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Meta Analysis

The Association Between Matrix Metalloproteinases-9–1562 C/T Polymorphism and Lung Cancer Susceptibility: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Matrix metalloproteinases (MMPs) are a family of zinc dependent proteinase. Several studies have reported the association between the single nucleotide polymorphisms(C/T) -1562 in the MMP-9 promoter and the risk of cancer. In this study we decided to carry out a comprehensive meta-analysis to obtain a reasonable result about the association between this polymorphism and the risk of lung cancer.

Materials and Methods: A complete literature review was conducted within the databases of ISI Web of Knowledge, google scholar and PubMed for studies on lung cancer published from 2002 to 2018. A meta-analysis was conducted which included more than 3000 case and control subjects. The pooled odds ratio (OR) and 95% confidence intervals (CI) were used for dominant, recessive and co-dominant MMP-9 genotypes to assess the strength of the association.

Results: Analysis indicated no significant association between MMP-9-1562C/T polymorphism and the risk of lung cancer, dominant model; [CT+TT/CC]: OR=0.972, 95% CI=0.811–1.164, recessive model [CC+CT/TT] OR= 1.027, 95% CI=0.651–1.618 and co-dominant model [TT/CC] OR=0.983, 95% CI=0.550–1.755.

Conclusions: No association was observed between the MMP9-1562 C/T polymorphism and the incidence of lung cancer. Meta-analysis demonstrated that this polymorphism can't serve as a diagnostic marker for lung cancer.

Keywords: MMP-9, Lung Cancer, Polymorphism

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Introduction

Lung cancer is the most common malignancy and has been the most common cause of deaths from cancer in the past few decades.[1] A total of 1.8 million new cases were estimated in 2012 which includes 12.9% of all newly diagnosed cancers. The patient's five-year survival rate is much lower than that of other cancers (17.8%).[2,3] The most important risk factors of lung cancer include tobacco smoking and aging. In addition to the mentioned factors, genetic background plays an important role in the development of this disease.[4] Matrix metalloproteases (MMPs) are a large family of zinc dependent proteinases consisting of more than 26 members; they act based on digestion of extracellular matrix (ECM) and basement membrane components. Since the ECM acts as an anchorage for stabilization of cells, increased MMPs level are required for invasion and migration of cancer cells.[5,6] The MMPs also act on cleavage of cell adhesion molecules such as growth factors, cell surface receptors, chemokines/cytokines and they may regulate angiogenesis in cancer process through the activation of proangiogenic factors.[7-9] The MMP-9 (type IV collagenase) is one of the most important members of the metalloproteinase family which plays a role in degrading of both basement membrane components and collagen attachments around the cells. A cytosine (C) to thymine (T) base substitution at position -1562 in the upstream of the MMP-9 transcription initiation site (MMP-9–1562C/T) causes MMP-9 over expression.[10]

Several studies have reported that CT and TT genotypes of MMP-9–1562C/T polymorphisms are associated with the occurrence and progression of some cancers, including colon, breast and lung cancer.[11-13] In previous studies, a significant association was found between the T allele and occurrence of breast cancer in the Iranian population. It was also found that T allele increases the plasma MMP-9 levels in breast cancer patients.[14,15] On the other hand, there are reports about the association between the presence of MMP-9 promoter T allele and lower risk of lung cancer in the Spanish,[16] Turkish[17] and French populations.[18] Another study published by Chinese researchers did not suggest a relevant association between MMP-9–1562 C/T polymorphism and lung cancer.[19]

A research on the Iranian population reports an association between the MMP-9–1562 C/T polymorphism T allele and lung cancer.[20] Therefore, considering the controversial results regarding the association between –1562 C/T polymorphism and cancers and the function of mmp-9 enzyme in lung cancer, we decided to perform a complete meta-analysis on all previous reports on MMP-9 -1562 C/T polymorphism and lung cancer.

Materials and Methods

Data Sources and Keywords

The electronic databases of PubMed, Embase, EBSCO and Google Scholar were systematically searched to retrieve articles which had studied the correlation between MMP-9 and lung cancer until august 2018. The search strategy used a combination of key words including: matrix metalloproteinase 9, MMP-9, collagenase IV or gelatinase IV and lung cancer and genetic polymorphism or single nucleotide polymorphism or SNP. In addition, references of the related articles and review articles were also screened. In all data sources, if data or data subsets were observed in more than one article, we only selected the data of studies with larger sample size.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) evaluating the association between the MMP-9 promoter polymorphism (-1562 C/T) and lung cancer; (2) reports of case-control studies (3) containing sufficient published genotypes data for the calculation of an OR with a 95% CI.[21] Investigators applied the inclusion criteria to each study by screening the title, abstract, and full text of the papers. In this process, all duplicate publications and studies with incomplete data were excluded (Figures 1 and 2).

Data Extraction

Two investigators independently evaluated all data for each included study, and the following information was collected: the first author's name, year of publication, number of case and control groups, study design, country and ethnicity of study population, methods of DNA extraction and genotyping. If the two investigators generated different results from one study, both investigators compared the results again to reach an agreement. For studies that provided no genotype data or incomplete data, like the study by Bayramoglu et al.[17] the MMP-9 genotype data were obtained through genotype calculations. The data about -1562 C/T polymorphism were divided into two subgroups including lung cancer and healthy controls.

Statistical Analysis

Meta-analysis was performed using the comprehensive meta-analysis 2.0 software (Corporation, NJ, USA). The association between promoter polymorphisms of MM-9 (-1562C/T) and susceptibility to lung cancer was evaluated using the pooled *p*-value, OR and 95% CI under the random effects model or the fixed effects model. The OR with the corresponding 95% CI was calculated for the dominant model (C/T+T/T *vs*. C/C), codominant model (C/C vs. T/T), and recessive model (C/C+C/T vs. T/T) respectively. The *P*-value less than 0.05 was considered statistically significant. Forest plots displayed the comparison of the OR and its 95% CI among all studies. According to heterogeneity results, random-effects model was used when heterogeneity was significant ($P<0.05$ or I^2 test exhibited >50%), and fixed-effect model was used to calculate the pooled OR with a 95% CI.[15,16] We considered *P* value < 0.1 as an indicator of significant heterogeneity for the random-effects model. Funnel plot was employed to ascertain potential publication bias to further confirm the result.

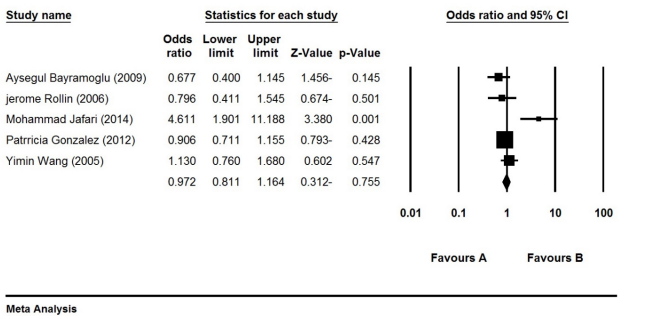

Figure 1. Meta-analysis for MMP9-1562 C/T Polymorphism and Lung Cancer Susceptibility in Dominant Model (CT+TT/CC).

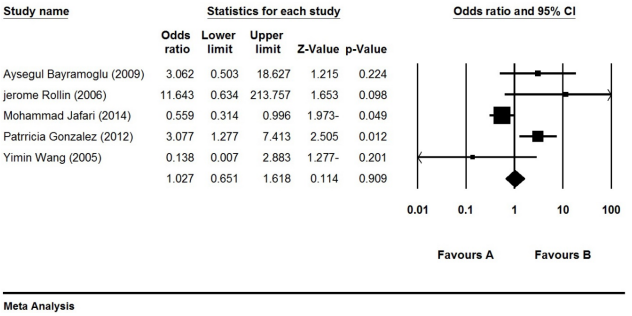

Figure 2. Meta-analysis for MMP9-1562 C/T Polymorphism and Lung Cancer Susceptibility in Recessive Genetic Model (CC+CT/TT).

Results

Characteristics of the Included Studies

Initially, 32 studies retrieved from electronic searches and manual searches in online databases which included three review article and 15 studies on other cancers as well as unrelated studies were eliminated and finally, five case-control studies published between 2005 and 2015, which included 1502 cancer patients and 1443 control subjects, were selected for the present meta-analysis. In all selected studies, the -1562 C/T polymorphism was analyzed by polymerase chain reaction with restriction fragment length polymorphism (PCR-RFLP) and direct sequencing. The characteristics of the selected studies in terms of *MMP9*-1562 C/T polymorphism and lung cancer, and the genotype frequencies distributions of the enrolled studies were consistent with Hardy-Weinberg equilibrium ($P>0.05$), except for the study of Jafari et al[20] ($P<0.05$).

The Association Between MMP-9-1562 C > T and LUNG CANCER SUSCEPTIBILITY

In this study, we first investigated the probability of T allele and increased risk of lung cancer. The results showed that there was no significant association between T allele and lung cancer. No significant association was observed in the analysis of T/T, C/T genotypes and T allele ($P > 0.05$). When the C/T genotype +T/T genotype of *MMP9*-1562 C/T polymorphism was compared with C/C genotype (dominant model), there was no significant association with the risk of lung cancer (OR=0.972, 95% CI== 0.811–1.164,). The recessive model [CC+CT vs TT] also showed no significant association (OR=1.027, 95% CI = 0.651–1.618). In addition, the MMP-9 co-dominant genotype models showed no association with lung cancer (TT/CC OR = 0.983 95% CI = 0.550–1.755) and CC/TT (OR = 1.018, 95% CI = 0.570–1.817) (Figure 3). We evaluated the possibility of publication bias using the funnel plot and Egger's test. The shape of the funnel plots suggested no evident publication bias for MMP-9 among the dominant, co-dominant and recessive genotype models. The *P* value < 0.05 was considered valid for all calculations (Figures 4 and 5).

Discussion

There are contradictory reports about the association between the MMP-9–1562 C/T polymorphisms CT and TT genotypes and occurrence or progression of lung cancer. Some studies reported an association between the MMP-9 promoter T allele and lung cancer occurrence.[16,17] We have already reported a

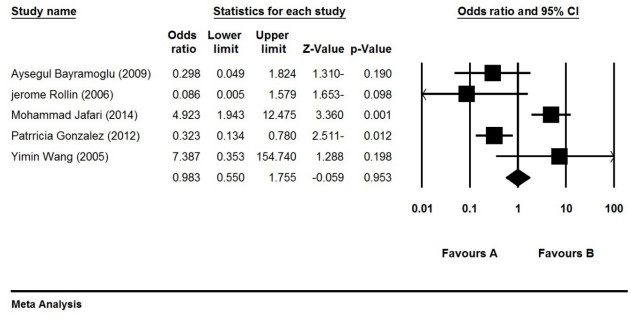

Figure 3. Meta-analysis for MMP9-1562 C/T Polymorphism and Lung Cancer Susceptibility in Co-dominant Genetic Model (TT/CC).

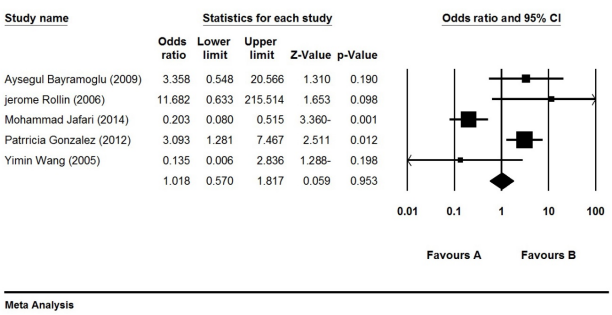

Figure 4. Meta-analysis for MMP9-1562 C/T Polymorphism and Lung Cancer Susceptibility in Co-dominant Genetic Model (CC/TT).

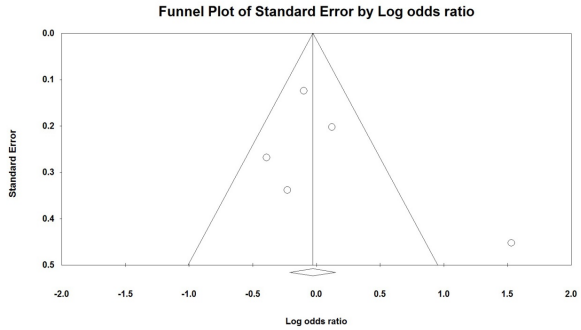

Figure 5. Funnel plots of the MMP-9 polymorphism studies: dominant model, Egger's test of the value from the funnel plot showed no statistical significance.

significant association between the MMP-9 promoter T allele and occurrence of breast cancer in the Iranian population, and we found that the MMP-9 promoter T allele increases the MMP-9 level in breast cancer patients.[14,15] Nevertheless, other studies reported no relevant association between MMP-9–1562 C/T polymorphism and lung cancer.[19] Therefore, a comprehensive meta-analysis study can help draw general conclusions about the association of this polymorphism with lung cancer.

The present meta-analysis involving more than 3000 cases and controls was performed to investigate the association between -1562 C/T polymorphism and lung cancer risk. According to our findings, the MMP-9–1562 C/T polymorphism does not increase the risk of lung cancer and this polymorphism cannot be considered as a risk factor for lung cancer. These results are in line with the results of Wang et al., which reported no association between the MMP-9–1562 C/T polymorphism and the risk of NSCLC. Furthermore, the genotype distribution between NSCLC patients with and without lymphatic metastasis was not significantly different.[19] In a meta-analysis based on 12 studies, Zhu et al reported no association between the MMP-9 -1562 C/T polymorphism and ovarian cancer risk.[22] In a recent meta-analysis, Meng et al. reported no association between the MMP-9 -1562 C/T polymorphism and the risk of urinary cancer.[23] These findings are in line with our findings regarding long cancer. A meta-analysis[22] based on nine published case–control studies including 2597 cases and 2618 controls, reported that MMP2-1306 C/T polymorphism may contribute to breast cancer susceptibility, but no significant association was found between any genotype of MMP9-1562 C/T and breast cancer. Another meta-analysis[23] based on 12 published case–control studies reported no association between MMP9-1562 C/T polymorphisms and the risk of colorectal cancer. In a meta-analysis based on 17 case- control studies, Hu et al. reported that MMP-9 -1562 polymorphism TT genotype decreases the risk of lung cancer.[24] In another meta-analysis based on nine case-control studies Peng et al. reported an association between the presence of MMP-9 -1562 polymorphism T allele and the occurrence of gastric cancer.[25]

Conclusions

In the present study, no association was found between the

MMP-9 -1562 polymorphism T or C alleles and the risk of lung cancer. There were some limitations in the present study, including the limited number of studies on this polymorphism, and also the fact that about half of the collected studies were excluded due to the lack of standard or incomplete results. Also, some studies have been performed on different populations, therefore a comprehensive meta-analysis with a larger sample size is recommended to confirm the findings of this study. Nevertheless, the results of this study are the results of the total published data up to this point which can be considered as a general conclusion. According to the results of this study, -1562 C/T polymorphism in the MMP-9 promoter region is not associated with the susceptibility of lung cancer and this polymorphism cannot serve as a diagnostic marker for lung cancer.

Authors' Contributions

FZ and MS contributed equally to this study.

Conflict of Interest Disclosures

The authors have declared no conflicts of interest.

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