No association between XRCC1 gene Arg194Trp polymorphism and risk of lung cancer: evidence based on an updated cumulative meta-analysis

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Abstract X-ray repair cross-complementing group 1 (XRCC1) gene Arg194Trp polymorphism has been reported to be associated with risk of lung cancer in many published studies. Nevertheless, the research results were inconclusive and conflicting. To reach conclusive results, several meta-analysis studies were conducted by combining results from literature reports through pooling analysis. However, these previous meta-analysis studies were still not consistent. Hence, we used an updated and cumulative meta-analysis to get a more comprehensive and precise result from 25 case–control studies searching through the PubMed database up to September 1, 2013. The meta-analysis was carried out by the Comprehensive Meta-Analysis software and the odds ratio (OR) with 95 % confidence interval (CI) was used to estimate the pooled effect. The result involving 8,876 lung cancer patients and 11,210 controls revealed that XRCC1 Arg194Trp polymorphism was not associated with lung cancer risk [(OR=0.97, 95 % CI=0.92–1.03) for Trp vs. Arg; (OR=0.92, 95 % CI=0.85–0.98) for ArgTrp vs. ArgArg; (OR=1.07, 95 % CI=0.92–1.23) for TrpTrp vs. ArgArg; (OR=0.93, 95 % CI=0.87–1.00) for (TrpTrp+ArgTrp) vs. ArgArg; and (OR=1.08, 95 % CI=0.94–1.25) for TrpTrp vs. (ArgTrp+ArgArg)]. The cumulative meta-analysis showed that the results maintained the same, while the ORs with 95 % CI were more stable with the accumulation of case–control studies. The sensitivity and subgroups analyses showed that the results were robust and not affected by any single study with no publication bias. Relevant studies might not be needed for supporting these results.

Keywords X-ray repair cross-complementing group 1 · XRCC1 · Lung cancer · Polymorphism · Risk · Meta-analysis

Introduction

X-ray repair cross-complementing group 1 (XRCC1) is involved in base excision repair protein that located on chromosome 19q13.2–13.3 with a length of 33 kb [1–4]. The polymorphisms of XRCC1 gene have been identified as three categories of codons 194(Arg to Trp), 280(Arg to His), and 399 (Arg to Gln) [5, 6]. One of them, Arg194Trp polymorphism was first reported in 1998 by Shen and coworkers [7]. In 2001, David-Beabes and coworkers [8] found that Arg194Trp polymorphism might contribute to lung cancer in African-American and Caucasian. Ratnasinghe and coworker [5] found similar results in Chinese during the same year. Later on, many molecular epidemiological studies reported the association of XRCC1 Arg194Trp with lung cancer susceptibility [5, 8–30]. However, these results remain conflicting and inconclusive. 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 [31–33]. 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 susceptibility with lung cancer risk remains unclear.

In order to obtain more comprehensive and precise results, we conducted cumulative meta-analysis [34, 35] to explore the truly association between Arg194Trp polymorphism and lung cancer risk based on 25 case–control studies. The meta-analysis is reported based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) [36] statement.

**Material and methods**

**Inclusion criteria**

A study met all of the following inclusion criteria was included: (1) to evaluate the association between XRCC1 Arg194Trp polymorphism and risk of lung cancer; (2) cohort or case–control design and the patients were diagnosed by histology or pathology;

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**Table 1** Characteristics of included studies

| References       | Country (ethnicity)     | Case Source | Control Source | Genotyping HWE |
|------------------|-------------------------|-------------|----------------|----------------|
|                  | N                       | ArgArg     | ArgTrp         | TrpTrp         |
|                  | N                       | ArgArg     | ArgTrp         | TrpTrp         |
| David-Beabes [8] | USA (Caucasian)         | 180         | 158            | 22             | 0              | 461         | 407       | 54        | 0              | PCR-RFLP 0.39 |
|                  | USA (African-Americans) | 154         | 142            | 10             | 2              | 243         | 205       | 36        | 2              | PCR-RFLP 0.67 |
| Ratnasinghe [5]  | China (Asian)           | 108         | 52             | 47             | 9              | 216         | 85        | 104       | 21             | TaqMan 0.22  |
| Chen [9]         | China (Asian)           | 109         | 48             | 44             | 11             | 109         | 57        | 40        | 5              | PCR-RFLP 0.79 |
| Chan [10]        | China (Asian)           | 75          | 50             | 22             | 3              | 162         | 79        | 67        | 16             | PCR-RFLP 0.71 |
| Hu [11]          | China (Asian)           | 710         | 335            | 311            | 64             | 710         | 339       | 308       | 63             | PCR 0.59     |
| Hung [12]        | European (Caucasian)    | 2,188       | 1,878          | 259            | 10             | 2,198       | 1,828     | 292       | 12             | PCR 0.87     |
| Schneider [13]   | Germany (Caucasian)     | 446         | 389            | 53             | 4              | 622         | 544       | 75        | 3              | PCR 0.74     |
| Shen [14]        | China (Asian)           | 118         | 65             | 41             | 12             | 112         | 64        | 40        | 8              | PCR 0.62     |
| Hao [15]         | China (Asian)           | 1,024       | 524            | 409            | 91             | 1,118       | 572       | 459       | 87             | PCR 0.77     |
| Landi [16]       | Europe (Caucasian)      | 295         | 118            | 143            | 34             | 314         | 123       | 149       | 42             | PCR 0.96     |
| Matullo [17]     | Europe (Caucasian)      | 116         | 98             | 16             | 2              | 1,094       | 951       | 141       | 2              | TaqMan 0.22  |
| Zienolddiny [18] | Norway (Caucasian)      | 336         | 309            | 26             | 1              | 405         | 368       | 35        | 2              | TaqMan 0.23  |
| De Ruyck [19]    | Belgium (Caucasian)     | 110         | 101            | 8              | 1              | 110         | 93        | 17        | 0              | PCR-RFLP 0.38 |
| Pachouri [20]    | India (Asian)           | 103         | 40             | 39             | 24             | 122         | 52        | 47        | 23             | PCR-RFLP 0.051 |
| Yin [21]         | China (Asian)           | 241         | 120            | 98             | 23             | 249         | 119       | 109       | 21             | PCR-RFLP 0.65 |
| Li [23]          | China (Asian)           | 350         | 184            | 136            | 30             | 350         | 196       | 133       | 21             | PCR-RFLP 0.89 |
| Improta [22]     | Italy (Caucasian)       | 94          | 42             | 41             | 11             | 121         | 53        | 61        | 7              | PCR-RFLP 0.15 |
| Chang [24]       | USA (Latinos)           | 113         | 89             | 23             | 1              | 299         | 223       | 66        | 10             | Illumina 0.1  |
| Chang [24]       | USA (African–Americans) | 255         | 221            | 34             | 0              | 280         | 248       | 31        | 1              | Illumina 0.97 |
| Tanaka [25]      | Japan (Asian)           | 50          | 28             | 15             | 7              | 50          | 25        | 23        | 2              | PCR 0.47     |
| Janik [26]       | Poland (Caucasian)      | 88          | 64             | 24             | 0              | 79          | 51        | 28        | 0              | PCR-SSCP 0.55 |
| Buch [27]        | USA (Caucasian)         | 720         | 682            | 36             | 2              | 928         | 839       | 83        | 6              | Illumina 0.03 |
| Wang [28]        | China (Asian)           | 209         | 105            | 83             | 21             | 256         | 137       | 96        | 23             | PCR-RFLP 0.59 |
| Guo [29]         | China (Asian)           | 684         | 314            | 302            | 68             | 602         | 265       | 274       | 63             | PCR-LDR 0.58  |

N total sample size, PB population-based controls, HB hospital-based controls, HWE Hardy–Weinberg equilibrium, PCR-RFLP polymerase chain reaction-restriction fragment length polymorphism, PCR-LDR polymerase chain reaction-ligase detection reaction, PCR-SSCP polymerase chain reaction-single strand conformation polymorphism.
The number of genotype distribution in both case and control group were directly reported or calculated from the reported data; and (4) the published language was English or Chinese.

Search strategy

The search terms ["XRCC1" or "X-ray repair cross-complementing group 1"] and "polymorphism" and ("lung cancer" or "lung carcinoma") were used to search the PubMed database up to September 1, 2013. The reference list of the included articles and relevant meta-analyses were manually searched.

Data extraction

Two authors independently chose 25 case–control studies, which were illustrated in Fig. 1. The data were independently extracted by authors according to the pre-specified table. The following data were extracted: the surname of first author, publication year, country origin and ethnicity, study design, cancer type, source of control, number and genotyping distribution of cases and controls, genotyping method, Hardy–Weinberg equilibrium (HWE) for controls. Disagreements were resolved through discussion with the third author.

Statistical analysis

Five genetic models [Trp vs. Arg; ArgTrp vs. ArgArg; TrpTrp vs. ArgArg; (TrpTrp + ArgTrp) vs. ArgArg; and TrpTrp vs. (ArgTrp + 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 was used firstly, if heterogeneity among included studies was detected by $I^2$ statistics ($I^2 \leq 40 \%$) [37], we shifted to random-effects model. Subgroups analysis were conducted based on the ethnicity, source of controls, cancer types, study design, and HWE for controls.

The influence of sample size on the overall risk estimation was carried out by cumulative meta-analysis [35], and the influence of single study on the overall risk estimation was determined through sensitivity analysis by omitting one study each time. The publication bias was detected by funnel plot analysis. All the analysis was performed using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey) [38].

Results

Study section and characteristics

The electronic searching yielded 128 studies, and the hand searching yielded 15 studies initially; finally, 23 articles

| Table 2 Results of overall and subgroup meta-analysis |
|-----------------------------------------------|
| **No. of studies** | **OR (95 % CI)** | **p for OR** | **I^2 (%)** | **OR (95 % CI)** | **p for OR** | **I^2 (%)** | **OR (95 % CI)** | **p for OR** | **I^2 (%)** |
| **Total** | 23 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |
| **Ethnicity** | | | | | | | | | | |
| Asian | 12 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |
| Caucasian | 10 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |
| Others | 3 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |
| **Source of controls** | | | | | | | | | | |
| HB | 14 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |
| PB | 11 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |
| HWE | Yes | 24 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |
| No | 1 | 0.97 (0.92–1.03) | 0.30 | 38.8 | 0.92 (0.85–0.99) | 0.017 | 95 | 0.93 (0.87–1.00) | 0.047 | 38.8 |

OR odds ratio, CI confidence interval, HB hospital-based controls, PB population-based controls, HWE Hardy–Weinberg equilibrium
involving 25 case–control studies [5, 8–29] contained 8,876 lung cancer patients and 11,210 controls were included. Figure 1 presents flow chart of study selection. The main characteristics of these eight studies were shown in Table 1.

### Table 1: Main Characteristics of Eight Studies

| Study name                  | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|-----------------------------|------------|-------------|-------------|---------|---------|
| David-Beabes C 2001         | 1.05       | 0.63        | 1.74        | 0.17    | 0.06    |
| David-Beabes AA 2001        | 0.53       | 0.28        | 0.99        | -1.98   | 0.05    |
| Rathnasinghe 2001           | 0.81       | 0.57        | 1.15        | -1.18   | 0.24    |
| Chen 2002                   | 1.45       | 0.94        | 2.24        | 1.69    | 0.09    |
| Chen 2005                   | 0.52       | 0.32        | 0.84        | -2.69   | 0.01    |
| Hu 2005                     | 1.02       | 0.87        | 1.19        | 0.20    | 0.84    |
| Hsu 2005                    | 0.87       | 0.73        | 1.03        | -1.66   | 0.10    |
| Schneider 2005              | 1.05       | 0.75        | 1.49        | 0.30    | 0.76    |
| Shen 2005                   | 1.14       | 0.75        | 1.73        | 0.62    | 0.54    |
| Hao 2006                    | 1.03       | 0.90        | 1.17        | 0.40    | 0.69    |
| Landi 2006                  | 0.94       | 0.75        | 1.19        | -0.49   | 0.63    |
| Matullo 2006                | 1.33       | 0.82        | 2.17        | 1.14    | 0.25    |
| Zienioldiny 2006            | 0.86       | 0.52        | 1.41        | -0.60   | 0.55    |
| De Ruyck 2007               | 0.57       | 0.25        | 1.27        | -1.39   | 0.17    |
| Pachouri 2007               | 1.19       | 0.81        | 1.73        | 0.89    | 0.37    |
| Yin 2007                    | 0.98       | 0.75        | 1.29        | -0.15   | 0.88    |
| Li 2008                     | 1.17       | 0.92        | 1.48        | 1.27    | 0.20    |
| Improta 2008                | 1.12       | 0.75        | 1.69        | 0.55    | 0.58    |
| Chang L 2009                | 0.74       | 0.46        | 1.19        | -1.24   | 0.21    |
| Chang AA 2009               | 1.14       | 0.70        | 1.87        | 0.52    | 0.60    |
| Tanaka 2010                 | 1.10       | 0.60        | 2.05        | 0.31    | 0.75    |
| Jank 2011                   | 0.73       | 0.41        | 1.33        | -1.03   | 0.31    |
| Buch 2012                   | 0.53       | 0.36        | 0.77        | -3.31   | 0.00    |
| Wang 2012                   | 1.11       | 0.84        | 1.48        | 0.73    | 0.47    |
| Guo 2013                    | 0.95       | 0.80        | 1.12        | -0.65   | 0.52    |
| Fixed                       | 0.97       | 0.92        | 1.03        | -1.04   | 0.30    |
| Random                      | 0.96       | 0.90        | 1.04        | -0.98   | 0.33    |

**Fig. 2** Forest plot based on Trp vs. Arg genetic model.

**Fig. 3** Forest plot for cumulative meta-analysis based on Trp vs. Arg genetic model.
Of them, three were multicenter studies [12, 16, 17], two articles were included two case–control studies [8, 24], and only one study was out of HWE [27].

Meta-analysis

Table 2 presented the overall and subgroups results of XRCC1 Arg194Trp polymorphism and lung cancer risk. Overall, the heterogeneity of all five genetic models were acceptable ($I^2 \leq 40\%$), and meta-analysis based on fixed-effects model showed that there was no association of XRCC1 Arg194Trp polymorphism with risk of lung cancer [(OR=0.97, 95 % CI=0.92–1.03) for Trp vs. Arg, Fig. 2; (OR=0.92, 95 % CI=0.85–0.98) for ArgTrp vs. ArgArg; (OR=1.07, 95 % CI=0.92–1.23) for TrpTrp vs. ArgArg; (OR=0.93, 95 % CI=0.87–1.00) for (TrpTrp + ArgTrp) vs.

![Fig. 4](Forest plot for sensitivity analysis based on Trp vs. Arg genetic model)

Fig. 4 Forest plot for sensitivity analysis based on Trp vs. Arg genetic model

![Fig. 5](Funnel plot based on Trp vs. Arg genetic model)

Fig. 5 Funnel plot based on Trp vs. Arg genetic model
ArgArg; and (OR=1.08, 95 % CI=0.94–1.25) for TrpTrp vs. (ArgTrp + ArgArg)].

The cumulative meta-analysis accumulated the studies according to the publication year and showed that there was no significant association between XRCC1 Arg194Trp polymorphism and lung cancer risk (Fig. 3). The sensitivity analysis showed that the results were robust and were not influenced by any single study (Fig. 4), with ORs in the range of 0.96–0.98 and 95 % CIs in the range of 0.90–1.05. Subgroup analysis upon source of control, ethnicity, and HWE also revealed similar results (Table 2).

Publication bias

Figure 5 shows the funnel plot of based on Trp vs. Arg genetic model. The relatively symmetric distribution indicated that there was no publication bias, which was confirmed by Egger’s test [(p=0.33 for Trp vs. Arg; p=0.12 for ArgTrp vs. ArgArg; p=0.65 for TrpTrp vs. ArgArg; p=0.25 for (TrpTrp + ArgTrp) vs. ArgArg; and p=0.50 for TrpTrp vs. (ArgTrp + ArgArg)].

Discussion

Meta-analysis is a statistical method of combining results across studies from literatures to resolve discrepancy in genetic association studies [39]. The meta-analysis of 25 case-control studies indicated that XRCC1 Arg194Trp polymorphism is not associated with lung cancer risk within human populations, and subgroup analysis upon source of controls, ethnicity, and HWE for controls is consistent with this result, which was also supported by cumulative meta-analysis and sensitivity analysis.

Compared to previously meta-analyses [31–33], the included studies of our analysis are most precise and comprehensive attributing to the largest sample size and accumulative meta-analysis method. Hence, the results are more precise and comprehensive. In addition, cumulative meta-analysis was performed to investigate the tendency of results by accumulating single study year by year. This analysis could be used to determine whether new relevant studies are needed or not. Indeed, we found that the results remained the same when studies were accumulated. Coincidentally, the sensitivity analysis indicated that the results were not influenced by any single study. Hence, our results were more precise and useful for appropriate care in lung cancer.

Obviously, there were potential to moderate level heterogeneity. From the subgroups analysis, we found that ethnicity and source of control might not be the source of heterogeneity (Table 2). When we deleted the study reported by Buch et al.[27], which was not according to HWE any more, the heterogeneity of all genetic models were decreased and the results of all five genetic models were of no significance (Table 2). This further indicated that violations and deviations in HWE might be one source of heterogeneity and do largely influence the results [40].

There were some limitations of our meta-analysis. First, there was heterogeneity among included studies. Although the heterogeneity was probably from the study reported by Buch et al. [27], we could not conclude whether the heterogeneity came from ethnicity or inconsistent results. Obviously, the homogeneity of Asians and Caucasian was good, but only the one combined with mixed ethnicities was significant. Second, although no obvious publication bias was detected; the funnel plot was not very symmetry. Our meta-analysis is limited to language and database restrictions. The PubMed database is the only search source and included published studies were either in English or Chinese [28]. Third, this meta-analysis was based on unadjusted data, lacking of detailed genotype information stratified by main confounding variables from original studies. Therefore, gene-gene and gene-environment interactions remain unclear.

In conclusion, this meta-analysis suggests that XRCC1 Arg194Trp polymorphism is not associated with lung cancer risk, either in Asians or Caucasians, either the controls were sourced with or without HWE. These results were not influenced by any single study, and relevant studies are not needed for supporting this result. Due to the limitations of this meta-analysis, current results should be viewed with caution and future studies should be conducted in gene-gene and gene-environment interactions.

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Conflicts of interest None

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