Original Article
XRCC1 polymorphisms and lung cancer risk in Caucasian populations: a meta-analysis

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Abstract: X-ray repair cross-complementing group 1 (XRCC1) plays an important role in the base excision repair. Many studies have reported the association of XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms with lung cancer risk, but the results remained controversial. In this meta-analysis, we performed a meta-analysis of ten published case-control studies in Caucasian populations to investigate the associations between lung cancer risk and XRCC1 Arg399Gln (2187 cases and 3453 controls from ten studies), Arg194Trp (857 cases and 2108 controls from six studies) and Arg280His (894 cases and 1133 controls from five studies). The results in total population showed that XRCC1 codon 399 polymorphism (OR=0.93, 95% CI=0.82-1.04) and codon 194 (OR=0.94, 95% CI=0.73-1.21) was significantly associated with lung cancer risk. However, no association was found between lung cancer risk and codon 280 (OR=1.17, 95% CI=0.89-1.54). In conclusion, this meta-analysis has demonstrated that codon 399 and codon 194 might have contributed to individual susceptibility to lung cancer in Caucasian populations. To further evaluate effect of XRCC1 polymorphisms, large studies with thousands of subjects are required to get conclusive results.

Keywords: X-ray repair cross-complementing group 1, lung cancer, polymorphism, meta-analysis

Introduction

Lung cancer is a major cause of cancer-related death in the worldwide and the overall survival rate has still an extremely poor [1]. According to cancer statistics 2012, lung cancer is expected to account for 26% of all female cancer deaths and 29% of all male cancer deaths [2]. Although cigarette smoking remains the predominant cause of lung cancer, it cannot fully explain epidemiologic characteristics of lung cancer in nonsmokers [3]. Currently, genetic susceptibility to environmental or occupational diseases is believed to play an important role in determining individual differences in the development of lung cancer [4, 5]. Moreover, genetic variations in DNA repair genes have been reported to be associated with the genomic instability and increasing risk of genomic damages [6].

X-ray repair cross-complementing group 1 (XRCC1), one of the >20 genes that participate in base excision repair (BER) pathway, encodes a protein that function in the repair of single-strand breaks [7]. XRCC1 plays a central role in the BER pathway by interacting with other DNA repair proteins [8, 9], giving the possibility that XRCC1 has some relationship with the response to therapy and the overall survival of lung cancer.

Three single nucleotide polymorphisms (SNPs) in XRCC1, Arg194Trp (exon 7), Arg280His (exon 10) and Arg399Gln (exon 11), are common and the most-studied SNPs in the XRCC1 gene. Some studies have reported the relationship between polymorphisms in XRCC1 gene and the risk of lung cancer patients [10-12], however the results were inconsistent. For Arg399Gln, many studies have shown that Arg399Gln is obvious associated with increased risk of lung cancer [13, 14]; while some non-significant or negative association are also reported by other studies [15, 16]. Furthermore, research has suggested that the effect of the XRCC1 SNPs on lung cancer may be dependent on ethnicity [17]. So we performed a systemic review and meta-analysis to assess the association of

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

First author-published year	Lung cancer cases			Controls		
	194	280	399	194	280	399
Vogel-2004		27/256	139/256		28/269	161/269
Zienolddiny-2006	27/336	33/329	202/331	37/405	27/377	240/391
Matullo-2006	18/116		65/116	143/1094		610/1094
Ryk-2006			100/177			94/153
De Ruyck-2007	9/110	4/109	71/109	17/110	14/110	63/109
López-Cima-2007			294/516			316/533
Improta-2008	16/94		52/94	17/121		68/121
Cote-2009			331/387			360/406
Chang-2009	24/113	26/112	59/113	76/299	56/298	143/298
Janik-2011	14/88	22/88	24/88	10/79	12/79	28/79

Codon 194: Arg/Trp and Trp/Trp genotypes compared with the total genotype. Codon 280: Arg/His and His/His genotypes compared with the total genotype. Codon 399: Arg/Gln and Gln/Gln genotypes compared with the total genotype.

XRCC1 polymorphisms on the risk of lung cancer.

Materials and methods

Identification and eligibility of relevant studies

We conducted a comprehensive literature search using the database of PubMed, Springer and Elsevier for relevant articles published in English between December 2003 and January 2012. We retrieved the relevant articles using the following terms: "XRCC1", "X-ray repair cross complementing protein 1", "lung cancer" and "polymorphism". Only full-text articles and the most recent studies were included in this meta-analysis.

Criteria for inclusion

The inclusion criteria were as follows: 1) the paper should be case-control or cohort association studies of lung cancer in Caucasian people with XRCC1 polymorphisms; 2) the paper should be included at least one of the three polymorphisms, Arg399Gln, Arg194Trp, and Arg280His; 3) the results were expressed as odds ratio (OR) and corresponding 95 percent confidence interval (95% CI); and 4) genotype distribution of control for a certain polymorphism must be in Hardy-Weinberg equilibrium (HWE).

The exclusion criteria were: 1) reviews or conference papers; 2) without control group; 3) studies with duplicate data; and 4) genotype information couldn't be extracted.

Quality assessment and data extraction

Two investigators independently extracted data and reached a consensus on all of the items. Any disagreement was subsequently resolved by discussion with another expert. The following information was extracted from each article: first author, year of publication, the exact data of total and exposed number in case and control groups, and genotyping information. Furthermore, we examined whether matching had been used and if the genotyping assay had been validated

Statistical analysis

The risks (ORs) of lung cancer associated with the XRCC1 polymorphisms were calculated directly from the data given in the eligible studies. We estimated the risks of the combined variant genotypes (i.e. Arg/Trp and Trp/Trp for Arg194Trp, and Arg/His and His/His for Arg280His, Arg/Gln and Gln/Gln for Arg399-Gln) versus their wild genotypes (Arg/Arg). Furthermore, in the analysis of pooled data, we combined using a fixed-effects model (the inverse variance-weighted method) and a random effects model (DerSimonian and Laird method) [18, 19]. The fixed-effects model is used when the effects are assumed to be homogenous, while the random effects model is used when they are heterogenous. Tests for heterogeneity between studies were performed with the Chi-square based Q test. The funnel plot and Egger's test were used to diagnose publication bias [20].
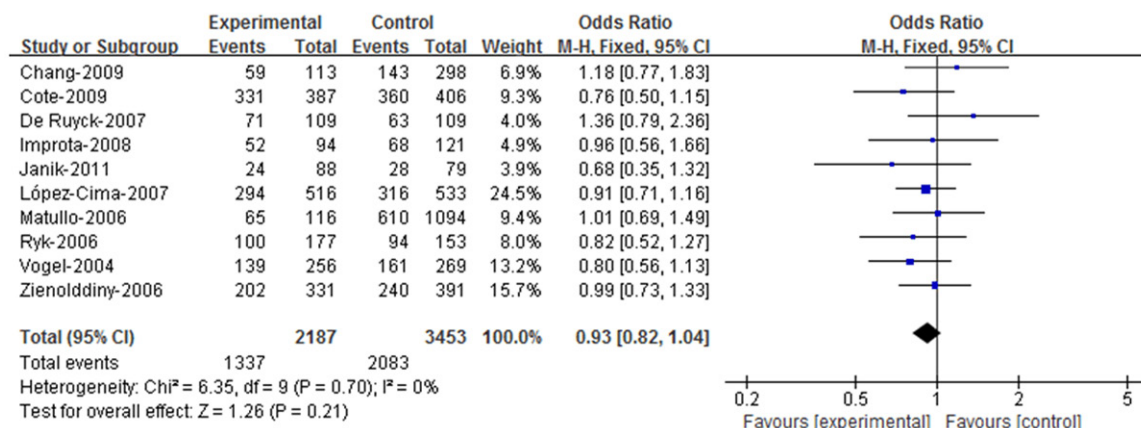
Figure 1. Meta-analysis with a fixed effect model for the ORs of lung cancer associated with XRCC1 Codon 399 for the Arg/Gln and Gln/Gln genotypes compared with the Arg/Arg genotype.
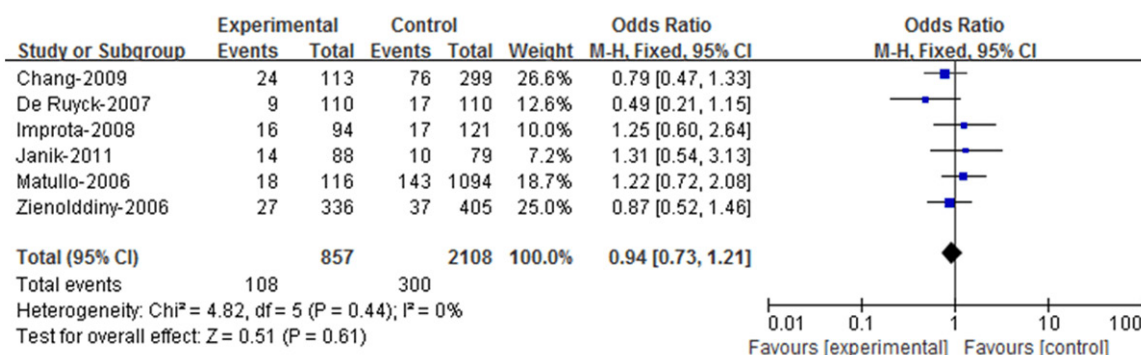

Figure 2. Meta-analysis with a fixed effect model for the ORs of lung cancer associated with XRCC1 codon 194 for the Arg/Trp and Trp/Trp genotypes compared with the Arg/Arg genotype.

To assess whether our results were substantially influenced by the presence of any individual study, we conducted a sensitivity analysis by systematically removing each study and recalculating the significance of the result.

All analyses were conducted in Review Manager (version 5.2, The Cochrane Collaboration). All the tests were two-sided and the significant level was 0.05.

Results

Literature search and meta-analysis databases

Relevant publications were retrieved and preliminarily screened [21-30]. **Table 1** list the essential information such as first author, the publication year and the numbers of lung cancer cases and controls for three XRCC1 poly-

morphisms, Arg399Gln, Arg194Trp, and Arg280His, respectively. There were ten case-control studies concerning the XRCC1 polymorphisms, including 3938 cases and 6694 controls.

Test of heterogeneity

All the ten case-control studies concern the Arg399Gln polymorphism, including 2187 cases and 3453 controls. **Figure 1** shows the association between the Arg399Gln polymorphism and lung cancer risk. We analyzed the heterogeneity for all ten case-control studies and the test value of Chi-square was 6.35 with 9 degree of freedom (d.f.) and P=0.70 in a fixed model.

A total of six case-control studies concern the Arg194Trp polymorphism, including 857 cases and 2108 controls. **Figure 2** showed the asso-
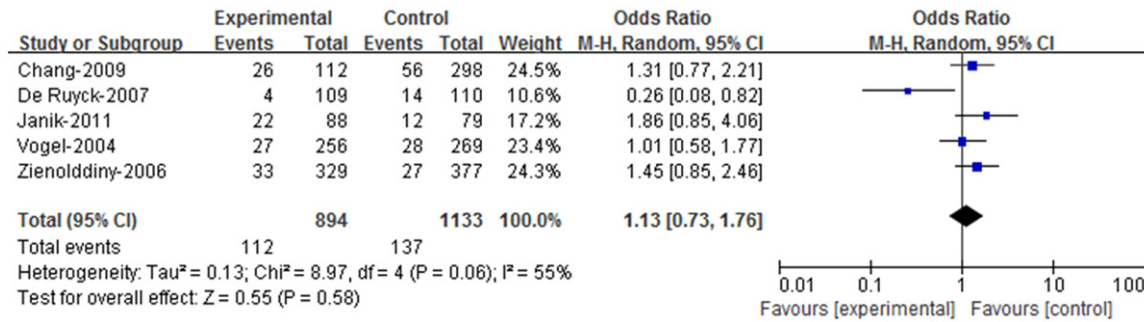
Figure 3. Meta-analysis with a fixed effect model for the ORs of lung cancer associated with XRCC1 codon 280 for the Arg/His and His/His genotypes compared with the Arg/Arg genotype.
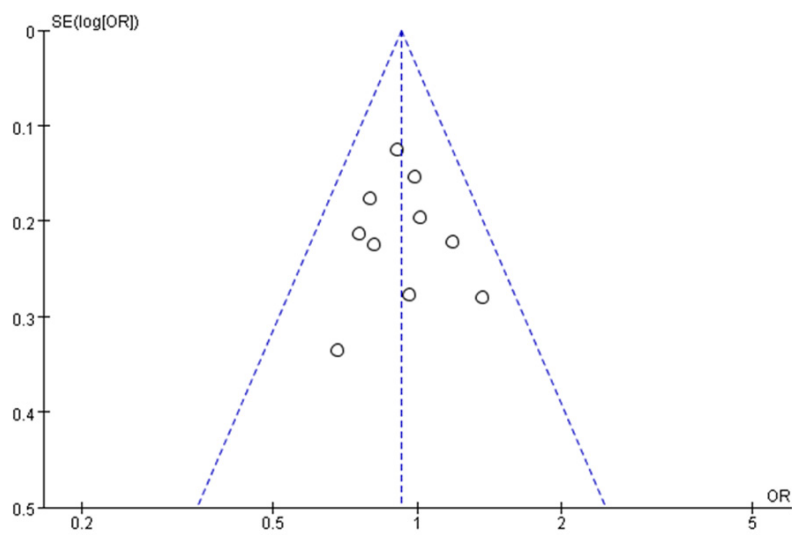

Figure 4. Funnel plot of the meta-analysis of lung cancer risk and the XRCC1 Arg399Gln polymorphism (Arg/Gln + Gln/Gln versus Arg/Arg).

each study. For the XRCC1 Arg399Gln polymorphism, the eligible studies included 1337 cases and 2083 controls which had the combined variant genotypes (Arg/Gln and Gln/Gln), and 850 cases and 1370 controls which had wild-type homozygote (Arg/Arg) of the XRCC1 Arg399Gln gene. The overall OR for the combined genotypes Arg/Gln and Gln/Gln versus Arg/Arg genotype was 0.93 (95% CI=0.82-1.04) in a fixed model (Z=1.26, P=0.21).

For the XRCC1 Arg194Trp polymorphism, 108 cases and 300 controls had the combined variant genotypes (Arg/Trp and Trp/Trp) and 749 cases and 1808 controls were wild-type homozygote (Arg/Arg) for the XRCC1 Arg194Trp gene in the eligible studies. The overall OR for the combined Arg/Trp and Trp/Trp genotypes versus Arg/Arg genotype was 0.94 (95% CI=0.73-1.21) in a fixed model (Z=0.51, P=0.61).

For the XRCC1 Arg280His polymorphism, the eligible studies had 112 cases and 137 controls combing the variant genotypes (Arg/His and His/His) and 782 cases and 996 controls including the wild-type homozygote (Arg/Arg) for the XRCC1 Arg280His gene. The overall OR for the combined variant genotypes versus the wild-type genotype was 1.13 (95% CI=0.73-1.76) as estimated in a random-effect mode (Z=0.55, P=0.58).

ciation between the Arg194Trp polymorphism and lung cancer risk. The Chi-square value for the heterogeneity of all six case-control studies was 4.82 with 5 d.f. and P=0.44 in a fixed model.

There are five case-control studies concerning the Arg280His polymorphism, including 894 cases and 1133 controls. **Figure 3** showed the association between genetic polymorphism of Arg280His and lung cancer risk. However, the Chi-square value for the heterogeneity of the five case-control studies was 8.97 with 4 d.f. and P=0.006 in a random-effect model.

Meta-analysis

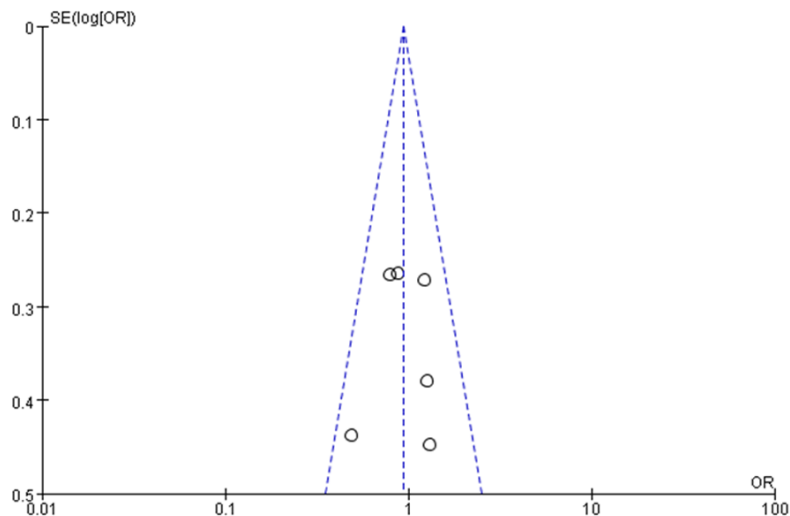The risks of lung cancer associated with XRCC1 genetic polymorphisms were estimated for

Figure 5. Funnel plot of the meta-analysis of lung cancer risk and the XRCC1 Arg194Trp polymorphism (Arg/Trp + Trp/Trp versus Arg/Arg).
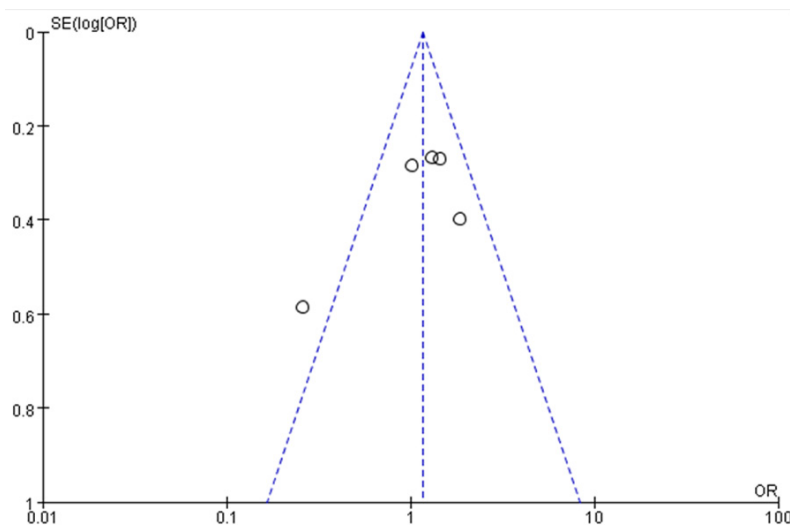

Figure 6. Funnel plot of the meta-analysis of lung cancer risk and the XRCC1 Arg280His polymorphism (Arg/His + His/His versus Arg/Arg).

Sensitivity analyses and publication bias

A single study included in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially changed.

The funnel plot was used to graphically assess the publication bias. For the three XRCC1 polymorphisms, Arg399Gln, Arg194Trp and Arg-280His, the shapes of the funnel plots appeared to be approximately symmetrical, suggest-ing that the publication bias can be neglected, and the magnitude of the main ORs was in dispersion around 1 (**Figures 4-6**). This meta-analysis indicated that publication biases might not have a significant effect on the results of three XRCC1 genes.

Discussion

DNA repair mechanisms are important for maintaining genome integrity and preventing carcinogenesis [31]. XRCC1, an important component of the BER pathway, has multiple roles in repairing DNA base damage and single-strand DNA breaks [32, 33]. A large number of molecular epidemiological studies have been conducted to evaluate the role of polymorphisms in the XRCC1 gene on lung cancer risk [34-36]; However, these original results are inconsistent and until now the lack of systematic review evaluation failed to give further insights on this issue. In this study, we carried out a meta-analysis of codon 194, codon 280 and codon 399 polymorphisms in XRCC1 gene to estimate the association of these three polymorphisms with lung cancer risk. Our results of this meta-analysis indicate that genetic variations of XRCC1 Arg399Gln and Arg194Trp may contribute to inter-individual susceptibility to lung cancer in Caucasian populations.

Three polymorphisms in XRCC1 Arg194Trp, Arg280His and Arg399Gln have been frequently examined in the studies on cancer susceptibility. The XRCC1 Arg399Gln polymorphism was the most common sequence variant among the three XRCC1 polymorphisms. Studies have shown that genetic polymorphism

of XRCC1 Arg399Gln was associated with risk of lung cancer [37, 38], and might be a candidate for contributing inter-individual difference in the overall survival of gemcitabine/platinum-treated advanced Non-Small-Cell Lung cancer patients [39]. However, several studies found no association, and one reported a protective effect of the variant allele [40-42]. Furthermore, two meta-analyses have demonstrated that codon 399 polymorphisms of XRCC1 gene might have contributed to individual susceptibility to lung cancer [36, 43]; While two other meta-analyses have shown that there is no association between XRCC1 Arg399Gln polymorphism and lung cancer risk [36, 44]. In our meta-analysis of the XRCC1 gene in Caucasian populations, the combined variant genotype (Arg/Gln and Gln/Gln) of the XRCC1 Arg399Gln polymorphism was significantly associated with lung cancer risk, as obtained from ten studies.

Previous meta-analysis of XRCC1 Arg194Trp polymorphisms on the risk of lung cancer showed that homozygous Trp/Trp variant genotype could increase lung cancer risk in total population, especially in Asians; However, the heterozygote Arg/Trp variant genotype might decrease the risk of lung cancer, especially in whites [35]. Our result showed that the combined variant genotype (Arg/Trp and Trp/Trp) of XRCC1 Arg194Trp polymorphism was also significantly associated with lung cancer risk, as obtained from six studies, whereas no statistically significant associations with lung cancer risk was observed for the XRCC1 Arg280His polymorphisms from five studies. However, the association between XRCC1 polymorphism and lung cancer risk was not consistent with previously reported meta-analyses [17, 45]: one has demonstrated that the XRCC1 Arg399Gln polymorphism was associated with an increased risk of lung cancer among Asians, but not among Caucasians; the other has demonstrated that the XRCC1 Arg280His polymorphisms may be biomarkers of cancer susceptibility and may play a role in cancer development [46].

Although we have put considerable effort and resources into testing possible association between XRCC1 gene polymorphisms and lung cancer risk, there are still some limitations inherited from the published studies. Firstly, lung cancer is a complex disease, and there are complex interactions between genetic background and environmental factors especially tobacco smoking. Secondly, gene-gene interactions were also possible in the association between XRCC1 polymorphism and lung cancer risk. Finally, selection bias could have played a role because all of the studies selected in this meta-analysis were published in English. Therefore, further studies are needed to assess the possible associations.

In summary, our meta-analysis measured the association between genetic polymorphisms in XRCC1 and lung cancer risk, and suggested that variant genotypes of Arg399Gln and Arg194Trp, but not Arg280His, might alter inter-individual susceptibility to lung cancer in Caucasian populations. Besides, further studies are needed to assess the possible gene-gene or gene-environment interactions in the association above.

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Disclosure of conflict of interest

None.

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