RESEARCH COMMUNICATION

Quantitative Assessment of the Effects of MMP-2 Polymorphisms on Lung Carcinoma Risk

Xiao-Tong Guo[1&], Jun-Feng Wang[2&], Lin-You Zhang[1*], Guang-Quan Xu[1]

Abstract

Background: Previous studies assessing associations between matrix metalloproteinase 2 (MMP-2) polymorphisms and lung cancer risk reported conflicting results. A meta-analysis was therefore performed to derive a more precise estimation. Method: Case-control studies assessing associations between MMP-2 C735T and C1306T polymorphisms and lung cancer risk were included. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated. Results: 7 studies with a total of 3,189 lung cancer cases and 3,013 controls were finally included into this meta-analysis. Overall, the MMP-2 C735T polymorphism was associated with lung cancer risk under the homozygote model (CC versus TT: OR =1.44, 95% CI = 1.03-2.02, I^2 = 0%), while the MMP-2 C1306T polymorphism also associated demonstrated links with all four models (all P values less than 0.05). Subgroup analyses by race suggested obvious associations between MMP-2 C735T and C1306T polymorphisms and lung cancer risk in Asians but not in Caucasians. There was no evidence for publication bias. Conclusion: Currently available evidence supports teh conclusion that MMP-2 C735T and C1306T polymorphisms influence susceptibility to lung cancer in Asians.

Keywords: MMP-2 - polymorphisms - lung carcinoma - meta-analysis - risk - Asians - Caucasians

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Introduction

Lung cancer is the most frequently occurring cancer and the leading cause of death from cancer worldly (Jemal et al., 2011). Among the lifestyle related causes of lung cancer, smoking is the primary risk factor for lung cancer, but lung cancer develops in less than 20% of people who smoke throughout their life, which suggests that other factors including genetic susceptibility also contribute to lung carcinogenesis (Herbst et al., 2008; Xiao et al., 2011). Examination of genetic polymorphisms may explain individual differences in cancer risk and explore the mechanism of lung carcinogenesis (Brennan et al., 2011). Matrix metalloproteinases (MMPs) are a large family of zincdependent neutral endopeptidases that play an important role in the degradation of all matrix components crucial for malignant tumor growth, invasion and metastasis (Bauvois, 2012). MMPs can promote cancer progression by increasing cancer-cell growth,migration, invasion, metastasis and angiogenesis, and their expression is often associated with poor survival (Cao et al., 2011; Im et al., 2012). MMP-2 is considered to play a critical role in metastasis, and the synthesis and secretion of MMP-2 can be stimulated by a variety of stimuli, including cytokines, during various pathological processes such as tumor invasion, atherosclerosis, and inflammation (Cao et al., 2011; Hahn et al., 2012). MMP-2 C735T and C1306T are two common polymorphisms in the MMP-2 gene, have allele-specific effects on the transcriptional activities of MMP gene promoters (Decock et al., 2008; Chetty et al., 2011). A number of studies have been performed to assess the associations between MMP-2 C735T and C1306T polymorphisms and lung cancer risk. However, previous studies assessing the associations between MMP-2 C735T and C1306T polymorphisms and lung cancer risk reported conflicting results. Thus, we performed a meta-analysis to derive a more precise estimation of the associations above.

Materials and Methods

Search strategy

We conducted a comprehensive search in the Pubmed, Web of Science and Chinese Biomedical Database (CBM) databases from their inception through March 22, 2012. We combined search terms for MMP-2 C735T and C1306T polymorphisms and lung cancer. Search terms included: (Matrix metalloproteinases 2, MMP-2, C735T, or C1306T) and (lung carcinoma, lung cancer, or lung tumor) and (polymorphism, polymorphisms, mutation, or genotype). There was no language limitation. All references cited in those included studies were also reviewed to identify additional published articles not indexed in the common database.

*[1]Department of Thoracic Surgery, the 2nd Affiliated Hospital of Harbin Medical University, [2]Department of Thoracic Surgery, the 3rd Affiliated Hospital of Harbin Medical University, Harbin, China [&]Equal contributors *For correspondence: zhanglyhh1956@sina.com*

Study eligibility

Eligibility criteria included the following: 1) Case–control design with the genotyping of individuals with and without lung cancer; 2) identification of lung cancer was confirmed pathologically; 3) sufficient reported genotypic frequencies in both cases and controls for estimating an odds ratio (OR) with a 95% confidence interval (95%CI). In studies with overlapping cases or controls, the most recent and/or the largest study with extractable data was included in the meta-analysis. Studies investigating progression, severity, phenotype modification, response to treatment, or survival were excluded from this meta-analysis.

Data extraction

Two investigators independently extracted data, and disagreements were resolved through consensus. Standardized abstraction sheets were employed for recording of data from individual studies. Data retrieved from the articles included the following: author, year of publication, study design, study population, ethnicity of the study population, racial decent of the study population (categorized as Caucasians, Asians and others), genotyping method, and genotype distributions of cases and controls for MMP-2 C735T and C1306T polymorphisms.

Quality assessment

Quality assessment for case-control studies in this meta-analysis was assessed using the Newcastle Ottawa scale (NOS) as recommended by the Cochrane Non-Randomized Studies Methods Working Group (Wells et al., 2000). This instrument was developed to assess the quality of nonrandomized studies, specifically cohort and case-control studies. Based on the NOS cohort studies were judged based on three broad perspectives: selection of study groups (1 criteria), comparability of study groups (4 criteria), and ascertainment of outcome of interest (3 criteria). Given the variability in quality of observational studies found on our initial literature search, we considered studies that met 5 or more of the NOS criteria as high quality.

Statistical analysis

We calculated the pooled OR with its corresponding 95%CI to assess the association between MMP-2 C735T and C1306T polymorphisms and lung cancer. We performed a meta-analysis to investigate the association between MMP-2 C735T and C1306T polymorphisms and lung cancer for the allele contrast (C versus T), homozygote (CC versus TT), recessive (CC versus CT and TT), and dominant (CC and CT versus TT) models. In our study, two models of meta-analysis for dichotomous outcomes were conducted: the random-effects model and the fixed-effects model. The random-effects model was conducted using the DerSimonian and Laird's method (DerSimonian and Laird, 1986). The fixed-effects model was conducted using the Mantel-Haenszel's method (Mantel and Haenszel, 1959). The I2 statistic to quantify the proportion of the total variation due to heterogeneity was calculated to assess the between-study heterogeneity (Higgins et al., 2003). If heterogeneity existed, the random-effects model was used to pool the results; otherwise, the fixed-effects model was used to pool the results. For additional analyses, the cases and controls were sub-grouped on the basis of their ethnicity. Racial descent was categorized into Caucasians, Asians and others according to ethnicity classifications for genetic studies. Publication bias was assessed by visual inspection of the funnel plots, in which the standard error of logor of each study was plotted against its logor, and an asymmetric plot suggested possible publication bias. All analyses were performed using Review Manager Version 5.1. A P value < 0.05 was considered statistically significant, except where otherwise specified.

Results

Study characteristics

With our search criterion, 26 abstracts were found. After discarding those which clearly did not meet the criteria and excluding 19 records, 7 full-text publications with a total of 3,189 lung cancer cases and 3,013 controls were included into this meta-analysis (Yu et al., 2002; Zhou et al., 2005; Rollin et al., 2007; Song et al., 2007; Jia, 2009; Aysegul et al., 2011; Gonzalez-Arriaga et al., 2012). Ethnic groups among these studies were as following: 3 from Caucasians and 4 from Asians. There were 4 studies with a total of 2,045 cases and 1913 controls on MMP-2 C735T polymorphism (Zhou et al., 2005; Rollin et al., 2007; Jia, 2009; Gonzalez-Arriaga et al., 2012), and there were 5 studies with a total of 2,004 cases and 1967 controls on MMP-2 C1306T polymorphism (Yu et al., 2002; Zhou et al., 2005; Rollin et al., 2007; Song et al., 2007; Aysegul et al., 2011). The number of cases varied from 89 to 816, with a mean of 456, and the numbers of controls varied from 90 to 852, with a mean of 430.

Meta-analysis results

The outcome for the association between MMP-2 C735T polymorphism lung cancer risk was showed in the Table 1. Overall, MMP-2 C735T polymorphism was associated with lung cancer risk under the homozygote model (CC versus TT: OR =1.44, 95% CI = 1.03-2.02, I^2 = 0%). Subgroup analyses by race suggested there were an obvious association between MMP2 C735T

Table 1. Meta-analysis of the Association Between MMP-2 C735T Polymorphism and Lung Cancer Risk

Contrast models	OR (95%CI)	P	I^2 (%)	Pooled model
Total population				
C versus T	1.16(0.93-1.44)	0.19	65%	Random effects
CC versus TT	1.44(1.03-2.02)	0.03	0%	Fixed effects
CC versus CT/TT	1.17(0.83-1.64)	0.34	80%	Random effects
CC/CT versus TT	1.33(0.96-1.85)	0.1	0%	Fixed effects
Caucasians				
C versus T	0.96(0.78-1.17)	0.66	0%	Fixed effects
CC versus TT	1.72(0.89-3.31)	0.1	0%	Fixed effects
CC versus CT/TT	0.88(0.70-1.10)	0.26	0%	Fixed effects
CC/CT versus TT	1.80(0.94-3.46)	0.08	0%	Fixed effects
Asians				
C versus T	1.32(1.15-1.52)	<0.001	31%	Fixed effects
CC versus TT	1.36(0.91-2.01)	0.13	0%	Fixed effects
CC versus CT/TT	1.39(1.03-1.87)	0.03	64%	Random effects
CC/CT versus TT	1.19(0.81-1.75)	0.39	0%	Fixed effects

Table 2. Meta-analysis of the Association Between MMP-2 C1306T Polymorphism and Lung Cancer Risk

Contrast models	OR (95%CI)	P	I^2 (%)	Pooled model
Total population				
C versus T	1.51(1.13-2.02)	0.005	74%	Random effects
CC versus TT	1.88(1.17-3.02)	0.009	0%	Fixed effects
CC versus CT/TT	1.60(1.14-2.24)	0.006	75%	Random effects
CC/CT versus TT	1.63(1.01-2.62)	0.04	0%	Fixed effects
Caucasians				
C versus T	0.94(0.67-1.31)	0.71	0%	Fixed effects
CC versus TT	1.03(0.29-3.70)	0.96	0%	Fixed effects
CC versus CT/TT	0.91(0.62-1.35)	0.65	0%	Fixed effects
CC/CT versus TT	1.07(0.30-3.82)	0.91	0%	Fixed effects
Asians				
C versus T	1.93(1.52-2.23)	<0.001	0%	Fixed effects
CC versus TT	2.07(1.24-3.47)	0.006	0%	Fixed effects
CC versus CT/TT	2.14(1.82-2.51)	<0.001	0%	Random effects
CC/CT versus TT	1.74(1.04-2.91)	0.03	0%	Fixed effects

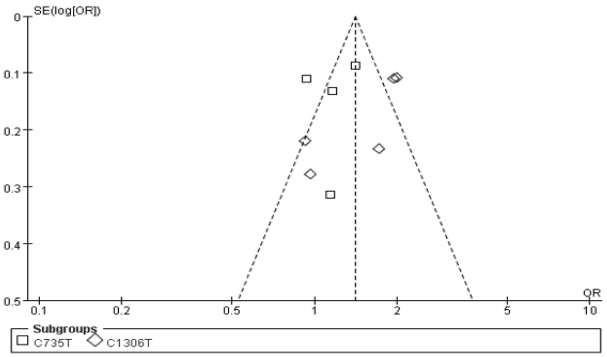

Figure 1. Funnel Plot for Assessing the Publication Bias Risk in This Meta-analysis (Allele Contrast Model C Versus T)

polymorphism and lung cancer risk in Asians (C versus T: OR =1.32, 95% CI = 1.15-1.52, I^2 = 31%; CC versus CT/TT: OR =1.39, 95% CI = 1.03-1.87, I^2 = 64%), but there was no association in Caucasians (Table 2).

The outcome for the association between MMP-2 C1306T polymorphism risk of lung cancer was showed in the Table 2. Overall, MMP-2 C1306T polymorphism was associated with lung cancer risk under all four models (All P values were less than 0.05). Subgroup analyses by race suggested there were an obvious association between MMP-2 C1306T polymorphism and lung cancer risk in Asians (All P values were less than 0.05), but there was no association in Caucasians (All P values were more than 0.05) (Table 2).

Publication bias

Funnel plot was used to assess the publication bias in this meta-analysis. Funnel plots' shape of all contrasts did not reveal obvious evidence of asymmetry, suggesting that publication bias was not evident in this meta-analysis (Figure 1).

Discussion

Many studies have investigated the role of MMP-2 polymorphisms in lung cancer risk, but have yielded inconsistent and inconclusive results (Yu et al., 2002; Zhou et al., 2005; Rollin et al., 2007; Song et al., 2007; Aysegul et al., 2011; Gonzalez-Arriaga et al., 2012). Meta-analysis is a quantitative approach in which individual study findings on the same topic are statistically integrated and analyzed, and recently, it has been used for the evaluation of cancer prognostic markers and genetic risk factors. Thus, derive a more precise estimation of the associations above, we performed this meta-analysis by including relevant studies. 7 studies with a total of 3189 lung cancer cases and 3013 controls were finally included into this meta-analysis. Overall, MMP-2 C735T polymorphism was associated with lung cancer risk under the homozygote model (CC versus TT: OR =1.44, 95% CI = 1.03-2.02, I^2 = 0%), while MMP-2 C1306T polymorphism was associated with lung cancer risk under all four models (All P values were less than 0.05). Subgroup analyses by race suggested there were obvious associations between MMP-2 C735T and C1306T polymorphisms and lung cancer risk in Asians but not in Caucasians. Thus, MMP-2 C735T and C1306T polymorphisms are susceptibility gene for lung cancer in Asians.

MMPs can regulate the tumor microenvironment, and their expression and activation is increased in almost all human cancers compared with normal tissue (Chetty et al., 2011; Wang et al., 2011). MMP-2 is over-expressed in various human cancer tissues and involves in tumor initiation, invasion, and metastasis (Egeblad and Werb, 2002). Previous studies suggest individuals with CC genotype of both MMP-2 C735T and C1306T polymorphisms have higher promoter activity and higher MMP-2 enzyme activity compared with those with the TT genotype, and thus may have obviously higher risk of lung cancer (Nelson et al., 2000; Price et al., 2001). Thus, there is biochemical evidence for the associations between MMP-2 polymorphisms and lung cancer risk.

The heterogeneity is a very important part of meta-analysis and finding the possible sources for the high heterogeneity is very important and can greatly affect the results of a meta-analysis (Ioannidis et al., 2007). There was high heterogeneity in some contrast models of this meta-analysis. Subgroup analyses by ethnicity showed the heterogeneity decreased obviously in the subgroup analyses of Asians or Caucasians, which suggested ethnicity was the major source of the heterogeneity in our meta-analysis. This heterogeneity may be explained by the race-specific effect of MMP-2 C735T and C1306T polymorphisms on the susceptibility to lung cancer.

Our analysis had several limitations that must be considered when interpreting the finding. Firstly, our main analysis was based on unadjusted estimates owing to the lack of adjusted estimates. However, a more precise analysis could be performed if adjusted estimates were available in all studies (Peters and Mengersen, 2008). Second, as no prospective studies have addressed our question, all included studies followed a retrospective case-control design. Thus, the possible increased reporting bias associated with case-control studies could not be eliminated in this meta-analysis, and this aspect should be one of the limitations of our meta-analysis. Future prospective studies can investigate whether routine screening for the presence of the MMP-2 C735T and C1306T polymorphisms can predicate the development of lung cancer. Finally, the association between MMP-2

C735T and C1306T polymorphisms and lung cancer may be affected by the different histological types of lung cancer. However, little data on this aspect was reported in those studies, and we were unable to make subgroup analyses by the different histological types of lung cancer. Further studies with large sample size are needed to identify this association in different histological types of lung cancer.

In conclusion, our study supports that MMP-2 C735T and C1306T polymorphisms are susceptibility gene for lung cancer in Asians. Besides, more studies with large sample need performing to further assess the associations between MMP-2 polymorphisms and lung cancer risk in Caucasians.

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The author(s) declare that they have no competing interests.

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