RESEARCH COMMUNICATION

XRCC1 Polymorphisms and Risk of Nasopharyngeal Carcinoma: a Meta-analysis

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Abstract

Objective: Previous studies on the association between X-ray repair cross-complementing protein 1 (XRCC1) polymorphisms and nasopharyngeal carcinoma (NPC) risk showed inconsistent results. The aim of this study was to evaluate the effects of XRCC1 variants on NPC risk. Methods: A meta-analysis was performed with all eligible studies covering a total of 1,341 cases and 1,425 controls for the Arg194Trp polymorphism, 1,260 cases and 1,207 controls for the Arg280His polymorphism, and 1,644 cases and 1,678 controls for the Arg399Gln polymorphism. Results: No associations was found between Arg194Trp and Arg280His polymorphisms with NPC risk under all contrast models (co-dominant, dominant, and recessive models). However a deleterious effect of the 399Gln genotype was observed under the co-dominant model (Gln/Gln versus Arg/Arg, OR = 1.30, 95% CI : 1.01-1.69, P = 0.04). Under the recessive model (Gln/Gln versus Arg/Arg+Arg/Gln), the P value was marginally significant (OR = 1.28, 95% CI : 1.00-1.65, P = 0.05). However, the effect of the 399Gln genotype on NPC became non-significant after excluding one study from the meta-analysis because of departure from Hardy-Weinberg equilibrium. Conclusions: No associations was found between Arg194Trp and Arg280His polymorphisms with NPC risk, whereas the Arg399Gln genotype was associated with increased risk.

Keywords: XRCC1 - polymorphism - NPC - risk

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy with an unusual geographical disparities. An estimated 92% of new cases occurs within economically developing countries (Jemal et al., 2011). Incidence rates are high in Malaysia, Indonesia, Singapore, a number of provinces in South-Eastern China including Guangdong and Hong Kong, and in other parts of Southern Asia (Guigay, 2008; Jemal et al., 2011). Genetic susceptibility, early-age exposure to chemical carcinogens (particularly Cantonese salted fish), and latent EBV infection are suggested to be three major aetiological factors for NPC (Tao and Chan, 2007). However, the precise genetic alterations during NPC development are still unclear.

The X-ray repair cross-complementing protein 1 (XRCC1) has multiple roles in base excision repair (BER) and single-strand breaks (SSBs), including bridging the steps in BER through protein interactions and promoting an S phase-specific mode of SSB repair (Thompson and West, 2000). XRCC1 interacts with many proteins involved in BER and SSB, and functions as a scaffold protein to coordinate and facilitate in various DNA repair pathways (Horton et al., 2008). Three single nucleotide polymorphisms on XRCC1 including Arg194Trp (exon6, C/T), Arg280His (exon9, G/A), and Arg399Gln (exon10, G/A) are most commonly studied. They are suggested to be of biological functionality in the XRCC1 interaction with other proteins (Laantri et al., 2011). Meta-analysis have revealed significant associations between XRCC1 SNPs and risk of breast cancer (Saadat and Ansari-Lari, 2009), lung cancer (Kiyohara et al., 2006) and esophageal cancer (Yin et al., 2009) among Asian (or Chinese).

The association between XRCC1 polymorphisms and NPC risk was first reported by Cho et al. and inconsistent conclusions were revealed by subsequent studies (Cho et al., 2003; Cao et al., 2006; Dai et al., 2007; Yang et al., 2007; Laantri et al., 2011). Most of the studies were conducted in Asians from high NPC incidence endemic area, except one in Maghrebian population from the intermediate incidence area of North Africa (Laantri, Jalbout et al., 2011). Due to the relatively small sample size and different patient population, studies on the XRCC1 polymorphisms and NPC risk showed contradict results. Therefore, a meta-analysis was performed from all eligible studies to evaluate the effect of XRCC1 variants

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(Arg194Trp, Arg280His and Arg399Gln) on NPC risk in this study.

Materials and Methods

Identification and eligibility of relevant publications

Computer searching of PubMed and Chinese National Knowledge Infrastructure (CNKI) was performed in English or Chinese before April 2011 with the following terms "XRCC1", "polymorphism" and "nasopharyngeal". We included all the case-control studies of NPC with polymorphism data for at least one of the three SNPs, Arg194Trp, Arg280His and Arg399Gln.

Data extraction

The following data was extracted from each study and entered into a database: first author, year of publication, ethnicity (country) of study population, numbers of cases and controls, and genotype frequency of cases and controls.

Statistical analysis

The odds ratio (OR) with 95% confidence interval (CI) of XRCC1 polymorphisms and NPC risk were estimated for each study. To assess the heterogeneity between studies, a $\chi 2$–based Q statistic test was performed. A P value of greater than 0.05 indicated a lack of heterogeneity, and the ORs were estimated using the fixed-effect model (Mantel-Haenszel method). Otherwise, the random-effect model (DerSimonian-Laird method) was used. The significance of the pooled ORs was assessed via Z-test. The co-dominant (B/B versus A/A; B was for the minor allele and A for the major allele), the dominant (B/B+A/B versus A/A), and the recessive model (B/B versus A/B+A/A) was performed respectively. Publication bias was investigated by funnel plot, and estimated using Egger's tests. Hardy-Weinberg equilibrium (HWE) was determined by Fisher's exact test. Analysis was performed using the software Review Manager (version 5.0).

Results

Eligibility

The characteristics of all the studies that were included in the meta-analysis were listed in Table 1. Six studies published until April 2011 were concerning XRCC1 polymorphisms and risk of NPC (Table 1). Four studies were about XRCC1 Arg194Trp polymorphism and NPC risk, with a total number of 1,341 cases and 1,425 controls (Table 2); four studies about XRCC1 Arg280His polymorphism and NPC risk, with a total number of 1,260 cases and 1,207 controls (Table 3); five studies about XRCC1 Arg399Gln polymorphism and NPC risk, with a total number of 1,644 cases and 1,678 controls (Table 4). The genotype distribution in the control groups in each study did not depart from the HWE except one with XRCC1 Arg399Gln polymorphism (Table 4) (Dai, YANG et al. 2007).

Meta-analysis results

XRCC1 Arg194Trp polymorphism: The results of meta-analysis under different contrast models (co-dominant, dominant, and recessive models) suggested no associations between Arg194Trp polymorphism and NPC risk when all eligible studies were pooled into meta-analysis. In the co-dominant model (Trp/Trp versus Arg/Arg), OR = 1.79, 95% CI : 0.50-6.40, P = 0.37 (Fig 1A); in the dominant model (Trp/Trp+Arg/Trp versus Arg/Arg), OR = 1.37, 95% CI : 0.80-2.34, P = 0.25 (Fig 1B); in the recessive model (Trp/Trp versus Arg/Arg+Arg/Trp), OR = 1.53, 95% CI : 0.53-4.41, P = 0.43 (Figure 1C).

XRCC1 Arg280His polymorphism: There was also no associations between Arg280His polymorphism and NPC risk under different contrast models (co-dominant, dominant, and recessive models). In the co-dominant model (His/His versus Arg/Arg), the pooled OR was 0.98 (95% CI : 0.50-1.94, P = 0.96, Fig 2A); in the dominant

Table 1. Characteristics of Studies Included in the Meta-analysis

First author (ref.)	Year	Area	Ethnicity	No. cases	No. controls	SNP studied
Laantri N	2011	N Africa	African	598	545	194,280,399
Yang ZH	2007	China	Asia	153	168	194,280,399
Dai Q(a)	2007	China	Asia	220	250	194,280
Dai Q(b)	2007	China	Asia	220	250	399
Cao Y	2006	China	Asia	462	511	194,399
Cho EY	2003	Taiwan	Asia	334	283	280,399

Table 2. Distribution of XRCC1 Codon 194 among NPC Cases and Controls Included in the Meta-analysis.

	Cases			Controls			HWE(control)	
First author(ref.)	Arg/ Arg	Arg/ Trp	Trp/ Trp	Arg/ Arg	Arg/ Trp	Trp/ Trp	$\chi 2$	p
Laantri N	492	55	4	470	41	1	0.011	0.915
Yang ZH	62	79	12	99	65	4	3.179	0.075
Dai Q(a)	116	91	13	168	73	9	0.093	0.760
Cao Y	232	166	19	235	217	43	0.508	0.476

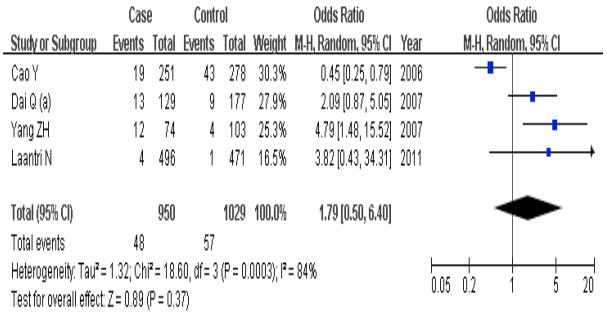
Table 3. Distribution of XRCC1 Codon 280 among NPC Cases and Controls Included in the Meta-analysis.

	Cases			Controls			HWE(control)	
First author(ref.)	Arg/ Arg	Arg/ Trp	Trp/ Trp	Arg/ Arg	Arg/ Trp	Trp/ Trp	$\chi 2$	p
Laantri N	431	114	10	405	92	9	1.923	0.166
Yang ZH	125	27	1	131	35	2	0.039	0.843
Dai Q(a)	173	43	4	209	37	4	2.326	0.127
Cho EY	275	55	2	215	66	2	1.631	0.202

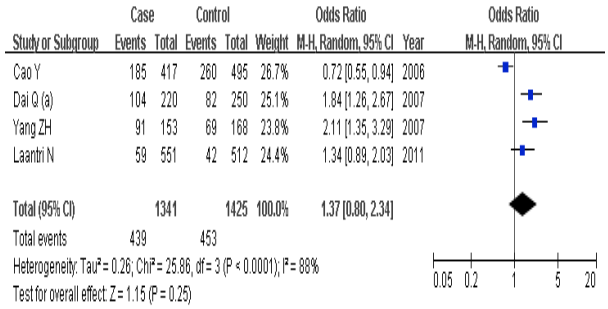
Table 4. Distribution of XRCC1 Codon 399 among NPC Cases and Controls Included in the Meta-analysis.

	Cases			Controls			HWE(control)	
First author(ref.)	Arg/ Arg	Arg/ Trp	Trp/ Trp	Arg/ Arg	Arg/ Trp	Trp/ Trp	$\chi 2$	p
Laantri N	274	193	45	279	163	35	2.637	0.104
Yang ZH	93	54	6	95	67	6	1.989	0.158
Dai Q(b)	116	68	36	147	72	31	17.684	<0.001
Cho EY	174	128	32	152	109	21	0.057	0.811
Cao Y	241	152	32	270	201	30	0.857	0.354

(A) XRCC1 codon 194 Trp/Trp vs. Arg/Arg



(B) XRCC1 codon 194 Trp/Trp+Arg/Trp vs Arg/Arg



(C) XRCC1 codon 194 Trp/Trp vs Arg/Arg+Arg/Trp

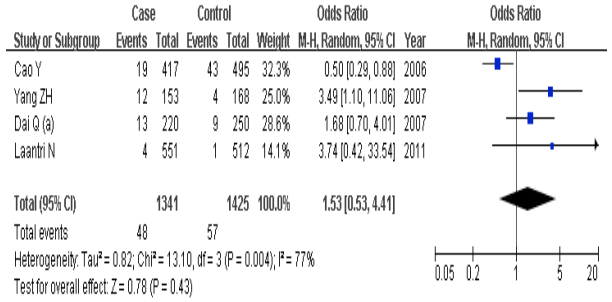
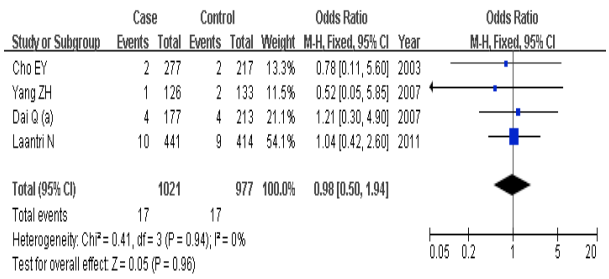
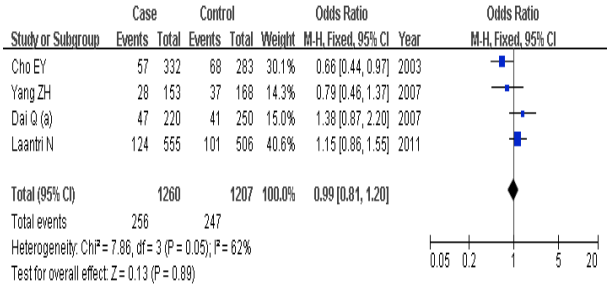


Figure 1. Forest Plots Show the Odd Ratios and Confident Intervals of the Association Between XRCC1 Arg194Trp Genotype and NPC Risk. A, Under the co-dominant model (Trp/Trp versus Arg/Arg); B, Under the dominant model (Trp/Trp+Arg/Trp versus Arg/Arg); C, Under the recessive model (Trp/Trp versus Arg/Arg+Arg/Trp)

(A) XRCC1 codon 280 His/His vs. Arg/Arg



(B) XRCC1 codon 280 His/His+Arg/His vs Arg/Arg



(C) XRCC1 codon 280 His/His vs. Arg/Arg+Arg/His

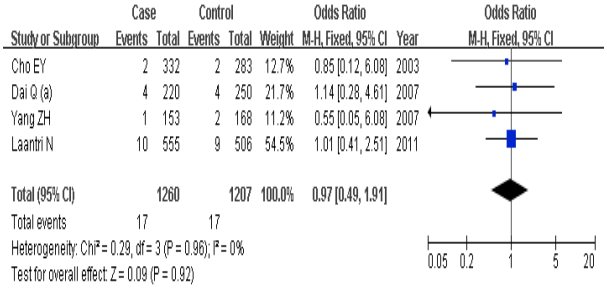


Figure 2. Forest Plots Show the Odd Ratios and Confident Intervals of the Association Between XRCC1 Arg280His Genotype and NPC Risk. A, under the Co-dominant model (His/His versus Arg/Arg); B, Under the dominant model (His/His+Arg/His versus Arg/Arg); C, Under the recessive model (His/His versus Arg/Arg+Arg/His)

model (His/His+Arg/His versus Arg/Arg), the pooled OR was 0.99 (95% CI : 0.81-1.20, P = 0.89, Fig 2B); in the recessive model (His/His versus Arg/Arg+Arg/His), the pooled OR was 0.97 (95% CI : 0.49-1.91, P = 0.43 Figure 2C).

XRCC1 Arg399Gln polymorphism: When all eligible studies were pooled into meta-analysis, the results showed significant associations between Arg399Gln polymorphism and NPC risk under co-dominant model, but not in dominant model and recessive model. In the co-dominant model (Gln/Gln versus Arg/Arg, OR = 1.30, 95% CI : 1.01-1.69, P = 0.04, Figure 3A), the homozygous genotype Gln/Gln showed a significant increased risk of NPC. In the dominant model (Gln/Gln+Arg/Gln versus Arg/Arg), OR = 1.06, 95% CI : 0.93-1.22, P = 0.39 (Fig 3C); and in the recessive model (Gln/Gln versus Arg/Arg+Arg/Gln), OR = 1.28, 95% CI : 1.00-1.65, P = 0.05 (Figure 3D). Nevertheless, when the study (Dai et al., 2007) in which genotype distribution of Arg399Gln in the controls was significantly deviated from HWE was removed from the meta-analysis, the results indicated no significant associations between Arg399Gln polymorphism and NPC risk under co-dominant model (OR = 1.26, 95% CI : 0.94-1.69, P = 0.12, Figure 3B).

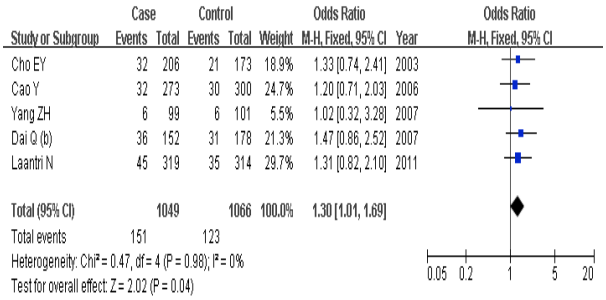
Publication bias

Publication bias was assessed by funnel plot, and estimated using Egger's tests under all contrast models. The results showed no publication bias in all comparison model (P > 0.05).

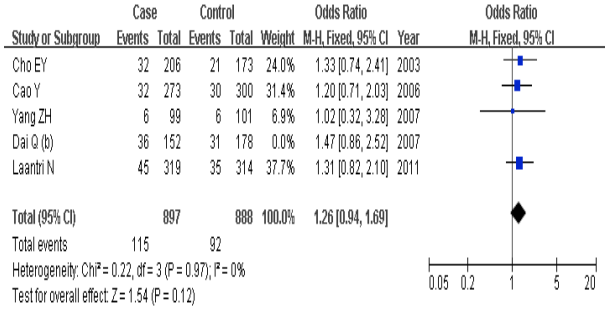
Discussion

In the present study, a meta-analysis was performed to provide the most comprehensive assessment of the association between XRCC1 single nucleotide polymorphisms (Arg194Trp, Arg280His and Arg399Gln) and risk of NPC. The results of current pooled data suggested no evidence for a major role of variants in NPC risk for Arg194Trp and Arg280His. Deleterious effect of

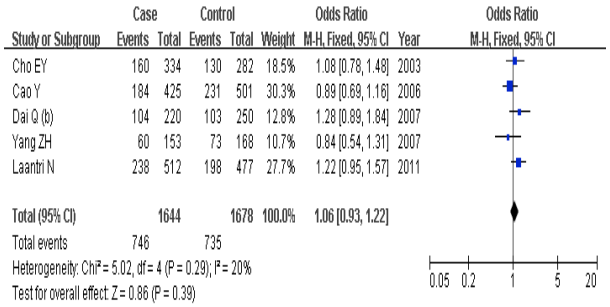
(A) XRCC1 codon 399 Gln/Gln vs. Arg/Arg



(B) XRCC1 codon 399 Gln/Gln vs. Arg/Arg without "Dai Q"



(C) XRCC1 codon 399 Gln/Gln+Arg/Gln vs Arg/Arg



(D) XRCC1 codon 399 Gln/Gln vs. Arg/Arg+Arg/Gln

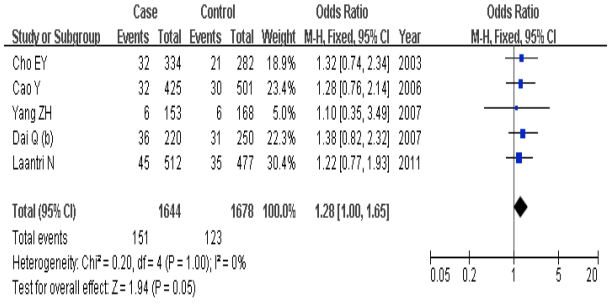


Figure 3. Forest Plots Show the Odd Ratios and Confident Intervals of the Association Between XRCC1 Arg399Gln Genotype and NPC Risk. A, Under the co-dominant model (Gln/Gln versus Arg/Arg); B, Under the co-dominant model (Gln/Gln versus Arg/Arg) without the study of Dai Q; C, Under the dominant model (Gln/Gln+Arg/Gln versus Arg/Arg); D, Under the recessive model (Gln/Gln versus Arg/Arg+Arg/Gln)

399Gln genotype was observed under the co-dominant model (OR = 1.30, 95% CI : 1.01-1.69, P = 0.04). Under the recessive model, the P value was marginally significant (OR = 1.28, 95% CI : 1.00-1.65, P = 0.05). However, insignificant effect of 399Gln genotype on NPC was found after excluding the study (Dai et al., 2007) from the meta-analysis because of departure from HWE.

To date, association between the XRCC1 gene polymorphisms and NPC risk has been reported by six studies. Cho et al. found no associations between Arg280His and Arg399Gln with NPC risk (Cho et al., 2003). Cao et al. indicated a significant protective effect of the 194Trp/Trp genotype whereas Yang et al. and Dai Q et al. reported a significant deleterious effect (Cao et al., 2006; Dai et al., 2007; Yang et al. 2007). Dai et al. (2007) observed no associations between Arg399Gln and NPC risk in the other report. The studies above were all carried out among Asian populations from high NPC incidence area. The only one study among Maghrebian population from the intermediate incidence area of North Africa was performed by Laantri et al. (2011) which maintained XRCC1 gene polymorphisms are not associated with NPC risk. These studies showed inconsistent conclusions probably due to the relatively small sample size and different population. We therefore conducted a meta-analysis to evaluate the effect of XRCC1 variants on NPC risk in this study. Deleterious effect of 399Gln genotype was observed under the co-dominant model. The effect of 399Gln was consistent with previous meta-analysis on esophageal cancer (Yin et al., 2009), breast cancer (Saadat and Ansari-Lari, 2009), and lung cancer (Kiyohara et al., 2006). However, protective effect of 399Gln genotype was observed on a meta-analysis on colorectal cancer (Jiang et al., 2010). Interestingly, another meta-analysis of XRCC1 polymorphism on colorectal cancer maintained no significant association between Arg399Gln polymorphism and colorectal cancer risk, probably because of different inclusion literatures (Wang, Wang et al. 2010).

XRCC1 was the first human gene involved in SSB repair to be cloned (Ladiges 2006). XRCC1-mutant in CHO cell lines led to hypersensitivity to genotoxins, reduced rate of SSBR and DSBR, and perturbation of DNA replication (Caldecott, 2003). XRCC1 also played an important role in sister-chromatid exchange (Wilson and Thompson, 2007). Polymorphisms of XRCC1 could influence its interaction with the other BER enzymes and consequently regulate DNA repair activity. Sister chromatoid exchange frequency was higher in homozygous carriers of the 399Gln allele in XRCC1 than those of 399Arg/Arg among current smokers (Duell et al., 2000). The 399Gln allele was significantly associated with higher levels of aflatoxin B1 DNA adducts (Lunn et al., 1999) and prolonged cell-cycle delay (Hu et al., 2001). These results were consistent with our meta-analysis that 399Gln genotype had a deleterious effect on NPC.

There are some limitations in this meta-analysis. First, selection bias. The genotype distribution of the XRCC1 Arg399Gln in controls was deviated from HWE in one study (Dai et al., 2007). Second, since negative results were less likely to be published, our findings were possibly biased toward a positive result. Third, limited literatures were included because of limited publication of XRCC1 polymorphism on NPC. With the consideration of these limitations, our results should be interpreted as preliminary.

In conclusion, our meta-analysis had suggested XRCC1 Arg194Trp and Arg280His polymorphisms had

no associations with NPC risk, whereas association was found between XRCC1 399Gln genotype and increased NPC risk under the co-dominant model among all subjects. However, further studies with large sample sizes are needed to clarify the association between XRCC1 polymorphisms and NPC risk.

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