Review Article

Association between XRCC1 Arg399Gln, Arg280His, Arg194Trp polymorphisms and cervical cancer risk: a pooled analysis based on Chinese individuals

Yan Cai*, Qi-Ming Wang*, Jin-Hui Feng, Liang Chen, Shi-Tong Zhang, Yong Huang

*Department of Gynecology and Obstetrics, Ningbo Women and Children's Hospital, Ningbo 315012, People's Republic of China. *Equal contributors.*

Abstract: Although various individual studies have evaluated the correlation between X-ray repair cross-complementing group 1 (XRCC1) polymorphisms and cervical cancer, the current results remain inconclusive. Therefore, we performed a pooled analysis based on Chinese individuals to provide comprehensive data on the association between XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and cervical cancer risk. Studies were identified using PubMed and Chinese databases through July 2016. A total of ten studies with 2049 cervical cancer cases and 2922 controls were included in this meta-analysis. It revealed that XRCC1 Arg399Gln and Arg194Trp polymorphisms were significantly associated with an increased risk of cervical cancer in our study. No significant association was observed between XRCC1 Arg280His and cervical cancer in all the models. In conclusion, this meta-analysis suggests that XRCC1 Arg399Gln and Arg194Trp polymorphisms may be associated with cervical cancer risk in Chinese individuals, while Arg280His polymorphism might not be a risk factor for cervical cancer.

Keywords: Meta-analysis, X-ray repair cross-complementing group 1, polymorphism, cervical cancer

Introduction

Cervical cancer is one of the most most common malignancy and the fourth leading cause of cancer death among women worldwide [1]. It has been reported that the incidence and mortality rates range from 2.4 to 4.6 per 100,000 women and 2 to 4 per 100,000 women respectively in urban areas of China [2]. Previous studies showed a strong correlation between human papillomavirus (HPV) infection and cervical cancer [3], however, only a small portion of women go on to develop cervical cancer following infection with HPV. Therefore, other factors, including environment and genetic susceptibility, may play an important role in the development of cervical cancer. The X-ray repair cross-complementing group 1 (XRCC1) gene polymorphisms may alter DNA repair activity by affecting the interaction of other enzyme protein with XRCC1, so as to increase the risk of cancer [4, 5]. In recent years, a number of studies were conducted to investigate the association between XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and cervical cancer risk. But these studies reported conflicting results. Differences in results may be related to the racial and regional differences in patients who have been studied, as well as a limited number of patients in each study. In order to reduce the influence of the diverse genetic backgrounds, we performed a pooled analysis based on Chinese individuals to assess the relationship between XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and cervical cancer risk.

Materials and methods

Search strategy and selection criteria

Using the databases of PubMed and Chinese databases, we searched all literature sources published before July 2016 for studies examining the relationship between XRCC1 polymorphisms and the risk of cervical cancer. The search keywords were (X-ray repair cross complementing protein 1 or XRCC1) and cervical
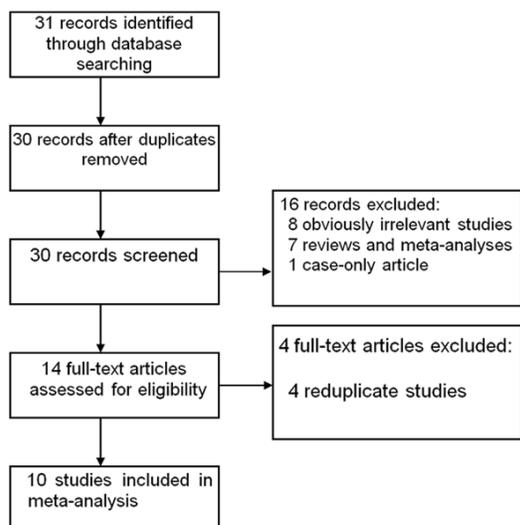
Figure 1. Flow diagram of the literature search.

cancer and (Chinese or China or Taiwan). The reference lists of extracted reviews and articles were also reviewed. No language restriction was applied.

Inclusion criteria: (1) case-control studies describing the association between XRCC1 polymorphisms and cervical cancer, (2) studies with sufficient genetypes data in cases and controls, (3) all participants were Chinese individuals. Exclusion criteria: (1) repeated literatures, (2) incomplete data, (3) case-only articles, (4) review articles and abstracts.

Data extraction

Two investigators independently extracted data from all eligible publications and entered them into a database. Titles and abstracts of all potentially relevant articles were screened firstly. Full articles were then scrutinized if the title and abstract were ambiguous. These information such as first author's name, publication year, source of controls, sample size, and available genotype data for XRCC1 polymorphisms were collected.

Statistical analysis

Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to assess the strength of the association between XRCC1 polymorphisms and cervical cancer risk. The heterogeneity among individual studies was assessed by chi-squarebased Q-test

[6]. The fixed-effect model (Mantel-Haenszel) or random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs according to the results of the heterogeneity test. The significance of the pooled OR was evaluated by a Z-test. Sensitivity analysis was performed by comparing the results of fixed- and random-effects models. Begg's funnel plot and Egger's linear regression test were employed to evaluate the publication bias. All statistical analyses were conducted using the Stata, version 12 (StataCorp LP, College Station, TX). A *P* value less than 0.05 was considered to be statistically significant.

Results

Description of included studies

Figure 1 illustrates the literature search process in the form of a flow chart. Thirty-one articles which examined the association between XRCC1 polymorphisms and cervical cancer were identified. According to the inclusion and exclusion criteria, ten studies [7-16] were included and 21 articles were excluded. The publication year of involved studies ranged from 2003 to 2015. In total, 2049 cervical cancer cases and 2922 controls were included in this meta-analysis. The source of controls in all included studies was population-based. Nine articles studied on XRCC1 Arg399Gln, 5 articles on Arg194Trp, and 4 articles on Arg280His. The characteristics of the included studies are listed in **Table 1**.

Meta-analysis results

The primary results of this meta-analysis on the association between XRCC1 gene polymorphisms and cervical cancer in Chinese individuals are shown in **Table 2**.

XRCC1 Arg399Gln, Arg194Trp polymorphisms and cervical cancer

Nine studies including 1926 cases and 2747 controls identified an association between the XRCC1 Arg399Gln polymorphism and cervical cancer risk in the Chinese population [7-15], while five studies including 1077 cases and 1698 controls for XRCC1 Arg194Trp [7, 8, 13, 14, 16]. Meta-analysis revealed that XRCC1 Arg399Gln and Arg194Trp polymorphisms were

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

References	Publication year	Source of controls	Case number	Control number	Studied polymorphisms
Wu et al. [7]	2003	Population-based	100	196	XRCC1 Arg399Gln, Arg194Trp, Arg280His
Huang et al. [8]	2007	Population-based	539	800	XRCC1 Arg399Gln, Arg194Trp, Arg280His
Hong et al. [9]	2008	Population-based	72	176	XRCC1 Arg399Gln
Jiang et al. [10]	2009	Population-based	436	503	XRCC1 Arg399Gln
Xiao et al. [11]	2010	Population-based	162	183	XRCC1 Arg399Gln
Ma et al. [12]	2011	Population-based	200	200	XRCC1 Arg399Gln
Zhang et al. [13]	2012	Population-based	80	177	XRCC1 Arg399Gln, Arg194Trp, Arg280His
Fan et al. [14]	2013	Population-based	235	350	XRCC1 Arg399Gln, Arg194Trp
Zhou et al. [15]	2015	Population-based	102	162	XRCC1 Arg399Gln
Wang et al. [16]	2010	Population-based	123	175	XRCC1 Arg194Trp, Arg280His

Table 2. Association of the XRCC1 polymorphisms on cervical cancer susceptibility

Polymorphism	n	ORr (95%CI)	ORf (95%CI)	P_h
XRCC1 Arg399Gln				
Gln vs. Arg	9	1.28 (1.08-1.53)	1.29 (1.17-1.41)	0.002
Gln/Gln vs. Arg/Arg	9	1.66 (1.05-2.62)	1.63 (1.30-2.04)	0.001
Arg/Gln vs. Arg/Arg	9	1.29 (1.09-1.53)	1.30 (1.15-1.48)	0.123
Gln/Gln vs. Arg/Arg+Arg/Gln	9	1.50 (0.98-2.30)	1.49 (1.19-1.85)	0.001
Gln/Gln+Arg/Gln vs. Arg/Arg	9	1.33 (1.10-1.61)	1.34 (1.19-1.51)	0.024
XRCC1 Arg194Trp				
Trp vs. Arg	5	1.26 (1.06-1.51)	1.30 (1.15-1.46)	0.110
Trp/Trp vs. Arg/Arg	5	2.09 (1.09-4.01)	2.11 (1.60-2.80)	0.008
Arg/Trp vs. Arg/Arg	5	1.12 (0.95-1.32)	1.12 (0.95-1.32)	0.513
Trp/Trp vs. Arg/Arg+Arg/Trp	5	2.00 (1.10-3.65)	2.03 (1.55-2.65)	0.014
Trp/Trp+Arg/Trp vs. Arg/Arg	5	1.23 (1.02-1.49)	1.24 (1.07-1.45)	0.263
XRCC1 Arg280His				
His vs. Arg	4	1.05 (0.85-1.28)	1.04 (0.86-1.26)	0.359
His/His vs. Arg/Arg	4	1.74 (0.86-3.61)	1.76 (0.87-3.55)	0.512
Arg/His vs. Arg/Arg	4	0.96 (0.78-1.19)	0.96 (0.77-1.19)	0.676
His/His vs. Arg/Arg+Arg/His	4	1.75 (0.85-3.61)	1.76 (0.87-3.54)	0.502
His/His+Arg/His vs. Arg/Arg	4	1.00 (0.82-1.24)	1.00 (0.81-1.23)	0.543

ORr: Odd ratio for random-effects model; ORf: Odd ratio for fixed-effects model; P_h: P value for heterogeneity test.

significantly associated with an increased risk of cervical cancer in four contrast models respectively (**Table 2**, **Figures 2** and **3**).

XRCC1 Arg280His polymorphism and cervical cancer

Four studies determined the relationship between the XRCC1 Arg280His polymorphism and cervical cancer risk in the Chinese population [7-8, 13, 16]. The total sample size for patients with cervical cancer and controls was 842 and 1348, respectively. No significant association was observed between XRCC1 Arg280His and cervical cancer in all the models (**Table 2**, **Figure 4**).

Sensitivity analysis and publication bias diagnosis

We compared the pooled results between fixed- and random-effects models to evaluate the sensitivity of the meta-analysis. All the corresponding pooled ORs were not materially altered except one model for XRCC1 Arg399Gln-Gln/Gln vs. Arg/Arg+Arg/Gln (**Table 2**). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures for XRCC1 Arg399Gln and cervical cancer. As showed in **Figure 5**, the shape of the funnel plot did not reveal obvious asymmetry. Similarly, the Egger's test indicated that there was no evidence of obvious publication bias in the 9 reviewed studies (t=-0.39, *p*=0.710). Due to the limited studies, we did not performed the publication bias assessment for XRCC1 Arg194Trp and Arg280His polymorphisms.
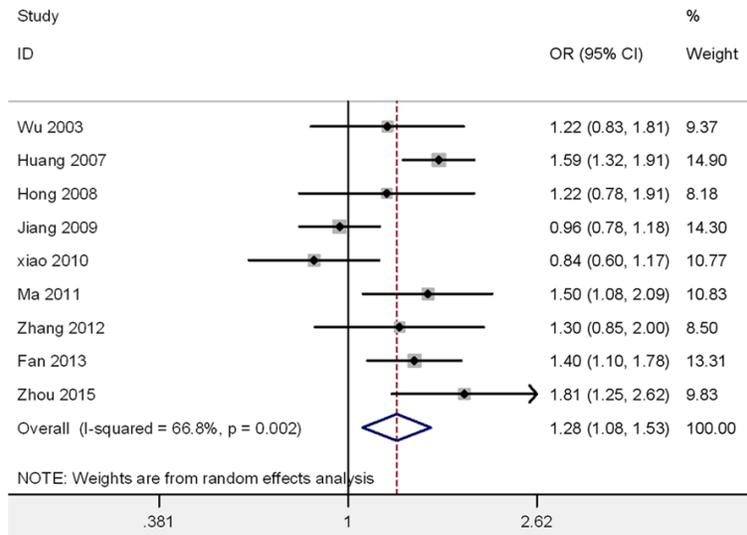
Figure 2. The forest plot on the association between XRCC1 Arg399Gln polymorphism and cervical cancer risk under allele model.

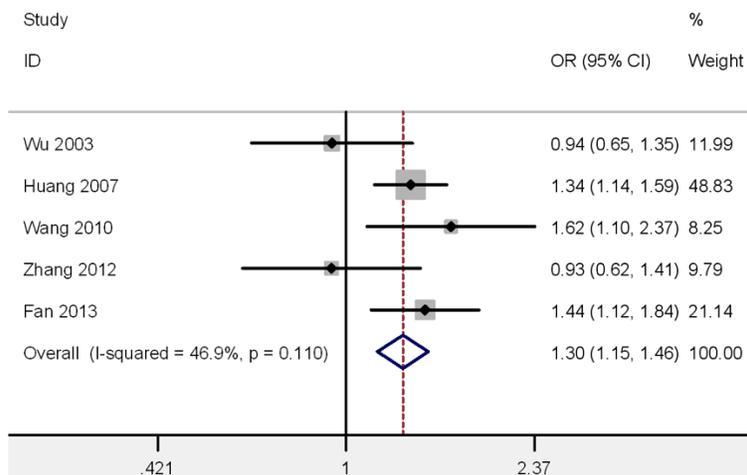**Figure 3.** The forest plot on the association between XRCC1 Arg194Trp polymorphism and cervical cancer risk under allele model.

ferent results. Therefore, we conducted this meta-analysis based on Chinese individuals to assess the effect of XRCC1 Arg399Gln, Arg194Trp, Arg28-0His polymorphisms on risk for cervical cancer.

A total of 10 studies with 2049 cervical cancer cases and 2922 controls were included in this meta-analysis. We found significant association of the XRCC1 Arg399Gln, Arg194Trp polymorphisms with susceptibility to cervical cancer in Chinese individuals. No association was found between XRCC1 Arg280His and cervical cancer in Chinese individuals. The reason could be its crucial role for XRCC1 variants in the facilitation of human cancer development [17]. Such as, the XRCC1 Arg399Gln polymorphism may alter the efficiency of the repair process because of its location in the poly (ADP-ribose) poly-merase-binding domain, and the functional significance of XRCC1 Arg194Trp is mainly due to its location in an evolutionarily conserved linker region [18, 19]. The null association between XRCC1 Arg280His polymorphism and cervical cancer risk was consistent with all the previous meta-studies on this polymorphism [19-21].

Discussion

It is well known that DNA repair gene has become an important determinant of cancer risk. XRCC1 protein is exclusively required for DNA base excision repair and strand break repair [17]. The first study on the association between XRCC1 Arg399Gln, Arg194Trp, Arg280His polymorphisms and cervical cancer was reported in Taiwan in 2003 [7]. After that, a number of studies have been performed and generated the conflicting results. Regional and racial differences may be the likely reasons for the different

Till now, there are serval published meta-analyses regarding XRCC1 polymorphisms and cervical cancer risk [19-24]. Of these, three meta-analyses [22-24] only studied on XRCC1 Arg-399Gln polymorphism, while the other three ones studied on XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms [19-21]. For XRCC1 Arg194Trp and Arg280His polymorphisms, the consistent conclusions have been draw that Arg194Trp polymorphism may be associated with cervical cancer risk , and there may be no association between Arg280His polymorphism and cervical cancer risk [19-21].
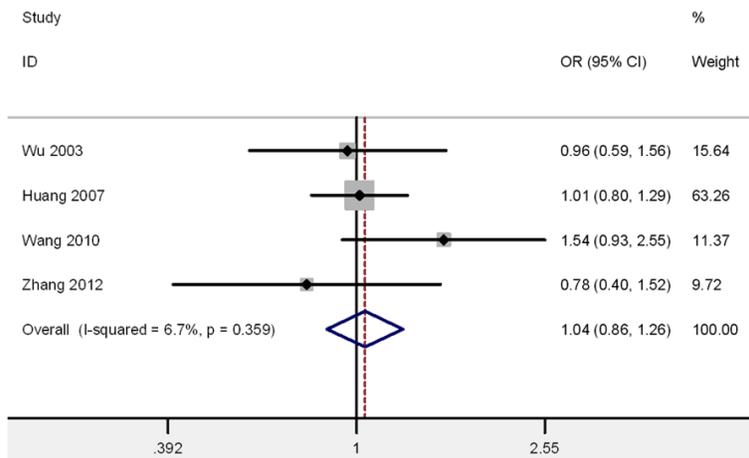
Figure 4. The forest plot on the association between XRCC1 Arg280His polymorphism and cervical cancer risk under allele model.
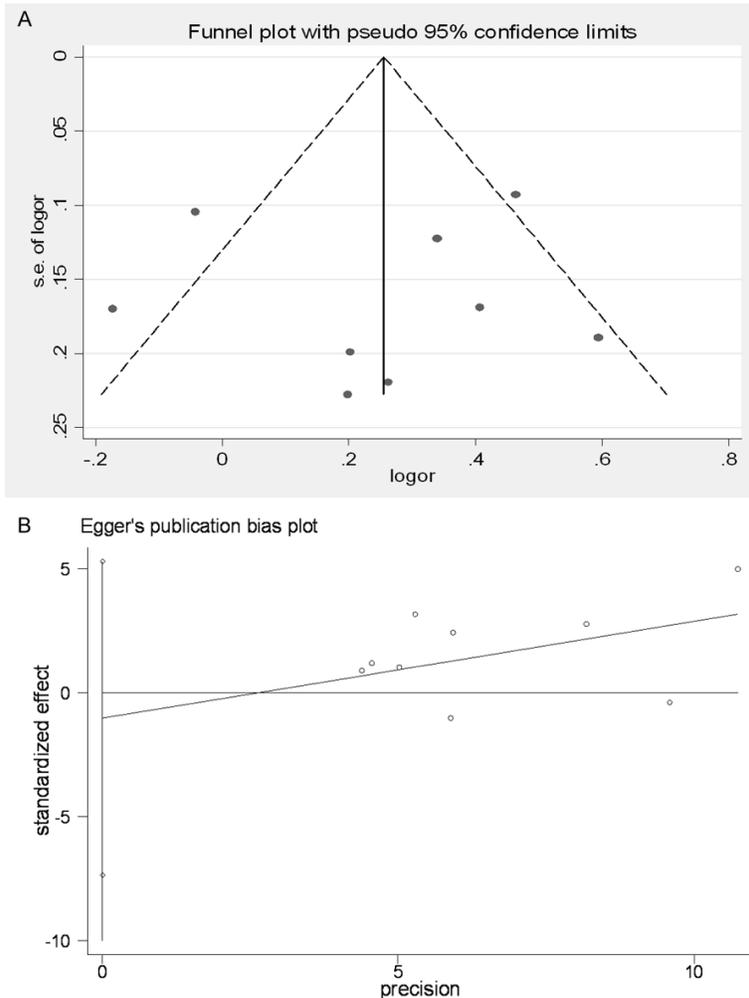

Figure 5. Publication bias assessment of XRCC1 Arg399Gln polymorphism and cervical cancer risk (A: Begg's funnel plot; B: Egger's linear regression).

For XRCC1 Arg399Gln polymorphism, most of the meta-analyses found that XRCC1 Arg399Gln polymorphism had a positive association with cervical cancer susceptibility, while Shuai et al. [20] failed to find the significant result. As compared to Zhang et al.'s meta-analysis in the Chinese population [24], it only studied on XRCC1 Arg399Gln polymorphism and cervical cancer in Chinese individuals. This current meta-analysis is strengthened by including several new studies and XRCC1 Arg-194Trp, Arg280His polymorphisms.

In conclusion, our meta-analysis suggests that XRCC1 Arg399Gln and Arg194Trp polymorphisms may be associated with cervical cancer risk in Chinese individuals, whereas there may be no association between Arg280-His polymorphism and cervical cancer risk.

Disclosure of conflict of interest

None.

Address correspondence to: Yong Huang, Department of Gynecology and Obstetrics, Ningbo Women and Children's Hospital, No. 339, Liuting Street, Ningbo 315012, People's Republic of China. Tel: +86 0574-87083300; E-mail: nbhuangy88@126.com

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