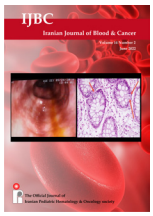
IJBC 2022; 14(2): 61-67

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir



Meta-analysis

Association between two functional polymorphisms in the MMP-2 promoter and lung cancer incidence in Asian population: a meta-analysis study

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ARTICLE INFO

Article History:
Received: 7/11/2021
Accepted: 4/6/2022

Keywords:
Matrix metalloproteinase-2
Lung cancer
Asian
Polymorphism

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Abstract

Background: Numerous experiments have been performed to determine the relationship between the Matrix metalloproteinase-2 (MMP-2) -1306C/T and -735C/T polymorphisms and the prevalence and progression of lung cancer in diverse populations. However, due to the small sample size and the different results of previous studies, we decided to perform a general meta-analysis on all previous studies about mmp-2 polymorphism and lung cancer in Asian population.

Methods: A complete literature review was conducted within the ISI Web of Knowledge, google scholar, and PubMed databases for studies about MMP-2 polymorphism and lung cancer published from 2002 to 2020. A meta-analysis was conducted, which included more than 2884 cases and 2768 controls. 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: A significant correlation was found between the MMP2 C 1306T polymorphism and lung cancer risk (C vs T: OR=1.705, P=0.029; CC vs CT+TT: OR=1.16, 95% P=0.000) and for MMP2 C 735T polymorphism (C vs T: OR=1.433, P=0.151; CC vs CT+TT: OR=1.698, P=0.000).

Conclusion: The present meta-analysis revealed a significant association between the MMP-2-735C/T and MMP-9-1562 C/T polymorphisms and the risk of lung cancer in Asian population.

Please cite this article as: khafaei M, Gharechahi J, sadeghi M. Association between two functional polymorphisms in the MMP-2 promoter and lung cancer incidence in Asian population: a meta-analysis study. IJBC 2022; 14(2): 61-67.

1. Introduction:

Matrix metalloproteinase-2 (MMP-2) is a member of the MMPs family that have a potential role in degrading or breaking down of extracellular matrix, a physical barrier that limits the increasing growth and migration of tumor cells [1-3]. Increased MMP-2 expression has been linked with invasive and metastatic cancer characteristics [4-6]. However, increasing research has shown that, in addition to disrupting the extracellular matrix and allowing tumor cells to invade and metastasize, MMP-2 is involved in many stages of cancer formation [7-9]. MMP-2 overexpression has also been

found in precancerous lesions and early stages of human cancer [10,11]; the human MMP2 gene sequence is variable, and two functional single nucleotide polymorphisms (SNPs) in the MMP2 promoter have been reported as a C>T polymorphism at nucleotide 1306 breaks an Sp1 regulatory element, resulting in the T allele having much lower promoter activity than the C allele [12-14]. Another C>T polymorphism at nucleotide 735 similarly disrupts an Sp1 binding region, with the T allele linked with substantially decreased promoter activity [15]. Interestingly, the 1306C>T and 735C>T polymorphisms are in linkage disequilibrium, and the T 1306 /T 735 haplotype exhibits even lower promoter activity and mRNA expression than the haplotype with a single T allele at the 1306 or 735 sites, indicating an interactive effect of these two SNPs on MMP2 transcriptional function [16]. Numerous researches have examined the relationship between the 1306C>T polymorphism and susceptibility to human malignancies. The 1306C allele has been linked to an increased risk of developing common malignancies, including lung, stomach, cardiac, breast, oral, and colorectal [17-21]. Recently association between the 735C>T polymorphism and the risk of lung cancer, either alone or in conjunction with the 1306C>T polymorphism, an increased risk of cancer not only with the 1306C allele but also with the 735C allele, furthermore an even stronger connection between an increased risk of developing lung cancer and haplotypes comprising the 1306C and 735C alleles [16]. Given the critical role of MMP-2 in cancer initiation and progression, a more comprehensive study is warranted to determine the effect of MMP2 promoter haplotypes as a genetic modifier in the etiology of lung cancer in Asian populations. In this study, we decided to perform a meta-analysis on the association between MMP-2, 1306C>T, and 735C>T polymorphisms and the incidence of lung cancer in the Asian population.

2. Methods:

2.1. Data Sources and Keywords

The research team independently searched PubMed, Embase, EBSCO, and Google Scholar for any possibly relevant studies. The queries included all possible combinations of the keywords 'carcinoma', 'cancer',, 'neoplasm','malignancy', or 'tumor' with 'MMP','metalloproteinase','collagenase','gelatinase', references to the recovered articles and reports were also screened. six studies to be eligible, one of the following requirements had to be encountered: They evaluated candidates using the following criteria: They have published experiments that examined at least one of the four functional polymorphisms of MMP2; they used an unrelated case-control design, and they used a suitable genotyping instrument and had sufficient data to calculate an odds ratio (OR) with a confidence interval (CI) and a P-value.

2.2. Data extraction

The following basic details were extracted from studies that fulfilled the inclusion requirements: first author, tumor type, publication year, area, the ethnic makeup of the study population, number of cases and controls, genotyping protocol, and confirmation of diagnosis. Two independent investigators gathered data, and any discrepancies were resolved by discussion.

2.3. Statistical Analysis

Meta-analysis was performed using the comprehensive meta-analysis 2.0 software (Corporation, NJ, USA). The association between MMP-2, -1306C>T, and -735C>T polymorphisms and susceptibility to lung cancer in the Asian population 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 were calculated for the dominant model (C/C+C/T vs. T/T), codominant model (C/C vs. T/T), and recessive model (T/ T+T/C vs. C/C), respectively. A P-value less than 0.05 was considered statistically significant. Forest plots compared the OR and its 95% CI among all studies. Fixed-effect model was used to calculate the pooled OR with a 95% CI. We considered the P value < 0.1 indicator of significant heterogeneity for the random-effects model. A funnel plot was employed to ascertain potential publication bias to confirm the result further.

3. Results

3.1. Characteristics of the Included Studies

After a whole search, 29 relevant studies were initially recruited. Finally, 22 unrelated studies and studies on other cancers were eliminated. six case-control studies published between 2002 and 2019 [17,22-26] were included (**Fig 1**), of which three were conducted on MMP-2-1306C>T polymorphisms [17,22,23], two were conducted on MMP-2-735C>T polymorphisms [24,25] and 1 was conducted on MMP-2-1306C>T and -735C>T and polymorphisms [26]. A total of 1779 cases and 1639 controls studying the MMP-2,

-1306C/T polymorphism and 1105 cases and 1129 controls studying the MMP-2, -735C/T polymorphism were included. All 6 studies were conducted in Asian populations. The basic characteristics of the eligible studies are shown in **Tables 1** and **2.** all selected studies, the -1306C>T and -735C>T polymorphism were analyzed by polymerase chain reaction with restriction fragment length polymorphism (PCR-RFLP) or direct sequencing. The genotype frequency distributions of the enrolled studies were consistent with Hardy-Weinberg equilibrium (P>0.05).

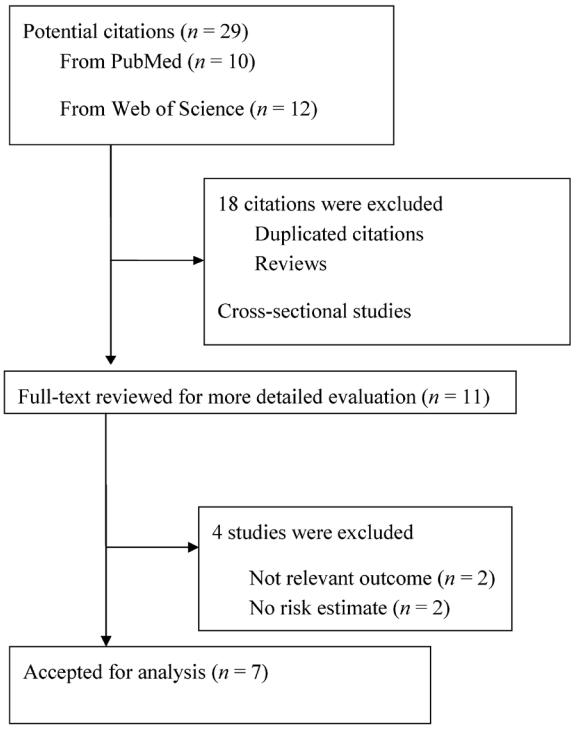

Figure 1: Flow chart of literature search and study selection

3.2. The association between the -1306C/T polymorphism and lung cancers in the Asian population

After a meta-analysis of the MMP-2, -1306C/T polymorphism, the results showed a significant association between C allele and lung cancer susceptibility. Our analysis showed that the -1306 CC genotype carriers had about 2-fold elevated risk for developing lung cancer (OR, 1.856; 95% CI, 1.600-2.153) compared with the non-carriers. (Figure 2). When the C/C genotype + C/T genotype of MMP-2, -1306 C/T polymorphism was compared with T/T genotype (dominant model), there was a significant association with the risk of lung cancer (OR, 1.705; 95% CI, 1.57-2.751),). The recessive model [TT+CT vs CC] showed no significant association (OR=0.519, 95% CI=0.448–0.601). 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-2, -1306 C/T polymorphism among the dominant and recessive genotype models. The P value < 0.05 was considered valid for all calculations **(Fig. 2)**

3.3. The association between the -735C>T polymorphism and lung cancers in Asian population

In the investigation of the MMP-2 -735C>T polymorphism in this study, we found a significant association between the C allele and lung cancer susceptibility in the Asian population. Our meta-analysis showed that the -735 C>T polymorphism CC genotype carriers had an about 1.6-fold elevated risk for developing lung cancer (OR, 1.698; 95% CI, 1.418-2.033) compared with CC and CT genotypes. **(Fig. 2)**. When the C/C genotype + C/T genotype of MMP-2, -1306 C/T polymorphism was compared with T/T genotype (dominant model), there was a significant association with the risk of lung cancer (OR, 1.705; 95% CI, 1.57-2.751),). The recessive model [TT+CT vs CC] showed no significant association (OR=0.519, 95% CI=0.448–0.601). The results showed no significant association between the 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 T/T genotype polymorphism was compared with T/T and C/T genotype, there was no significant association with the risk of lung cancer (OR=0.607, 95% CI== 0.371–0.993). **(Fig. 3)**.

3.4. Publication bias analyses

We evaluated the possibility of publication bias using the funnel plot and Egger's test. The shape of the funnel plots suggested no statistical evidence of publication bias for MMP-2-1306C>T polymorphism and MMP-2 -735C>T polymorphism among the dominant, co-dominant, and recessive genotype models in the Asian population. The P-value < 0.05 was considered valid for all calculations **(Fig. 4)**.

4. Discussion

There are many reports about the association between the MMP2 polymorphisms and lung cancer in different populations but have yielded inconsistent and inconclusive results about the role of the MMP2 polymorphisms in lung cancer to evaluate a more

Table 1: Characteristics of the included studies of MMP-2 polymorphism

Study name	Year	Country	Technique	No. of cases	No. of controls	NOS score
-1306 C/T						
Bayramoglu	2011	Turkey	PCR-RFLP	200	100	6
Yu	2002	China	PCR-DHPLC	781	852	8
Song	2007	China	PCR-RFLP	163	148	7
Zhou	2005	China	PCR-LDR	635	539	8
-735 C/T						
Zhou	2005	China	PCR-LDR	635	539	8
Jia	2009	China	PCR-RFLP	370	436	7
Keshvary	2009	Iran	PCR-RFLP	100	154	6

Table 2: MMP-2 polymorphisms genotype distribution and allele frequency in cases and controls

Study name	Case/Control	Cases			Controls			
		CC	CT	TT	CC	CT	TT	PHWE
-1306 C/T								
Bayramoglu	200/100	123	73	4	65	32	3	0.6923
Yu	781/852	644	127	10	585	248	19	0.222
Song	163/148	129	32	2	100	44	4	0.747
Zhou	770/777	635	124	11	539	220	18	0.074
-735 C/T								
Zhou	370/436	260	96	14	292	123	21	0.092
Jia	100/154	82	16	2	65	32	3	0.393
Keshvary	770/777	506	230	34	425	313	39	0.074

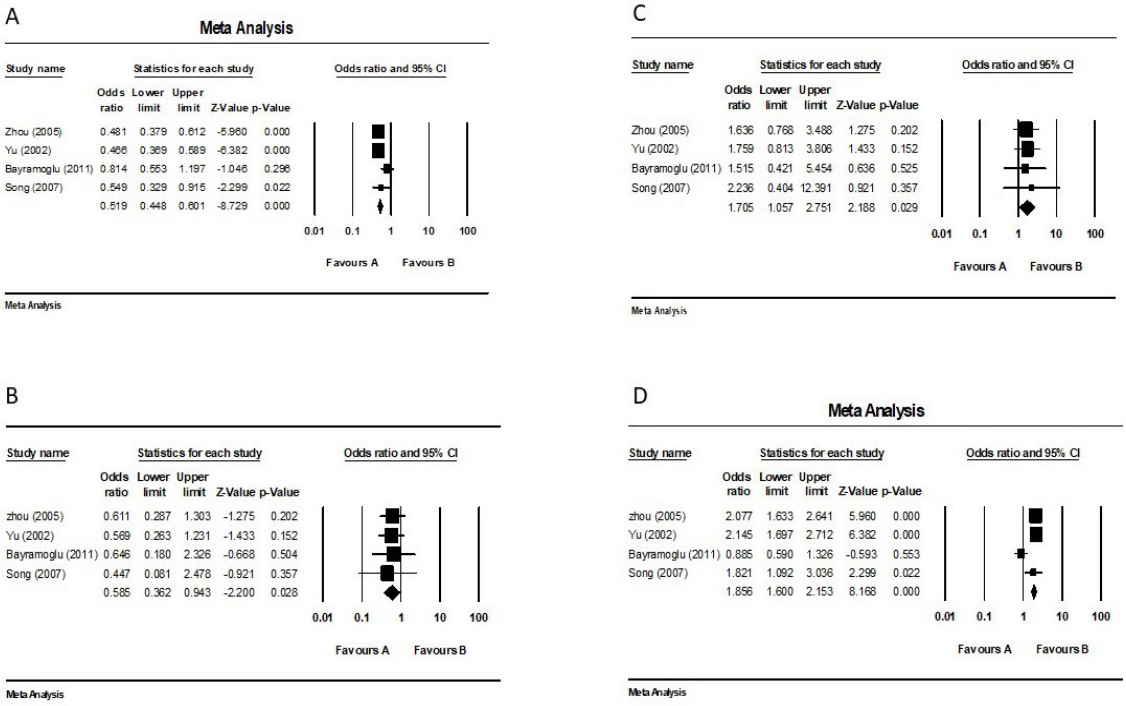

Figure 2: Forest plot of the meta-analysis of the MMP-2 -1306C/T polymorphism. (**A**) T allele; (**B**) Dominant model (**C**) C allele; and (**D**) recessive model. CI, confidence interval.

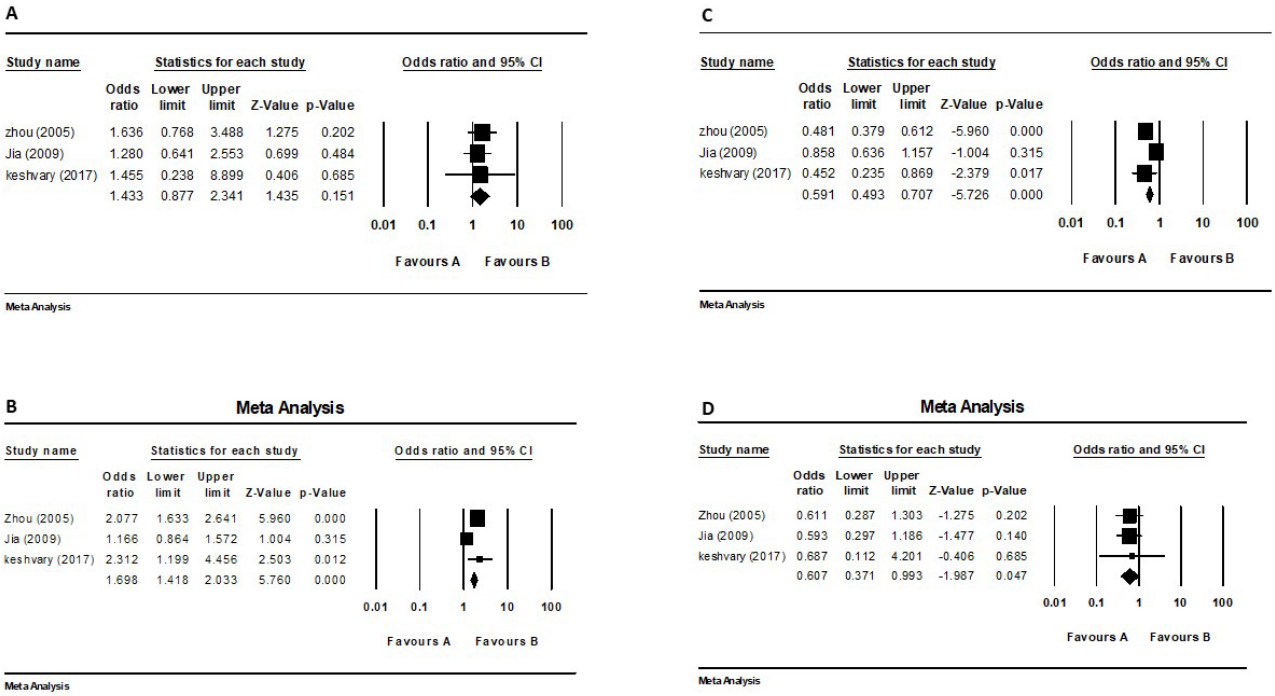

Figure 3: Forest plot of the meta analysis of the MMP-2 -735C/T polymorphism. (A) C allele; (B) Dominant model (C) T allele; and (D) recessive model. CI, confidence interval.

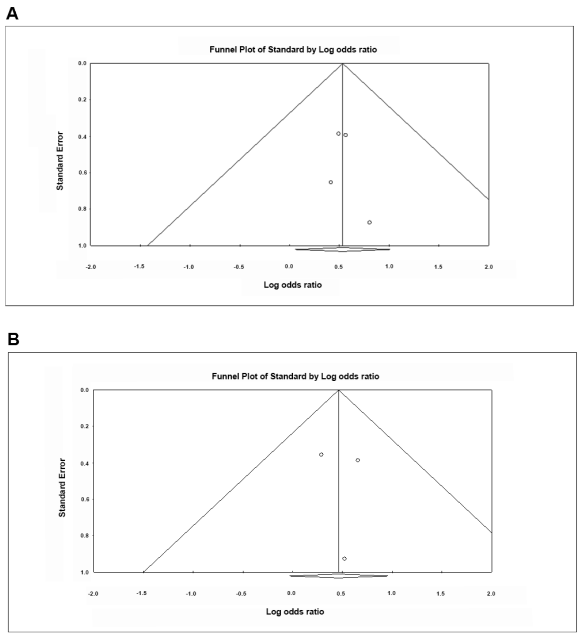

Figure 4: Funnel plots of the MMP-2 -1306C/T polymorphism. (A); Funnel plots of the MMP-2 -735 C/T polymorphism (B); Egger's test of the value from the funnel plot showed no statistical significance.

precise role the MMP2 polymorphisms in lung cancer, we performed a present meta-analysis. After a meta-analysis of the MMP-2, -1306C/T polymorphism, the results showed a significant association between the C allele and lung cancer susceptibility. Our analysis showed that the -1306 CC genotype carriers had an about 2-fold a higher risk for developing lung cancer than CT and TT genotypes. In investigation of the MMP-2 -735C>T polymorphism, we found a significant association between C allele and lung cancer susceptibility in Asian population. Our meta-analysis showed that the -735 C>T polymorphism CC genotype carriers had about 1.6-fold elevated risk for developing lung cancer compared with CC and CT genotypes. The -735CC and -1306CC genotypes were in linkage disequilibrium and interacted with haplotypes [16]. The current study extended the findings to lung cancer, demonstrating that not only the -1306CC but also the -735CC genotypes were susceptibility factors and these two genotypes interacted strongly within a haplotype to influence cancer risk. MMP-2 overexpression has been implicated in the development of various human malignancies, including lung cancer [27,28], Indicating that MMP-2 overexpression is most likely the

result of transcriptional alterations rather than gene amplification or activating mutation. MMP2 as one of the enzymes involved in collagen digestion as one of the basic constituents of the basement membrane plays an essential role in the attachment of cells to the basement membrane [29,30]. Previous studies have shown that MMP2 over-expression is associated with angiogenesis invasion, and metastasis of lung cancer cells [31]. Therefore, MPP2 can be considered as an important diagnostic factor in lung cancer and increased expression of MPP9 should be considered as a major factor in reducing survival in lung cancer patients. [32]. Our meta-analysis is based on six case–control studies on Asian population and found that MMP2 C735T and C1306T polymorphisms are both associated with lung cancer risk, and Asian people with MMP2 C735T and C1306T CC genotype are at increased risk of lung. In previous studies, Yang et al. In a meta-analysis of seven case–control studies of the Caucasus population and the Asian population reported that individuals with TT genotype of both MMP2 C735T and C1306T polymorphisms had obviously decreased risk of lung cancer compared with those with CC genotype, which were consistent with the findings of our study of the Asian population [33]. Another meta-analysis performed by McColgan et al, reported the associations between MMP2 C735T and C1306T polymorphisms CC genotype and lung cancer risk, which was in line with our meta-analysis findings, but their study only included two studies on MMP2 C735T polymorphism and three studies on MMP2 C1306T polymorphism, and the sample was relatively small [34]. In a recent meta-analysis of the Asian and Caucasian population Lee et al, reported decreased lung cancer risk in MMP2 -735 C/T and MMP-2 C1306T heterozygote model and dominant model in Asian population but this association was lost in Caucasians [35]. These findings were in line with our results on the Asian population. the C→T substitution in −1306 or −735 MMP-2 promoter position abolishes a Sp-1 binding site and causes lower promoter activity and lower MMP-2 expression in individuals with the T allele [36,37]. In this meta-analysis, we first examined the association between these two polymorphisms and lung cancer in the Asian population we found a significant association between the presence of CC genotype in MMP2 -735 C/T and MMP2 C1306T polymorphisms and increased risk of lung cancer, it seems that the presence of C allele in these two polymorphisms increases the expression of mmp-2, thereby increasing the digestion of collagen in the basement membrane and thus increasing the risk of lung cancer in these individuals. In this study, we encountered limitations, including the small number of studies on the Asian population.

5. Conclusion

In conclusion, our results suggested that MMP2 -735 C/T and MMP-2 C1306T are potential risk factors for lung cancer in Asians. To confirm the association identified in our meta-analysis, it is recommended to conduct studies with larger samples size and different ethnic groups.

Acknowledgment

We sincerely thank the human genetic research center of Baqiyatallah University of Medical Sciences for its technical and financial support. We would also like to thank Dr. Rouhollah Akbarpour, and Rahim Ramezani for their help with the statistical analysis.

Conflict of Interest

The authors have no conflicts of interest to declare.

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