRCC1 Arg399Gln polymorphism were relatively small, the results may not be sufficient to examine the real associations statistically; (ii) the current study was based on unadjusted OR estimates because not all included trials presented adjusted ORs or when they did, the ORs were not adjusted by the same factors, such as race, age and smoking status; (iii) obvious heterogeneity among studies in the pooled analysis was found in all allele models.

In conclusion, present meta-analysis estimates the association between genetic polymorphism

and endometrial cancer risk; and found that the polymorphism of XRCC1 Arg399Gln may be associated with endometrial cancer risk in Caucasian population. Since the number of subjects included in present meta-analysis was relatively small, well-designed and larger multicenter case-control studies are needed in order to re-evaluate the association and further enrich the present findings.

#### Disclosure of conflict of interest

None.

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