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Original Article

X-ray repair cross-complementing protein 1 polymorphisms and risk of nasopharyngeal carcinoma: a meta-analysis in the Chinese population

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Abstract: Previous studies investigating the association between X-ray repair cross-complementation group 1 (XRCC1) polymorphisms and nasopharyngeal carcinoma (NPC) risk has provided inconsistent results. To further evaluate the influence of XRCC1 polymorphisms on NPC risk, we conducted a meta-analysis in the Chinese population. To identify eligible studies, we searched on PubMed and Chinese databases through April 2016. To determine the strength of the associations, we utilized pooled odds ratios (ORs) and 95% confidence intervals (CIs). This meta-analysis included 6 studies with 1450 NPC cases and 1571 controls. In general, our findings indicated that a significant association existed between XRCC1 Arg399Gln polymorphism and the risk of NPC in the studied Chinese population, and there may be no association between Arg280His, Arg194Trp polymorphisms and NPC risk. In conclusion, this meta-analysis provides evidence that XRCC1 Arg399Gln polymorphism is associated with NPC in the Chinese population. Further studies in other ethnic groups are required for definite conclusions.

Keywords: Meta-analysis, X-ray repair cross-complementation group 1, polymorphism, nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor of the nasopharynx that has a strong geographical distribution [1]. There were an estimated 84400 incident cases of NPC and 51600 deaths in 2008, representing about 0.7% of the global cancer burden [1]. It was also found that 80% of patients with NPC lived in China with the southern part of China having the highest incidence of the disease [2, 3]. A growing body of evidence indicates that epstein-Barr virus infection [4], tobacco smoking, alcohol consumption [5], occupational exposure to wood dust [6] and consumption of a high-salt diet [7, 8] may may induce the disease. However, the carcinogenesis of various cancers is associated with interaction between environmental carcinogens and individuals' genetic background. Polymorphisms in cancer-related genes have been suggested to be the genetic basis of individuals' susceptibility to NPC.

Recently, some commonly inherited low-penetrance genes have been recognized as genes possibly responsible for susceptibility to NPC. One of their major representatives is X-ray repair cross-complementing group 1 (XRCC1), which is involved in base excision repair and the repair of single-strand breaks. Loss of XRCC1 may result in decreased genetic stability, including increased frequencies of spontaneous and/or induced chromosome translocations and deletions [9]. XRCC1 gene included at least 21 single nucleotide polymorphisms with the amino acid substitutions, in which the Arg194Trp (exon6, C/T), Arg280His (exon9, G/A), and Arg399Gln (exon10, G/A) are most commonly studied. Some studies have explored the association between XRCC1 polymorphisms and NPC susceptibility; however, no definite consensus has been made. Differences in findings may be due to race and clinical heterogeneity in patients who have been studied, as well as a limited number of patients in each study. In evaluating the association of XRCC1

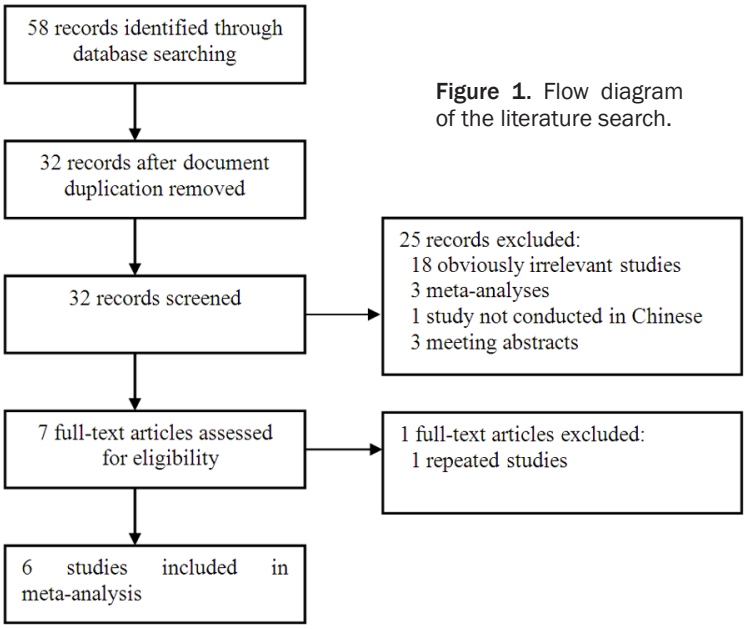

Figure 1. Flow diagram of the literature search.

polymorphisms with the risk of NPC in a solely Chinese population, we conducted the present updated meta-analysis to reduce the influence of the diverse genetic backgrounds.

Materials and methods

Search strategy and selection criteria

Using the databases of PubMed and Chinese databases, we searched all literature sources published before April 2016 for studies examining the relationship between XRCC1 polymorphisms and the risk of NPC. The search keywords were used: (XRCC1 or X-ray repair cross-complementing group 1) and (nasopharyngeal carcinoma or NPC) and (Chinese or China or Taiwan). Furthermore, we carefully inspected the lists with references of the articles and reviews that had been extracted. No language restriction was applied.

To be eligible for inclusion, the investigations had to have fulfilled the following requirements: (1) case-control studies describing the association between XRCC1 polymorphisms and NPC, (2) studies with sufficient genetypes data in cases and controls, (3) all participants were Chinese population. The following studies were excluded: (1) non-cohort or non-case-control investigations; (2) duplicates of earlier publications; (3) their data were incomplete; (4) reviews, letters, editorial articles, or meta-analyses.

Data extraction

Data were extracted from all eligible publications and entered into a database. Extraction was performed by two reviewers independently. For conflicting evaluations, an agreement was reached following a discussion. The following information was collected from each study: first author's name, publication year, sources of controls, sample size, and available genotype information from the XRCC1 polymorphisms. Hardy-Weinberg equilibrium in controls were calculated from corresponding genotype distributions. Sources of controls were stratified to population based [PB] and hospital based [HB]. In this meta-analysis, the quality assessment of individual study was conducted according to the nine-star Newcastle-Ottawa Scale [10].

Statistical analysis

We performed meta-analyses using: (1) allelic contrast, (2) contrast of homozygotes, (3) recessive, and (4) dominant models. Allele frequencies at the XRCC1 polymorphisms from the respective studies were determined by the allele counting method. The pooled odds ratio (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the relationship between XRCC1 polymorphisms and NPC risk. The between-study heterogeneity was assessed by chi-square based Q-test [11]. Depending on the results of the heterogeneity test among individual studies, the fixed-effect model (Mantel-Haenszel) or random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs. The significance of the pooled OR was determined by a Z-test. We employed Begg's funnel plot and Egger's linear regression tests to evaluate the publication bias. All statistical tests were performed using the Stata, version 12 (StataCorp LP, College Station, TX). A *P* value less than 0.05 was considered to be statistically significant.

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

References	Genotyping method	Study design	Quality score	Sources of controls	Case number	Control number	Cases			Controls			HWE for controls	
													X^2	*P*
XRCC1 Arg399Gln							Arg/Arg	Arg/Gln	Gln/Gln	Arg/Arg	Arg/Gln	Gln/Gln		
Cho 2003	PCR-RFLP	Case-control	8	PB	334	282	174	128	32	152	109	21	0.06	0.81
Cao 2006	PCR-RFLP	Case-control	8	HB	425	501	241	152	32	270	201	30	0.86	0.35
Dai 2007	PCR-RFLP	Case-control	6	PB	220	226	116	68	36	147	32	47	94.86	0.00
Yang 2007	PCR-RFLP	Case-control	7	PB	153	168	93	54	6	95	67	6	1.99	0.16
Li 2013	PCR-CTPP	Case-control	7	PB	231	300	92	117	22	166	114	20	0.01	0.94
Zhu 2014	PCR- RFLP	Case-control	7	PB	87	94	57	27	3	66	26	2	0.09	0.76
XRCC1 Arg194Trp							Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg	Arg/Trp	Trp/Trp		
Cao 2006	PCR-RFLP	Case-control	8	HB	417	495	232	166	19	235	217	43	0.51	0.48
Dai 2007	PCR-RFLP	Case-control	6	PB	220	250	116	91	13	168	73	9	0.09	0.76
Yang 2007	PCR-RFLP	Case-control	7	PB	153	168	62	79	12	99	65	4	3.18	0.07
Zhu 2014	PCR-RFLP	Case-control	7	PB	87	94	34	50	3	31	56	7	7.09	0.01
XRCC1 Arg280His							Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His		
Cho 2003	PCR-RFLP	Case-control	8	PB	332	283	275	55	2	215	66	2	1.63	0.20
Dai 2007	PCR-RFLP	Case-control	6	PB	220	250	173	43	4	209	37	4	2.33	0.13
Yang 2007	PCR-RFLP	Case-control	7	PB	153	168	125	27	1	131	35	2	0.04	0.84

Table 2. OR and 95% CI in each included study.

References	OR (95% CI)	Adjusted OR (95% CI)	Adjusted factors
XRCC1 Arg399Gln	Gln/Gln vs. Arg/Arg		
Cho 2003	1.3 3 (0.74-2.41)	1.0 (0.74-1.5)	Age, gender, and ethnicity
Cao 2006	1.20 (0.71-2.03)	1.20 (0.69-2.06)	Age, sex, smoking status
Dai 2007	0.97 (0.59-1.60)	-	-
Yang 2007	1.02 (0.32-3.28)	-	-
Li 2013	1.98 (1.03-3.83)	1.96 (1.02~3.78)	Age, gender, smoking status, and family history of cancer
Zhu 2014	1.69 (0.25-14.97)	-	-
XRCC1 Arg194Trp	Trp/Trp vs. Arg/Arg		
Cao 2006	0.45 (0.25-0.79)	0.48 (0.27-0.86)	Age, sex, smoking status
Dai 2007	2.09 (0.87-5.05)	-	-
Yang 2007	4.79 (1.48-15.52)	-	-
Zhu 2014	0.41 (0.08-1.65)	-	-
XRCC1 Arg280His	His/His vs. Arg/Arg		
Cho 2003	0.78 (0.11-5.60)	0.66 (0.09-4.7)	Age, gender, and ethnicity
Dai 2007	1.21 (0.30-4.90)	-	-
Yang 2007	0.52 (0.05-5.85)	-	-

Table 3. Association of the XRCC1 gene polymorphisms on NPC susceptibility

Polymorphism		N	Orr (95% CI)	ORf (95% CI)	P_h
XRCC1 Arg399Gln	Gln vs. Arg	6	1.14 (0.96-1.34)	1.13 (1.01-1.27)	0.093
	Gln/Gln vs. Arg/Arg	6	1.25 (0.96-1.64)	1.25 (0.96-1.63)	0.668
	Gln/Gln vs. Arg/Arg+Arg/Gln	6	1.12 (0.86-1.46)	1.12 (0.86-1.45)	0.518
	Gln/Gln+Arg/Gln vs. Arg/Arg	6	1.20 (0.91-1.59)	1.17 (1.01-1.35)	0.005
XRCC1 Arg194Trp	Trp vs. Arg	4	1.15 (0.70-1.88)	1.04 (0.90-1.20)	0.000
	Trp/Trp vs. Arg/Arg	4	1.14 (0.35-3.70)	0.88 (0.59-1.30)	0.000
	Trp/Trp vs. Arg/Arg+Arg/Trp	4	1.05 (0.41-2.72)	0.85 (0.58-1.26)	0.006
	Trp/Trp+Arg/Trp vs. Arg/Arg	4	1.21(0.67-2.20)	1.09 (0.91-1.31)	0.000
XRCC1 Arg280His	His vs. Arg	3	0.90 (0.60-1.35)	0.89 (0.70-1.13)	0.067
	His/His vs. Arg/Arg	3	0.92 (0.33-2.58)	0.91 (0.33-2.54)	0.827
	His/His vs. Arg/Arg+Arg/His	3	0.92 (0.33-2.58)	0.91 (0.33-2.54)	0.871
	His/His+Arg/His vs. Arg/Arg	3	0.89 (0.56-1.42)	0.87 (0.67-1.13)	0.051

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

Results

Description of included studies

Figure 1 illustrates the literature search process in the form of a flow chart. We identified 58 articles that examined the association between XRCC1 polymorphisms and risk of NPC in various databases. According to the inclusion and exclusion criteria, six studies [12-17] were included and 52 articles were excluded. The publication year of involved studies ranged from 2003 to 2014. In total, 1450 NPC cases and 1571 controls were included in this meta-analysis. The source of controls in 5 studies was population-based. Six articles studied on XRCC1 Arg399Gln, 4 articles on Arg194Trp, and 3 articles on Arg280His. The properties of included investigations are listed in **Tables 1** and **2**.

Meta-analysis

The summary of the meta-analysis on the association between XRCC1 gene polymorphisms and NPC in the Chinese population is shown in **Table 3**.

XRCC1 Arg399Gln polymorphism and NPC

Six studies determined the relationship between the XRCC1 Arg399Gln polymorphism and

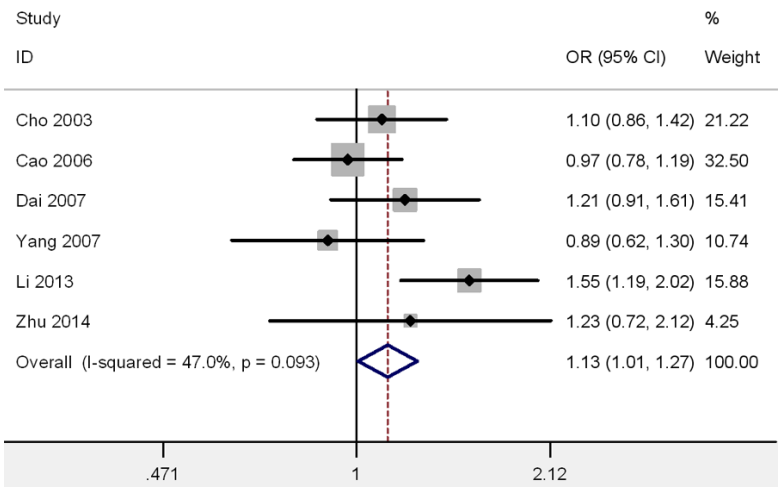

Figure 2. The forest plots on the association between XRCC1 Arg399Gln polymorphism and NPC risk under allele model.

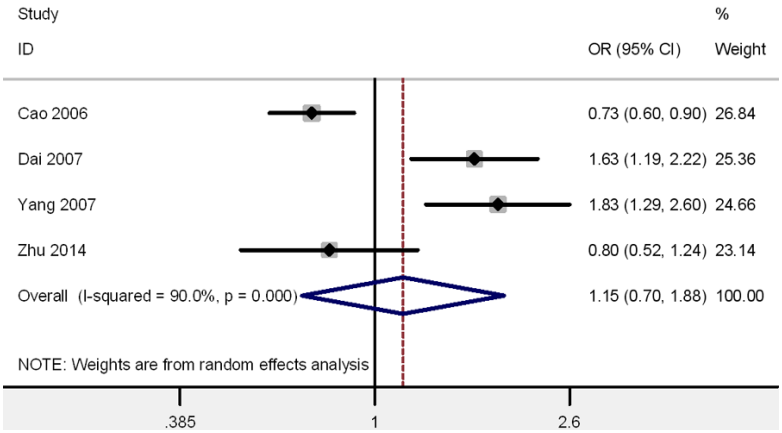

Figure 3. The forest plots on the association between XRCC1 Arg194Trp polymorphism and NPC risk under allele model.

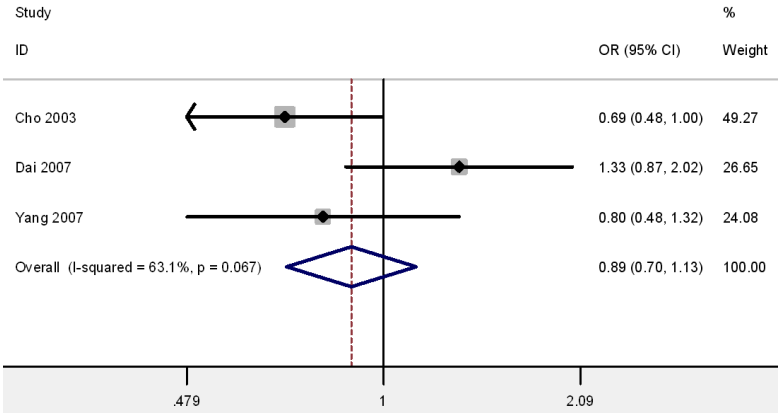

Figure 4. The forest plots on the association between XRCC1 Arg280His polymorphism and NPC risk under allele model.

NPC risk in the Chinese population [12-17]. The total sample size for patients with NPC and controls was 1450 and 1571, respectively. Meta-analysis revealed that XRCC1 Gln variant was significantly associated with an increased risk of NPC in the allelic contrast model (Gln vs. Arg: OR=1.13, 95% CI=1.01-1.27, **Figure 2**). No statistical significant results were found in homozygotes, recessive, and dominant models (Gln/Gln vs. Arg/Arg: OR=1.25, 95% CI=0.96-1.63; Gln/Gln vs. Arg/Arg+Arg/Gln: OR=1.12, 95% CI=0.86-1.45; Gln/Gln +Arg/Gln vs. Arg/Arg: OR= 1.20, 95% CI=0.91-1.59).

XRCC1 Arg194Trp, Arg280His polymorphisms and NPC

Four studies including 877 cases and 1007 controls identified an association between the XRCC1 Arg194Trp polymorphism and NPC risk in the Chinese population [13-15, 17], while three studies including 705 cases and 701 controls for XRCC1 Arg280His [12, 14, 15]. No significant association was observed between XRCC1 Arg194Trp, XRCC1 Arg280His and NPC in all the models (**Figures 3**, **4**).

Publication bias diagnosis and sensitivity analysis

The Begg's funnel plot and Egger's test were performed to access the publication bias of literatures for XRCC1 Arg399Gln and NPC. As showed in **Figure 5**, the shape of the funnel plots did not reveal obvious asymmetry. Similarly, the Egger's test indicated that there was no

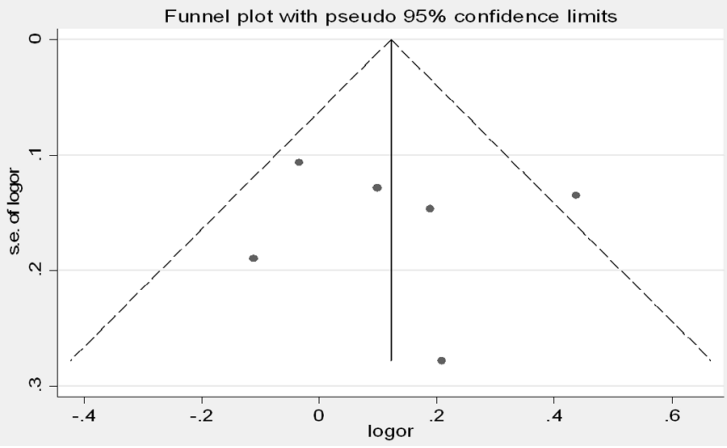

Figure 5. Publication bias assessment of XRCC1 Arg399Gln polymorphism and NPC risk.

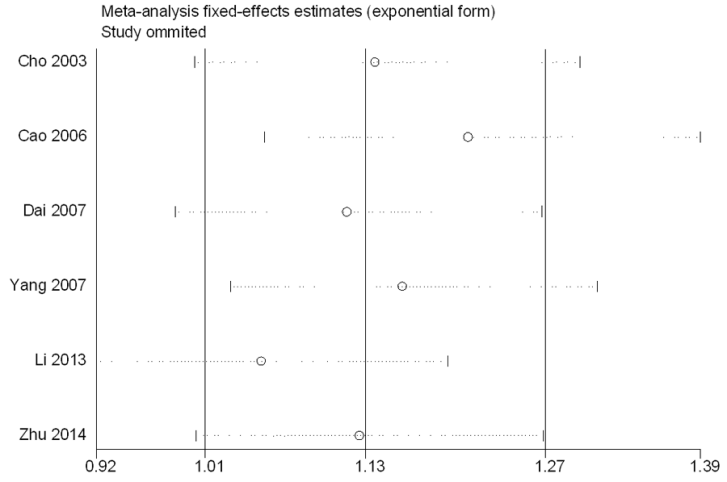

Figure 6. Sensitivity analysis to evaluate the stability of the meta-analysis.

evidence of obvious publication bias in the 6 reviewed studies (t=0.70, *P*=0.521). To estimate the sensitivity of our meta-analysis, a leave-one-out sensitivity analysis was performed. The results did not substantially alter when any single study was deleted, suggesting that the results of this meta-analysis were comparatively credible and stable (**Figure 6**).

Discussion

At present, it is accepted that NPC is a multifactorial disease, and individual susceptibility to NPC is determined by environmental factors and genetic variations. The XRCC1 protein is an important component of the base excision repair (BER) pathway, which fixes base damage and DNA singlestrand breaks caused by ionizing radiation and alkylating agents. Mutations of XRCC1 may increase the risk of cancers by impairing the interaction of XRCC1 with other enzymatic proteins and consequently altering DNA repair activity [18, 19]. XRCC1 polymorphisms have been reported to be associated with increased risk of NPC but the results remain inconclusive. Regional and racial differences is one likely reason for the conflict results. Therefore, we performed this meta-analysis to assess the effect of the XRCC1 polymorphisms on risk for NPC in the Chinese population specifically, in order to reduce the impact of genetic background.

Three polymorphisms in XRCC1 (Arg194Trp, Arg280His and Arg399Gln) have been frequently examined in the studies on cancer susceptibility. In this meta-analysis, we found that XRCC1 Arg399Gln polymorphism might be a low penetrant risk factor for NPC in the Chinese population, and there may be no association between Arg280His, Arg194Trp polymorphisms and NPC risk. The explanation for the results may be that functional variants in the XRCC1 gene may play a crucial role in the facilitation of human cancer development because of the alteration of BER functions [20]. Such as, the XRCC1 Arg399Gln may alter the efficiency of the repair process because of its location in the poly (ADP-ribose) poly-merase-binding domain [20-22]. The null association between XRCC1 Arg194Trp, Arg280His polymorphisms and NPC risk may be because there were only limited studies in the analysis.

As compared to the previous meta-analyses [23, 24], they only included a smaller number of studies which were conducted in Chinese populations. This current meta-analysis is strengthened by including several new studies. We were able to explore the association between XRCC1 polymorphisms and NPC may not be

influenced by genetic backgrounds. Sensitivity analyses and publication bias test confirmed the reliability and stability of the meta-analysis. Therefore, our results indicated that XRCC1 Arg399Gln polymorphism is associ ated with NPC in individuals from China.

Several limitations of this study should be figured out. First, our results are solely applicable in Chinese patients with NPC since the data that included in the ethnic-specific meta-analysis were obtained only in this ethnic group. Second, the current meta-analysis was based predominantly on unadjusted effect estimates and CIs; thus the confounding factors were not evaluated. Third, gene-gene, and gene-environmental interactions were not addressed in this meta-analysis because of the lack of sufficient data. Finally, due to the limitations of funnel plotting, which requires a range of studies, we did not evaluate publication bias for Arg194Trp and Arg280His in this meta-analysis.

In conclusion, the results of this meta-analysis suggest that the XRCC1 Arg399Gln polymorphism is associated with susceptibility to NPC in the Chinese population. Ethnicity seems to play an important role in the genetic association of the disease. Further studies in other ethic groups are required in order to explore the broader role that these polymorphisms play in the pathogenesis of NPC.

Disclosure of conflict of interest

None.

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