RESEARCH ARTICLE

Updated Assessment of the Association of the XRCC1 Arg399Gln Polymorphism with Lung Cancer Risk in the Chinese Population

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Abstract

Background: Published studies have reported relationships between X-ray repair cross-complementing group 1 (XRCC1) Arg399Gln polymorphism and lung cancer risk in Chinese population. However, the epidemiological results remained controversial. The objective of this study was to clarify the association of XRCC1 Arg399Gln polymorphism with lung cancer risk in the Chinese population. Materials and Methods: Systematic searches were performed through the database of Medline/Pubmed, Web of Science, Embase, CNKI and WanFang Medical Online. Odds ratios (ORs) with 95% confidence interval (95%CI) were calculated to estimate the strength of the association. Results: Overall, we observed an increased lung cancer risk among subjects carrying XRCC1 codon 399 Gln/Gln genotype (OR=1.36, 95%CI: 1.09-1.71) in the Chinese population on the basis of 19 studies with 5,416 cases and 5,782 controls. We did not observe any association between XRCC1 codon 399 Arg/Gln and Arg/Gln+Gln/Gln polymorphisms and lung cancer risk (OR=1.00, 95%CI: 0.92-1.08 and OR=1.05, 95%CI: 0.97-1.13, respectively). Limiting the analysis to studies with controls in agreement with Hardy-Weinberg equilibrium (HWE), we observed an increased lung cancer risk among subjects carrying XRCC1 codon 399 Gln/Gln genotype (OR=1.18, 95%CI: 1.01-1.38). When stratified by source of control, we observed an increased lung cancer risk among subjects carrying XRCC1 codon 399 Arg/Gln+Gln/Gln genotype on the basis of hospitalized patient-based controls (OR=1.21, 95%CI: 1.04-1.42) and among subjects carrying XRCC1 codon 399 Gln/Gln genotype on the basis of healthy subject-based controls (OR=1.22, 95%CI: 1.04-1.43). Conclusions: Our findings indicated that certain XRCC1 Arg399Gln variants might affect the susceptibility of lung cancer in Chinese population. Larger sample size studies are required to confirm our findings.

Keywords: Lung cancer - risk - XRCC1 Arg399Gln - polymorphism - meta-analysis - Chinese

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Introduction

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally, and among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death (Jemal et al., 2011). The global incidence of lung cancer is 1, 608, 800 per year, with an annual mortality rate of 1, 378, 400. For the year 2000, an estimated 85% of lung cancer in men and 47% of lung cancer in women is the consequence of tobacco smoking (Parkin et al., 2005). But the rest of lung cancers occur in non-smokers, which suggests that genetic factors might also play important roles in the development of lung cancer. Recently, common genetic polymorphisms in genes involved in DNA repair have been reported to be of importance in determining an individual's susceptibility (Yu et al., 2011; Kazma et al., 2012; Zhong et al., 2012; Wang et al., 2014).

X-ray repair cross-complementing group 1 (XRCC1) is a major DNA repair protein involved in base excision repair (BER) and single-strand breaks (SSBs) repair and plays an important role in the maintenance of genomic integrity. A polymorphism of Arg399Gln (rs25487) has been identified in the XRCC1 gene, which leads to amino acid substitutions (exon 10, G-A) (Shen et al., 1998). This mutation may alter XRCC1 function, diminish repair kinetics and influence susceptibility to cancers. To date, a series of studies have reported the association of XRCC1 Arg399Gln polymorphism with lung cancer risk in Chinese population (Ratnasinghe et al., 2001; Chen et al., 2002; Song et al., 2004; Chan et al., 2005; Hu et al., 2005; Shen et al., 2005; Zhang et al., 2005a; Zhang et al., 2005b; Yu et al., 2006; Yin et al., 2007; Li et al., 2008; Su et al., 2008; Li et al., 2011; Qian et al., 2011; Du et al., 2012; Wang et al., 2012a; Guo et al., 2013; Ouyang et al., 2013; Du et al., 2014). However, the results from epidemiological studies have been conflictive rather than conclusive. Moreover, two meta-analyses have reported the association between XRCC1 Arg399Gln polymorphism and lung cancer risk

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in Chinese population (Zheng et al., 2009; Li et al., 2013). But, there are some key limitations in the previous meta-analyses. For example, several overlapping data (Li et al., 2005a; Li et al., 2005b; Li et al., 2005c; Hao et al., 2006; Yin et al., 2009) were not excluded from Li et al's study (Li et al., 2013) and one eligible paper published before 2013 (Ratnasinghe et al., 2001) was missing. For Zheng et al's paper (Zheng et al., 2009), four eligible papers published before 2008 (Ratnasinghe et al., 2001; Chan et al., 2005; Hu et al., 2005; Zhang et al., 2005b) were not included. Therefore, the conclusions from these two studies were not entirely reliable. In order to obtain a more precise estimation of this relationship, a meta-analysis including a total of 19 selected studies was performed, which may provide the more comprehensive evidence for the association of XRCC1 Arg399Gln polymorphism with lung cancer risk in Chinese population.

Materials and Methods

Literature and methods

Systematic searches were carried out through the database of Medline/Pubmed, Web of Science, Embase, WanFang Medical Online and Chinese National Knowledge Infrastructure (CNKI), covering all papers publishing before December 5, 2014 with the following search terms: "lung cancer" or "lung carcinoma" and "XRCC1 Arg399Gln" or "rs25487" and "Polymorphism" and "China" or "Chinese". Additional studies were identified by the references lists of the selected papers.

Data inclusion criteria: (a) Papers investigating lung cancer risk and XRCC1 Arg399Gln polymorphism; (b) Papers focusing on Chinese population; (c) Case-control studies and cohort studies; (d) Papers offering the sample size, odds ratio (OR) and their 95% confidence interval (95%CI) or the information that can help infer the results. Accordingly, articles that could not offer essential information were excluded; reviews and repeated or overlapping literatures were excluded, too. For overlapping papers, the most recent population or publication including more information was included.

In total, twenty-seven published papers were identified with the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese population. We reviewed all papers in the light of the criteria defined above and excluded two reviews (Zheng et al., 2009; Li et al., 2013) and six overlapping articles (Li et al., 2005a; Li et al., 2005b; Li et al., 2005c; Hao et al., 2006; Yin et al., 2009; Wang et al., 2012b). Therefore, 19 studies were determined to enter our study.

Data extraction

Two authors (Siyu Yang and Fuye Shao) tabulated the data first, and then inputted them into an electronic database independently. The following information was subtracted from each paper: authors' name, publishing year, area, source of controls, total number of cases and controls, genotype frequency of case and control, and stratified factors. Characteristics of individual study were summarized in Table 1.

Quantitative data synthesis

To estimate the association of XRCC1 Arg399Gln polymorphism with lung cancer risk in Chinese population, we conducted a meta-analysis of selected studies. Data were combined to calculate the summary OR and 95%CI using a fixed-effects model and a random-effects model (DerSimonian et al., 1986). The Cochrane Q statistics test was used to assess the heterogeneity among studies. If the effects are assumed to be homogenous, the fixed-effects model is used. Otherwise, a random-effects model is used if the effects are heterogeneous. The funnel plot was drawn to assess publication bias visually. Egger's test and Begg's test were also used to assess the publication bias (Begg et al., 1994; Egger et al., 1997). We tested whether genotype frequencies of controls were in Hardy-Weinberg equilibrium (HWE) using the χ^2 test.

All of the statistical analyses were performed by using Review Manager (Version 5.0.24, the Cochrane Collaboration) and STATA10.0 software package (Stata Corporation, College Station, Texas). All the tests were two-sided, a P value <0.05 for any test or model was considered to be statistically significant.

Results

Meta-analysis databases

A database was established according to the extracted information from each article. All essential information was listed in Table 1, which showed first author, publishing year, area, source of control, number of case and control, stratified factors and P value of HWE. There were a total of 19 studies with 5, 416 cases and 5, 782 controls concerning the relationship between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese population.

Test of heterogeneity

The heterogeneity of XRCC1 codon 399 Arg/Gln *vs* Arg/Arg, Gln/Gln *vs* Arg/Arg and Arg/Gln+Gln/Gln *vs* Arg/Arg was analyzed for 19 case-control studies. Our results showed that XRCC1 codon 399 Gln/Gln *vs* Arg/Arg for total population and hospitalized patients-based control, and Arg/Gln+Gln/Gln *vs* Arg/Arg for adenocarcinomas had the heterogeneity with a P value less than 0.05 (Table 2). Therefore, a random-effects model was used to analyze the summary odds ratios for them. A fixed-effects model was used to analyze the summary odds ratios for the rest.

Quantitative data synthesis

Overall, we observed an increased lung cancer risk among subjects carrying XRCC1 codon 399 Gln/Gln genotype (OR=1.36, 95%CI: 1.09-1.71) in Chinese population on the basis of 19 studies with 5, 416 cases and 5, 782 controls (Figure 1A). We did not observe any association between XRCC1 codon 399 Arg/Gln and Arg/Gln+Gln/Gln polymorphisms and lung cancer risk in Chinese population (OR=1.00, 95%CI: 0.92-1.08 and OR=1.05, 95%CI: 0.97-1.13, respectively) (Figure 1B and 1C). Limiting the analysis to the studies with controls in agreement with HWE, we observed an increased lung

Table 1. General Information of Selected Articles

First author	Year	Area	Source of control	Number of case	Number of control	HWE	Stratified factors
(Chan et al., 2005)	2005	Hong Kong	Healthy subjects	75	162	0.879127	
(Chen et al., 2002)	2002	Jiangsu	Healthy subjects	103	99	0.853812	
(Du et al., 2012)	2012	Shanghai	Healthy subjects	100	100	0.000006	Smoke and histological type
(Du et al., 2014)	2014	Shanghai	Healthy subjects	120	120	0.000000	Smoke and histological type
(Guo et al., 2013)	2013	Heilongjiang	Hospitalized patients	684	602	0.005453	
(Hu et al., 2005)	2005	Jiangsu	Healthy subjects	710	710	0.679058	
(Li et al., 2008)	2008	Liaoning	Hospitalized patients	350	350	0.239615	Histological type
(Li et al., 2011)	2011	Chongqing	Healthy subjects	455	443	0.052370	Smoke and histological type
(Ouyang et al., 2013)	2013	Hunan	Healthy subjects	82	201	0.148702	
(Qian et al., 2011)	2011	Tianjin	Healthy subjects	581	603	0.411222	
(Ratnasinghe et al., 2001)	2001	Yunnan	Healthy subjects	107	208	0.572907	
(Shen et al., 2005)	2005	Yunnan	Healthy subjects	116	109	0.053219	
(Song et al., 2004)	2004	Jiangsu	Hospitalized patients	104	104	0.466350	Smoke and histological type
(Su et al., 2008)	2008	Shanxi	Healthy subjects	162	244	0.848338	Histological type
(Wang et al., 2012a)	2012	Henan	Healthy subjects	209	256	0.302191	
(Yin et al., 2007)	2007	Liaoning	Hospitalized patients	205	193	0.198358	
(Yu et al., 2006)	2006	Hubei	Healthy subjects	104	121	0.288300	
(Zhang et al., 2005a)	2005	Henan	Healthy subjects	149	157	0.853973	Smoke
(Zhang et al., 2005b)	2005	Beijing	Healthy subjects	1000	1000	0.079392	Histological type

Table 2. Summary Odds Ratios of the Relation of XRCC1 Codon 339 Polymorphism to Lung Cancer Risk in Chinese Population

Genotype	Case/Control	Heterogeneity test		Summery	Hypothesis test		df	Begg's test		Egger's test	
		Q	*P*	OR (95% CI)	*Z*	*P*		*Z*	*P*	*t*	*P*
Total											
Arg/Gln *vs* Arg/Arg	4943/5383	21.13	0.27	1.00(0.92-1.08)	0.03	0.98	18	0.49	0.624	0.45	0.657
Gln/Gln *vs* Arg/Arg	3395/3576	34.41	0.01	1.36(1.09-1.71)	2.69	0.007	18	0.56	0.576	0.39	0.700
Arg/Gln+Gln/Gln *vs* Arg/Arg	5416/5782	26.36	0.09	1.05(0.97-1.13)	1.23	0.22	18	1.12	0.263	1.07	0.298
Stratification by HWE											
Yes											
Arg/Gln *vs* Arg/Arg	4133/4600	20.42	0.16	1.00(0.92-1.09)	0.10	0.92	15	0.41	0.685	0.37	0.719
Gln/Gln *vs* Arg/Arg	2271/3024	23.69	0.07	1.18(1.01-1.38)	2.13	0.03	15	0.59	0.558	0.15	0.881
Arg/Gln+Gln/Gln *vs* Arg/Arg	4512/4960	22.40	0.1	1.03(0.95-1.12)	0.74	0.46	15	0.59	0.558	0.59	0.564
Stratification by source of control											
Healthy subjects-based control											
Arg/Gln *vs* Arg/Arg	3710/4199	11.33	0.66	0.96(0.87-1.05)	0.92	0.36	14	0.30	0.767	0.28	0.784
Gln/Gln *vs* Arg/Arg	2562/2781	20.51	0.11	1.22(1.04-1.43)	2.39	0.02	14	0.49	0.621	1.42	0.179
Arg/Gln+Gln/Gln *vs* Arg/Arg	4073/4533	16.91	0.26	1.00(0.92-1.09)	0.07	0.94	14	1.09	0.276	0.83	0.420
Hospitalized patients-based control											
Arg/Gln *vs* Arg/Arg	1233/1184	6.50	0.09	1.14(0.97-1.34)	1.59	0.11	3	1.02	0.308	2.40	0.139
Gln/Gln *vs* Arg/Arg	833/795	8.97	0.03	1.46(0.75-2.86)	1.12	0.26	3	1.70	0.089	3.64	0.068
Arg/Gln+Gln/Gln *vs* Arg/Arg	1343/1249	5.13	0.16	1.21(1.04-1.42)	2.42	0.02	3	1.02	0.308	0.98	0.431
Stratification by smoking status											
Smokers											
Arg/Gln+Gln/Gln *vs* Arg/Arg	386/335	1.19	0.55	0.97(0.72-1.30)	0.21	0.84	2	1.04	0.296	12.94	0.049
Nonsmokers											
Arg/Gln+Gln/Gln *vs* Arg/Arg	276/322	4.29	0.12	1.12(0.81-1.55)	0.71	0.48	2	0.00	1.000	0.62	0.648
Stratification by histological type											
Squamous cell carcinoma											
Arg/Gln+Gln/Gln *vs* Arg/Arg	508/1348	6.06	0.05	1.10(0.89-1.35)	0.86	0.39	2	0.00	1.000	2.96	0.208
Adenocarcinoma											
Arg/Gln+Gln/Gln *vs* Arg/Arg	798/2342	16.00	0.007	1.12(0.81-1.53)	0.68	0.49	5	0.38	0.707	0.03	0.974

*HWE: Hardy-Weinberg equilibrium

cancer risk among subjects carrying XRCC1 codon 399 Gln/Gln genotype (OR=1.18, 95%CI: 1.01-1.38) (Table 2). When stratified by source of control, we observed an increased lung cancer risk among subjects carrying XRCC1 codon 399 Arg/Gln+Gln/Gln genotype on the basis of hospitalized patients-based control (OR=1.21, 95%CI: 1.04-1.42) and among subjects carrying XRCC1 codon 399 Gln/Gln genotype on the basis of healthy subjects-based control (OR=1.22, 95%CI: 1.04-1.43) (Table 2). We did not observe any association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese population in the additional subgroup analyses by smoking status and histological type (Table 2).

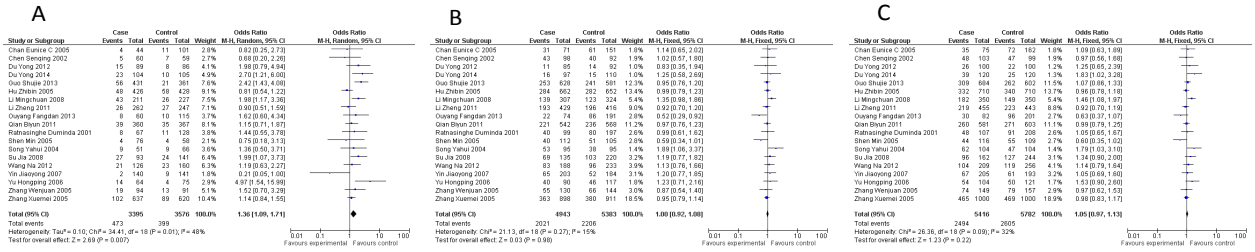

Figure 1. Forest Plots for the Association between XRCC1 Arg399Gln Polymorphism and Lung Cancer Risk in Chinese Population. A) Gln/Gln *vs* Arg/Arg; **B)** Arg/Gln *vs* Arg/Arg; **C)** Arg/Gln+Gln/Gln *vs* Arg/Arg)

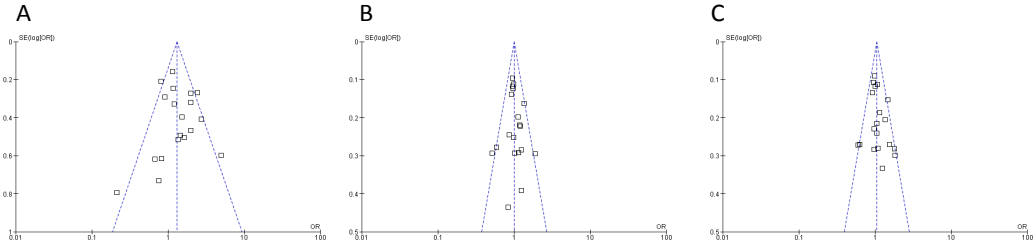

Figure 2. Funnel Plots for the Association between XRCC1 Arg399Gln Polymorphism and Lung Cancer Risk in Chinese Population in the Heterozygous Model. A) Gln/Gln *vs* Arg/Arg; **B)** Arg/Gln *vs* Arg/Arg; **C)** Arg/Gln+Gln/Gln *vs* Arg/Arg)

Bias diagnosis

The shape of funnel plots seemed to be approximately symmetrical for Gln/Gln *vs* Arg/Arg, Arg/Gln *vs* Arg/Arg and Arg/Gln+Gln/Gln *vs* Arg/Arg (Figure 2A, 2B and 2C). Egger's test and Begg's test suggested that publication biases may not have a significant influence on the results of the association between XRCC1 Arg399Gln polymorphism and lung cancer risk, except for XRCC1 codon 399 Arg/Gln+Gln/Gln *vs* Arg/Arg in smokers since there was some uncertainty with the P value being equal to 0.049 in Egger's test (Table 2).

Sensitivity analysis

Sensitivity analyses were carried out to determine the effect of the individual study on the summary ORs by sequentially deleting each eligible study. The overall effects were not altered when the studies were homogenous for Gln/Gln *vs* Arg/Arg among total population by deleting some studies (Data not shown).

Discussion

XRCC1 is an important component of the base excision repair system, which is a predominant DNA repair pathway for small base lesions resulting from oxidation and alkylation damage (Almeida et al., 2007). XRCC1 gene is mapped at human chromosome 19q13.2-13.3, which is 32.354 kilobases in length and consists of 16 introns and 17 exons. It encodes a 70-kDa scaffolding protein consisting of 633 amino acids, which coordinates a lot of protein-protein interactions, including DNA ligase III and DNA polymerase at the site of damage (Kubota et al., 1996; Vidal et al., 2001). It has been reported that more than 300 validated single nucleotide polymorphisms were identified in XRCC1 gene. Among them, XRCC1 Arg399Gln of exon 10 (rs25487) was the most extensively studied polymorphic site. Recently, meta-analysis studies have reported the association between XRCC1 Arg399Gln polymorphism and several kinds of cancer risk in Chinese population, such as colorectal cancer (Tian et al., 2013), esophageal cancer (Dai et al., 2009; Zhang et al., 2013) and hepatocellular carcinoma (Duan et al., 2012). In this study, we performed a systematic literature review to comprehensively evaluate the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese population. We also estimated the possible effect modifications by source of control, smoking status, histological type and HWE in control. In summary, we observed an association of XRCC1 Arg399Gln polymorphism with lung cancer risk in Chinese population.

It is widely acknowledged that deviation from HWE may point to methodological weaknesses, such as biased selection of subjects or genotyping errors. The results of genetic association studies might be spurious if the distribution frequency of genotypes in the control group was not in agreement with HWE (Salanti et al., 2005). To address this issue, a stratified analysis was performed by HWE in control group in this study. When three studies (Du et al., 2012; Guo et al., 2013; Du et al., 2014) that significantly deviated from HWE were removed from this meta-analysis, no substantial modification of the results was observed, suggesting that this factor might not affect the combined effects in this current meta-analysis.

This meta-analysis should be expounded within the context of its limitations. Firstly, only published papers were included in this study, which may cause publication bias. To address this issue, Egger's test and Begg's test were performed. Our results signified that there was no significant publication bias in this study, except for subgroup analysis by smoking status. Secondly, each study had different eligibility criteria for subjects and different source of controls, which should be taken into consideration while interpreting the combined estimates. When subgroup analysis was performed by source of control, we observed an association between XRCC1

Arg399Gln polymorphism and lung cancer risk among healthy subjects-based control. We also observed an association between XRCC1 Arg399Gln polymorphism and lung cancer risk among hospitalized patients-based control, but our results should be verified by larger sample size study, since only four studies were included in this meta-analysis. Thirdly, some factors such as sex, age, tobacco smoking, environment factors and histological type may influence the summary effects. We only performed subgroup analysis by smoking status and histological type in this study and did not observe any association between XRCC1 Arg399Gln polymorphism and lung cancer risk. Fourthly, but not the last one, the heterogeneity existed when comparing Gln/Gln genotype with Arg/Arg genotype in total population. To address this issue, sensitivity analysis was conducted. We still observed an increased lung cancer risk among subjects carrying XRCC1 codon 399 Gln/Gln genotype when the study was homogenous by removing some studies.

In conclusion, this systematic review demonstrates that XRCC1 Arg399Gln polymorphism appears to be a risk factor of lung cancer in Chinese population. Studies with large sample size are required to confirm the results from this current meta-analysis.

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