Original Article

Matrix metalloproteinase family gene polymorphisms and lung cancer susceptibility: an updated meta-analysis

Xiaoliang Li[1#], Caiyang Liu[1#], Ran Ran[2], Gaohua Liu[1], Yanhui Yang[1], Wenzhuo Zhao[3], Xiaoyang Xie[1], Ji Li[1]

[1]Department of Cardiothoracic Surgery, The First People's Hospital of Neijiang, Neijiang 641000, China; [2]Department of endocrine Breast Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China; [3]Department of Psychiatry, The First Affiliated Hospital of Southwest Medical University, Luzhou 646000, China

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[#]These authors contribute to this work equally and thus are co-first authors.

Correspondence to: Ji Li. Department of Cardiothoracic Surgery, The First People's Hospital of Neijiang, No. 1866, West Section of Hanan Avenue, Shizhong District, Neijiang 641000, China. Email: njyyxxwklcy@163.com.

Background: Many studies have investigated the association between matrix metalloproteinase polymorphisms and lung cancer susceptibility. However, the results are still controversial. To clarify these associations, we conducted a meta-analysis.

Methods: A systematic search of studies was conducted in PubMed, Embase, and China National Knowledge Infrastructure. Overall and subgroup analysis stratified by ethnicity was conducted. OR with 95% CI was used to assess the strength of the association. Furthermore, false-positive report probability (FPRP) tests were also performed for associations obtained in this meta-analysis.

Results: Twenty-four studies, including 10,099 cases and 9,395 controls, were analyzed. Nine polymorphisms were reported. For MMP1 -1607 1G/2G and MMP7 -181 A/G, increased lung cancer risk was found in Asians. For MMP2 -1306 C/T and MMP2 -735 C/T, decreased lung cancer risk was found in both "diverse populations" and Asians. For MMP9 -1562, C/T decreased lung cancer risk was found in both "diverse populations" and Caucasians. For MMP13 -77A/G, the A/G genotype decreased lung cancer risk in Asians. However, only associations between MMP1 -1607 1G/2G, MMP2 -1306 C/T, MMP2 -735 C/T, and MMP7 -181 A/G and lung cancer risk were considered noteworthy according to FPRP tests. There was no association between MMP3 -1171 5A/6A, MMP9 R279Q, and MMP12 -82A/G and lung cancer risk.

Conclusions: Our meta-analysis suggested that MMP1 -1607 1G/2G and MMP7 -181 A/G were risk factors for lung cancer, while MMP2 -1306 C/T, MMP2 -735 C/T, MMP9 -1562 C/T, and MMP13 -77A/G might be protective factors. However, results for MMP9 -1562 C/T and MMP13 -77A/G should be interpreted with caution due to the probability of false-positive reports.

Keywords: Matrix metalloproteinases; polymorphisms; lung cancer; meta-analysis

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Introduction

Lung cancer is one of the leading causes of cancer-related death globally and is still a huge health threat to human beings (1,2). Although tobacco smoking is the major risk factor for lung cancer, lung cancer develops in less than 20% throughout life smokers, indicating that other factors such as genetic susceptibility may also contribute to lung carcinogenesis (3,4). The matrix metalloproteases (*MMPs*) family, including at least 26 human *MMPs* belong to a larger family of proteases named metzincin superfamily. They are

zinc-dependent endopeptidases that collectively degrade all extracellular matrix (ECM) components (5,6). According to the main substrates, *MMPs* are traditionally classified as collagenases (e.g., *MMP-1*, *MMP-8* and *MMP-13*), gelatinases (e.g., *MMP-2* and *MMP-9*), stromelysins (e.g., *MMP-3*, *MMP-10* and *MMP-11*), matrilysins (e.g., *MMP-7* and *MMP-26*) and macrophage metalloelastase (e.g., *MMP-12*) (7). Egeblad *et al.* demonstrated that these *MMPs* influenced tumor cell behavior and played an important role in several steps of cancer development, including immune surveillance, angiogenesis, and regulation of cell growth and apoptosis (8).

MMP-1 and *MMP-13*, belong to the collagenase, is related to the ability of neoplastic cells to cross the basal membrane of both the vascular endothelium and the epithelium (9). Studies have reported that *MMP-1* might contribute to tumor growth and spread by altering the cellular microenvironment to favor tumor formation (8,10), and overexpression of *MMP-13* is related to poor prognosis and more aggressive tumors (11,12). *MMP-2* and *MMP-9*, members of gelatinases, can degrade the major basal membrane component-type IV collagen and, therefore, are involved in cancer invasion and metastasis (13). *MMP-7*, the member of the matrilysins, can degrade proteoglycans, elastin, type IV collagen, and fibronectin (14). Also, *MMP-7* has the so-called "sheddase function" that cleave non-matrix substrates from the cell surface, such as pro-tumor necrosis factor from thecadherin (15). Several studies have proved that *MMP-7* has a statistically significant positive correlation with invasive tumor potential and contributes to early tumor development (16-18). *MMP-12*, known as macrophage metalloelastase, exhibits the same ability as *MMP-7* to degrade elastin. The roles of *MMP-12* in cancers are still controversial. However, overexpression of *MMP-12* is reported to be positively associated with not only tumor invasion and progression but also the poor outcome of patients in multiple cancers, including lung cancer (19-21). *MMP-3* belongs to the stromelysins, is known to induce the synthesis of other *MMPs* (9).

Last decades, a surge of studies investigating the association between genetic polymorphisms and lung cancer risk was published. Polymorphisms in *MMP* genes were also considered to be related to lung cancer risk. However, the results remained ambiguous and controversial because the relatively small sample size of a single study was underpowered to detect the effect of these polymorphisms. Several meta-analyses have been conducted to assess the association between *MMP* polymorphisms and lung cancer risk (22-24). Nevertheless, the latest one was published four years ago, and the data were updated. Therefore, we conducted this meta-analysis based on 24 case-control studies and aimed to better assess the association between *MMP* polymorphisms and lung cancer risk to date.

Methods

Identification of eligible studies

Two independent investigators conducted a systematic search strategy. Firstly, we searched Pubmed, EMBASE, and China National Knowledge Infrastructure (CNKI) with the terms: "lung cancer or lung carcinoma" and "*MMP* or matrix metallopeptidase" on or before Sept 30, 2019. Secondly, after the title and abstract manually screened, all references cited in relevant studies were also reviewed to identify other studies.

Inclusion and exclusion criteria

Studies included in this meta-analysis must meet the following inclusion criteria: (I) case-control study about the association between *MMP* polymorphisms and lung cancer risk; (II) genotype and allele data were available; (III) all studies must conform to Hardy-Weinberg equilibrium (HWE) in the control group. Exclusion criteria: (I) duplication of publications; (II) studies that were not about *MMP* polymorphisms and the etiology of lung cancer; (III) no sufficient data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). If more than one study using the same case series was published, only the study with the largest sample size was included.

Data extraction

Two investigators (Li and Liu) extracted data from eligible studies independently and then followed by data exchange and cross-check. Any disagreement was settled by rechecking the original data and further discussion together. The following contents were collected: first author, publication year, country of origin, genes and polymorphisms, source of control (hospital-based or population-based), ethnicity, genotyping methods, number of cases and controls, and genotype distributions in cases and controls.

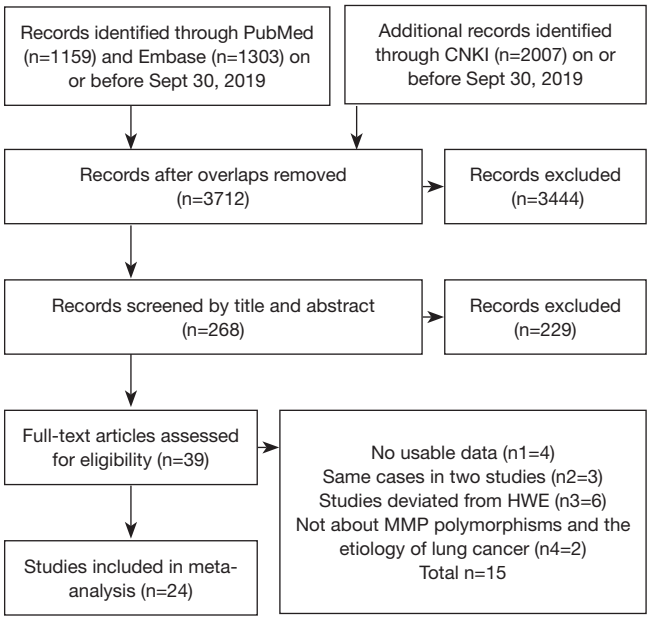

Figure 1 Selection of studies.

Quality assessment

We assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS) (25). The NOS rating system was based on three aspects of the case-control study: selection, comparability, and exposure. For each of the three aspects, four, one, and three parameters were assigned, respectively. Scores were ranged from 0 to 9, and studies were of high quality if scores ≥7. Two investigators assessed the quality of the studies through consultations to reach consensus.

Statistics analysis

We evaluated HWE for each study in control groups by the chi-square goodness-of-fit test, and P<0.05 was considered a significant departure from HWE. ORs assessed the strength of association between *MMP* polymorphisms and lung cancer risk with 95% CIs. The pooled ORs were performed for five genetic models: allelic model (x versus X), heterozygote model (Xx versus XX), homozygote model (xx versus XX), dominant model (xx + Xx versus XX) and recessive model (xx versus Xx + XX), x represented the minor allele and X represented the major allele. Z-test determined the statistical significance level with a P value of less than 0.05. Heterogeneity was evaluated by both Q statistic and the I^2 statistic. A P value of less than 0.1 and I^2 greater than 50% was a significant inconsistency (26). The random effects model was used if there was significant inconsistency; otherwise, the fixed-effects model was used (27). For each genetic comparison, subgroup analysis stratified by ethnicity was conducted. Sensitivity analysis was also performed by omitting each study in each turn to evaluate the effect of each study on the combined ORs. Potential publication bias was checked by Egger's test (28) and Begg's funnel plots (29). The P value of Egger's test less than 0.05, and an asymmetric plot was considered a significant publication bias. All statistical analyses were performed using Stata version 12.0 (StataCorp LP, College Station, TX, USA).

False-positive report probability (FPRP) tests

We performed FPRP tests for all the significant associations obtained in this meta-analysis. FPRP was determined by three parameters: the observed P value, the prior probability, and the statistical power of the test. The approach developed by Wacholder *et al.* was used (30). He advocated presetting the FPRP noteworthiness value at 0.2, and the prior probability of 0.01 and power OR 1.5 were used in our study. FPRP values were calculated by the excel spreadsheet offered by Wachoder *et al.*

Results

Characteristics of studies

A total of 4,469 articles were retrieved from PubMed, Embase, and CNKI databases due to less stringent terms we used. The literature selection process was shown in *Figure 1*. Full-text assessment was conducted for 39 articles and ,as a result, 15 articles were excluded, among which 4 had no usable data (31-34), 3 used the same case series as another study (35-37), 6 deviated from HWE (38-43), and 2 were not about *MMP* polymorphisms and the etiology of lung cancer (44,45). Finally, 24 eligible case-control studies were included in our meta-analysis (21,46-68). Five studies presented genotype distributions of more than one polymorphisms separately; thus, each of them was treated as separate studies (21,50,51,57,58). Nine polymorphisms (*MMP1* -1607 1G/2G, *MMP2* -1306 C/T and -735 C/T, *MMP3* -1171 5A/6A, *MMP*7 -181 A/G, *MMP9* -1562 C/T and R279Q, *MMP12* -82A/G, and *MMP13* -77A/G) were reported in the 24 included studies containing a total of 10,099 cases and 9,395 controls. For most of the polymorphisms, studies were conducted in "diverse

Table 1 Characteristics of studies included in the meta-analysis

First author	Year	Country	Ethnicity	Source of control	Genotyping method	Cases/ controls	Genes	Polymorphisms	NOS, total scores
Bayramoglu	2009	Turkey	Asian	HB	PCR-RFLP	200/100	MMP9	–1562 C/T	6
Bayramoglu	2011	Turkey	Asian	HB	PCR-RFLP	200/100	MMP2	–1306 C/T	6
Fakhoury	2012	Lebanon	Caucasian	PB	PCR-RFLP	41/51	MMP1	–1607 1G/2G	8
Fang	2005	China	Asian	PB	PCR-RFLP	243/350	MMP3	–1171 5A/6A	8
Gonzalez-Arriaga	2012	Spain	Caucasian	HB	PCR-RFLP	716/534	MMP3, MMP9	–1171 5A/6A, –1562 C/T	6
Gonzalez-Arriaga	2008	Spain	Caucasian	HB	PCR-RFLP	501/510	MMP1, MMP13	–1607 1G/2G, –77 A/G	7
Hart	2011	Norway	Caucasian	PB	TaqMan	436/434	MMP1	–1607 1G/2G	9
Hu	2005	China	Asian	PB	PCR-RFLP	744/747	MMP9	R279Q	8
Jia	2009	China	Asian	PB	PCR-RFLP	370/436	MMP2	–735 C/T	8
Liu	2011	China	Asian	PB	PCR-RFLP	825/825	MMP1	–1607 1G/2G	9
Lu	2017	China	Asian	PB	PCR-RFLP	260/219	MMP7	–181 A/G	8
Peng	2010	China	Asian	PB	PCR-RFLP	420/419	MMP12, MMP13	–82 A/G, –77 A/G	8
Rollin	2007	France	Caucasian	HB	PCR-RFLP	90/90	MMP2, MMP9	–1306 C/T, –735 C/T, –1562 C/T	7
Sanli	2013	Turkey	Asian	PB	PCR-RFLP	132/80	MMP7	–181 A/G	7
Song	2007	China	Asian	PB	PCR-RFLP	163/148	MMP2	–1306 C/T	8
Su	2006	USA	Caucasian	PB	TaqMan	2,014/1,323	MMP1, MMP3, MMP12	–1607 1G/2G, –1171 5A/6A, –82 A/G	7
Wang	2013	China	Asian	PB	PCR-RFLP	300/300	MMP12	–82 A/G	8
Wang	2013	China	Asian	PB	PCR-RFLP	300/300	MMP13	–77 A/G	8
Yu	2002	China	Asian	PB	PCR-DHPLC	781/852	MMP2	–1306 C/T	8
Zhang	2005	China	Asian	PB	PCR-RFLP	243/350	MMP7	–181 A/G	8
Zhang	2006	China	Asian	PB	PCR-RFLP	150/200	MMP1	–1607 1G/2G	8
Zhao	2007	China	Asian	PB	PCR-RFLP	50/50	MMP9	R279Q	8
Zhou	2005	China	Asian	PB	PCR-RFLP	770/777	MMP2	–735 C/T	8
Zhang	2005	China	Asian	PB	PCR-RFLP	150/200	MMP9	–1562 C/T	8

HB, hospital-based; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-DHPLC, polymerase chain reaction-denaturing high-performance liquid chromatography.

populations", while studies about *MMP*7 -181 A/G and *MMP9* R279Q focused on Asians. Different genotyping methods were utilized, including polymerase chain reaction-restriction fragment length polymorphism, TaqMan, and polymerase chain reaction-denaturing high-performance liquid chromatography. The genotype distributions in the controls of all studies were consistent with HWE. More details about the characteristics of these studies were shown in *Table 1*. Genotype counts, and the P value of HWE were shown in *Table 2*.

Table 2 Genotype counts of the analyzed polymorphisms included in the meta-analysis

Study	Ethnicity	Cases/controls	Cases			Controls			P_{HWE}
			1G/1G	1G/2G	2G/2G	1G/1G	1G/2G	2G/2G	
MMP1 -1607 1G/2G									
Su	Caucasian	2,014/1,323	541	1,015	458	367	642	314	0.310
Gonzalez-Arriaga	Caucasian	501/510	128	248	125	119	259	132	0.712
Hart	Caucasian	436/434	115	207	114	132	198	104	0.081
Liu	Asian	825/825	74	323	428	100	367	358	0.691
Fakhoury	Caucasian	41/51	5	17	19	7	16	28	0.081
Zhang	Asian	150/200	32	70	48	60	98	42	0.865
MMP2 -1306 C/T			CC	CT	TT	CC	CT	TT	
Yu	Asian	781/852	644	127	10	585	248	19	0.220
Rollin	Caucasian	90/90	60	28	2	60	29	1	0.217
Bayramoglu	Asian	200/100	123	73	4	65	32	3	0.692
Song	Asian	163/148	129	32	2	100	44	4	0.747
MMP2 -735 C/T			CC	CT	TT	CC	CT	TT	
Zhou	Asian	770/777	506	230	34	425	313	39	0.052
Rollin	Caucasian	89/90	69	18	2	67	21	2	0.816
Jia	Asian	370/436	260	96	14	292	123	21	0.092
MMP3 -1171 5A/6A			5A/5A	5A/6A	6A/6A	5A/5A	5A/6A	6A/6A	
Fang	Asian	243/350	7	73	163	8	105	237	0.358
Su	Caucasian	2,014/1,323	485	1,012	517	325	648	350	0.466
Gonzalez-Arriaga	Caucasian	716/534	164	367	185	119	276	139	0.417
MMP7 -181 A/G			A/A	A/G	G/G	A/A	A/G	G/G	
Zhang	Asian	243/350	200	40	3	316	33	1	0.888
Sanli	Asian	132/80	120	10	2	79	1	0	0.955
Lu	Asian	260/219	182	78	0	176	43	0	0.107
MMP9 -1562 C/T			CC	CT	TT	CC	CT	TT	
Zhang	Asian	150/200	83	60	7	155	42	3	0.936
Rollin	Caucasian	90/90	68	22	0	64	21	5	0.085
Bayramoglu	Asian	200/100	150	48	2	67	30	3	0.871
Gonzalez-Arriaga	Caucasian	762/649	581	174	7	483	148	18	0.110
MMP9 R279Q			RR	RQ	QQ	RR	RQ	QQ	
Hu	Asian	744/747	357	323	64	343	323	81	0.704
Zhao	Asian	50/50	24	20	6	14	28	8	0.335

Table 2 (*continued*)

Table 2 (*continued*)

Study	Ethnicity	Cases/controls	Cases			Controls			P_{HWE}
			1G/1G	1G/2G	2G/2G	1G/1G	1G/2G	2G/2G	
MMP12 -82A/G			A/A	A/G	G/G	A/A	A/G	G/G	
Su	Caucasian	2,014/1,323	1,535	449	30	1,008	289	26	0.324
Wang	Asian	300/300	290	10	0	287	13	0	0.701
Peng	Asian	420/419	404	16	0	399	20	0	0.617
MMP13 -77A/G			A/A	A/G	G/G	A/A	A/G	G/G	
Gonzalez-Arriaga	Caucasian	501/506	248	208	45	267	197	42	0.508
Wang	Asian	300/300	85	132	83	55	156	89	0.354
Peng	Asian	420/419	105	207	108	91	227	101	0.085

P_{HWE}, P value of Hardy-Weinberg Equilibrium.

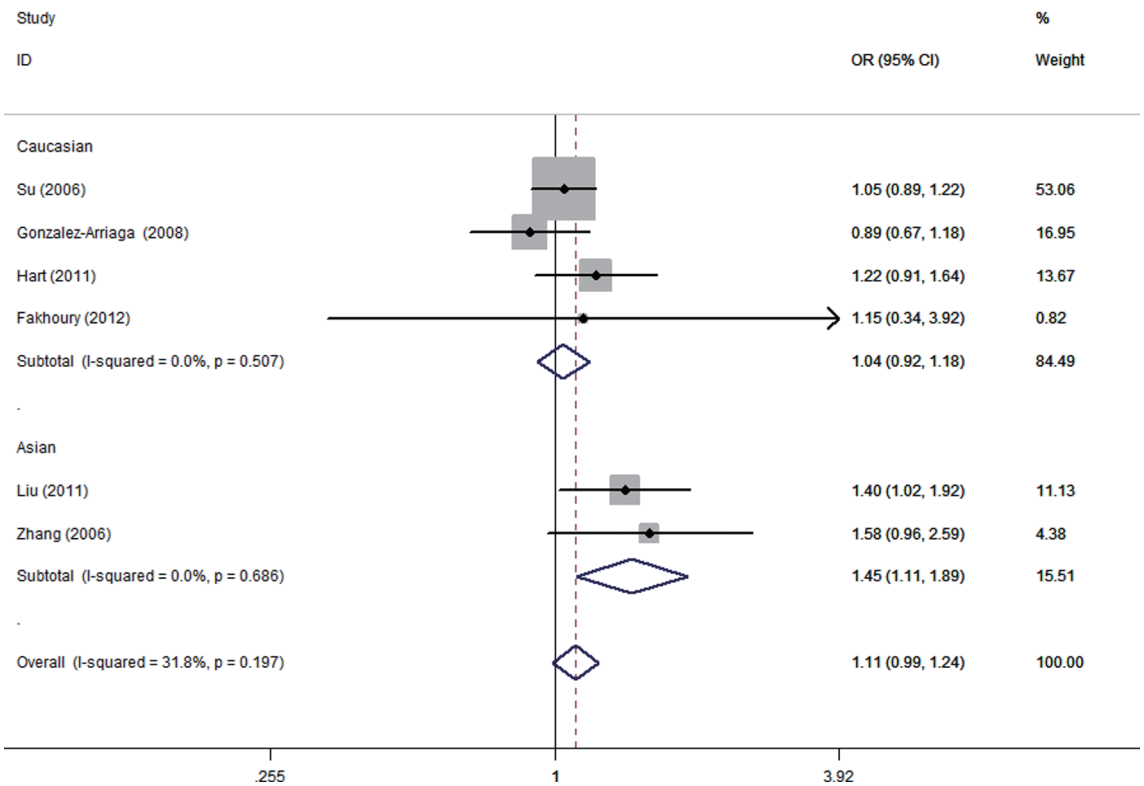

Figure 2 The association between *MMP1* -1607 1G/2G and lung cancer risk (dominant model: OR =1.11, 95% CI: 0.99–1.24, P=0.077; P=0.197 for heterogeneity; fixed-effects model).

MMP1 -1607 1G/2G and lung cancer susceptibility

Six studies involving 3,967 cases and 3,343 controls were pooled. The random effects model was used in the allelic model, homozygote model, and recessive model. A fixed-effects model was used in the other two genetic models. Overall, no significant association was identified in any of the genetic models. Next, subgroup analysis stratified by ethnicity was conducted and increased lung cancer risk

Table 3 Summary of pooled ORs in the meta-analysis and FPRP

Ethnicity	N †	Allelic model			Heterozygote model			Homozygote model			Dominant model			Recessive model		
		OR	I^2 (%)	FPRP‡	OR	I^2 (%)	FPRP	OR	I^2 (%)	FPRP	OR	I^2 (%)	FPRP	OR	I^2 (%)	FPRP
MMP1 -1607 1G/2G																
Asian	2	1.34 (1.18–1.53)	0.0	0.002	1.23 (0.93–1.63)	0.0	–	1.73 (1.29–2.31)	0.0	0.107	1.45 (1.11–1.89)	0.0	0.498	1.45 (1.21–1.74)	0.0	0.010
Caucasian	4	1.00 (0.93–1.09)	0.0	–	1.06 (0.93–1.21)	0.0	–	1.01 (0.87–1.18)	0.0	–	1.04 (0.92–1.18)	0.0	–	0.97 (0.85–1.10)	0.0	–
Total	6	1.12 (0.97–1.29)	70.0	–	1.09 (0.97–1.23)	0.0	–	1.22 (0.95–1.58)	61.6	–	1.11 (0.99–1.24)	31.8	–	1.13 (0.92–1.39)	67.2	–
MMP2 -1306 C/T																
Asian	2	0.53 (0.43–0.64)	0.0	0.000	0.48 (0.39–0.60)	0.0	0.000	0.46 (0.23–0.93)	0.0	0.953	0.48 (0.39–0.59)	0.0	0.000	0.55 (0.27–1.10)	0.0	–
Caucasian	1	1.04 (0.60–1.79)	–	–	0.97 (0.51–1.81)	–	–	2.00 (0.18–22.65)	–	–	1.00 (0.54–1.86)	–	–	2.02 (0.18–22.71)	–	–
Total	3	0.64 (0.44–0.93)	64.1	0.821	0.58 (0.39–0.87)	56.6	0.770	0.52 (0.27–1.02)	0.0	–	0.59 (0.39–0.89)	61.2	0.808	0.61 (0.31–1.18)	0.0	–
MMP2 -735 C/T																
Asian	2	0.76 (0.66–0.87)	31.1	0.007	0.72 (0.51–1.01)	69.4	–	0.74 (0.50–1.09)	0.0	–	0.72 (0.53–0.97)	64.1	0.814	0.84 (0.57–1.24)	0.0	–
Caucasian	1	0.87 (0.47–1.62)	–	–	0.83 (0.41–1.70)	–	–	0.97 (0.13–7.09)	–	–	0.84 (0.42–1.68)	–	–	1.01 (0.14–7.34)	–	–
Total	3	0.76 (0.66–0.88)	0.0	0.024	0.73 (0.56–0.95)	43.1	0.717	0.75 (0.51–1.10)	0.0	–	0.73 (0.58–0.92)	34.9	0.493	0.85 (0.58–1.24)	0.0	–
MMP3 -1171 5A/6A																
Asian	1	0.96 (0.71–1.30)	–	–	0.79 (0.28–2.29)	–	–	0.79 (0.28–2.21)	–	–	0.79 (0.28–2.20)	–	–	0.97 (0.69–1.38)	–	–
Caucasian	2	0.99 (0.91–1.08)	0.0	–	1.02 (0.88–1.19)	0.0	–	0.98 (0.83–1.16)	0.0	–	1.01 (0.88–1.16)	0.0	–	0.97 (0.85–1.11)	0.0	–
Total	3	0.99 (0.91–1.07)	0.0	–	1.02 (0.88–1.18)	0.0	–	0.98 (0.83–1.15)	0.0	–	1.01 (0.88–1.15)	0.0	–	0.97 (0.86–1.10)	0.0	–
MMP7 -181 A/G																
Asian	3	1.89 (1.41–2.54)	29.7	0.037	1.92 (1.40–2.63)	0.0	0.072	4.11 (0.67–25.80)	0.0	–	1.98 (1.44–2.70)	2.0	0.038	3.81 (0.61–23.86)	0.0	–
Total	3	1.89 (1.41–2.54)	29.7	–	1.92 (1.40–2.63)	0.0	–	4.11 (0.67–25.80)	0.0	–	1.98 (1.44–2.70)	2.0	–	3.81 (0.61–23.86)	0.0	–
MMP9 -1562 C/T																
Asian	1	0.68 (0.43–1.08)	–	–	0.72 (0.42–1.23)	–	–	0.30 (0.05–1.82)	–	–	0.68 (0.40–1.15)	–	–	0.33 (0.05–1.99)	–	–
Caucasian	2	0.83 (0.67–1.02)	0.0	–	0.98 (0.77–1.24)	0.0	–	0.27 (0.12–0.62)	0.0	0.924	0.89 (0.71–1.12)	0.0	–	0.27 (0.12–0.62)	0.0	0.924
Total	3	0.80 (0.67–0.97)	0.0	0.704	0.93 (0.75–1.16)	0.0	–	0.28 (0.13–0.59)	0.0	0.878	0.86 (0.69–1.05)	0.0	–	0.28 (0.13–0.59)	0.0	0.878
MMP9 R279Q																
Asian	2	0.88 (0.76–1.02)	45.5	–	0.71 (0.32–1.56)	69.8	–	0.73 (0.52–1.03)	0.0	–	0.69 (0.33–1.45)	68.9	–	0.78 (0.55–1.07)	0.0	–
Total	2	0.88 (0.76–1.02)	45.5	–	0.71 (0.32–1.56)	69.8	–	0.73 (0.52–1.03)	0.0	–	0.69 (0.33–1.45)	68.9	–	0.78 (0.55–1.07)	0.0	–
MMP12 -82A/G													–			
Asian	2	0.78 (0.47–1.32)	0.0	–	0.78 (0.46–1.32)	0.0	–	–	–	–	0.78 (0.46–1.32)	0.0	–	–	–	–
Caucasian	1	0.98 (0.84–1.13)	–	–	1.02 (0.86–1.21)	–	–	0.76 (0.45–1.29)	–	–	1.00 (0.85–1.18)	–	–	0.75 (0.44–1.28)	–	–
Total	3	0.96 (0.83–1.11)	0.0	–	0.99 (0.85–1.17)	0.0	–	0.76 (0.45–1.29)	–	–	0.98 (0.84–1.14)	0.0	–	0.75 (0.44–1.28)	–	–
MMP13 -77A/G																
Asian	2	0.88 (0.72–1.08)	46.7	–	0.67 (0.47–0.96)	45.3	0.849	0.76 (0.50–1.16)	49.5	–	0.70 (0.48–1.01)	55.3	–	1.01 (0.80–1.27)	0.0	–
Caucasian	1	1.10 (0.91–1.34)	–	–	1.14 (0.88–1.47)	–	–	1.15 (0.73–1.82)	–	–	1.14 (0.89–1.46)	–	–	1.09 (0.70–1.69)	–	–
Total	3	0.95 (0.79–1.14)	59.4	–	0.81 (0.54–1.22)	78.3	–	0.87 (0.61–1.24)	51.1	–	0.83 (0.56–1.23)	78.3	–	1.02 (0.83–1.26)	0.0	–

†, N number of included studies; ‡, FPRP false-positive report probabilities (power OR =1.5, prior probability =0.01).

was found in Asians (allelic model: OR =1.34, 95% CI: 1.18–1.53, P<0.001; homozygote model: OR =1.73, 95% CI: 1.29–2.31, P<0.001; dominant model: OR =1.45, 95% CI: 1.11–1.89, P=0.006, *Figure 2*; recessive model: OR =1.45, 95% CI: 1.21–1.74, P<0.001, *Table 3*). No significant association was found in Caucasians.

MMP2 -1306 C/T and lung cancer susceptibility

Three studies involving 1,034 cases and 1,090 controls were pooled after one study (47) excluded according to the sensitivity analysis (*Table S1*). Random effects model was used in allelic model, heterozygote model, and dominant model. Fixed-effects model was used in the other two genetic models. Decreased lung cancer risk was found in "diverse populations" (allelic model: OR =0.64, 95% CI: 0.44–0.93, P=0.020; heterozygote model: OR =0.58, 95% CI: 0.39–0.87, P=0.007; dominant model: OR =0.59, 95% CI: 0.39–0.89, P=0.011,*Table 3*) and Asians (allelic model: OR =0.53, 95% CI: 0.43–0.64, P<0.001; homozygote model: OR =0.48, 95% CI: 0.39–0.60, P<0.001; heterozygote model: OR =0.46, 95% CI: 0.23–0.93, P=0.032; dominant model: OR =0.48, 95% CI: 0.39–0.59, P<0.001, *Table 3*). No significant association was found in Caucasians.

MMP2 -735 C/T and lung cancer susceptibility

Three studies involving 1,229 cases and 1,303 controls were pooled. Although no obvious heterogeneity was found in the overall analysis, significant heterogeneity was identified in subgroup analysis under the heterozygote model and dominant model. So, the random-effects model was used in these two genetic models. As a result, decreased lung cancer risk was found (allelic model: OR =0.76, 95% CI: 0.66–0.87, P<0.001; heterozygote model: OR =0.73, 95% CI: 0.56–0.95, P=0.019; dominant model: OR =0.73, 95% CI: 0.58–0.92, P= 0.007, *Table 3*). When subgroup analysis stratified by ethnicity was conducted, this association was lost in Caucasians.

MMP3 -1171 5A/6A and lung cancer susceptibility

Three studies involving 2,973 cases and 2,207 controls were pooled. No significant heterogeneity was identified, so a fixed-effects model was used. There was no association between *MMP3* -1171 5A/6A polymorphism and lung cancer risk in both overall and subgroup analysis (*Table 3*).

MMP7 -181 A/G and lung cancer susceptibility

Three studies performed in Asians involving 635 cases and 649 controls were pooled. No significant heterogeneity was identified, so the fixed-effects model was used. As a result, increased lung cancer risk was found (allelic model: OR =1.89, 95% CI: 1.41–2.54, P<0.001; heterozygote model: OR =1.92, 95% CI: 1.40–2.63, P<0.001; dominant model: OR =1.98, 95% CI: 1.44–2.70, P<0.001, *Table 3*).

MMP9 -1562 C/T and lung cancer susceptibility

Three studies involving 1,052 cases and 839 controls were pooled after one study (68) excluded according to the sensitivity analysis (*Table S1*). No significant heterogeneity was identified, so the fixed-effects model was used. Decreased lung cancer risk was found in overall analysis (allelic model: OR =0.80, 95% CI: 0.67–0.97, P=0.021; homozygote model: OR =0.28, 95% CI: 0.13–0.59, P=0.001; recessive model: OR =0.28, 95% CI: 0.13–0.59, P=0.001, *Table 3*). The same association was also found in Caucasians (homozygote model: OR =0.27, 95% CI: 0.12–0.62, P=0.002; recessive model: OR =0.27, 95% CI: 0.12–0.62, P=0.002, *Table 3*).

MMP9 R279Q and lung cancer susceptibility

Two studies performed in Asians involving 794 cases and 797 controls were pooled. The random-effects model was used in the heterozygote model and the dominant model. A fixed-effects model was used in the other three genetic models. There was no association between *MMP9* R279Q polymorphism and lung cancer risk (*Table 3*).

MMP12 -82A/G and lung cancer susceptibility

Three studies involving 2,734 cases and 2,042 controls were pooled. No significant heterogeneity was identified, so the fixed-effects model was used. There was no association between *MMP12* -82A/G polymorphism and lung cancer risk in both overall and subgroup analysis. It was worth noting that there was no GG genotype in two studies (57,61), therefore pooled ORs under the homozygote model and recessive model were not available (*Table 3*).

MMP13 -77A/G and lung cancer susceptibility

Three studies involving 1,221 cases and 1,225 controls were

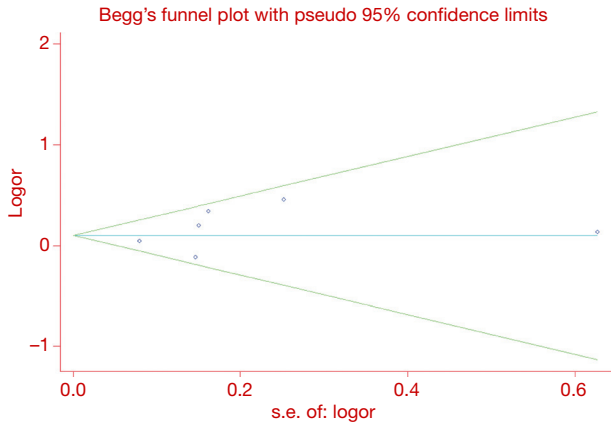

Figure 3 Begg's funnel plot for the association between *MMP1* -1607 1G/2G and lung cancer risk (dominant model: Z=0.75, P=0.452).

pooled. The random-effects model was used in all genetic models except for the recessive model. No significant association was found in the overall analysis, but A/G genotype decreased the risk of lung cancer in Asians (OR =0.67, 95% CI: 0.47–0.96, P=0.029, *Table 3*).

Sensitivity analysis and publication bias

Sensitivity analyses were performed to assess the stability of results by removing each study once in every polymorphism and genetic model. The corresponding results were materially altered after a single study was excluded at a time for 6 polymorphisms (*Table S1*). Positive results for three polymorphisms were notable. For *MMP2* -1306 C/T and *MMP2* -735 C/T, excluding Ayşegül *et al.* (47) study and Zhou *et al.* (67) study respectively could reverse the results under the allelic model, heterozygote model, and dominant model. For *MMP9* -1562 C/T, the exclusion of Zhang *et al.* (68) study could reverse the results under the allelic model, homozygote model, and recessive model.

Interestingly, heterogeneity between studies was decreased after these three studies were excluded, indicating that these studies might contribute as a source of heterogeneity. Ayşegül *et al.* (47) study and Zhang *et al.* (68) study were finally excluded from our meta-analysis but not Zhou *et al.* (67) study because the other two studies investigating *MMP2* -735 C/T were relatively small. No publication bias for the association between *MMP1* -1607 1G/2G and lung cancer susceptibility was identified by Begg's test (P=0.452) or Egger's test (P=0.376) under the dominant model. Symmetrical funnel plots were also obtained in all the genetic models (*Figure 3*). We did not evaluate publication bias of the rest polymorphisms owing to the limited study number.

FPRP tests

We performed FPRP tests for all the significant associations obtained in this meta-analysis. Eleven associations involved 4 SNPs (*MMP1* -1607 1G/2G, *MMP2* -1306 C/T, *MMP2* -735 C/T, and *MMP*7 -181 A/G) were considered to be noteworthy (FPRP value less than 0.2), indicating a true association, *Table 3*.

Discussion

Twenty-four eligible case-control studies, including 10,099 cases and 9,395 controls about nine polymorphisms in *MMP* genes, were analyzed. We found that *MMP1* -1607 1G/2G and *MMP*7 -181 A/G increased lung cancer risk and *MMP2* -1306 C/T, *MMP2* -735 C/T, *MMP9* -1562 C/T, and *MMP13* -77A/G might confer protection against lung cancer. No association was found between *MMP3* -1171 5A/6A, *MMP9* R279Q, and *MMP12* -82A/G and lung cancer risk. However, when FPRP tests were performed, only associations between *MMP1* -1607 1G/2G, *MMP2* -1306 C/T, *MMP2* -735 C/T, and *MMP*7 -181 A/G and lung cancer risk were considered noteworthy.

MMPs, degrading basal membranes, and ECM, as we know, was involved in many critical physiological and pathological processes of lung cancer and inflammation (5,6,58,63). Nowadays, a large number of studies have reported that the expression of *MMPs* plays a critical role in tumor development, invasion, and poor prognosis of multiple cancers, including lung cancer (8,46,58,63). Polymorphisms in *MMP* genes were widely studied. Functional analyses are indicating alterations in the gene expression due to the modulatory effect of these polymorphisms on transcriptional activity (69-73). It could be presumed that *MMP* polymorphisms contributed to the development of lung cancer, and this conclusion might be biologically plausible.

MMP1 -1607 1G to 2G substitution might lead to significantly higher transcriptional activity because the 2G allele created an E26 (ETS) transcription factor binding site and increased transcription capacity (70). The study had reported that the Ets site was a notable correlation with the expression of *MMP-1* (74). Enhancing Ets activity up-

regulated the expression of *MMP-1*, and a reduction in Ets activity led to suppression (75,76). Two studies in Asians supported that individuals carrying the 2G/2G genotype had a higher risk of developing lung cancer than 1G/1G genotype (55,65). Our meta-analysis also observed that 2G/2G genotype carriers had a 1.73-fold increased risk of developing lung cancer compared with 1G/1G genotype carriers in Asians.

Nevertheless, no association was found in Caucasians. Besides, no heterogeneity between studies was found after subgroup analysis stratified by ethnicity was conducted. So, the loss of association in Caucasians could be explained by different frequencies of the polymorphism between different ethnicities.

MMP2 -1306 C/T and -735 C/T were in linkage disequilibrium (77). These two genotypes, within a haplotype, had a strong interaction and were correlated with lung cancer risk. Earlier studies demonstrated that CC genotype had higher promoter activity compared with the TT genotype, thus leading to the overexpression of *MMP-2* (72,73). Although the differences resulting from polymorphisms were subtle, a long-time overexpression of *MMP-2* might also increase the risk of lung cancer. Zhou *et al.* (67) reported that individuals with -1306 C/C or -735 C/C genotype were more likely to develop lung cancer, and the risk was even higher in smokers. However, Rollin *et al.* (58) observed opposite results due to different ethnicities and limited sample size. Our meta-analysis revealed that the T allele was a protective factor for lung cancer. That was exactly consistent with Zhou *et al.* (67) study. However, we did not investigate genetic-environment interaction effects.

The study has shown that *MMP*7 -181 G allele has a 2- to 3-fold higher promoter activity than that of the 181 A allele (78). Higher promoter activity induced an elevated level of *MMP*-7 mRNA and subsequently led to overexpression of MMP-7. "Sheddase function" of *MMP*-7 protein and the ability to increase activation of other *MMPs* worked together might predispose to malignant transformation (78,79). Although, to the best of our knowledge, all of the association studies investigating *MMP*7 -181 A/G were conducted in Asians, inconsistent results were still reported by previous studies. The reason might be listed as follows limited sample size and low frequency of the G allele. Our meta-analysis pooled data from 3 studies, suggesting that G allele increased lung cancer risk in Asians. However, further studies that focus on Caucasians are called for.

MMP9 -1562 C/T, the presence of the T allele was found to be involved in the decrease of the capacity of a putative transcription repressor protein with a subsequent increase in gene expression (71). *MMP13* -77A/G, reduced the transcriptional activity of the *MMP13* gene due to the modification of a PEA3 binding site (80). These two polymorphisms were also found significantly associated with lung cancer susceptibility. However, as Wacholder *et al.* reminded us, we should "protect ourselves from overinterpreting statistically significant findings that are not likely to signify a true association" (30). FPRP tests were indicating the probability of false-positive reports on these two polymorphisms. So, results for *MMP9* -1562 C/T and *MMP13* -77A/G should be interpreted with caution, and more studies were needed to replicate these findings.

The association between polymorphisms in *MMP* genes and lung cancer susceptibility has been investigated by several meta-analyses (22-24). The latest one was conducted by Li *et al.* (23) in 2015 and, in agreement with our meta-analysis, they demonstrated that significantly increased and reduced lung cancer risk were found in Asians for *MMP1* -1607 1G/2G and *MMP2* -1306 C/T, -735 C/T respectively. However, opposite to our result, they found a significantly increased risk for *MMP9* -1562 C/T while a decreased risk was identified in ours. They yielded this result based on only one study (68), which was excluded in ours according to the sensitivity analysis. Our finding was consistent with another meta-analysis performed by Hu *et al.* (22). Compared with Li's work, we excluded one letter (31) but identified more eligible studies (49,53,56,59,61,64,66). We also found two significant associations that were not observed in Li's study—*MMP13* -77A/G decreased lung cancer risk and *MMP*7 -181 A/G increased lung cancer risk. Furthermore, data for three new polymorphisms (*MMP*7 -181 A/G, *MMP9* R279Q, and *MMP12* -82A/G), which have never been investigated by previous meta-analyses, were also analyzed.

Our meta-analysis has several strengths. First, less stringent terms were used in the literature search, and no limitation was made. Thus, selection bias was well controlled. Additionally, compared with the prior meta-analyses, more studies were included, and three new polymorphisms were also explored. Finally, we performed FPRP tests to confirm if the obtained associations were noteworthy or not. However, some limitations should also be addressed. Firstly, for several polymorphisms, the number of included studies limited further analysis. Secondly, significant heterogeneity was detected. Although we used the random effects model to calculate the pooled ORs, the precision of the outcome would be affected.

Finally, the lack of more detailed individual data preventing a more precise evaluation with adjusted ORs.

In conclusion, our results suggested that *MMP1* -1607 1G/2G and *MMP*7 -181 A/G were risk factors for lung cancer in Asians, while *MMP2* -1306 C/T, *MMP2* -735 C/T, *MMP9* -1562 C/T, and *MMP13* -77A/G might be protective factors. There was no association between *MMP3* -1171 5A/6A, *MMP9* R279Q, and *MMP12* -82A/G and lung cancer risk. However, results for *MMP9* -1562 C/T and *MMP13* -77A/G should be interpreted with caution. Well-designed studies with larger sample sizes and more ethnic groups are required to confirm the association identified in our meta-analysis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Positive results from the sensitivity analysis

Study omitted	Allelic model			Heterozygote model			Homozygote model			Dominant model			Recessive model		
	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)
MMP1 -1607 1G/2G															
Su										1.17 (1.00–1.38)	0.050	36.5			
Gonzalez-Arriaga										1.15 (1.02–1.30)	0.023	14.3			
Hart										1.09 (0.96–1.23)	0.171	41.4			
Liu										1.07 (0.95–1.20)	0.272	18.3			
Fakhoury										1.11 (0.99–1.24)	0.079	45.4			
Zhang										1.08 (0.97–1.22)	0.167	23.1			
Combined										1.11 (0.99–1.24)	0.077	31.8			
MMP2 -1306 C/T															
Yu	0.86 (0.58–1.29)	0.479	54.0	0.87 (0.54–1.38)	0.546	53.3	0.69 (0.25–1.87)	0.467	0.0	0.86 (0.53–1.37)	0.517	56.3			
Rollin	0.67 (0.43–1.05)	0.082	78.4	0.66 (0.38–1.16)	0.153	81.6	0.49 (0.26–0.94)	0.030	0.0	0.65 (0.38–1.12)	0.118	81.0			
Bayramoglu	0.64 (0.44–0.93)	0.020	64.1	0.58 (0.39–0.86)	0.007	56.6	0.52 (0.27–1.02)	0.055	0.0	0.59 (0.39–0.89)	0.011	61.2			
Song	0.81 (0.46–1.41)	0.452	84.4	0.79 (0.40–1.55)	0.486	85.2	0.57 (0.30–1.10)	0.096	0.0	0.79 (0.40–1.53)	0.479	85.4			
Combined	0.74 (0.49–1.11)	0.142	76.8	0.72 (0.44–1.16)	0.176	77.8	0.55 (0.30–1.00)	0.051	0.0	0.71 (0.44–1.14)	0.160	78.2			
MMP2 -735 C/T															
Zhou	0.86 (0.68–1.10)	0.228	0.0	0.87 (0.65–1.16)	0.340	0.0				0.86 (0.65–1.13)	0.266	0.0			
Rollin	0.76 (0.66–0.87)	0.000	31.1	0.72 (0.51–1.01)	0.061	69.4				0.72 (0.53–0.97)	0.032	64.1			
Jia	0.72 (0.61–0.85)	0.000	0.0	0.63 (0.52–0.78)	0.000	0.0				0.65 (0.53–0.79)	0.000	0.0			
Combined	0.76 (0.66–0.88)	0.000	0.0	0.73 (0.56–0.95)	0.019	43.1				0.73 (0.58–0.92)	0.007	34.9			
MMP9 -1562 C/T															
Zhang	0.80 (0.66–0.97)	0.021	0.0				0.29 (0.14–0.62)	0.002	0.0				0.30 (0.14–0.64)	0.002	0.0
Rollin	1.12 (0.56–2.23)	0.758	91.4				0.75 (0.13–4.29)	0.746	80.8				0.69 (0.15–3.20)	0.641	75.2
Bayramoglu	1.12 (0.54–2.34)	0.758	91.0				0.61 (0.07–5.02)	0.644	82.7				0.56 (0.08–3.74)	0.552	78.6
Gonzalez-Arriaga	1.05 (0.43–2.56)	0.923	90.5				0.60 (0.06–6.44)	0.673	77.7				0.58 (0.07–4.79)	0.612	72.0
Combined	1.00 (0.57–1.75)	0.988	87.9				0.53 (0.11–2.53)	0.426	75.1				0.51 (0.13–2.07)	0.348	68.8
MMP9 R279Q															
Hu										0.42 (0.18–0.97)	0.041	–			
Zhao										0.92 (0.75–1.13)	0.424	–			
Combined										0.69 (0.33–1.45)	0.330	68.9			
MMP13 -77A/G															
Gonzalez-Arriaga				0.67 (0.47–0.96)	0.029	45.3									
Wang				0.96 (0.68–1.37)	0.838	64.1									
Peng				0.80 (0.39–1.64)	0.548	88.5									
Combined				0.81 (0.54–1.22)	0.312	78.3									