Research Paper

Association between XRCC1 polymorphisms and the risk of cervical cancer: a meta-analysis based on 4895 subjects

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ABSTRACT

The present meta-analysis was intended to explore the relationship between the X-ray repair cross complementing 1 (XRCC1) polymorphisms (Arg194Trp, Arg280His and Arg399Gln) and cervical cancer risk. Several electronic databases were searched systematically and bibliographies of relevant papers were identified carefully. Then, a meta-analysis was performed based on eligible studies in various genetic models. Pooled odds ratios (OR) with 95% confidence intervals (95% CI) were employed to evaluate the strength of associations between the XRCC1 polymorphisms and cervical cancer risk. Additionally, heterogeneity analysis and sensitivity analysis were done if necessary. Totally, 11 articles involving 2092 cases and 2803 controls were included. Taken together, there was no obvious association between the Arg194Trp or Arg280His polymorphism and cervical cancer risk. Considering the great heterogeneity, subgroup analysis was done, but the pooled result remained stable. Nevertheless, the association between the Arg399Gln polymorphism and cervical cancer risk showed distinct statistic significance in the allele model, dominant model, homozygous model and heterozygous model. In view of the exiting heterogeneity, we did subgroup analysis stratified by ethnicity, resulting in the fact that the Arg399Gln polymorphism was related to the decreased risk of cervical cancer. The Begg's test and Egger's test were used to find no publication bias. To conclude, the current meta-analysis indicated that the XRCC1 Arg399Gln polymorphism decreased the risk of cervical cancer, while the Arg194Trp and Arg280His polymorphisms were not associated with cervical caner risk. Certainly, a well-designed large-scale multicenter study is warranted to confirm the finding.

INTRODUCTION

Nowsdays, cervical cancer is one of the most common genital tract carcinomas and has become a challenging health issue confronted by women throughout the world. It seriously threatens women's quality of life arising from reproductive endocrine function's damage caused by this malignancy, and brings about great morbidity and economic burden. Infection with high-risk types of human papillomavirus (HPV) is the main causative factor for developing cervical intraepithelial neoplasia (CIN) which is a precursor lesion for cervical cancer. While, not all women who are infected with HPV will certainly progress into cervical cancer, suggesting that there are still other factors playing a role in the pathogenesis of cervical cancer. For example, ultraviolet, ionizing radiation and environmental chemical agents can lead to DNA damage, initiating certain human cancers [1–9].

In human body, DNA repair genes are considerable factors in the prevention of genomic injury and sequential carcinogenesis. So variants of DNA repair genes might be able to impair DNA repair ability and have been suggested to be associated with cancer risk. X-ray repair cross complementing group 1 (XRCC1) gene is a typical DNA repair gene. It is located at chromosome 19q13.2-13.3 and encodes the scaffolding protein [10]. The protein functions in the repair of single-strand breaks which is the most common lesions in cellular DNA [11]. Both biological and biochemical evidence indicate XRCC1 interacts with a complex of DNA repair proteins, such as poly(ADP-ribose) polymerase [11–13]. There are three most common polymorphisms in XRCC1, contributing to amino acid

substitutions in XRCC1 at codon 194 (exon 6, base C to T, amino acid Arg to Trp), codon 280 (exon 9, base G to A, amino acid Arg to His), and codon 399 (exon 10, base G to A, amino acid Arg to Gln) (http://egp.gs.washington. edu). And eventually these variants alter XRCC1 function.

A great many epidemiologic studies have been conducted to evaluate the role of the XRCC1 polymorphisms (Arg194Trp, Arg280His and Arg399Gln) on cervical cancer risk [14–24]. But the results were inconclusive. For example, Zhang et al. found the XRCC1 Arg194Trp polymorphism showed no significant association with CIN and squamous cervical carcinomas (SCC), while the Arg280His polymorphism acted as a protective factor for SCC, and the Arg399Gln polymorphism increased CIN risk among women who first gave birth before 22 years old [14]. Bajpai et al. suggested XRCC1 polymorphisms (Arg194Trp, Arg280His and Arg399Gln) increased cervical cancer risk greatly [23]. Barbisan et al. convinced that XRCC1 polymorphisms (Arg194Trp and Arg399Gln) genotypes and haplotypes contributed to reducing the risk of cervical cancer development in Argentin women [22]. Facing the contradictory, we assumed that a meta-analysis of various studies involving more subjects would offer a more precise conclusion. Thus, we aimed to obtain the summary risk estimating the association between the above mentioned three polymorphisms of XRCC1 and cervical cancer risk through a meta-analysis.

RESULTS

Characteristics of included studies

We initially retrieved 46 articles through various electronic databases. After removing reviews, meta-analysises, basic experimental studies, we got 32 articles needing screening the full-text. While 20 articles did not present available data and one was a duplicate study [25]. Consequently, a total of 11 articles involving 2092 cases and 2803 controls were recruited in the present meta-analysis [14–24] (Figure 1). Among these articles, 7 articles were about Arg194Trp (rs1799782) [14, 16, 17, 20–23], 4 articles were about Arg280His (rs25489) [14, 15, 20, 23], and 11 articles were about Arg399Gln (rs25487) [14–24]. However, we only recruited 10 studies when analyzing the association between Arg399Gln polymorphism and cervical cancer risk because an article offered data concerning CIN and cervical cancer as a whole [16]. Yet the study was included in the subgroup analysis stratified by the degree of cervical lesions.

The included studies were all performed in recent years. The objects in eight studies were of Caucasians, two were of Asian and one was Mixed. Eight out of eleven control groups were population-based or healthy-based participants and the ramaining three were hospital-based. The largest number of subjects was 1339, almost 10-fold of the smallest number (n = 133). (Table 1) The quality

assessment of included studies showed that all the studies were of high quality except that one study scored 5 points. (Table 2)

Hardy-Weinberg equilibrium (HWE) examination results of the included studies and the XRCC1 polymorphisms genotype distribution in cases and controls were displayed in Table 3. All studies were consistent with HWE except for three studies for Arg194Trp [17, 21, 22], one study for Arg280His [23], and one study for Arg 399Gln [24].

Meta-analysis results

For XRCC1 Arg194Trp polymorphism, there were seven studies, involving 1315 cases and 1633 controls, evaluating the connection between it and cervical cancer susceptibility. All the studies were done among the Asian population apart from one study [22]. Overall, there was no obvious statistic significance between the polymorphism and cervical cancer in all five models ($P > 0.05$). considering the moderate to great heterogeneity among studies, we performed subgroup analysis stratified by the degree of cervical lesion. However, the finding that the pooled OR still incorporated 1.0 showed that the Arg194Trp polymorphism had no association with the risk of cervical cancer. Then we excluded three studies which were not consistent with HWE [17, 22, 23] and reassessed the relationship between this locus and cervical cancer risk. The final results did not change substantially. (Table 4).

With regard to XRCC1 Arg280His polymorphism, four articles including 2015 objects (784 cases and 1231 controls) offered data about the association between it and cervical cancer risk. On the whole, the heterogeneity among studies were quite huge, the random model was employed to weigh the strength of the association. While the remarkable link between this genetic locus and cervical cancer wasn't witnessed in all models ($P > 0.05$). However, the heterogeneity among studies dropped to zero when excluding the study which didn't conform to HWE. Despite of this, the pooled results stayed stable when we eliminated the one [23]. (Table 4)

In terms of XRCC1 Arg399Gln polymorphism, ten studies involving 1635 cancer patients and 2361 controls presented available data about this locus and cervical cancer risk. The Arg399Gln polymorphism decreased cervical cancer susceptibility in four genetic models: allele model (Gln vs. Arg: OR = 0.39, 95% CI = 0.29–0.51, $P < 0.00001$), dominant model (GlnGln + ArgGln vs. ArgArg: OR = 0.08, 95% CI = 0.04–0.18, $P < 0.00001$), homozygous model (GlnGln vs. ArgArg: OR = 0.50, 95% CI = 0.33–0.75, $P = 0.0009$), heterozygous model (ArgGln vs. ArgArg: OR = 0.57, 95% CI = 0.45–0.72, $P < 0.00001$). (Figures 2–5) While there was no significant difference in recessive model (GlnGln vs. ArgGln + ArgArg: OR = 0.80, 95% CI = 0.63–1.01, $P = 0.06$). All the stuies

were in accordance with HWE except one study [24]. The trend of summary ORs remained stable after excluding the one. The subgroup analysis stratified by ethnicity revealed that there still exited obvious association between this polymorphism and decreased cervical cancer among the Asian (Gln vs. Arg: OR = 0.34, 95% CI = 0.26–0.43, P = 0.00001; GlnGln + ArgGln vs. ArgArg: OR=0.06, 95% CI = 0.03–0.12, P < 0.00001; GlnGln vs. ArgGln + ArgArg: OR = 0.70, 95% CI = 0.61–0.81, P < 0.00001; GlnGln vs. ArgArg: OR = 0.44, 95% CI = 0.28–0.68, P = 0.002; ArgGln vs. ArgArg: OR = 0.54, 95% CI = 0.40-0.72, P < 0.0001) and the Caucasian (Gln vs. Arg: OR = 0.63, 95% CI = 0.51–0.79, P < 0.0001; GlnGln + ArgGln vs. ArgArg: OR = 0.28, 95% CI = 0.11–0.68, P = 0.005; ArgGln vs. ArgArg: OR = 0.63, 95% CI = 0.41–0.97, P = 0.03). (Figure 6) In the subgroup analysis by the degree of cervical lesion (cervical cancer, cervical cancer + CIN), the Arg399Gln polymorphism reduced the risk of both cervical cancer and CIN. (Table 4)

Detection for heterogeneity

Considering the great heterogeneity among studies, the random-effect model was applied and subgroup analysis stratified by ethnicity (Figure 6) and the degree of cervical lesion was performed. Nevertheless, the comprehensive results stayed stable. Furthermore, the meta-regression of ethnicity showed no obvious difference (P > 0.05), implying that the ethnicity exerted no influence on the association between the XRCC1 Arg399Gln polymorphism and the risk of cervical cancer.

Sensitivity analysis

Although some studies wasn't consistent with the balance of HWE in control groups (P < 0.05), yet the final results were not substantially altered after excluding those. Simultaneously, the studies with quite large or small sample sizes were deleted one by one in order to test the stability of pooled results. Moreover, sequential deletion of each study was utilized to perform sensitivity analysis in all models. However, the pooled ORs did not show quantitative changes when excluding any study, suggesting that the results of this meta-analysis were stable and reliable. Sensitivity analysis of the association between the XRCC1 Arg399Gln polymorphism and the risk of cervical cancer in homozygous model was showed Figure 7.

Publication bias

The Begg's test and Egger's test were done in all models showing that there was no statistical evidence for publication bias. Publication bias of the XRCC1 Arg399Gln polymorphism in homozygous model was shown in Figure 8 (P > 0.05).

DISCUSSION

Cervical cancer is still the second most common malignant tumor among women and heavily threatens women's health in the world. To improve this embarrassing situation, risk factors concerning cervical cancer should be indentified timely and controlled effectively. There
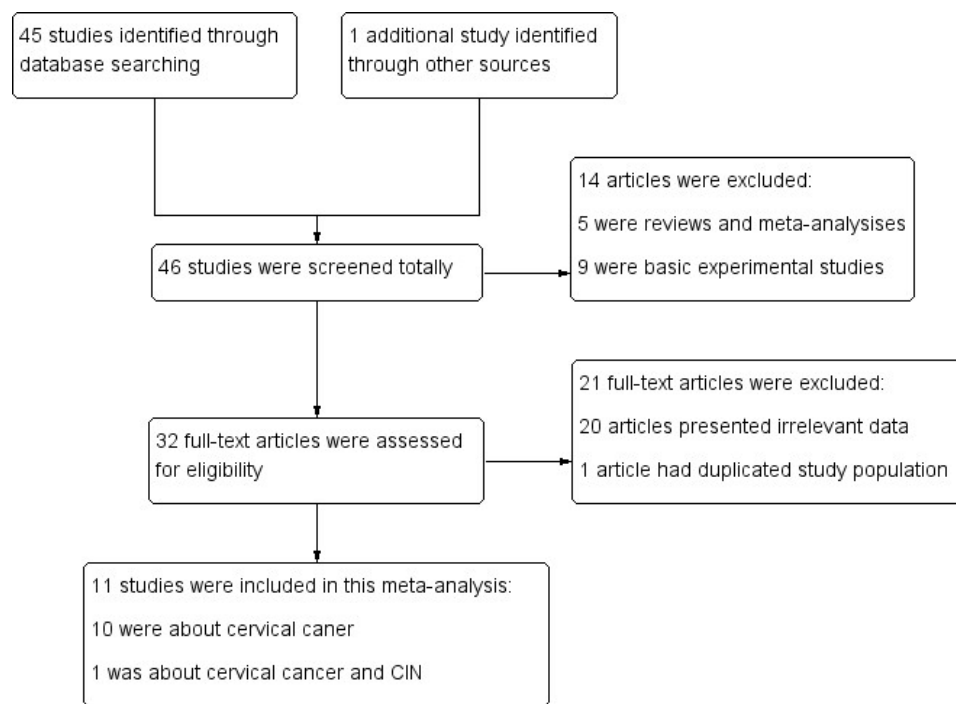

Figure 1: Search flow diagram.

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

First author	Year	Country	Ethnicity	Source of controls	Genotyping method
Alsbeih et al. [24]	2013	Saudi Arabia	Asian	Hospital-based	PCR
Bajpai et al. [23]	2016	India	Asian	Hospital-based	PCR-RFLP
Barbisan et al. [22]	2011	Argentina	Caucasian	Population-basd	PCR
Djansugurova et al. [21]	2013	Kazakhstan	Asian	Healthy-based	PCR
Huang et al. [20]	2007	China	Asian	Population-basd	MA-PCR
Rozak et al. [18]	2011	Poland	Caucasian	Hospital-based	PCR-RFLP
Niwa et al. [19]	2005	Japan	Asian	Healthy-based	PCR
Setthetham-Ishida et al. [17]	2011	Thailand	Asian	Healthy-based	PCR-RFLP
Wang et al. [16]	2009	Costa Rica	Mixed	Population-basd	Taqman
Wu et al. [15]	2004	Taiwan	Asian	Population-basd	PCR-RFLP
Zhang et al. [14]	2012	China	Asian	Healthy-based	PCR

PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism.

Table 2: Quality assessment of studies based on the modified scoring system [31]

Study name	Representativeness of cases	Source of controls	HWE in controls	Genotyping examination blinded	Association assessment	Total
Alsbeih 2013	2	1	1	0	1	5
Bajpai 2016	2	1	2	0	2	7
Barbisan 2011	1	2	2	0	1	6
Djansugurova 2013	2	2	2	0	1	7
Huang 2007	2	2	2	0	2	8
Rozak 2011	2	1	2	0	1	6
Niwa 2005	2	2	2	0	1	7
Setthetham-Ishida 2011	2	2	2	0	2	8
Wang 2009	2	2	2	0	1	7
Wu 2004	1	2	2	0	2	7
Zhang 2012	2	2	2	0	2	8

HWE : Hardy-Weinberg equilibrium.

have exited several case-control studies focusing on the relationship between individual susceptibility or genetic variants and cervical cancer [17, 18, 21, 24, 26]. However, the results remained conflicting rather than conclusive. Because a single study may have been underpowered to detect the effect of XRCC1 polymorphisms on cervical cancer risk, yet a quantitative synthesis of accumulative data from all available studies may provide convincing evidence. So a meta-analysis of ten available studies involving 2092 cervical cancer cases and 2803 controls was performed, expecting to derive a more precise estimation of the association between the XRCC1 polymorphism and cervical cancer susceptibility. Our results showed that there was no obvious association between XRCC1 Arg194Trp or Arg280His and cervical cancer susceptibility. Although we did subgroup analysis and sensitivity analysis, the trend of pooled results still remained identical, suggesting that the comprehensive results were quite stable. As to

the Arg399Gln polymorphism, it reduced the risk of cervical cancer sharply. Likewise, we performed subgroup analysis and sensitivity analysis, the summary results still hinted a positive relationship between the Arg399Gln polymorphism and the decreased risk of cervical cancer.

Certainly, there have emerged several other meta-analysises concerning the link between XRCC1 polymorphisms and cervical cancer risk. A latest meta-analysis exploring the association between the Arg399Gln polymorphism and cervical cancer showed that the Arg399Gln polymorphism increased the risk of cervical cancer [27]. The result contradicted ours and the reasons may include the following. On the one hand, the number of databases we searched was bigger, resulting in more available studies in English were included. On the another, the quantity of subjects involving in present meta-analysis was greater, which surely strengthened the persuasive power of this research. Another meta-analysis noted that the Arg399Gln polymorphism elevated the risk of cervical

Table 3: XRCC1 polymorphisms genotype distribution and allele frequency in cases and controls

First author	Genotype (N)							Allele frequency (N)				HWE
	Case				Control			Case		Control		
Arg194Trp(rs1799782)	Total	TrpTrp	ArgTrp	ArgArg	Total	TrpTrp	ArgTrp	ArgArg	Trp	Arg	Trp	Arg	
Bajpai et al. [23]	65	38	16	11	68	13	11	44	92	38	37	99	1.07
Barbisan et al. [22]	103	4	20	79	114	4	12	98	28	178	20	208	< 0.05
Djansugurova et al. [21]	217	6	48	163	160	15	40	105	60	374	70	250	< 0.05
Huang et al. [20]	539	78	220	241	800	63	330	407	376	702	456	1144	0.73
Setthetham-Ishida et al. [17]	111	9	49	53	118	2	51	65	67	155	55	181	0.02
Wu et al. [15]	100	9	43	48	196	16	93	87	61	139	125	267	0.20
Zhang et al. [14]	80	8	31	41	177	19	71	87	47	113	109	245	0.43
Arg280His (rs25489)	Total	HisHis	ArgHis	ArgArg	Total	HisHis	ArgHis	ArgArg	His	Arg	His	Arg	
Bajpai et al. [23]	65	39	6	20	58	3	7	48	84	46	13	103	< 0.05
Huang et al. [20]	539	6	117	416	800	9	171	620	129	949	189	1411	0.46
Wu et al. [15]	100	2	24	74	196	1	55	140	28	172	57	335	0.07
Zhang et al. [14]	80	1	11	68	177	1	34	142	13	147	36	318	0.49
Arg399Gln (rs25487)	Total	GlnGln	ArgGln	ArgArg	Total	GlnGln	ArgGln	ArgArg	Gln	Arg	Gln	Arg	
Alsbeih et al. [24]	100	14	34	52	100	1	40	59	62	62	158	42	0.04
Bajpai et al. [23]	65	31	22	12	68	12	33	23	84	84	79	57	0.989
Barbisan et al. [22]	103	18	31	54	114	18	59	37	67	67	133	95	0.49
Djansugurova et al. [21]	217	20	119	78	160	4	90	66	159	159	222	98	4.21
Huang et al. [20]	539	47	203	289	800	37	235	528	297	297	1291	309	0.10
Rozak et al. [18]	189	39	101	49	308	40	152	116	179	179	384	232	0.37
Niwa et al. [19]	131	13	49	69	320	26	109	185	75	75	479	161	0.097
Setthetham-Ishida et al. [17]	111	4	41	66	118	5	44	69	49	49	182	54	0.54
Wu et al. [15]	100	8	38	54	196	9	73	114	54	54	301	91	0.53
Zhang et al. [14]	80	6	31	43	177	10	58	109	43	43	276	78	0.54

HWE: Hardy-Weinberg equilibrium.

cancer in Chinese population [28]. However, the number of included studies was seven, less than the present one. Moreover, it only included the Chinese population, which undoubtedly weakened the strength of the conclusion. Li et al. held that the Arg194Trp polymorphism increased the risk of cervical cancer, while there was no association between the Arg399Gln or Arg280His polymorphism and cervical cancer risk [29]. But the meta-analysis was done five years ago and the number of databases was less than the present, which may explain the discrepancy in the results. Mei et al. showed that the Arg194Trp polymorphism increased the risk of cervical cancer and the Arg399Gln polymorphism elevated the risk of cervical cancer only in Asian population, while there was no association between the Arg280His polymorphism and cervical cancer risk [30]. While the meta-analysis was performed based on only two databases and it included studies without language limits, which may account for the distinction. As you see, the previous meta-analysises either focused on only one polymorphism or only one race or included fewer studies. Yet the present meta-analysis involved all studies of moderate to high quality according to prescribed inclusion and exclusion criteria, so the strength of this study was stronger than those past studies. Simultaneously, even though we performed subgroup analysis and sensitivity analysis, the pooled results still remained stable, supporting that this study was of great credit and persuasiveness.

Likewise, some limitations of this meta-analysis should be mentioned even though considerable effort and resources have been put into testing the possible association between the XRCC1 polymorphism and cervical cancer risk. On the one hand, we retrieved relevant articles only through electronic databases, leading to a potential bias caused by the lack of unpublished articles which would not be available in the electronic databases. On the other, although the great heterogeneity among studies had no effect on the pooled result, yet the heterogeneity could not be neglected completely.

To conclude, the current meta-analysis indicated that the XRCC1 Arg399Gln polymorphism decreased the risk of cervical cancer, while the Arg194Trp and Arg280His polymorphisms were not associated with cervical caner risk. Certainly, to further evaluate the association between

Table 4: Meta-analysis results

Subgroup Analysis		OR	95% CI	*P* value	Heterogeneity		Effects model
					I²	*P* value	
XRCC1 Arg194Trp		Allele model (Trp vs. Arg)					
Overall		1.04	0.80–1.36	0.75	72%	0.001	R
Degree of cervical lesion	CC	1.03	0.65–1.62	0.91	78%	0.004	R
	CC+CIN	1.66	0.83–3.31	0.15	94%	< 0.00001	R
		Dominant model (TrpTrp + ArgTrp vs. ArgArg)					
Overall		1.12	0.96–1.31	0.61	49%	0.07	F
Degree of cervical lesion	CC	1.03	0.66–1.61	0.89	65%	0.04	R
	CC+CIN	1.80	0.77–4.21	0.18	92%	< 0.00001	R
		Recessive model (CC vs. GC + GG)					
Overall		1.08	0.60–1.94	0.81	72%	0.002	R
Degree of cervical lesion	CC	1.03	0.35–3.10	0.95	72%	0.01	R
	CC+CIN	1.76	0.95–3.24	0.07	71%	0.03	R
		Homozygous genetic model (TrpTrp vs. ArgArg)					
Overall		1.13	0.61–2.12	0.69	71%	0.002	R
Degree of cervical lesion	CC	0.54	0.40–0.74	0.95	14%	0.004	R
	CC+CIN	0.75	0.57–0.97	0.12	87%	0.0005	R
		Heterozygous genetic model (ArgTrp vs. ArgArg)					
Overall		1.07	0.91–1.26	0.43	10%	0.35	F
Degree of cervical lesion	CC	0.56	0.41–0.77	0.84	43%	0.15	R
	CC+CIN	0.89	0.67–1.16	0.23	87%	0.0004	R
XRCC1 Arg280His		Allele model (His vs. Arg)					
Overall		1.78	0.63–5.01	0.28	95%	< 0.00001	R
		Dominant model (HisHis + ArgHis vs. ArgArg)					
Overall		1.16	0.94–1.43	0.17	90%	< 0.00001	R
		Recessive model (HisHis vs. ArgHis + ArgArg)					
Overall		4.08	0.58–28.75	0.16	82%	0.0009	R
		Homozygous genetic model (HisHis vs. ArgArg)					
Overall		4.12	0.55–30.79	0.17	83%	0.0006	R
		Heterozygote genetic model (ArgHis vs. ArgArg)					
Overall		0.97	0.77–1.21	0.78	0%	0.41	F
XRCC1 Arg399Gln		Allele model (Gln vs. Arg)					
Overall		0.39	0.29–0.51	< 0.00001	83%	< 0.00001	R
Ethnicity	Asian	0.34	0.26–0.43	0.00001	72%	0.0008	R
	Caucasian	0.63	0.51–0.79	< 0.0001	0%	0.51	R
Degree of cervical lesion	CC	0.41	0.31–0.54	< 0.00001	72%	0.001	R
	CC+CIN	0.39	0.24–0.65	0.0003	93%	< 0.00001	R
		Dominant model (GlnGln + ArgGln vs. ArgArg)					
Overall		0.08	0.04–0.18	< 0.00001	92%	< 0.00001	R
Ethnicity	Asian	0.06	0.03–0.12	< 0.00001	86%	< 0.00001	R
	Caucasian	0.28	0.11–0.68	0.005	81%	0.02	R

		OR	95% CI	P	I²	P	Model
Degree of cervical lesion	CC	0.07	0.03–0.17	< 0.00001	90%	< 0.00001	R
	CC+CIN	0.11	0.04–0.33	< 0.0001	95%	< 0.00001	R
Recessive model (GlnGln vs. ArgGln + ArgArg)							
Overall		0. 80	0.63–1.01	0.06	63%	0.003	R
Ethnicity	Asian	0.70	0.61–0.81	< 0.00001	0%	0.43	R
	Caucasian	1.14	0.30–4.38	0.85	94%	< 0.0001	R
Degree of cervical lesion	CC	0.90	0.67–1.22	0.50	64%	0.01	R
	CC+CIN	0.79	0.53–1.16	0.22	81%	0.0001	R
Homozygous genetic model (GlnGln vs. ArgArg)							
Overall		0.50	0.33–0.75	0.0009	55%	0.02	R
Ethnicity	Asian	0.44	0.28–0.68	0.0002	42%	0.10	R
	Caucasian	0.77	0.23–2.53	0.67	84%	0.01	R
Degree of cervical lesion	CC	0.56	0.32–0.99	0.05	61%	0.02	R
	CC+CIN	0.68	0.31–1.48	0.33	85%	0.0002	R
Heterozygous genetic model (ArgGln vs. ArgArg)							
Overall		0.57	0.45–0.72	< 0.00001	36%	0.13	F
Ethnicity	Asian	0.54	0.40–0.72	< 0.0001	48%	0.06	F
	Caucasian	0.63	0.41–0.97	0.03	0%	0.59	F
Degree of cervical lesion	CC	0.57	0.37–0.89	0.01	36%	0.15	R
	CC+CIN	0.83	0.48–1.43	0.50	69%	0.02	R

CC: cervical cancer; CIN: cervical intraepithelial neoplasia; F: fixed-effect model; R: random-effect model; OR: odds ratio; 95% CI : 95% confidence interval.
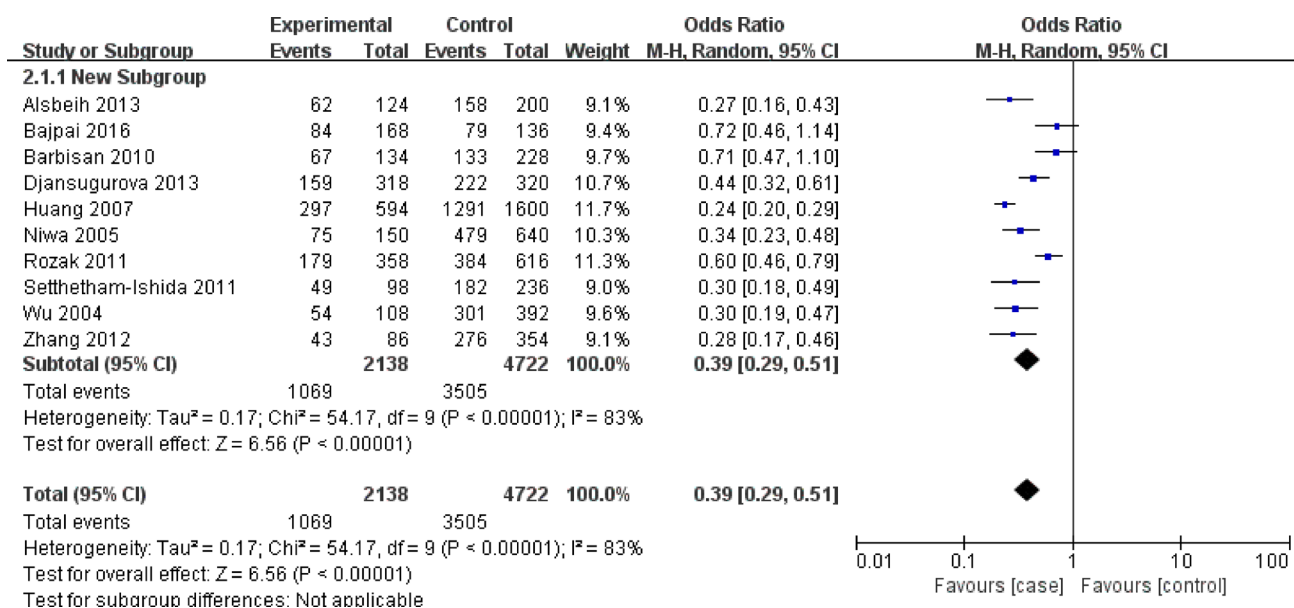

Figure 2: Meta-analysis of the association between XRCC1 Arg399Gln polymorphism and the risk of cervical cancer in allele model. CI: confidence interval; OR: odds ratio.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Alsbeih 2013	48	100	99	100	6.3%	0.01 [0.00, 0.07]	
Bajpai 2016	53	65	56	68	10.0%	0.95 [0.39, 2.29]	
Barbisan 2010	49	103	96	114	10.7%	0.17 [0.09, 0.32]	
Djansugurova 2013	139	217	156	160	9.5%	0.05 [0.02, 0.13]	
Huang 2007	250	539	763	800	11.3%	0.04 [0.03, 0.06]	
Niwa 2005	62	131	294	320	10.9%	0.08 [0.05, 0.13]	
Rozak 2011	140	189	268	308	11.1%	0.43 [0.27, 0.68]	
Setthetham-Ishida 2011	45	111	113	118	9.7%	0.03 [0.01, 0.08]	
Wu 2004	46	100	187	196	10.3%	0.04 [0.02, 0.09]	
Zhang 2012	37	80	167	177	10.3%	0.05 [0.02, 0.11]	
Total (95% CI)		1635		2361	100.0%	0.08 [0.04, 0.18]	
Total events	869		2199				

Heterogeneity: Tau² = 1.25; Chi² = 108.43, df = 9 (P < 0.00001); I² = 92%
Test for overall effect: Z = 6.53 (P < 0.00001)

0.01 0.1 1 10 100
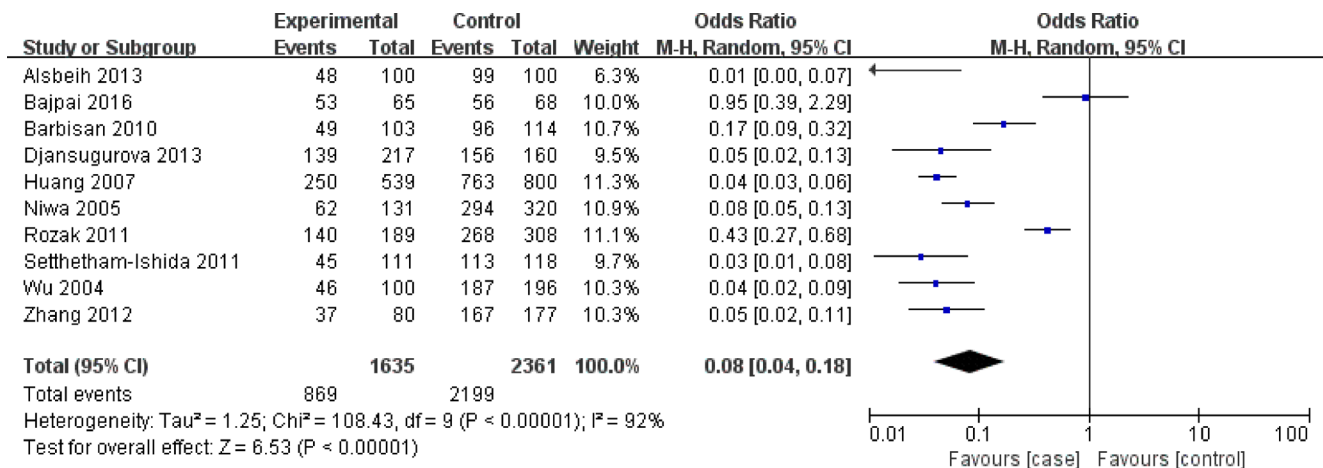Favours [case]   Favours [control]

Figure 3: Meta-analysis of the association between XRCC1 Arg399Gln polymorphism and the risk of cervical cancer in dominant model. CI: confidence interval; OR: odds ratio.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Alsbeih 2013	52	66	59	60	3.3%	0.06 [0.01, 0.50]	
Bajpai 2016	12	43	23	35	9.5%	0.20 [0.08, 0.53]	
Barbisan 2010	54	72	37	55	11.7%	1.46 [0.67, 3.17]	
Djansugurova 2013	78	98	66	70	8.0%	0.24 [0.08, 0.73]	
Huang 2007	289	336	528	565	16.2%	0.43 [0.27, 0.68]	
Niwa 2005	69	82	185	211	12.5%	0.75 [0.36, 1.53]	
Rozak 2011	49	88	116	156	14.8%	0.43 [0.25, 0.75]	
Setthetham-Ishida 2011	66	70	69	74	6.3%	1.20 [0.31, 4.65]	
Wu 2004	54	62	114	123	9.1%	0.53 [0.19, 1.46]	
Zhang 2012	43	49	109	119	8.5%	0.66 [0.23, 1.92]	
Total (95% CI)		966		1468	100.0%	0.50 [0.33, 0.75]	
Total events	766		1306				

Heterogeneity: Tau² = 0.21; Chi² = 20.11, df = 9 (P = 0.02); I² = 55%
Test for overall effect: Z = 3.32 (P = 0.0009)

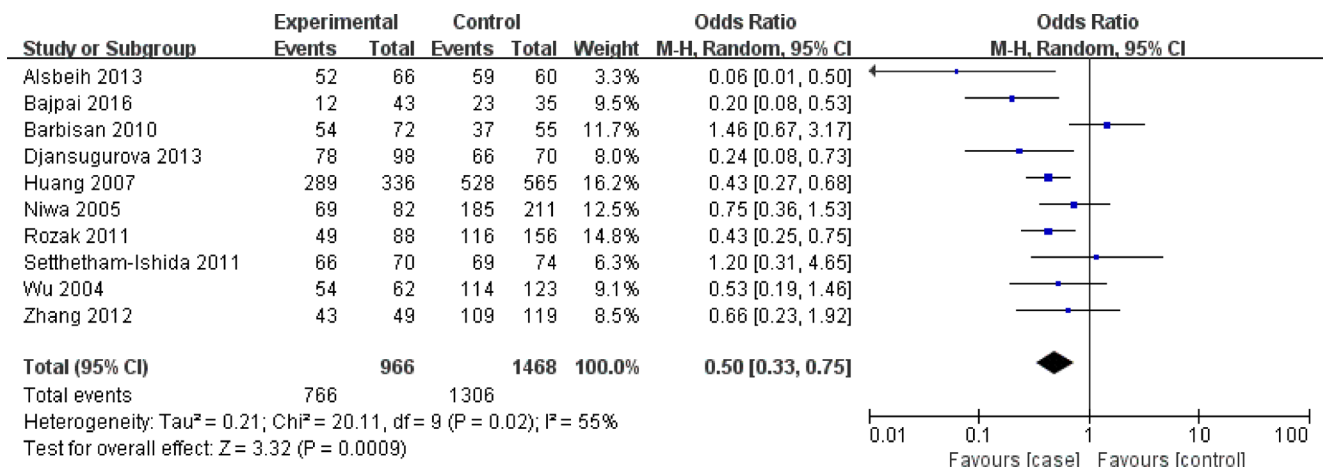0.01 0.1 1 10 100
Favours [case]   Favours [control]

Figure 4: Meta-analysis of the association between XRCC1 Arg399Gln polymorphism and the risk of cervical cancer in homozygous model. CI: confidence interval; OR: odds ratio.
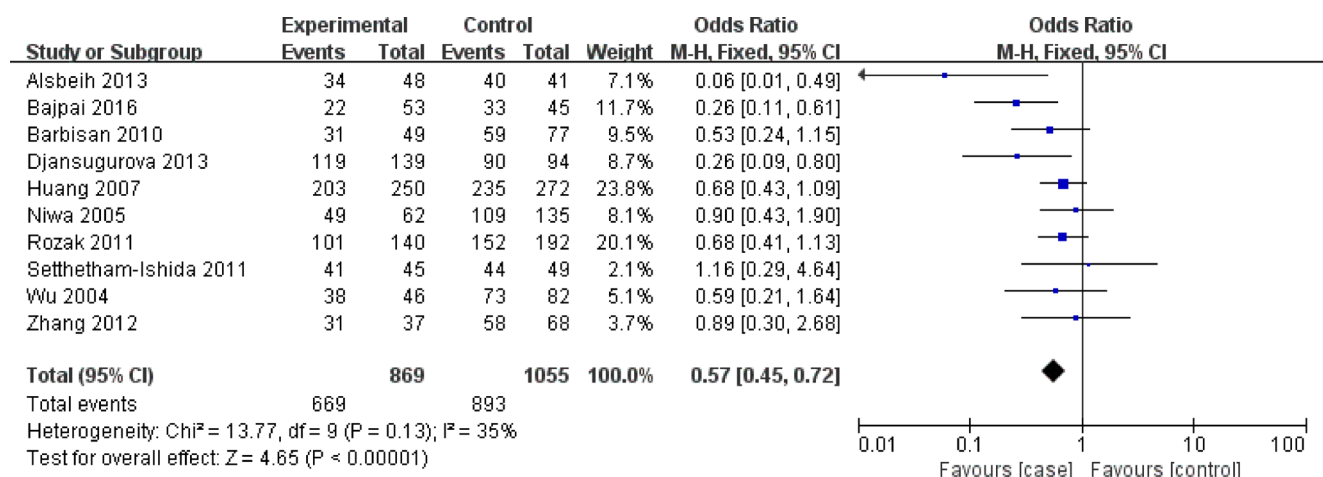
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Alsbeih 2013	34	48	40	41	7.1%	0.06 [0.01, 0.49]	
Bajpai 2016	22	53	33	45	11.7%	0.26 [0.11, 0.61]	
Barbisan 2010	31	49	59	77	9.5%	0.53 [0.24, 1.15]	
Djansugurova 2013	119	139	90	94	8.7%	0.26 [0.09, 0.80]	
Huang 2007	203	250	235	272	23.8%	0.68 [0.43, 1.09]	
Niwa 2005	49	62	109	135	8.1%	0.90 [0.43, 1.90]	
Rozak 2011	101	140	152	192	20.1%	0.68 [0.41, 1.13]	
Setthetham-Ishida 2011	41	45	44	49	2.1%	1.16 [0.29, 4.64]	
Wu 2004	38	46	73	82	5.1%	0.59 [0.21, 1.64]	
Zhang 2012	31	37	58	68	3.7%	0.89 [0.30, 2.68]	
Total (95% CI)		869		1055	100.0%	0.57 [0.45, 0.72]	
Total events	669		893				

Heterogeneity: Chi² = 13.77, df = 9 (P = 0.13); I² = 35%
Test for overall effect: Z = 4.65 (P < 0.00001)

0.01 0.1 1 10 100
Favours [case]   Favours [control]

Figure 5: Meta-analysis of the association between XRCC1 Arg399Gln polymorphism and the risk of cervical cancer in heterozygous model. CI: confidence interval; OR: odds ratio.
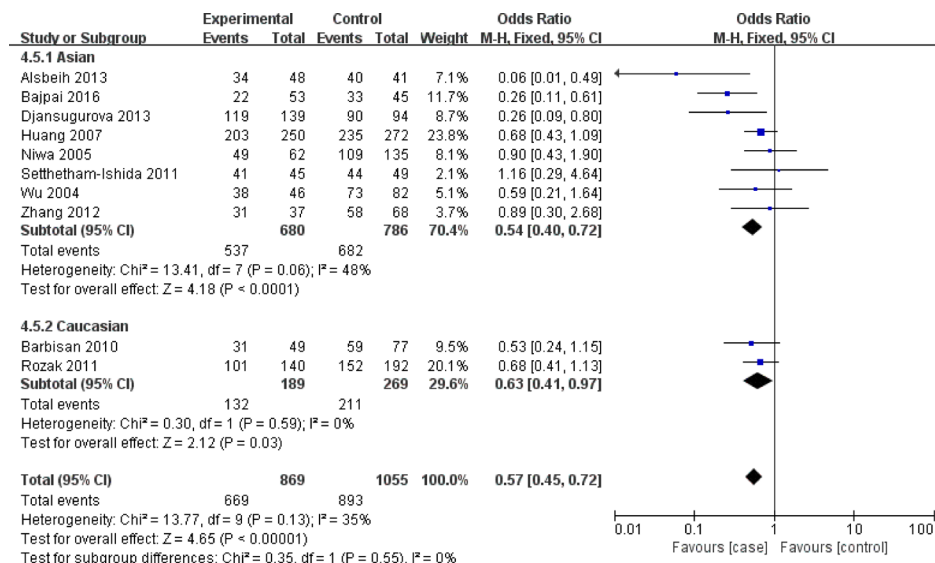
Figure 6: Subgroup analysis of the association between XRCC1 Arg399Gln polymorphism and the risk of cervical cancer stratified by ethnicity in heterozygous model. CI: confidence interval; OR: odds ratio.
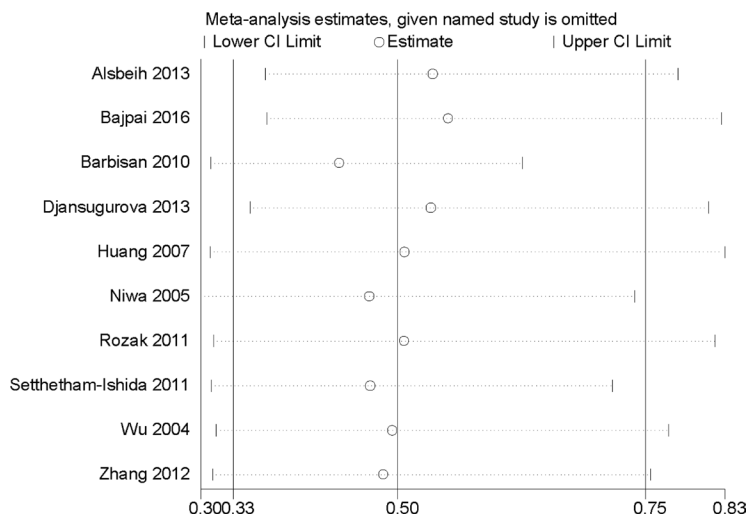

Figure 7: Sensitivity analysis of the association between XRCC1 Arg399Gln polymorphism and the risk of cervical cancer in homozygous model.
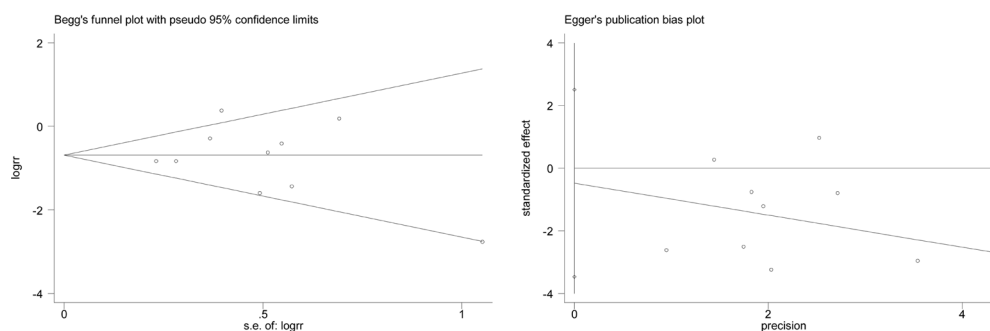

Figure 8: Publication bias of XRCC1 Arg399Gln polymorphism in homozygous model was assessed by Begg's test and Egger's test, suggesting that there was no statistical evidence for publication bias in this meta-analysis ($P > 0.05$).

XRCC1 polymorphisms and cervical cancer susceptibility, a well-designed large-scale multicenter study is warranted to confirm the finding.

MATERIALS AND METHODS

Literature searching strategy

A systematic literature search was done through PubMed, Web of Science, EMBASE and the Cochrane Library up to July 2016 in English. The search terms included "X-ray repair cross complementing protein 1", "XRCC1", "Arg194Trp", "rs1799782", "Arg280His", "rs25489", "Arg399Gln" or "rs25487"; "poly-morphism", "variant", "genotype", "polymorphism" or "SNP"; "cervical" or "cervix"; "cancer", "carcinoma", "neoplasm", "tumor" or " malignancy "and the combinations. Besides, the relevant references of identified studies were screened carefully for potential articles.

Inclusion and exclusion criteria

The included studies have to meet the following criteria: 1) investigating the association between XRCC1 polymorphisms (Arg194Trp, Arg280His and Arg399Gln) and risk of cervical cancer; 2) studies on human beings; 3) genotype frequencies were available both in case and control groups; 4) subjects in control groups should have no cancer history, previous radiotherapy and chemotherapy history and a family history of tumor; 5) the diagnosis of the cases was based on pathology. The study with the following criteria was excluded: 1) abstracts, case reports, letters, comments, editorials, reviews and mata-analysises; 2) studies lacking relevant data. What's more, the most recent study was included once the studies were duplicated. Any one study was screened by two authors independently and disagreements were resolved by discussing with a third author.

Data extraction and synthesis

Two investigators simultaneously extracted characteristics of the included studies according to the inclusion and exclusion criteria and the results were checked by a third reviewer. The data extracted from each study included first author, year of publication, country of origin, ethnicity, source of the control group, genotyping method and numbers of case and control subjects. Ethnicity was classified as ''Caucasian'', ''Asian'' and ''Mixed''.

Quality assessment

The methodological quality assessment was performed based on the modified scoring system used for studies in genetic epidemiological issues. [31] Points were awarded on the basis of representativeness of cases, source of controls, HWE in controls, genotyping examination and association assessment. Total score ranged from 0 (lowest quality) to 8 (highest quality). A study with a score of 6 or higher was classified as high quality and vice versa.

Statistical analysis

Review Manage version 5.2.0 (The Cochrane Collaboration, 2012) and STATA version 11.0 software (StataCorp LP, College Station, TX) were applied to carry out statistical analysis. The association between XRCC1 polymorphisms and cervical cancer risk was estimated in the allele model, the dominant model, the recessive model, the homozygous genetic model and the heterozygous genetic model. To evaluate the strength of associations, the summary odds ratio (OR) and 95% confidence interval (CI) were calculated through fixed/random effects mode. $P < 0.05$ was considered statistically significant. To test the heterogeneity among studies, we assumed the I^2 and Q statistic. We adopted random effect model if there was great heterogeneity (I^2 greater than 50%). Otherwise, we adopted the fixed effect model. At the same time, we conducted a subgroup analysis according to ethnicities. To assess the stability of the finding, we performed sensitivity analysis. Each study involved in this meta-analysis was deleted respectively to reflect the influence of the individual data exerted on the pooled OR. HWE of the genotype frequencies in the control group of each study was assessed by χ^2 test and $P > 0.05$ was considered to be consistent with HWE [32]. For the studies which did not live up to HWE, we reassessed the association by eliminating them. The Begg's funnel plot and Egger's test were used to evaluate the possibly exiting publication bias [33, 34].

CONFLICTS OF INTEREST

The authors have declared that no conflicts of interest exists.

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