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Association between the -77T>C polymorphism in the DNA repair gene *XRCC1* and lung cancer risk

B.B. Sun, J.Z. Wu, Y.G. Li and L.J. Ma

Department of Respiratory Medicine,
People's Hospital Affiliated to Zhengzhou University, Zhengzhou, China

Corresponding author: L.J Ma
E-mail: malj1med@126.com

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ABSTRACT. Numerous studies have evaluated the association between the X-ray repair cross-complementing group 1 (*XRCC1*) DNA repair gene polymorphism -77T>C and lung cancer risk. However, this association is controversial. We used PubMed and Embase to identify 5 case-control studies, which included 2488 lung cancer cases and 2576 controls, for inclusion in a comprehensive meta-analysis in order to assess this association. Two independent reviewers extracted data from the studies, and ORs with 95%CIs were calculated. When all studies were pooled, we found a significant association between the -77T>C polymorphism and lung cancer risk (TT *vs* CC: OR = 0.52, 95%CI = 0.34-0.80, P = 0.49; TT *vs* CT: OR = 0.71, 95%CI = 0.62-0.81, P = 0.69; dominant model: OR = 1.45, 95%CI = 1.27-1.66, P = 0.64; recessive model: OR = 0.54, 95%CI = 0.36-0.82, P = 0.24). In a subgroup analysis of nationalities, the -77T>C polymorphism was significantly associated with lung cancer risk in Asian patients. In conclusion, the *XRCC1* -77T>C polymorphism might be related to increased risk of lung cancer

in Asians. Future studies are needed for conclusive evidence about this association.

Key words: -77T>C polymorphism; Lung cancer; XRCC1

INTRODUCTION

Lung cancer is a common type of cancer, and it has a high mortality rate. Additionally, current knowledge about the molecular basis of lung cancer susceptibility is limited (Mitsudomi, 2010). In addition to smoking, which has been established as the most important environmental factor that causes lung cancer, other notable contributors to lung cancer risk include age, radon exposure, environmental pollution, occupational exposures, gender, race, and pre-existing lung disease. However, not all people with these risk factors develop lung cancer, and other people with unknown risk factors do develop cancer, which indicates the importance of genetic influences (De Groot and Munden, 2012). In recent years, genome-wide association studies have shown that genetic factors also play an important role in lung cancer pathogenesis (Herbst et al., 2008).

The X-ray repair cross-complementing group 1 (*XRCC1*) gene encodes the XRCC1 protein. XRCC1 is an important component of the base excision repair pathway that is directly associated with polymerase beta, DNA ligase III, and poly ADP ribose polymerase, and functions in a complex to facilitate base excision repair and single strand break repair (Thompson and West, 2000). The human *XRCC1* gene is located at the chromosomal locus 19q13.2, contains 17 exons, and encodes a 633 amino acid protein (Lindahl and Wood, 1999). Recently, a novel T>C transition located at nucleotide -77 (-77T>C) in the promoter region of *XRCC1* was identified by re-sequencing the *XRCC1* gene. The -77T>C polymorphism may be associated with reduced *XRCC1* expression, thereby rendering a phenotype variation, which could affect cancer susceptibility. In the past decade, a number of epidemiological studies have assessed the association between the -77T>C polymorphism and lung cancer risk. However, the results have been inconsistent. Meta-analysis can be a useful tool for detecting associations that would otherwise remain masked by the sample sizes of the individual studies. This is especially true when evaluating rare allele frequency polymorphisms (Attia et al., 2003). The aim of this study was to investigate the association between the -77T>C polymorphism and lung cancer susceptibility by conducting a meta-analysis of all eligible case-control studies that are currently published.

MATERIAL AND METHODS

Literature and search strategy

Two reviewers (B.B.S. and L.J.M.) searched the PubMed and Embase databases to retrieve papers that linked the -77T>C polymorphism and lung cancer risk that were available by September 2013. The searches, which were not subject to language restrictions, used the following key words: -77T>C, lung cancer, polymorphism, single nucleotide polymorphism (SNP), and genetic polymorphism. The reference lists of major textbooks, reviews, and included articles were identified through manual searches to find other potentially eligible studies.

Inclusion criteria and data extraction

To be eligible for inclusion in this meta-analysis, studies had to meet the following criteria: i) case-control studies that included lung cancer cases and healthy controls; ii) studies of the association between the -77T>C polymorphism and lung cancer susceptibility; iii) studies that included sufficient genotype data for extraction; iv) healthy controls were in Hardy-Weinberg equilibrium (HWE). The exclusion criteria were as follows: i) reports that were not case-control studies evaluating the association between the -77T>C polymorphism and lung cancer risk; ii) case reports, letters, reviews, meta-analyses, and editorial articles; iii) studies based on incomplete raw data and those with no usable data reported; iv) studies that included duplicate data or had healthy controls that were not in HWE.

Data extraction

To gather the necessary information, 2 reviewers (J.Z.W. and Y.G.L.) used a standardized form to independently extract data from published studies. Disagreements were resolved by discussion. The following information was extracted from each of the included articles: first author, year of publication, country, nationality, number of patients and controls, gene polymorphisms, and evidence of HWE. When there were conflicting evaluations, the reviewers discussed the issue and reached an agreement.

Statistical analysis

We assessed HWE in the controls of each study using chi-square tests, and $P < 0.05$ was considered to be a statistically significant difference. The strength of the association between the -77T>C polymorphism and lung cancer susceptibility was estimated using ORs and 95%CIs under a homozygote comparison (TT *vs* CC), a heterozygote comparison (TT *vs* CT), a dominant model (CC + CT *vs* TT), and a recessive model (TT + CT *vs* CC). We quantified the effect of heterogeneity using the I^2 test. I^2 values range from 0% to 100% and represent the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. The random effects model was used for meta-analysis when the heterogeneity across studies was found to be $I^2 > 50\%$; otherwise, the fixed effects model was used. Subgroup analyses were performed to explore and explain the diversity among the results of different studies and to evaluate ethnicity-specific effects. There was only 1 study aiming at Europe (De Ruyck et al., 2007), and the result of the ethnicity-specific subgroup analysis was not performed for Europeans. Sensitivity analysis was performed using the values from the random effect model compared to the values from the fixed effect model. Funnel plot asymmetry was assessed using Begg's test to estimate potential publication bias ($P < 0.05$ was considered to be statistically significant). Meta-analysis was performed using the Stata package, version to be 12.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Study characteristics

Our search strategy identified 22 potentially relevant studies. On the basis of our inclusion criteria, 5 case-control studies with full texts were chosen for inclusion in this meta-analysis (Hu et al., 2005; Hao et al., 2006; De Ruyck et al., 2007; Li et al., 2008; Hsieh et al., 2009), and 17 studies were excluded. Study selection is summarized by the flow chart in Figure 1. The 5 studies that were selected included a total of 2488 cases and 2576 healthy controls. All reports included were from case-control studies that evaluated the association between the -77T>C polymorphism and lung cancer risk. The year of publication of the studies included ranged from 2005 to 2009. All the articles were written in English. The controls were mainly taken from healthy populations. The HWE test was performed on the genotype distribution of the controls, and all of them were in HWE ($P > 0.05$). Baseline characteristics and methodological quality of all included studies are summarized in Table 1. The genotype distribution and risk allele frequency are summarized in Table 2.

Significant heterogeneity ($P < 0.05$ or $I^2 > 50\%$) between studies was not observed in the comparisons of positive allele *vs* negative allele and positive homozygote plus heterozygote *vs* negative homozygote. Therefore, the fixed effects model was used to pool the results. A summary of the meta-analysis findings about the association between the -77T>C polymorphism and lung cancer risk is shown in Figure 2 and Table 2. Meta-analysis results showed significant associations between the -77T>C polymorphism and lung cancer risk in all comparisons of the positive allele *vs* the negative allele (TT *vs* CC: OR = 0.52, 95%CI = 0.34-0.80, P = 0.49; TT *vs* CT: OR = 0.71, 95%CI = 0.62-0.81, P = 0.69; dominant model: OR = 1.45, 95%CI = 1.27-1.66, P = 0.64; recessive model: OR = 0.54, 95%CI = 0.36-0.82, P = 0.24).

In a subgroup analysis where the data was separated according to ethnicity, our analysis confirmed that the -77T>C polymorphism was significantly associated with lung cancer risk in the Asian population (TT *vs* CC: OR = 0.42, 95%CI = 0.25-0.71, P = 0.76; TT *vs* CT: OR = 0.70, 95%CI = 0.61-0.81, P = 0.67; dominant model: OR = 1.48, 95%CI = 1.28-1.70, P = 0.66; recessive model: OR = 0.41, 95%CI = 0.24-0.69, P = 0.51).

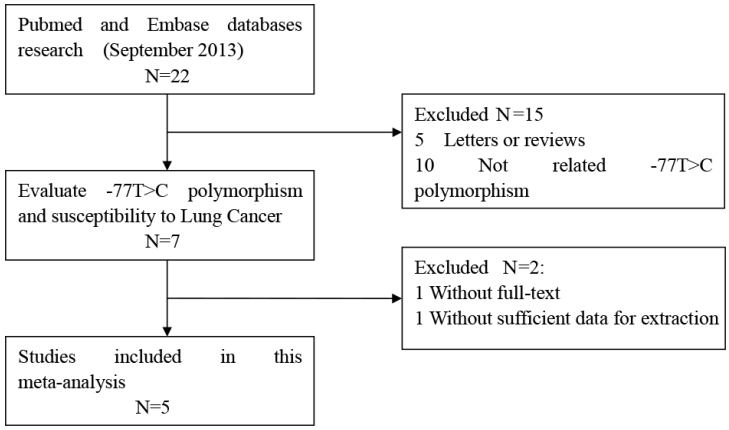

Figure 1. Flow diagram of study searching and selection process.

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

Study included	Year	Area	Race	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test
					TT	CT	CC	TT	CT	CC	
Hu et al.	2005	China	Asian	710/710	500	198	12	558	148	4	0.08
Hao et al.	2006	China	Asian	1024/1118	783	223	18	924	182	12	0.37
De Ruyck et al.	2007	Belgium	Europe	110/110	37	53	19	40	52	18	0.87
Li et al.	2008	China	Asian	350/350	264	75	11	291	55	4	0.45
Hsieh et al.	2009	China	Asian	294/288	251	40	3	250	37	1	0.76

Table 2. Summary ORs and 95%CI of XRCC1 -77T>C polymorphism and lung cancer risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2	P	OR	95%CI	z	P
Overall	TT *vs* CC	2488	2576	Fixed	0.0%	0.49	0.52	0.34-0.80	0.24	0.81
	TT *vs* CT			Fixed	0.0%	0.69	0.71	0.62-0.81	0.24	0.81
	Dominant model			Fixed	0.0%	0.64	1.45	1.27-1.66	0.24	0.81
	Recessive model			Fixed	27.1%	0.24	0.54	0.36-0.82	0.24	0.81
Asians	TT *vs* CC	2378	2466	Fixed	0.0%	0.76	0.42	0.25-0.71	0.34	0.73
	TT *vs* CT			Fixed	0.0%	0.67	0.70	0.61-0.81	0.34	0.73
	Dominant model			Fixed	0.0%	0.66	1.48	1.28-1.70	0.34	0.73
	Recessive model			Fixed	0.0%	0.51	0.41	0.24-0.69	0.34	0.73

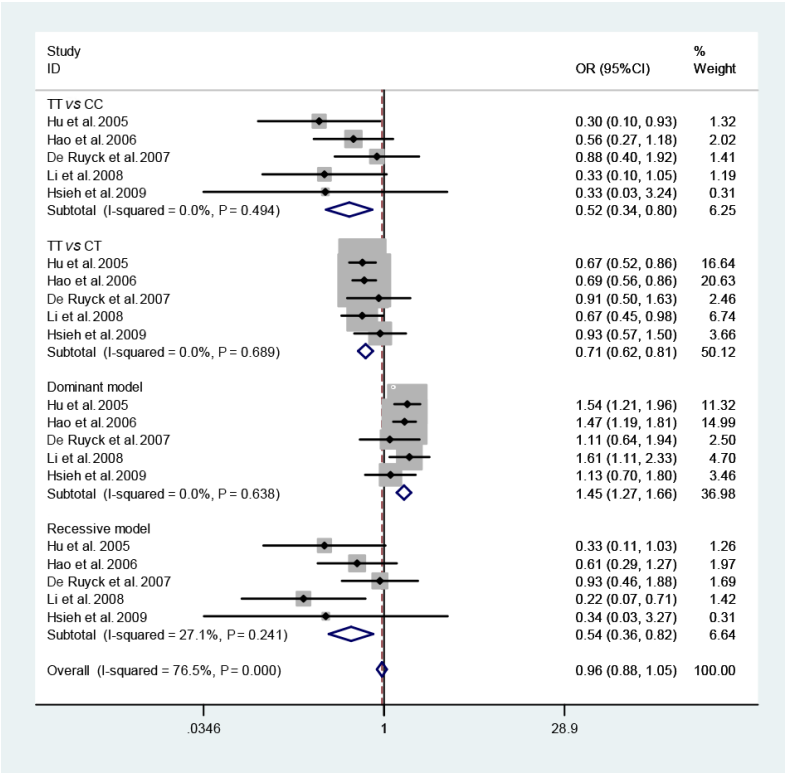

Figure 2. Meta-analysis of the relationship between the -77T>C polymorphism and lung cancer risk in the total population.

Publication bias and sensitivity analysis

Sensitivity analyses were conducted by altering the statistical models. No material alterations were detected, indicating that our results were statistically robust. Publication bias in the literature was assessed by Begg's funnel plot (Figure 3 and Table 2). The asymmetry of the funnel plot was assessed. The results of the Begg's funnel plot test are shown in Table 2. Our results found that there was no publication bias (all $P > 0.05$).

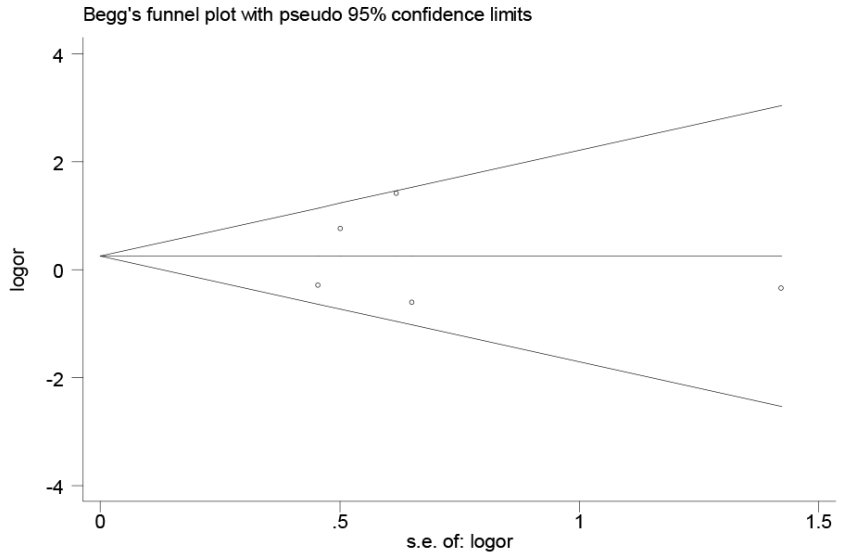

Figure 3. Begg's funnel plot test of publication bias for the association of the -77T>C polymorphism and lung cancer.

DISCUSSION

Lung cancer is a major cause of cancer-related deaths worldwide, and the overall survival rate of this disease is extremely poor (Jemal et al., 2008). Although the cause of most lung cancer cases is well known, this disease is still difficult to diagnose early and treat successfully. This problem reflects the fact that we have only made limited advances in our understanding of the molecular mechanisms underlying lung carcinogenesis and individual susceptibility to lung cancer. Genetic polymorphisms that alter protein expression levels are anticipated to have a substantial influence on disease activity (Tahara et al., 2009). A novel -77T>C polymorphism has been identified in the 5' untranslated region of the *XRCC1* gene. Hao et al. (2006) reported that the XRCC1 -77T>C polymorphism was associated with lung cancer development, but these results are controversial. The aim of this meta-analysis was to combine similar studies to increase the sample size and statistical power, thereby yielding a more authentic result.

This is the first systematic study of the association between the -77T>C polymorphism and lung cancer risk that has used meta-analysis. In the end, 5 case-control studies were included and assessed, giving a combined pool of 2488 cases and 2576 healthy controls. The

results revealed that the maternal -77T>C polymorphism in the *XRCC1* gene was significantly associated with lung cancer susceptibility (TT *vs* CC: OR = 0.52, 95%CI = 0.34-0.80, P = 0.49; TT *vs* CT: OR = 0.71, 95%CI = 0.62-0.81, P = 0.69; dominant model: OR = 1.45, 95% CI = 1.27-1.66, P = 0.64; recessive model: OR = 0.54, 95%CI = 0.36-0.82, P = 0.24). To account for differences in genetic backgrounds and living environments, we also performed an ethnicity-specific subgroup analysis. We found a significant association between the -77T>C polymorphism and lung cancer risk in the Asian population. There was only 1 study performed in Europe (De Ruyck et al., 2007), and the ethnicity-specific subgroup analysis was not performed for Europeans. Further sensitivity analysis confirmed the significant association between the maternal -77T>C polymorphism and lung cancer risk. There was no evidence of publication bias in this meta-analysis of the -77T>C polymorphism. The number of studies eligible for this meta-analysis was limited, so these results still require further investigation.

The mechanism by which the *XRCC1* gene -77T>C polymorphism is related to lung cancer risk is still unclear. Potential functions of the -77T>C polymorphism might be affected by gene-gene and gene-environment interactions. A previous study demonstrated that the haplotype -77T>C, Arg194Trp, and Arg399Gln increased lung cancer risk, while the *XRCC1* Arg194Trp or Arg399Gln polymorphisms alone did not increase lung cancer risk (Hu et al., 2005). In addition, heavy smokers and people exposed to cooking oil fumes who have -77C variant alleles are more susceptible to lung cancer (Hu et al., 2005; Li et al., 2008). However, for only one study aiming at -77T>C polymorphism exposed to cooking oil fumes or smoking, which could not be included in our meta-analysis, and further studies of gene-gene and gene-environment interactions should be undertaken to add to our knowledge about assessment of lung cancer risk.

Some limitations of our meta-analysis should be addressed. First, some relevant studies could not be included in our analysis because they contained incomplete, raw data. Second, gene-gene and gene-environment interactions were not tested in the present study, due to the lack of information from the original studies. Finally, the number of studies published was not sufficiently large for a comprehensive analysis, and some included studies of small size might not have had enough statistical power to explore the real association between *XRCC1* gene -77T>C polymorphism and susceptibility to lung cancer.

In conclusion, the -77T>C polymorphism in the *XRCC1* gene might be associated with increased risk of lung cancer in the Asian population. Few studies are available in this field, and current evidence of this association remains limited; therefore, large studies of adequate methodological quality that obtain valid results by properly controlling for potential confounding factors are greatly needed.

Conflicts of interest

The authors declare no conflict of interest.

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