The Arg194Trp Polymorphism in the XRCC1 Gene Have No Associated With Lung Cancer Risk: A Meta-Analysis

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Abstract

X-ray repair cross-complementing group 1(XRCC1) gene Arg194Trp polymorphism has been implicated in correlation with risk of lung cancer in some published studies, however, results of different studies have been inconsistent and some are totally different. In this study, we conducted a cumulative meta-analysis to get more comprehensive results of XRCC1 polymorphism of Arg194Trp and the risk of lung cancer from 27 case-control studies searching through the Pubmed, EBSCO and Embase database up to April 1, 2016. The meta-analysis was carried out by the Revman manager 5.3 Meta-Analysis software and the odds ratio (OR) with 95 % confidence interval (CI) was used to estimate the pooled effect. The results involving 9730 lung cancer patients and 13314 healthy controls revealed that XRCC1 Arg194Trp polymorphism was not associated with lung cancer risk [(OR= 0.90, 95 % CI=0.8-1.10) for ArgTrp vs. ArgArg; (OR=1.20, 95% CI=0.92-1.56) for TrpTrp vs. ArgArg; (OR=0.94, 95 % CI=0.83-1.07 for (TrpTrp+ArgTrp) vs. ArgArg]. The sensitivity and subgroups analysis showed that the results were robust and not affected by any single study with no publication bias. Our meta-analysis suggested that XRCC1 Arg194Trp polymorphism is not related with lung cancer.

Keywords: X-ray repair cross-complementing group 1; XRCC1; Polymorphism; Lung cancer; Meta-analysis

Introduction

Cancer is a major public health problem all over the world. Currently, lung cancer has become the leading cause of cancer death worldwide, with the rate as high as more than one-quarter (27%) of all cancer deaths due to lung cancer [1,2]. In 2015, an estimated 221,210 new cases of lung and bronchial cancer will be diagnosed, and 158,040 deaths are estimated to occur. Studies showed that various factors including tobacco and alcohol have been associated with lung cancer pathogenesis [3]. DNA repair genes are considerable factors in the prevention of genomic injury and sequential carcinogenesis. The single nucleotide polymorphism (SNP) of DNA repair genes might be able to impair DNA repair ability and have been suggested to be associated with cancer risk [4-6]. X-ray repair cross-complementing group 1(XRCC1) is a protein that function in the repair of single strand breaks, playing a central role in the base excision repair (BER) pathway by interacting with other DNA repair proteins [7]. There are relatively common XRCC1 SNPs: amino acid substitutions at codon 194(Arg194Trp), codon 280 (Arg280His), and codon 399(Arg399Gln). In 2001, David-Beabes and [8] and Ratnasinghe [9] found that Arg194Trp polymorphism might contribute to lung cancer. There are more studies showed the relationship of XRCC1 polymorphism with the susceptibility of lung cancer. However, some researches showed that there was no association between XRCC1 gene Arg194Trp polymorphism and risk of lung cancer [10,11]. To reach conclusive results, several meta-analysis studies were conducted by combining results across studies from literatures through pooling analysis. However, these previous meta-analysis investigations were still not consistent [12,13]. Furthermore, new published research studies were coming out, but the inconclusive results are still a problem to be resolved. Therefore, the association of Arg194Trp with lung cancer risk remains inconclusive and unclear.

In order to have more comprehensive and precise results, we conducted cumulative meta-analysis to explore the association between Arg194Trp SNP and lung cancer risk based on 27 case-control studies.
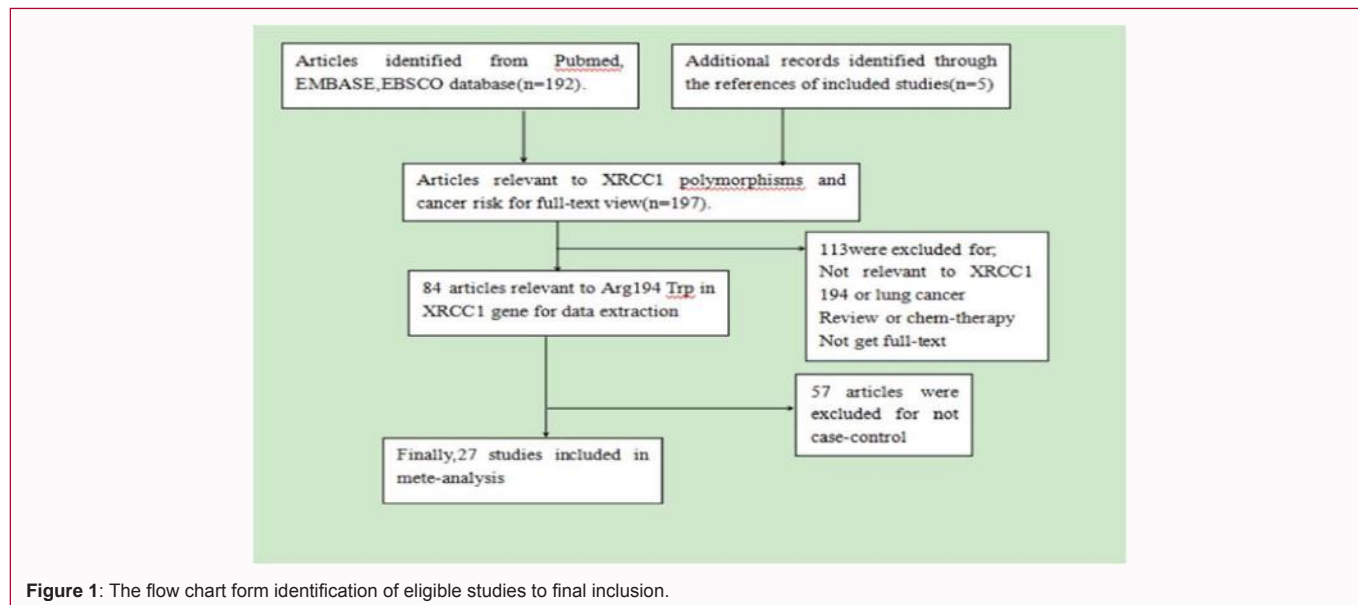
Figure 1: The flow chart form identification of eligible studies to final inclusion.

Figure 2: Forest plots for the association of XRCC1 Arg194Trp polymorphism with lung cancer risk. A. Trp/Trp *vs* Arg/Arg; B. Arg/Trp *vs* Arg/Arg; C. (Arg/Trp+Trp/Trp) *vs* Arg/Arg; D. Trp/Trp vs Arg/Trp.

Material and Methods

Publication search

Pubmed, EBSCO, EMBASE Data were searched to identify studies that had investigated the association between XRCC1 polymorphisms and the risk of lung cancer from inception through to April, 2016. The broad search terms were: "XRCC or X-ray repair cross complementing 1 and SNP or polymorphism and DNA repair

or variant and lung cancer or lung neoplasm or cancer of the lung". The reference also list of the included articles and relevant meta-analyses were manually searched.

Inclusion criteria

All data from studies included in this meta-analysis followed the criteria: [1] the papers should include lung cancer risk and polymorphisms of XRCC1 Arg194Trp [2]; the papers should be
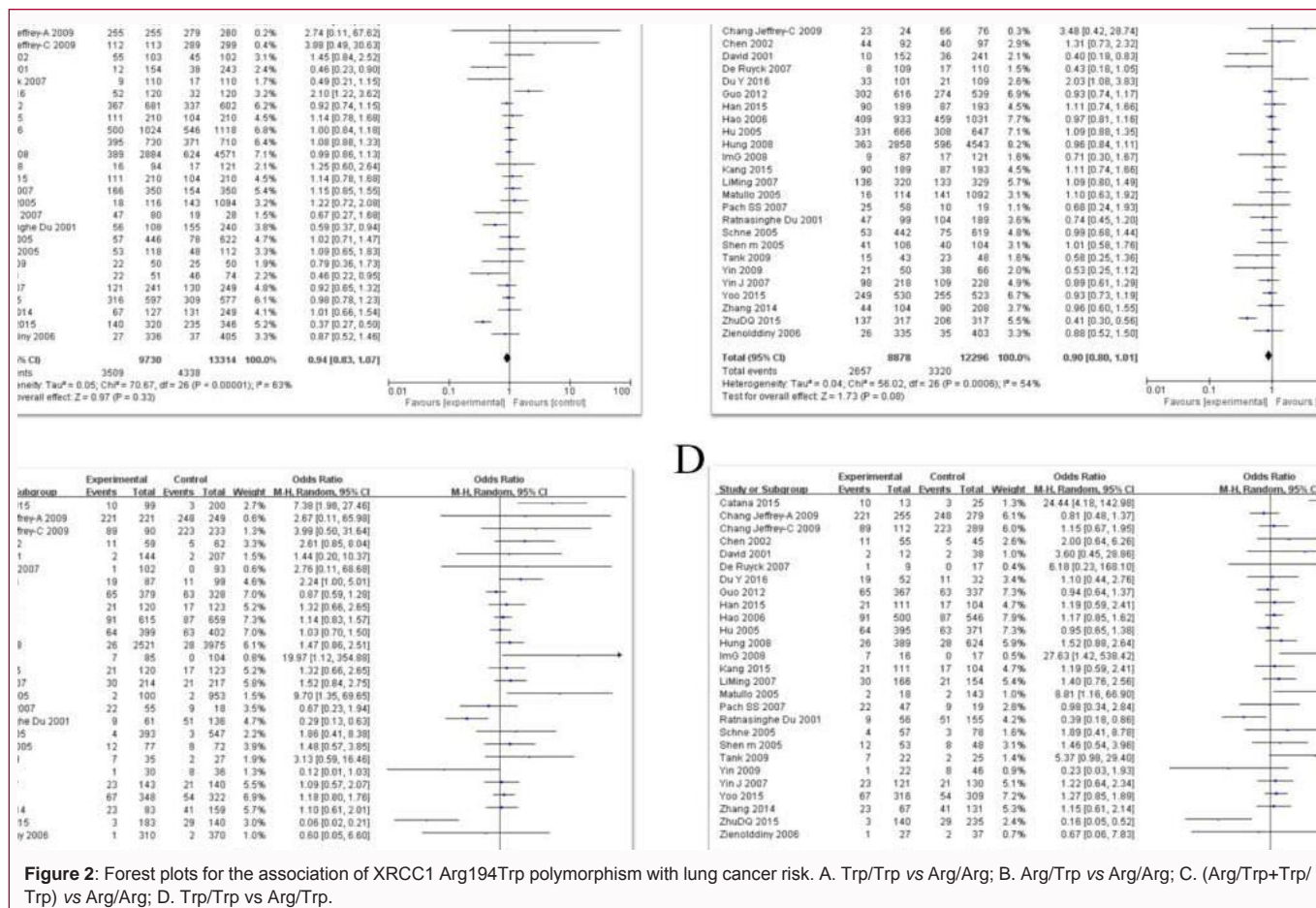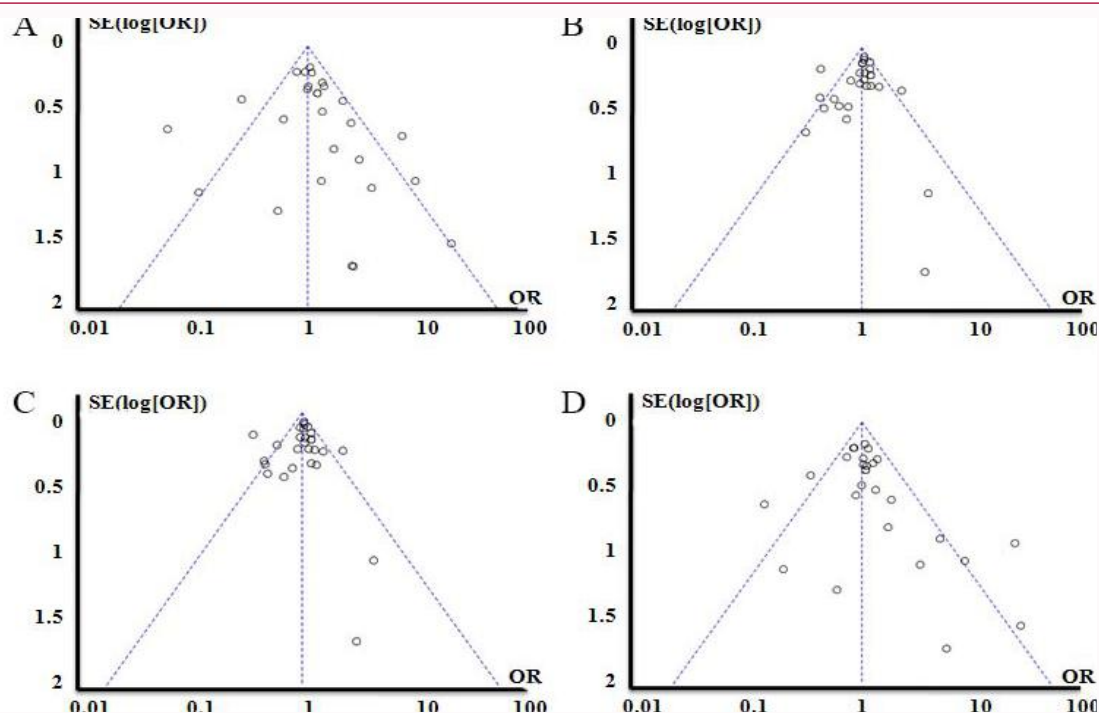
Figure 3: Funnel plots for the association of XRCC1 Arg194Trp polymorphism with lung cancer risk. A. Trp/Trp *vs* Arg/Arg; B. Arg/Trp *vs* Arg/Arg; C. (Arg/Trp+Trp/Trp) *vs* Arg/Arg ; D. Trp/Trp *vs* Arg/Trp.

published between January 1980 and April 2016 [3]; only the case-control studies and cohort studies were considered [4]; the number of genotype distribution in both case and control group were directly reported or calculated from the reported data [5]; the published language was English.

Data extraction

Two investigators extracted data from each included studies A third reviewer's decision was required when there was disagreement between the two reviewers. The following data were collected: the surname of first author, publication year, Ethnicity, genotyping-methods, case number of XRCC1 and genotyping distribution, control number of XRCC1 and genotyping distribution.

Statistical analysis

Four genetic models [ArgTrp vs. ArgArg; TrpTrp vs. ArgTrp; TrpTrp vs. ArgArg; (TrpTrp +ArgTrp) vs. ArgArg] were used to calculate the pooled odds ratio (OR) and its 95 % confidence interval (CI) to present the strength of associations between XRCC1 Arg194Trp polymorphism and risk of lung cancer. The fixed effects model is used when the effects are assumed to be homogenous, while the random effects model is used when they are heterogeneous. For heterogeneity among included studies $I^2 \geq 50$ % when detected by I^2 statistics (Figure 2) [14,15], random-effects model was used instead. The funnel plot was drawn to assess publication bias and Egger's test was used to test for the funnel plot symmetry. All the statistical analyses were performed with Review Manager (Version 5.3, The Cochrane Collaboration).

Results

Selection of studies

Based on our system search strategy, 197 (192 and 5 additional) potentially studies form designated databases were identified after careful examination of the titles and abstracts. All this 197 studies

are articles relevant to XRCC1 polymorphisms and cancer risk for full-text view. After excluded 113 papers due to the reasons of not relevant of XRCC1 194 or lung cancer/ reviews/ concerning therapy/ cannot get full text from the original 197 studies, eighty four studies remained in this analysis. Another 57 papers were excluded for the studies were not case-control study. Finally, a total of 27 studies Catana et al. [16], Chang et al. [17], Chen et al. [18], David-Beabes et al. [9], De Ruyck et al. [19], Du et al. [20], Guo et al. [21], Han et al. [22], Hao et al. [23], Hu et al. [24], Hung et al. [25], Improta et al. [26], Kang et al. [27], Li et al. [28], Matullo et al. [29], Pachouri et al. [30], Ratnasinghe et al. [10], Schneider et al. [31], Shen et al. [32], Tanaka et al. [33], Yin et al. [34], Yin et al. [35], Yoo et al. [36], Zhang et al. [37], Zhu et al. [38], Zienolddiny et al. [39], were included in the final meta-analysis, all were written in English.

Study characteristics

A total of 9730 lung cancer patients and 13314 controls from 27 studies were included in this meta-analysis. In all reports, classical polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) was utilized for detection of XRCC1 polymorphisms in the peripheral blood cells. The relevant characteristics of the 27 eligible studies are listed in (Table 1).

Arg194Trp allete and lung cancer risk

XRCC1 Arg194Trp polymorphism [ArgTrp vs. ArgArg; TrpTrp vs. ArgTrp; TrpTrp vs. ArgArg; (TrpTrp +ArgTrp) vs. ArgArg] Meta-analysis based on fixed-effects model showed that there was no association of XRCC1 Arg194Trp polymorphism with risk of lung cancer [(OR= 0.90, 95 % CI=0.8–1.10) for ArgTrp vs. ArgArg; (OR=1.20, 95 % CI=0.92–1.56) for TrpTrp vs. ArgArg; (OR=0.94, 95 % CI=0.83–1.07 for (TrpTrp+ArgTrp) vs. ArgArg] (Figure 2). No association was observed between the Arg194Trp polymorphism and lung cancer risk (OR=0.94, 95 % CI=0.83–1.07; Arg/Trp and Trp/Trp genotypes combined versus Arg/Arg genotype.

Table 1: Main characteristics of studies included in the meta-analysis.

Authors	Ethnicity	Methods	Case				Control			
			N	AA	AT	TT	N	AA	AT	TT
Catana A 2015	European	PCR	102	89	3	10	222	197	22	3
ChangJeffrey-A2009	Afrian	PCR	255	0	34	221	280	1	31	248
Chang Jeffrey-C2009	Amerian	PCR	113	1	23	89	299	10	66	223
Chen S 2002	China	PCR-RFLP	109	48	44	11	109	57	40	5
David B 2001	USA	PCR-RFLP	154	142	10	2	243	205	36	2
De Ruyck 2007	Belgium	PCR-RFLP	110	101	8	1	110	93	17	0
Du Y 2016	China	PCR	120	68	33	19	120	88	21	11
Guo S 2012	China	PCR-LDR	684	314	302	65	602	265	274	63
Han JC 2004	China	PCR-RFLP	245	99	90	21	257	106	87	17
Hao B 2006	China	PCR	1024	524	409	91	1118	572	459	87
Hu Z 2005	China	PCR-RFLP	710	335	331	64	710	339	308	63
Hung RJ 2008	European	PCR	2569	2495	363	26	4178	3947	596	28
Improta G 2008	Italy	PCR-RFLP	94	78	9	7	121	104	17	0
Kang S 2015	China	PCR-RFLP	210	99	90	21	210	106	87	17
Li M 2007	China	PCR-RFLP	350	184	136	30	350	196	133	21
Matullo G 2005	European	Tap-man	134	98	16	2	1094	951	141	2
Pachouri S 2007	India	PCR-RFLP	103	33	25	22	122	9	10	9
Ratnasinghe D 2001	China	PCR	108	52	47	9	240	85	104	51
Schne L 2005	Germany	PCR	446	389	53	4	622	544	75	3
Shen M 2005	USA	PCR	122	65	41	12	122	64	40	8
Tanaka Y 2009	Japan	PCR	50	28	15	7	50	25	23	2
Yin YY 2008	China	PCR	51	29	21	1	74	28	38	8
Yin JY 2006	China	PCR-RFLP	241	120	98	23	249	119	109	21
Yoo S 2015	Korea	Tap-man	597	281	249	67	577	268	255	54
Zhang L 2014	China	PCR	127	60	44	23	248	118	90	41
Zhu DQ 2015	China	CRS-PCR	320	180	137	3	346	111	206	29

Publication bias

No obvious publication bias was revealed after assessing the funnel plot for the eligible studies (Figure 3). Furthermore, the results from Egger's test for the studies evaluating XRCC1 Arg194Trp in lung cancer did not reveal obvious publication bias (Egger's=0.33). The shape of funnel plots seemed to be approximately symmetrical (Figure 3). Both Egger's test results suggested no evidence of publication biases existed in this meta-analysis (Table 2). The presence of publication bias showed that not significant or negative finding remain unpublished.

Discussion

Meta-analysis is a statistical method of combining results from literatures to resolve discrepancy in association studies [40]. We summarized the previous studies to estimate the association between the polymorphisms of XRCC1 codon 194 and lung cancer risk. Previously, many people made a subgroup analysis, analysis of each ethnicity of meta analysis. Considering the number of samples, we didn't see the each ethnicity of the relationship between XRCC1 polymorphism and lung cancer susception. In this study, we choose researches published only in English to avoid bias in some aspects. In further study, the understanding of the people went a step further; we may have further subgroup analysis. The meta-analysis of 27 case

control studies indicated that XRCC1 Arg194Trp polymorphism is not associated with lung cancer risk within human populations, which was also supported by cumulative meta-analysis and sensitivity analysis [41].

Compared to previously meta-analyses, the included studies of our analysis are should provide a stronger statistical power and have less risk of bias. Hence, the results are more precise and comprehensive. However, we should mention the test of heterogeneity, an important aspect on the evaluate quality of a meta-analysis, which may be produced due to unreliable data. Therefore, we will mention original statistical carefully. What's more, we found that the results remained the similar when studies were accumulated. Now, lung cancer patient mainly treated by chemotherapy because of there is no better treatment. People are also exploring actively the relationship between lung cancer and gene in order to treat lung cancer better. Several limitations should be pointed out in our meta-analysis. The funnel plot was not very symmetry despite there is no obvious publication bias. For another, this meta-analysis was based on unadjusted data, lacking of detailed genotype information stratified by main confounding variables from original studies.

Conclusion

In summary, we observed there is not associated between XRCC1

codon 194 with lung cancer, which is consistent with Kiyohara et al. [42]. These results were not influenced by any single study. We should be more focused on other factors associated with lung cancer such as microenvironment of lung cancer. Given a handful of studies included in this meta-analysis, the present conclusion should be considered with more high-quality prospective cohort studies next.

Acknowledgements

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