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Original Article

Genetic polymorphisms of matrix metalloproteinase-1 is associated with the risk of cancer metastasis: an update meta-analysis

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Abstract: Background: Matrix metalloproteinase-1 is the most expressed interstitial collagenase among Matrix metalloproteinases (MMPs), which play a central role in the degradation of basement membranes and the extracellular matrix. Accumulating evidences have elucidated that the genetic polymorphisms of Matrix metalloproteinase-1 (MMP-1) were associated with cancer invasion and metastasis with inconsistent results. To derive a more precise and reliable evaluation of the relationship between MMP-1(-1607)1G/2G polymorphism and cancer metastasis, we carried out this comprehensive meta-analysis. Methods: A systematic search of PubMed, EMBASE and Web of Science was conducted for relevant studies. A total of twenty-three eligible studies were included in this meta-analysis. The odds ratios (ORs) with 95% confidence intervals (95% CIs) calculated by Stata software were used to assess the associations between MMP-1(-1607)1G/2G polymorphism and cancer metastasis. We used Q test, I^2 value, and funnel plot to examine heterogeneity and publication bias, respectively. Results: Twenty-three studies containing 3208 cancer cases (1546 metastasis-positive cases and 1662 metastasis-negative cases) were pooled together in this meta-analysis. The results showed that MMP-1(-1607)1G/2G polymorphism was significantly associated with the increased risk of cancer metastasis (dominant model: 2G2G + 1G2G vs. 1G1G, OR = 1.28, 95% CI = 1.01-1.62, P = 0.040; recessive model: 2G2G vs. 1G2G + 1G1G, OR = 1.34, 95% CI = 1.02-1.76, P = 0.040; allele model: 2G vs. 1G, OR = 1.27, 95% CI = 1.11-1.45, P < 0.001). Stratified analysis based on ethnicity revealed that MMP-1(-1607)1G/2G polymorphism significantly increased the risk of cancer metastasis in Europeans. Besides, no obvious publication bias was observed in the analysis. Conclusions: In summary, our results of this meta-analysis indicated that MMP-1(-1607)1G/2G polymorphism was significantly associated with cancer progress overall and 2G allele at the MMP-1 promoter region could be seen as a risk factor of cancer invasion and metastasis.

Keywords: MMP-1, polymorphism, cancer metastasis, risk, meta-analysis

Introduction

Cancer is the primary cause of death and the major threat to public health all over the world. The incidence rates of this malignancy are progressively increasing since 1990 [1]. Cancer metastasis, the spread of malignant cells from the primary location to new distant sites, is regarded as the cause of ninety percent of deaths from solid tumors [2] and re-attracts researchers' attention nowadays. Metastasis is a multi-step progress of tumor cells ranging over escape from anoikis, protelysis of extracellular matrix, invasion of lymph, escape from immune surveillance and angiogenesis and so on [3]. It's obvious that extracellular matrix and basal membrane constitute main physical barriers of cancer metastasis.

Matrix metalloprpteinases (MMPs) are a family of metal-dependent proteolytic enzymes in relation to cell immigration, embryogenesis, tissue remodeling, and wound repair and the like. The most significant function of MMPs is to degrade not only basement membrane, and extracellular matrix like elastin, collagen, gelatin, but also growth-factor-binding proteins, receptor tyrosine kinases, and cell-adhesion

molecules and that counts among the causes of initiation, invasion and metastasis of cancer [4, 5]. Matrix metalloproteinase-1 (MMP-1), known as interstitial collagenase located on chromosome11q, is an important member of MMPs family and expressed in many normal cells. Previous studies indicated that MMP-1 gene facilitated growth of cancer and metastasis of lymph node [6, 7] and the expression level of it was high in many neoplasms instead of low in normal physiological tissues [8]. Meanwhile, the level of expression of MMP-1 gene could also be influenced by a functional single nucleotide polymorphism located in -1607 bp in *MMP-1* promoter region [9]. A single nucleotide polymorphism is the most common genetic variation which underlies differences in susceptibility to diseases in human beings. *MMP-1(-1607)1G/2G* (rs1799750) polymorphism is located at position 1607 bp upstream of the *MMP-1* promoter region with the insertion of a guanine (G) and capable of enhancing the transcription activities of MMP-1 gene by creating a core binding site for Ets family of transcription factors [10-12]. Individuals with the 2G2G genotype of *MMP-1(-1607)1G/2G* polymorphism were detected to have higher MMP-1 level. Highly expressed MMP-1 played a remarkable role in degrading collages I and III which was very important to cancer metastasis. In a sense, it heralded poorer prognosis in malignant patients [13].

To date, although a variety of studies have demonstrated the relationship between *MMP-1(-1607)1G/2G* polymorphism and neoplasm metastasis [6, 14-34], the results remain inconsistent and conflicting. Therefore, we performed this systematic meta-analysis of all eligible published studies from 2000 to 2015 to derive a more accurate and deeper evaluation of associations between *MMP-1(-1607)1G/2G* polymorphism and cancer metastasis.

Materials and methods

Identification of eligible studies

We executed a systematic search on PubMed, EMBASE and Web of Science databases for relevant case-control studies that investigated the associations between *MMP-1(-1607)1G/2G* polymorphism and metastasis up to July 1, 2015. The following keywords used for search were "MMP-1 OR Matrix metalloproteinase-1", "interstitial collagenase", "polymorphism OR variation" and "cancer OR carcinoma". The references of retrieved original articles were screened by manually searched as well.

Inclusion and exclusion criteria

All eligible studies included in this meta-analysis must meet the following criteria: (a) discussion about the correlation between *MMP-1(-1607)1G/2G* polymorphism and cancer; (b) independent case-control study; (c) sufficient data of genotype frequency to obtain odds ratios with 95% confidence intervals. The exclusion criteria were (a) not case-control study; (b) insufficient information about genotype frequency; (c) duplicate data of earlier publications; (d) reviews, comments or meta-analyses.

Date extraction

Two reviewers (Dongdong Wu and Bo Fu) independently extracted all available data from eligible studies. When encountering divergence, the third reviewer (Peng Song) was invited to verify data until a consensus was reached. We collected information including author's first name, publication year, cancer type, country origin, ethnicity of study population, the number of metastasis-positive and metastasis-negative cases and respective genotype distributions for *MMP-1(-1607)1G/2G* polymorphism from each available study. Referring to TNM Classification of Malignant Tumours (7^{th} edition), we divided all cases into metastasis-positive group and metastasis-negative group depending on whether lymph nodes invasion or distant metastasis was detected at the time of diagnosis or follow-up visit. It is noted that we gave priority to refer to lymph nodes metastasis if lymph nodes metastasis and distant metastasis were discussed together in respective studies.

Statistical analysis

We evaluated the strength of the correlation between *MMP-1(-1607)1G/2G* polymorphism and cancer metastasis by means of pooled odds ratios (ORs) and 95% confident intervals (CIs). The effect of study size of eligible studies on the results was assessed by the weight. The risk ORs of cancer metastasis associated with *MMP-1(-1607)1G/2G* polymorphism were esti-

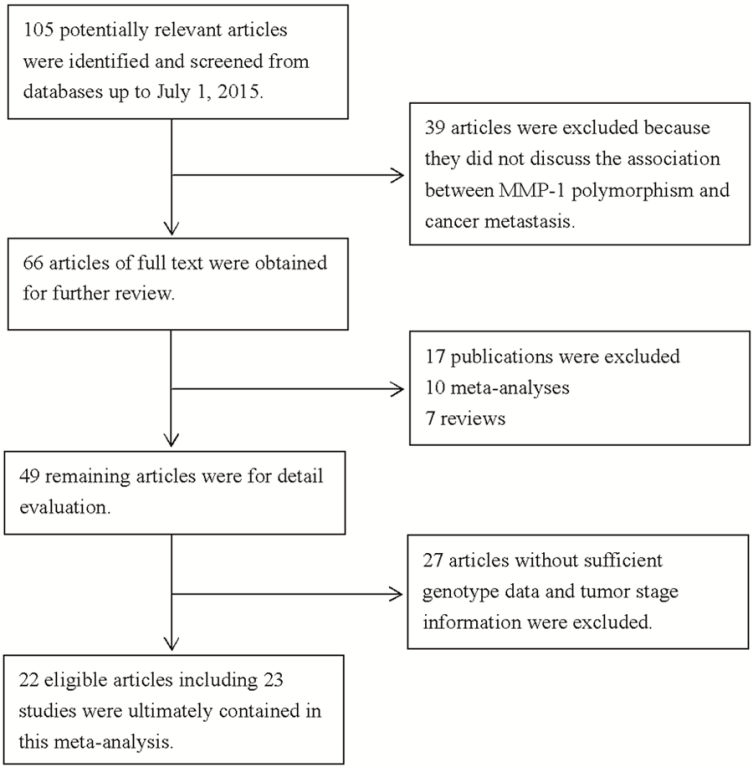

Figure 1. Flow diagram of studies identification for this meta-analysis.

mated for every study. The pooled ORs were calculated under dominant model comparison (2G2G + 1G2G *vs*. 1G1G), recessive model comparison (2G2G *vs*. 1G2G + 1G1G) and allele model comparison (2G *vs*. 1G), respectively. Z-test was applied to estimate the statistical significance of the ORs and a P value < 0.05 was considered significant. The heterogeneity between different studies was checked by ^{2}-based Q test and I^2 index. A fixed-effects model (the Mantel-Haenszel method) was applied if Q test indicated absence of prominent heterogeneity across all qualified studies, $P_{heterogeneity}$ > 0.05 and/or I^2 < 50% [35]. Otherwise, the random-effects model was conducted (Der Simonian and Laird method) [36]. Stratified analyses were performed by cancer types and ethnicity of study population. A cancer type was grouped into other cancers if it was investigated in a single study. Sensitivity analysis was also tested by removing one study at a time to evaluate the overall heterogeneity and effect size. The publication bias was diagnosed by Begg's funnel plot. Funnel plot asymmetry was assessed by Egger's linear regression test. (P < 0.05 suggested the statistically significant publication bias) [37]. All statistical analyses were carried out with Stata software (version 12.0, Stata Crop, College Station, TX, USA).

Result

Characteristics of studies

Eventually, 105 studies were retrieved according to the search strategy. 22 qualified articles [6, 14-34] containing 23 independent studies were involved in this meta-analysis after carefully reviewing. The publications selection progress was showed in **Figure 1**. All eligible case-control studies included 3208 cancer cases which were comprised of 1546 metastasis-positive cases and 1662 metastasis-negative cases. Among these studies, 7 studies described head and neck cancer, 3 studies focused on gastric cancer, 5 studies discussed colorectal cancer, 2 studies analyzed breast cancer and the remainders investigated other cancers. In addition, there were 15 studies of Asians, 6 studies of Europeans and 1 study of mixed population. All detailed characteristics of these studies were neatened in **Table 1**.

Quantitative data synthesis

This update meta-analysis pooled 23 eligible studies together to explore the associations between *MMP-1(-1607)1G/2G* polymorphism and cancer metastasis. The main results of this meta-analysis were shown in **Table 2**. The overall analysis indicated that genetic variant 2G allele was significantly associated with increased risk of cancer invasion and metastasis, compared with 1G allele (OR = 1.27, 95% CI = 1.11-1.45, P < 0.001, $P_{heterogeneity}$ < 0.001, I^2 = 72.1%, **Figure 2A**). Meanwhile, we found that *MMP-1* 2G2G and 1G2G variant genotypes also had a high risk of cancer metastasis compared with patients carrying 1G1G genotype for dominant model (2G2G + 1G2G *vs*. 1G1G: OR = 1.28, 95% CI = 1.01-1.62, P = 0.040, $P_{heterogeneity}$ = 0.083, I^2 = 35.0%, **Figure 2B**) and recessive model (2G2G *vs*. 1G2G + 1G1G: OR = 1.34,

Table 1. Characteristics of MMP-1 polymorphism distribution included in the Meta-analysis

Study	Year	Cancer type	Country	Ethnicity	Total		Genotypes					
					M(+)	M(-)	M(+)			M(-)		
							1G1G	1G2G	2G2G	1G1G	1G2G	2G2G
O-charoenrat	2006	head/neck	Thailand	Asian	181	119	75[a]	-	106	76[a]	-	43
Hashimoto	2004	head/neck	Japan	Asian	43	86	20[a]	-	23	40[a]	-	46
Vairaktaris	2007	head/neck	Greece	European	68	88	14	26	28	22	42	24
Nishizawa	2007	head/neck	Japan	Asian	56	114	3	26	27	11	53	50
Cao	2005	head/neck	China	Asian	67	29	27[a]	-	40	14[a]	-	15
Kondo	2005	head/neck	Japan/Taiwan	Asian	40	43	6	-	34[b]	4		39[b]
Nasr	2007	head/neck	Tunisia	European	118	56	5	37	76	8	26	22
Shimizu	2008	head/neck	Japan	Asian	19	50	9[a]	-	10	23[a]	-	27
Jin	2005	esophageal	China	Asian	59	72	6	24	29	12	29	31
Matsumura	2004	gastric	Japan	Asian	89	126	11	42	36	15	46	65
Dey	2014	gastric	India	Asian	119	26	18	-	101[b]	5	-	21[b]
Jin	2005	gastric	China	Asian	46	48	2	16	28	7	16	25
Hinoda	2002	colorectal	Japan	Asian	42	59	20[a]	-	22	23[a]	-	36
Woo	2006	colorectal	Korea	Asian	79	106	2	23	54	5	31	70
De Lima	2009	colorectal	Brazil	Mixed	43	38	31[a]	-	12	22[a]	-	16
Ghilardi	2001	colorectal	Italy	European	17	43	6[a]	-	11	31[a]	-	12
Kouhkan	2008	colorectal	Iran	Asian	69	81	10	21	38	20	40	21
Hughes	2007	breast	London	European	52	88	12	20	20	26	43	19
Przbylowska	2006	breast	Poland	European	141	129	33	57	51	44	58	27
Fang	2005	lung	China	Asian	123	74	13	41	69	8	24	42
Fong	2004	chondrosarcoma	Taiwan	Asian	14	53	6	8	0	12	26	15
Lai	2005	cervical	Taiwan	Asian	51	89	12	22	17	8	38	43
Albayrak	2007	prostate	Turkey	European	10	45	3	-	7[b]	7	-	38[b]

M(+)/M(-): cases of metastasis positive and metastasis negative. [a]means the number of 1G1G + 1G2G. [b]means the number of 1G2G + 2G2G.

Table 2. Stratified analysis of *MMP-1(-1607)1G/2G* polymorphism on cancer metastasis

Stratification	M(+)/M(-)	2G2G + 1G2G *vs.* 1G1G				2G2G *vs.* 1G2G + 1G1G			
		OR (95% CI)	P	Ph	I^2 (%)	OR (95% CI)	P	Ph	I^2 (%)
Total	1546/1662	1.28 (1.01-1.62)	0.040	0.083	35.0	1.34 (1.02-1.76)	0.040	< 0.001	65.2
Cancer type									
Head/neck	592/585	1.50 (0.89-2.51)	0.126	0.206	34.4	1.69 (1.20-2.31)	0.020	0.156	35.6
Gastric	254/200	1.33 (0.73-2.43)	0.351	0.339	7.5	0.90 (0.41-1.97)	0.792	0.108	61.3
Colorectal	250/327	1.93 (0.91-4.08)	0.086	0.988	0.0	1.43 (0.66-3.11)	0.370	0.001	78.2
Breast	193/217	1.60 (1.02-2.48)	0.039	0.693	0.0	2.18 (1.40-3.40)	0.001	0.902	0.0
Other	257/333	0.74 (0.47-1.15)	0.177	0.123	44.9	0.81 (0.56-1.17)	0.755	0.128	47.3
Ethnicity									
Asian	1097/1175	1.10 (0.80-1.50)	0.570	0.108	36.4	1.14 (0.83-1.56)	0.429	< 0.001	62.5
European	449/487	1.54 (1.08-2.20)	0.016	0.270	22.7	2.35 (1.72-3.21)	0.001	0.707	0.0

2G2G + 1G2G *vs.* 1G1G: dominant model; 2G2G *vs.* 1G2G+1G1G: recessive model. OR: odds ratio; CI: confidence interval; Ph: *P* value for heterogeneity test. Random model was used for data pooling when $P_{heterogeneity}$ < 0.05 and/or I^2 > 50%; otherwise fixed model was used. Two-sided test for genotype distribution.

95% CI = 1.02-1.76, *P* = 0.040, $P_{heterogeneity}$ < 0.001, I^2 = 65.2%, **Figure 2C**). In the stratified analysis by cancer type, significant associations were observed in breast cancer under the dominant model (OR = 1.60, 95% CI = 1.02-2.48, *P* = 0.039, $P_{heterogeneity}$ = 0.693, I^2 = 0.0%) and recessive model (OR = 2.18, 95% CI = 1.40-3.40, *P* = 0.001, $P_{heterogeneity}$ = 0.902, I^2 = 0.0%). Besides, there were significant associations in head and neck cancer subgroup under

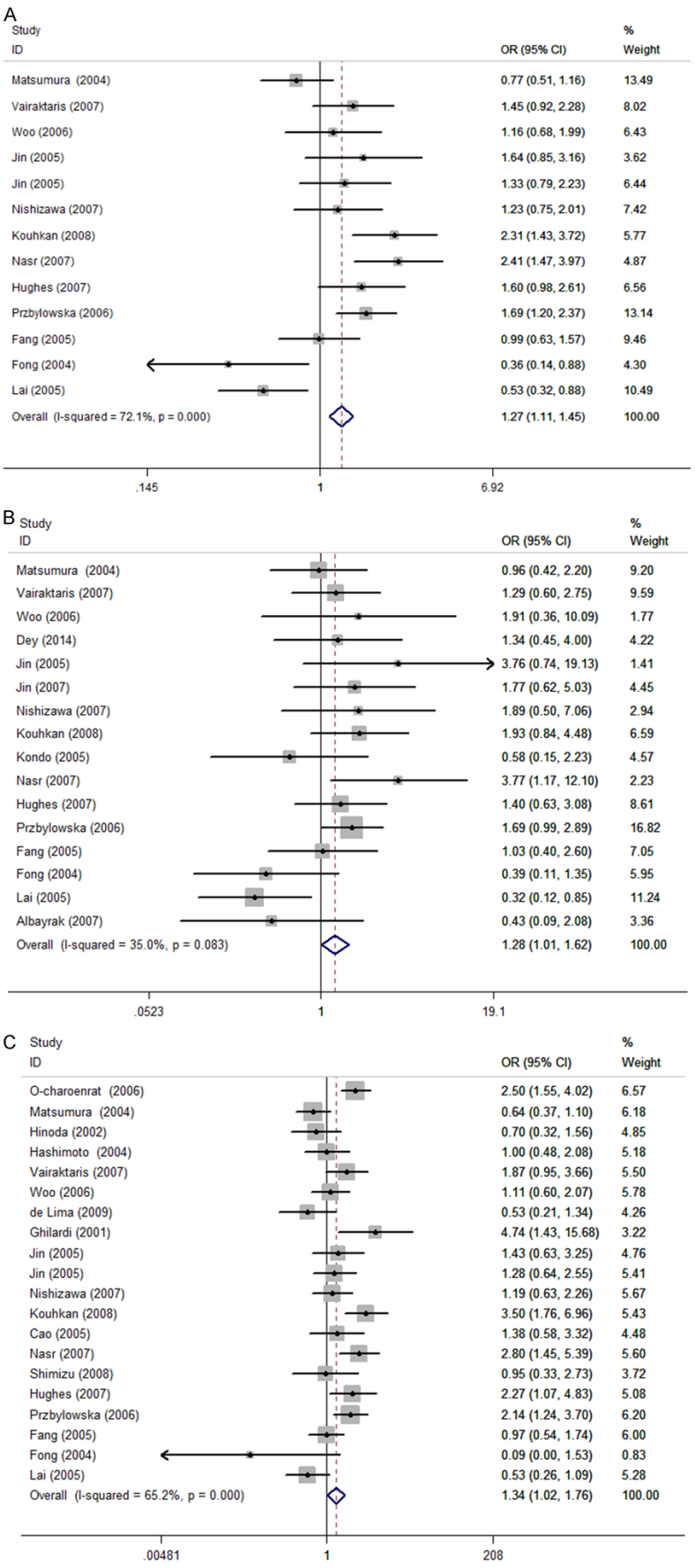

Figure 2. Forest plot of cancer metastasis associated with MMP-1(-1607)1G/2G polymorphism. A. 2G allele vs. 1G allele. B. The dominant model. C. The recessive model. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflected the weight. The diamond represented the pooled OR and 95% CI.

recessive model (OR = 1.69, 95% CI = 1.20-2.31, P = 0.020, $P_{heterogeneity}$ = 0.156, I^2 = 35.6%). Nevertheless, no significant associations with the risk of cancer metastasis were found in gastric cancer, colorectal cancer or other cancers under dominant model and recessive model. Under the dominant model and recessive model, subgroup analysis based on ethnicity was carried out. The results suggested that genetic variant 2G2G or 1G2G genotype strongly increased the risk of cancer metastasis in Europeans (dominant model: OR = 1.54, 95% CI = 1.08-2.20, P = 0.016, $P_{heterogeneity}$ = 0.270, I^2 = 22.7%; recessive model: OR = 2.35, 95% CI = 1.72-3.21, P = 0.001, $P_{heterogeneity}$ = 0.707, I^2 < 0.1%). On the contrary, there was no significant associations in Asians (dominant model: OR = 1.10, 95% CI = 0.80-1.50, P = 0.570, $P_{heterogeneity}$ = 0.108, I^2 = 36.4%; recessive model: OR = 1.14, 95% CI = 0.83-1.56, P = 0.429, $P_{heterogeneity}$ = 0.001, I^2 = 60.5%).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each study on the pooled ORs by deletion of individual study at a time. Through the analysis, we got

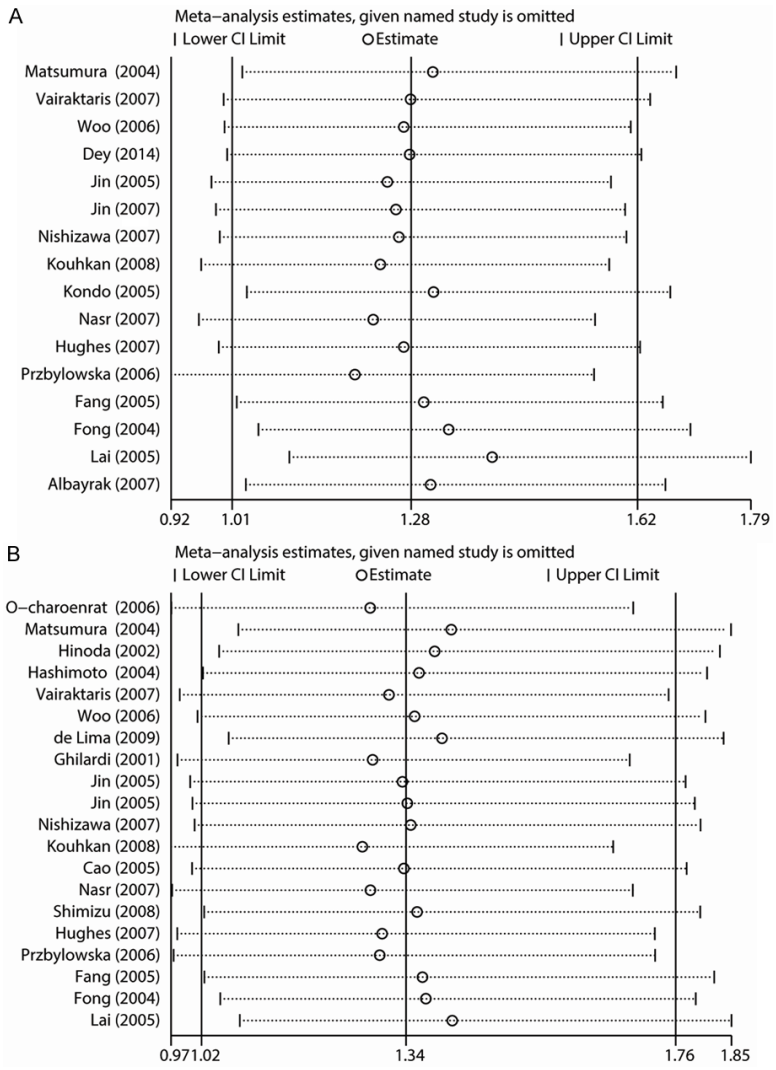

Figure 3. Influence analysis of summary odds ratio coefficients on associations between MMP-1(-1607)1G/2G polymorphism and cancer metastasis in this meta-analysis. A. The dominant model. B. The recessive model. The summary ORs were calculated by omitting each study in order.

to know that the study conducted by Lai et al. [33] significantly affected the overall result in dominant model (**Figure 3A**). After omitting this study, the result of this meta-analysis was not influenced apparently (OR = 1.40, 95% CI = 1.10-1.79, P = 0.007, $P_{heterogeneity}$ = 0.384, I^2 = 6.2%). The result in recessive model showed that no single study obviously influenced pooled ORs (**Figure 3B**). In general, no single study materially affected the pooled ORs which indicated that our results were statistically reliable and stable.

Heterogeneity analysis

Moderate heterogeneity was detected among these studies in recessive model (2G2G *vs*. 1G2G + 1G1G) and allele model (2G *vs*. 1G) but not in dominant model (2G2G + 1G2G *vs*. 1G1G). Hence, a fixed-effect model was utilized to pool ORs in dominant model while A random-effects model was used to pool ORs of other models. Stratified analysis was conducted by ethnicity of study population and cancer type to evaluate the source of heterogeneity. As showed in **Table 2**, we found that studies of gastric cancer, colorectal cancer and Asian population contributed to heterogeneity for recessive model. One possible explanation may be that the sample size of gastrointestinal cancer was relatively small and most of studies on gastrointestinal cancer were Asian population. To further investigate which study accounted for the major source of heterogeneity, we conducted a Galbraith radial plot. Five studies [14, 23, 28, 32, 33] which could be the potential source of heterogeneity were excluded from the pooled results (**Figure 4**). The associations between *MMP-1(-1607)1G/2G* polymorphism and cancer metastasis were still existed in recessive model (OR = 1.398, 95% CI = 1.162-1.681, P < 0.001, $P_{heterogeneity}$ = 0.052, I^2 = 40.6%). The same method was performed with allele model and we found three studies [23, 32, 33] contributing to the major cause of heterogeneity. The result remained stable after elimination of the above studies (OR = 1.53, 95% CI = 1.28-1.82, P < 0.001, $P_{heterogeneity}$ = 0.212, I^2 = 25.1%).

Publication bias

There was no evidence of publication bias found in this meta-analysis by use of the Begg's funnel plot and Egger's test. The shape of the funnel plot did not reveal any obvious asymmetry in dominant model and recessive model

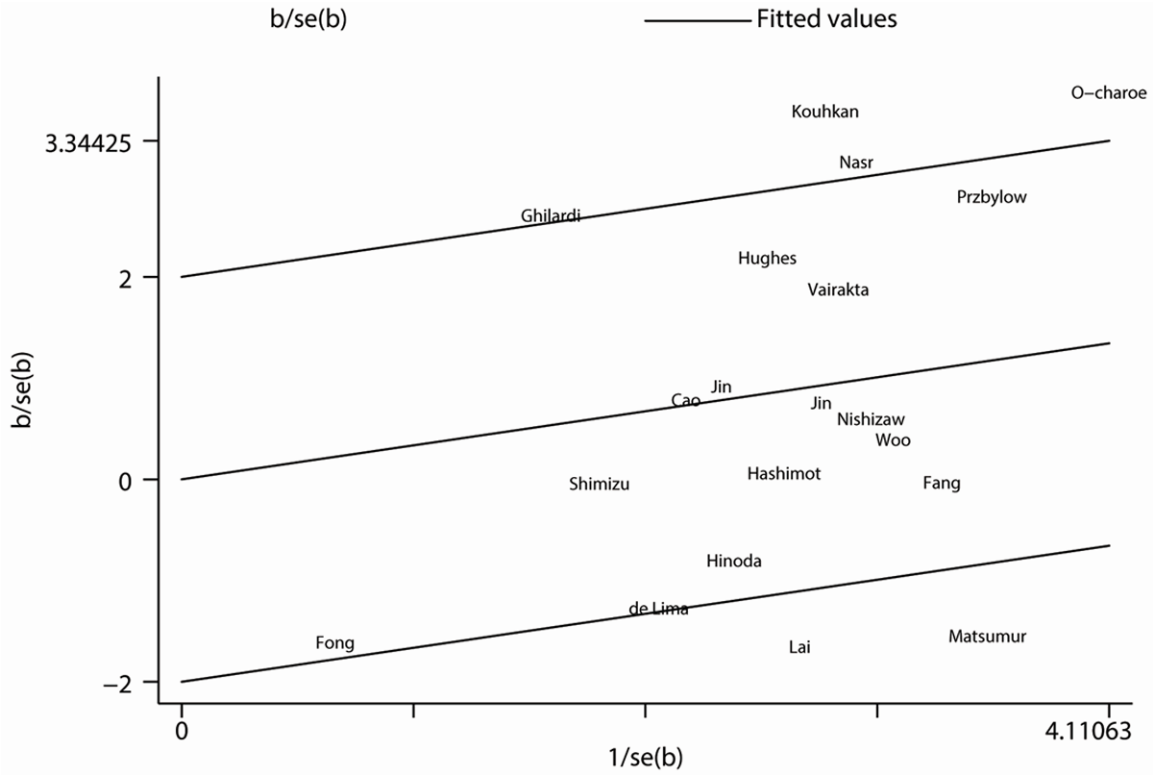

Figure 4. Galbraith radial plot for the recessive model. The figure showed the contribution of individual studies to the heterogeneity. There were five studies [14, 23, 28, 32, 33] accounting for the major cause of the heterogeneity.

(**Figure 5A** and **5B**). Egger's test was utilized to provide statistical evidence of funnel plot symmetry and the results were similar. (t = -0.61, *P* = 0.550 for dominant model; t = -1.09, *P* = 0.290 for recessive model).

Discussion

Cancer metastasis is a multi-step progression with complicated molecular mechanisms of regulation. Migration and invasion of malignant cells are regarded as the pivotal point of the progress of metastasis. An increasing number of studies have demonstrated that MMPs were involved in a variety of tumors geneses and developments through facilitating the breakdown of extracellular matrix, basement membranes, collagen, and fibronectin which were seen as normal barriers under physiological conditions [38]. In addition, MMPs also have an effect on the regulation of growth and proliferation of primary and metastatic tumors [39].

Among the MMPs family, MMP-1 is the most conspicuous and intriguing member partially because of its most ubiquitous expression. *MMP-1* gene is located in the chromosome 11q22 and is widely expressed not only in diverse normal physiological cells but also in various tumor cells [40]. As an interstitial collagenase with proteolytic activities, MMP-1 can specifically degrade fibrillar collagens, the abundant component of human connective tissues [30]. To our knowledge, the expression of MMP-1 is regulated by mitogen activated protein kinase (MAPK) pathway. Activator protein-1 and polyoma enhancing activity-3/E26 virus transcription factors can recognize the common bind sites in the *MMP-1* gene promoter region and directly affect the expression of MMP-1 [41]. Compared with low expression in normal cells and tissues, MMP-1 is overexpressed in various tumor tissues such as head and neck cancer, esophageal cancer, gastric cancer and colorectal cancer and so on [14, 22, 23, 25] which have brought an expectation of being a potential biomark in cancer progress for MMP-1. Growing evidences indicated that MMP-1 plays an important role in tumorigenesis progression and metastasis. Murray GI et al. [42, 43] had indicated that poor prognosis of gastric cancer, colorectal cancer and esophageal cancer was related to the overexpression

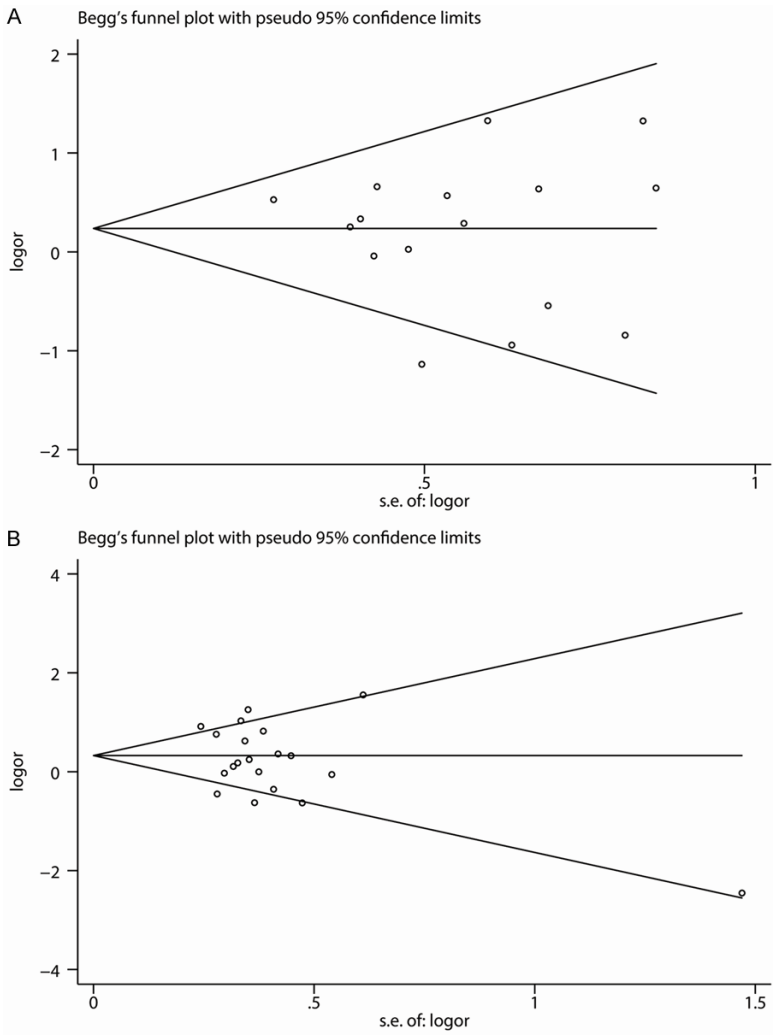

Figure 5. Begg' s funnel plot for publication bias test of overall meta-analysis. A. The dominant model. B. The recessive model. Each point represented a separate study for the indicated association.

of MMP-1. Study of Moser PL et al. [44] about invasive cervical cancer showed the positive associations between the overexpression of MMP-1 in cancer cells and lymphovascular space invasion and lymph node metastasis. In chondrosarcoma patients, elevated expression of MMP-1 was detected in patients with recurrence while relatively low level of MMP-1 expression in patients remaining disease-free [45]. It is well-known that SNP is a DNA sequence variation which is common in human beings. Some SNPs occurring in the gene promoter region can regulate gene expression by influencing the activities of transcription factors [46]. Joni L. Rutter et al. initially reported that a functional SNP (*MMP-1(-1607)1G/2G* polymorphism) located at the -1607 bp locus of *MMP-1* promoter region with the insertion of a G nucleotide could generate a 5'-GGAT-3' sequence, a core binding site for Ets family of transcription factors which gave rise to significantly elevated transcription activity for mutant 2G allele compared to wild-type 1G allele [13]. Higher level expression of MMP-1 were detected in cancer tissues of patients with 2G allele than those with 1G allele [47]. Thus, we surmised that *MMP-1(-1607)1G/2G* polymorphism was associated with tumorigenesis progress and invasion. In recent decades, A series of studies had explored the associations between *MMP-1(-1607)1G/2G* polymorphism and susceptivity and metastasis of malignancy but the results yet remained controversial and inconsistent. A meta-analysis had pointed out that *MMP-1(-1607)1G/2G* polymorphism was associated with an increased risk of cancer [48]. Dan Liu et al. indicated that 2G allele increased the risk of metastasis only under the recessive model in their meta-analysis [49]. To further reveal the impact of *MMP-1(-1607)1G/2G* polymorphism on cancer invasion and derive a more precise and deeper evaluation of the associations between *MMP-1(-1607)1G/2G* polymorphism and cancer metastasis, we performed this update meta-analysis.

In our analysis, we found that 2G allele at *MMP-1* promoter region significantly elevated the risk of tumor metastasis. Meanwhile, significant associations between *MMP-1(-1607)1G/2G* polymorphism and cancer metastasis were also found under both dominant model (2G2G + 1G2G *vs*. 1G1G) and recessive model (2G2G *vs*. 1G2G + 1G1G). There was moderate heterogeneity in the analysis of recessive model and allele model but no obvious heterogeneity in dominant model. To diagnose the source of heterogeneity, we carried

out stratified analysis, sensitivity analysis and a Galbraith radial plot. The results showed that our analysis was stable and reliable.

In stratified analysis based on cancer type, we found significant associations in breast cancer under the dominant model and recessive model. Besides, there was a significant increased risk of cancer metastasis in the subgroup of head and neck cancer under recessive model, whereas no significant associations were found in gastric cancer, colorectal cancer or other cancers. There is an earlier research which indicated that *MMP-1(-1607)1G/2G* polymorphism was related to the risk of lymph node metastasis and poor prognosis in breast cancer and that is in agreement with our results [29]. One possible explanation is that different tumors in different sites have various microenvironment and carcinogenetic mechanisms and *MMP-1(-1607)1G/2G* polymorphism may reflect varying values in different tumors. In subgroup analysis by ethnicity, significant associations between *MMP-1(-1607)1G/2G* polymorphism and increased risk of cancer metastasis were found in Europeans but not in Asians. Diverse genetic backgrounds, various living environments and lifestyles of different ethnicity may partially account for the phenomenon. Besides, the differences in results of Asians and Europeans may be due to chance because of inadequate sample size and further studies with larger sample size need to be performed to confirm our conclusions.

We have to admit that there are some limitations in our meta-analysis. First, moderate heterogeneity emerged from eligible studies. Differences in surroundings and genetic backgrounds of research objects may contribute to the heterogeneity, as well as tumor characteristics, when evaluating synthetic results of diverse studies and that is inevitable. Only eliminating the influence of heterogeneity in all eligible studies can obtain a statistical powerful prediction. Second, the sample size of our meta-analysis was not large enough especially in stratified analysis which may lead to false positive or negative results. Third, we did not analysis some other potential risk factors of cancer metastasis or interactions between different genes and environment. A better-designed analysis with more detailed data should be performed to check our findings. Fourth, though we did not find any obvious publication bias with Begg's funnel plot and Egger's test, some potential publication bias was still exist on account of ignoration of unpublished studies in our analysis.

Conclusion

In summary, our update meta-analysis definitely put forward for the first time that *MMP-1(-1607)1G/2G* polymorphism 2G allele could be seen as a risk factor of cancer invasion and metastasis especially in Europeans. Individuals with variant heterozygous 1G2G genotype or homozygous 2G2G genotype both increased the risk of tumor invasion and metastasis. Our results provided a possibility that *MMP-1(-1607)1G/2G* polymorphism 2G allele could be a potential biomark to predict cancer metastasis and poor prognosis in some ways.

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Disclosure of conflict of interest

None.

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