Effect of HLA-B-associated Transcript 3 Polymorphisms on Lung Cancer Risk: A Meta-Analysis

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Background: The association between the HLA-B-associated transcript 3 polymorphisms and lung cancer risk is a subject of debate. We conducted a meta-analysis to evaluate the association between these polymorphisms and lung cancer susceptibility.

Material/Methods: A systematic search of electronic databases (PubMed, EMBASE, Wanfang, and China National Knowledge Infrastructure) was performed. Data were extracted and pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: Ten case-control studies with 37,945 and 56,807 controls were included in this meta-analysis. Overall, a significant association between rs1052486 polymorphism and lung cancer susceptibility was observed (OR=1.07, 95% CI 1.01–1.12, P=0.01). In addition, a significant association was found for rs3117582 polymorphism (OR=1.29, 95% CI 1.22–1.37, P<0.01).

Conclusions: This meta-analysis suggested that HLA-B-associated transcript 3 polymorphisms are risk factors for lung cancer.

MeSH Keywords: Lung Neoplasms • Meta-Analysis • Polymorphism, Genetic

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META-ANALYSIS

Background

Lung cancer is the most common cancer in the world and represents a major public health problem, accounting for ~1.2 million cancer-related deaths worldwide each year. Although >80% of the population-attributable risk of lung cancer can be ascribed to tobacco smoking, several lines of evidence indicate that inherited genetic factors influence the development and progression of lung cancer.

HLA-B-associated transcript 3 is a member of the Bcl-2-associated anthanogene (BAG) family of proteins. HLA-B-associated transcript 3 was first discovered as a member of a group of genes located within the Class III region of the human major histocompatibility complex on chromosome 6, and has been extensively studied for its role in regulating apoptosis under various stress conditions such as DNA damage and endoplasmic reticulum-related stress [1,2]. Several studies have investigated the association between HLA-B-associated transcript 3 polymorphisms and lung cancer risk. However, the results were inconclusive [3–12]. Meta-analysis is a useful method for investigating associations between genetic factors and diseases, because a quantitative approach is used to combine the results from different studies on the same topic, thereby providing more reliable conclusions. Thus, we performed a meta-analysis to assess the association of HLA-B-associated transcript 3 polymorphisms with lung cancer. To our knowledge, this is the first meta-analysis of the association between HLA-B-associated transcript 3 polymorphisms and the risk of lung cancer.

Material and Methods

Publication search

In this meta-analysis, we searched the articles using the search terms “HLA-B-associated transcript 3”, “lung cancer” and “polymorphism” in the PubMed, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases, and the last search was updated March 2014. Additional studies were identified by a hand search of references of original studies or review articles on the association between HLA-B-associated transcript 3 polymorphisms and lung cancer. No publication date or language restrictions were imposed.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) evaluation of the HLA-B-associated transcript 3 polymorphisms and lung cancer risk, (2) using a case-control design, and (3) genotype distributions in both cases and controls should be available for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies were excluded if any of the following existed: (1) not relevant to lung cancer or HLA-B-associated transcript 3 polymorphisms, (2) not designed as case-control studies, (3) genotype frequencies or number not included, (4) animal studies, and (5) editorials, reviews, and abstracts. If more than 1 study used the same cases, the study with the most comprehensive population was included.

Data extraction

The following data were collected from each study: first author’s surname, year of publication, ethnicity, histology of cancer, smoking status, and sample size.

Statistical analysis

The strength of the associations between the HLA-B-associated transcript 3 polymorphisms and lung cancer risk was measured by ORs and 95% CIs. The random-effects model was used. The statistical significance of summary OR was determined with the Z test. The Q statistic and the I2 statistic were used to assess the degree of heterogeneity among the studies included in the meta-analysis. Subgroup analyses were carried out by ethnicity, history, and smoking. Sensitivity analysis was performed through sequentially excluding individual studies to assess the stability of the results. The potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry was tested using Egger’s test [13]. All statistical tests were performed using STATA 11.0 software (Stata Corporation, College Station, TX, USA). A P value <0.05 was considered statistically significant.

Results

Study characteristics

A total of 10 case-control studies with 37 945 and 56 807 controls on the association between HLA-B-associated transcript 3 polymorphisms and lung cancer risk were included in this meta-analysis [3–12]. There were 6 studies of rs1052486 and 5 studies of rs3117582. The characteristics of each case-control study are listed in Table 1.

Overall and subgroup meta-analysis results

rs1052486

The association between HLA-B associated transcript 3 rs1052486 polymorphism and lung cancer risk was investigated in 6 case-control studies with a total of 14 557 cases and 17 183 controls. The result suggested that this...
polymorphism was associated with lung cancer risk (OR=1.07, 95% CI 1.01–1.12, P=0.01). In the subgroup analysis by ethnicity, a significant association was found among whites (OR=1.07, 95% CI 1.01–1.12, P=0.02), but not among Asians (OR=1.15, 95% CI 0.97–1.38, P=0.11). The sensitivity analysis did not influence the result excessively by omitting any single study (data not shown). Funnel plot and Egger’s test were both performed to access the publication bias of this meta-analysis. The shape of the funnel plot appeared symmetrical (data not shown). Egger’s test showed no evidence of publication bias (P=0.48) (Figure 1).

rs3117582

The association between HLA-B associated transcript 3 rs3117582 polymorphism and lung cancer risk was investigated in 5 case-control studies with a total of 27 829 cases and 44 718 controls. The result suggested that this polymorphism was associated with lung cancer risk (OR=1.29, 95% CI 1.22–1.37, P<0.01). In the subgroup analysis by ethnicity, a significant association was found among whites (OR=1.29, 95% CI 1.22–1.37, P<0.01). Subgroup analysis was also performed by the type of lung cancer. The significant association was observed among squamous carcinoma patients (OR=1.30, 95% CI 1.11–1.52, P<0.01). In the subgroup analysis according to smoking status, increased lung cancer risk was found among smokers (OR=1.24, 95% CI 1.06–1.47, P<0.01). A summary of results is listed in Table 2. Statistically similar results were obtained after sequentially excluding each study (data not shown). The shape of the funnel plot was symmetrical (data not shown). Egger’s test did not find evidence of publication bias (P=0.34) (Figure 2).
Discussion

The main finding of this meta-analysis was that rs1052486 and rs3117582 polymorphisms were potential risk factors for developing lung cancer. In the subgroup analysis of rs1052486 by ethnicity, a significant association was found in whites. However, no study with Asians was included in this meta-analysis. Thus, more studies with Asians should be conducted to determine the association between rs1052486 polymorphism and lung cancer. In the subgroup analysis of rs3117582 by ethnicity, no significant association was found in Asians, but lung cancer risk was increased in whites. It is possible that different lifestyles, diets, and environments may account for this apparent discrepancy. These issues should be investigated in future studies. In the subgroup analysis by histology, we observed that there was a significant association between this polymorphism and squamous carcinoma risk, suggesting that rs3117582 polymorphism might influence the etiology of squamous carcinoma. In the subgroup analysis stratified by smoking, rs3117582 polymorphism was associated with increased lung cancer risk in smokers. Wang et al. [7] suggested that this polymorphism plays no role in the development of lung cancer. This result indicated that even the same variant in the same gene may have a different effect on the pathogenesis of lung cancer in different individuals.

**Table 2. Detailed results of meta-analysis.**

|                   | Association | Heterogeneity |
|-------------------|-------------|---------------|
|                   | OR (95% CI) | P Value | P Value | I² (%) |
| rs1052486         |             |         |         |       |
| Overall           | 1.07 (1.02–1.12) | 0.01    | 0.04    | 57.0   |
| Caucasian         | 1.07 (1.01–1.12) | 0.02    | 0.04    | 61.0   |
| Asian             | 1.15 (0.97–1.38) | 0.11    | 0.85    | 0.0    |
| rs3117582         |             |         |         |       |
| Overall           | 1.29 (1.22–1.37) | <0.01   | 0.16    | 39.0   |
| Caucasian         | 1.29 (1.22–1.37) | <0.01   | 0.16    | 39.0   |
| Adenocarcinoma    | 1.01 (0.82–1.24) | 0.93    | 1.00    | 0.0    |
| Squamous carcinoma| 1.30 (1.11–1.52) | <0.01   | 0.91    | 0.0    |
| Small cell lung cancer | 1.05 (0.92–1.20) | 0.49    | 0.65    | 0.0    |
| Smoker            | 1.24 (1.06–1.47) | <0.01   | 0.17    | 47.0   |

**Figure 2. Meta-analysis of the association between HLA-B-associated transcript 3 rs3117582 polymorphism and lung cancer risk.**
associated with lung cancer. Tsukahara et al. suggested that HLA-B-associated transcript 3 regulated apoptotic cell death induced by papillomavirus-binding factor in human osteosarcoma [17]. However, the role of polymorphisms in the HLA-B-associated transcript 3 gene in the development of lung cancer is still uncertain and the exact mechanism should be elucidated.

Some limitations should be acknowledged. First, only published studies that were included in the selected electronic databases were identified. It is possible that some relevant published or unpublished studies may have been missed. Second, the effects of gene-gene and gene-environment interactions were not addressed in this meta-analysis, because of limited available data. Third, our meta-analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs.

Conclusions

This meta-analysis found significant associations between HLA-B-associated transcript 3 polymorphisms and lung cancer risk. Further studies in more ethnic groups are warranted to validate these results.

Conflicts of interest

None.

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