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Meta analysis of XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia

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ABSTRACT

Objective: To assess the relation between XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia. **Methods:** Related studies of XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia were collected through searching the Pubmed, Embase Library, SPRINGER, CNKI and CSSCL. **Results:** According to the entry criteria, there were 8 case-control studies in the assessing system and there were 6 321 study cases, including 3 215 patients with lung cancer and 3 106 cases without cancers. Meta analysis results showed the combined OR value of the ratio of genotype Thr/Met-Met/Met and Thr/Thr was 1.03 (95%CI: 0.89–1.20) ($P>0.05$). **Conclusions:** XRCC3 Thr241Met polymorphism may not related to lung cancer susceptibility of populations in East Asia. Allele 241Met did not increase the risk of lung cancer.

1. Introduction

The daily habits such as smoking, pickled food usually make people supposed to the environment of carcinogenic aromatic amine, consequently leading to the DNA damage by DNA chemical compound[1,2]. Multiple restoration systems within human body have the function of sustaining the integrity of genotypes. Therefore, the defect of gene restoration functions caused by mutation or polymorphism can often cause the instability of genotypes. In turn, such a kind of instability was not only related to the instability of chromosomes, but also closely related to the occurrence and development of multiple cancers[3].

XRCC3 encodes a kind of proteins which play a part in homologous recombination repair and cross link repair

of broken double-stranded DNA within mammalian cells. In the homologous recombination repair, protein XRCC3 and protein Rad51 interacts with each other and they both sustain the stability of chromosomes[4,5]. The gene polymorphism is usually embodied in exon 7, often causing the replacement of Thr241Met in 241 sites, which consequently has an effect on the enzyme activity as well as its restoration function of damaged DNA[6]. Many studies related to molecular epidemiology have proved that XRCC3 Thr241Met polymorphism is related to breast cancer, lung cancer, skin cancer and colorectal cancer[7].

In our study, the author has studied the all the papers published in Pubmed and Chinese Medical Library and adopted Meta analysis method to discuss the relation between the polymorphism of DNA restoration gene XRCC3 Thr241Met (rs861539) and lung cancer susceptibility of populations in East Asia. Besides, the relation between the mutant genotypes and the risk of lung cancer was analyzed comprehensively in multiple case-control studies.

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2. Materials and methods

2.1 Search strategy

The computer was used to search Pubmed, Embase library, SPRINGER, CNKI and CSSCI and the time period was from the establishment of library to Nov. 2013. The references studied were searched for supplementary information. Case-control studies related to XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia were collected. The search strategy was to adopt the principle of combining key words and free words. The Chinese terms included lung cancer, susceptibility, XRCC3, gene polymorphism.

2.2 Inclusion and exclusion criteria

Inclusion criteria of references were: (1) case-control studies related to XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia; (2) all the cases in the study was proved to suffer lung cancer and the cases in control group did not suffer the cancer; (3) all the cases in the study offered complete the materials of genotypes or allele frequency; (4) the study area included China, Japan, Korea and the North Korea. Exclusion criteria of references were: (1) non-case-control studies; (2) abstract, review, review of the literature and conference paper; (3) materials of genotypes or allele frequency were not complete or cannot extract; (4) important published papers.

2.3 Data extraction

Literature information was extracted by two researchers independently, including the first author, article date, nation, distribution of study area, the number of cases, race, average age, diagnostic criteria, histologic type, clinical stages, test methods of polymorphism, genotypes or allele frequency, genetic Hardy-Weinberg balance.

2.4 Statistically processing

Software Review Magager 5 was used to do Meta analysis. Odds ratio (OR) and 95% of the credibility interval (CI) were used to assess the relation between XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia. Heterogeneity analysis among studies was assessed by Cochran's Q examination and I^2 examination. The effect size range of I^2 examination was 0%–100%. The larger the percentage of effect was, the tinier the heterogenicity among groups was. When the heterogenicity existed in the study ($I^2 > 50\%$), random effect model was used

to make analysis. If there was no heterogenicity, fixed effect model was used to make analysis. Z examination was used to judge whether combined OR value was statistical significant and the examination standard was set as 0.05.

Before the assessment of Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia by Meta analysis, χ^2 examination was adopted to judge whether genotype frequency in control group was fit for the HW balance. Each study was deleted one by one and sensitivity analysis was carried out to assess the effect of weight on the overall results. Funnel chart was used to assess publication bias and there was publication bias in the study when $P \leq 0.10$. The data was inputted by two researchers and calculated through the computer to ensure the accuracy of the results.

3. Results

3.1 Basic features of cases

There were 39 related literatures in the primary search, including 27 English literatures and 12 Chinese literatures. Screening was carried out exactly according to the inclusion and exclusion criteria. Abstracts as well as the whole papers were further read carefully and then 31 literatures were excluded. Finally, 8 case-control studies were included. There were totally 6 321 subjects in the 8 case-control studies, including 3 215 cases with lung cancer and 3106 contrast cases without cancers. All the literatures were the case-control studies of XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia; the article dates were from 2005 to 2013, among which there were respectively 4 Chinese and English literatures; among the 8 literatures, there were two whose subjects were Japanese^[8,9] and the rest were all Chinese^[10–15]. Reports about other nations such as Korea have not been found. In the case group, there were patients with lung cancer proved by pathology. In the control group, there were healthy people and cases with pulmonary disease rather than lung cancer. The allele distributions of cases in the study were all fit for HW balance. The basic information and the distribution of allele frequency of the cases in the study were showed in Table 1 and Figure 2. Meta analysis results of the 8 studies showed that in the study of Guo *et al*, there was remarkable difference between the genotype distribution frequency of case group and that of control group ($P < 0.05$) while in the other 7 studies, there was no obvious difference between the genotype distribution frequency of case group and that of control group ($P > 0.05$) (Table 2).

3.2. Meta analysis results

In the Chinese area, there were 6 items, 2 649 patients and 2 607 control cases; in Japanese area, there were 2 items, 566 cases and 499 control cases. Since the few mutations of homozygote, the homozygous mutant genotype Met/Met and the heterozygous mutant genotype Thr/Met were combined. Then they were compared with the wild homozygous genotype Thr/Thr. The combined OR value was used to assess the relation between gene polymorphism and lung cancer susceptibility. Through the heterogeneity test of XRCC3 Thr241Met results of each study, it was gained that $\chi^2=12.46$ and $I^2=44\%$. Therefore, the heterogeneity among the included studies was at a low level ($I^2<50\%$) while the homogeneity was relatively good (Figure 1). Random effect

model was used to make analysis and then the combined OR value was 1.03 (95%CI: 0.89-1.20), Z value was 0.43 ($P=0.67$). So it was thought that there was no relation between XRCC3 Thr241Met polymorphism and lung cancer susceptibility of populations in East Asia ($P>0.05$).

Meanwhile, random effect model was used to make sensitivity analysis of the 8 literatures included in the study. The combined OR value did not change remarkably. 95% of CI was close to that when fixed effect model was used. So the results were stable.

Regarding the OR value as horizontal axis and $\log(OR)$ as vertical axis, the results in Figure 2 showed that there was no significant publication bias in the studies. Since that Review Manager 5 could not make quantitative judgment of the publication bias, Begg's test and Egger's test were

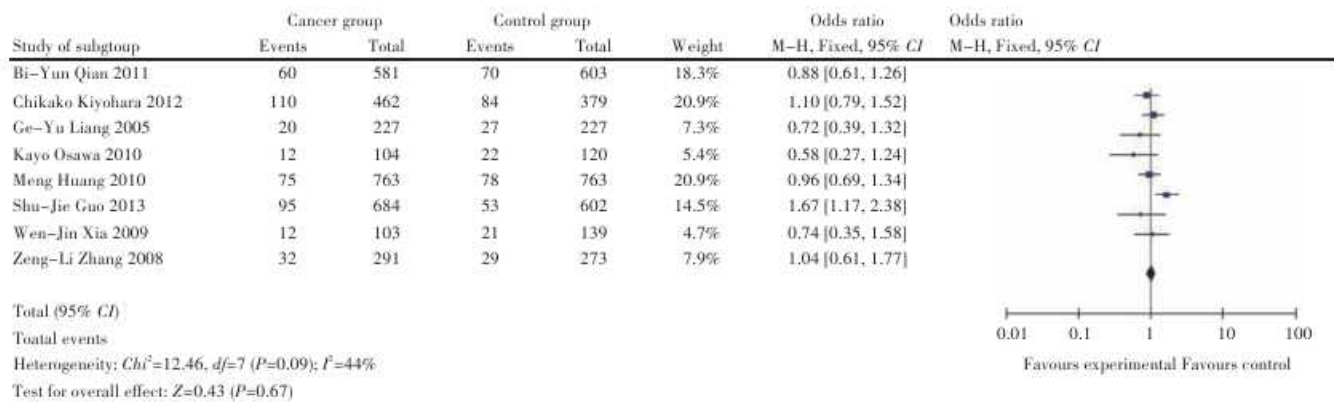


Figure 1. Forest map of the analysis of the relation between XRCC3 Thr241Met polymorphism of populations in East Asia and lung cancer.

Table 1

Basic information of cases.

| First author | Article date | Study area | Language | Subjects (n) | | Gender (F/M) | |
|--------------|--------------|------------|----------|--------------|----------|--------------|----------|
| | | | | Cases | Contrast | Cases | Contrast |
| Qian B | 2011 | China | English | 581 | 603 | 434/147 | 461/142 |
| Kiyohara C | 2012 | Japan | English | 462 | 379 | 287/175 | 283/96 |
| Liang G | 2005 | China | Chinese | 227 | 227 | 168/59 | 168/59 |
| Osawa K | 2010 | Japan | English | 104 | 120 | 69/35 | 73/47 |
| Huang M | 2010 | China | Chinese | 763 | 763 | 573/208 | 573/208 |
| Guo S | 2013 | China | English | 684 | 602 | 498/186 | 400/202 |
| Xia W | 2009 | China | Chinese | 103 | 139 | 85/18 | 113/26 |
| Zhang Z | 2008 | China | Chinese | 291 | 273 | 195/96 | 176/97 |

Table 2

Distribution of genotype frequency.

| Author | Case group | | | | Control group | | | | χ^2 Value | P Value |
|------------|------------|---------|---------|------|---------------|---------|---------|------|----------------|---------|
| | Thr/Thr | Thr/Met | Met/Met | RF | Thr/Thr | Thr/Met | Met/Met | RF | | |
| Qian B | 521 | 60 | 0 | 0.05 | 533 | 67 | 3 | 0.06 | 3.11 | 0.21 |
| Kiyohara C | 352 | 97 | 13 | 0.13 | 295 | 77 | 7 | 0.12 | 0.94 | 0.63 |
| Liang G | 207 | 20 | 0 | 0.04 | 200 | 27 | 0 | 0.06 | 1.16 | 0.28 |
| Osawa K | 92 | 12 | 0 | 0.06 | 98 | 22 | 0 | 0.09 | 2.00 | 0.16 |
| Huang M | 688 | 71 | 4 | 0.05 | 685 | 75 | 3 | 0.05 | 0.26 | 0.88 |
| Guo S | 589 | 93 | 2 | 0.07 | 549 | 52 | 1 | 0.04 | 8.14 | 0.02 |
| Xia W | 91 | 12 | 0 | 0.06 | 118 | 21 | 0 | 0.08 | 0.60 | 0.44 |
| Zhang Z | 259 | 30 | 2 | 0.06 | 244 | 28 | 1 | 0.05 | 0.27 | 0.87 |

RF: risk allele frequency,

adopted (Figure 3). The figure 3 showed the parameters in Begg's test such as the adjusted kendall value, statistics Z value, P value, adjusted statistics Z value and P value and so on. Adjusted statistics z value was 1.11 and its responsive P value was $0.266 > 0.10$, indicating the results were not statistically significant and there was no publication bias in the 8 studies. In the Egger's test of the same stage, the P value was $0.980 > 0.10$, which was similar to the results of Begg's test, indicating here was no publication bias in the 8 studies.

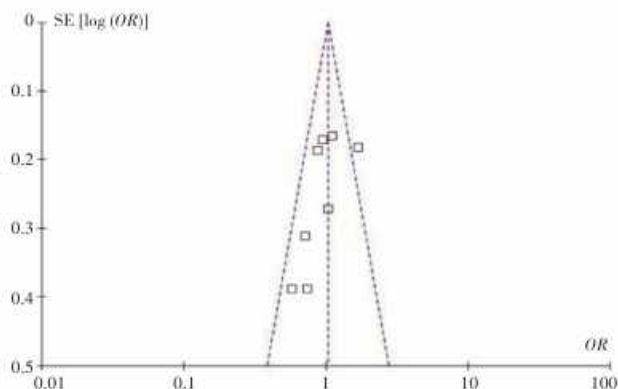


Figure 2. Funnel chart of the analysis of the relation between XRCC3 Thr241Met polymorphism of populations in East Asia and lung cancer.

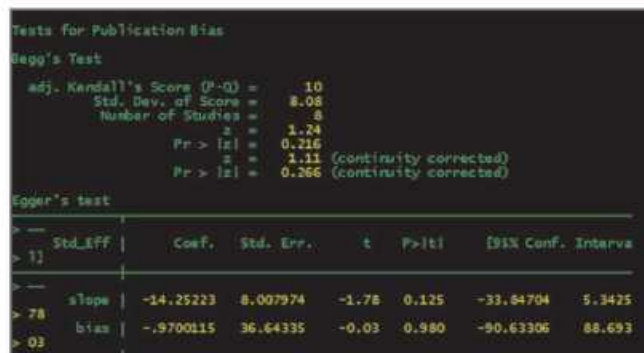


Figure 3. Publication bias results detected by Begg's test and Egger's test.

4. Discussion

Lung cancer is usually caused by the joint actions of multiple factors. The study argued that XRCC3 Thr241Met polymorphism can affect the expression of XRCC3 proteins and consequently influence the restoration function of DNA[20]. Then it becomes an important factor of lung cancer susceptibility. So far, there have been many reports about the relation between XRCC3 Thr241Met polymorphism and the occurrence of lung cancer[16,17]. In our study, there were 8 case-control studies in total. Through exact screening, there were 6 reports about Chinese and 2 reports about Japanese. Reports about the relation between gene polymorphism

and the occurrence of lung cancer of populations in Korean Peninsula have not been found. In the 8 case-control studies, there were 3 215 cases with lung cancer and 3 106 control cases (cases without cancer). Only the study of Guo et al[11] showed there was remarkable difference between the genotype distribution frequency in case group and that in control group ($P < 0.05$) while the other 7 studies showed there was no remarkable difference ($P > 0.05$). Meta analysis results argued that XRCC3 Thr241Met polymorphism was not related to the lung cancer susceptibility of populations in East Asia.

However, the study of Guo et al[11] reported that the XRCC3 Thr241Met polymorphism can help XRCC1 Arg399Gln polymorphism to influence the occurrence of lung cancer of populations in Northeast China. The study of Zhang et al showed that XRCC3 Thr241Met polymorphism may have an effect on lung cancer susceptibility and may have positive relation to smoking. The reasons showed that the experimental design involved in the synergistic action of other factors (such as other gene polymorphism or smoking) and XRCC3 Thr241Met polymorphism and consequently caused the results which were different from others'. Given the similarity of races in East Asia, our study made a comprehensive analysis of the related case-control studies in the area and was the first to prove that rs861539 polymorphism was not related to the lung cancer susceptibility of populations in East Asia by using the method of meta analysis. However, in West countries, researchers usually got an opposite conclusion. For example, the subjects of the study of Improta et al[18] were populations in Southern Italy. Their study argued that there was significant difference between the distribution of allele at the site of populations with cancer and that of those without cancer. Besides, the polymorphism at the site was related to the occurrence of colorectal cancer and lung cancer and 241Met allele gene can increase the risk of the cancer. XRCC3 protein can promote the uncoiling mediated by Rad51 and single-strand exchange. It can also repair DNA double-strand break to sustain the stability of genome. The polymorphism of this gene may weaken the ability to repair damaged DNA[19,20]. It cannot be denied that the difference of studied races was the primary reason of the inconformity with other studies. Besides, different exposed factors can cause the damage of DNA and consequently the change in lung cancer susceptibility of individuals or races cannot be neglected[21,22].

Though our study made a systemic discussion about the relation between the polymorphism of XRCC3 241 codon and lung cancer susceptibility in China and Japan, the

included region was not popular enough (currently there has not been related reports in Korea or North Korea). So the study of relation between rs861539 polymorphism and lung cancer susceptibility of populations in East Asia needs further case-control studies with broader range of research area to further prove the reliability of the results. To sum up, rs861539 polymorphism may not be related to lung cancer susceptibility and 241Met allele cannot increase the risk of lung cancer in the area.

Conflict of interest statement

We declare that we have no conflict of interest.

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