

Review Article

Association between MMP-12-82A/G polymorphism and cancer risk: a meta-analysis

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Abstract: Background: Numerous studies have focused on the association between MMP-12-82A>G polymorphism and cancer risk, but produced inconsistent results. Therefore, we performed a meta-analysis of case-control study to evaluate the association of MMP-12-82A>G polymorphism and cancer risk. Methods: A systematic literature search was conducted among PubMed, Web of Science, Science Direct, China National Knowledge Infrastructure (CNKI) and Wangfang databases updated on May 1st, 2015. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of association between this polymorphism and cancer risk. Results: A total of seventeen case-control studies with 7,450 cases and 7,348 controls were identified and analyzed. Overall, there was no statistically significant association between MMP-12-82A>G polymorphism and increased risk of cancer under all genetic models. Subgroup analysis by ethnicity observed that there is no strong relationship between MMP-12-82A>G polymorphism and cancer risk among Asian and European populations. Furthermore, stratified analysis based on the source of control revealed no statistically significant association between MMP-12-82A>G polymorphism and cancer risk either in hospital-based or population-based studies. However, when we stratified analysis based on cancer type, significant association was found in ovarian cancer, but not in other types of cancer. Conclusion: This meta-analysis suggests that MMP-12-82A>G polymorphism is not significantly associated with overall cancer risk. However, MMP-12-82A>G polymorphism may increase the susceptibility to ovarian cancer.

Keywords: Matrix metalloproteinases-12, polymorphism, cancer risk, meta-analysis

Introduction

Cancer is a leading cause of death and remains to be a major public health problem. About 14.1 million new cancer cases and 8.2 million cancer deaths occurred in 2012 worldwide [1]. It is well known that cancer is a complex disease involving multiple environmental factors and genetic factors. In particular, the association between genetic factors and cancer risk has been studied extensively, recently. Growing epidemiological evidence suggested that host genetic susceptibility plays a vital role in the pathogenesis of various types of cancer [2-4].

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that degrades virtually all extracellular matrix components [5]. Several types of MMPs are crucially involved in tumor invasion and metastasis

[6-8]. Among them Matrix metalloproteinase-12 (MMP-12) plays an important role in cancer development and progression, including cancer cell growth, migration, invasion, and metastasis [9-11]. Moreover, it has been reported that MMP-12 is highly expressed in a wide range of human cancers, including colorectal cancer, gastric cancer, nasopharyngeal carcinoma and lung cancer [12-15]. In recent years, several single nucleotide polymorphisms (SNPs) in the promoter region of *MMP-12* gene have been reported and the SNP of MMP-12-82A>G (rs2276109) is the most extensively studied. The MMP-12-82A>G polymorphism could affect transcriptional activity and lead to alterations in *MMP-12* gene expression. A number of studies have focused on the association between MMP-12-82A>G polymorphism and cancer risk, but the results are controversial. Therefore, in this study we performed a meta-analysis to better

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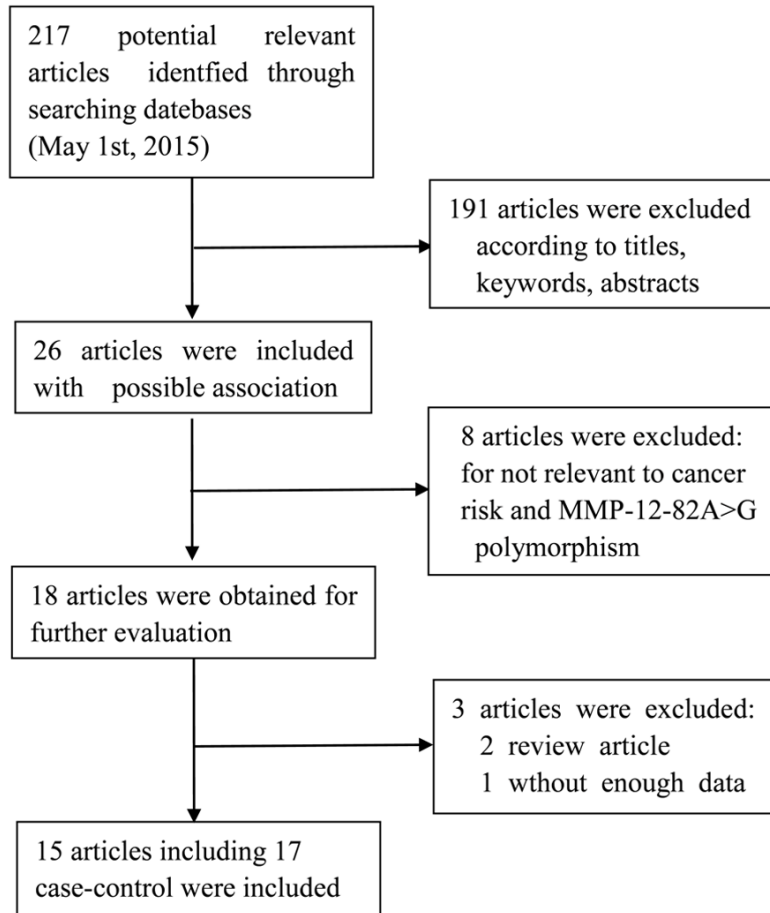


Figure 1. Search strategy of the studies included in this meta-analysis.

evaluate the association between MMP-12-82A>G polymorphism and cancer risk.

Methods

Search strategy

To identify all the articles on the association between the MMP-12-82A>G polymorphism and cancer risk, a systematic literature search was performed on electronic databases of PubMed, Web of Science, Science Direct, CNKI and Wanfang databases updated on May 1st, 2015. The search terms used were as follows: “Matrix metalloproteinases-12 or MMP-12”, “SNP or variant or polymorphism” and “cancer or carcinoma or neoplasm”.

Inclusion and exclusion criteria

The following inclusion criteria were applied: (1) case-control studies; (2) investigating the association of MMP-12-82A>G polymorphism with

cancer risk; (3) sufficient published data to calculate an odds ratio (OR) with a 95% confidence interval (CI) and *P*-value; (4) the distribution of genotypes among controls were consistent with the Hardy-Weinberg equilibrium.

The following exclusion criteria were applied: (1) not case-control studies; (2) studies without sufficient data and information; (3) reviews and repeated reports.

Data extraction

The data were extracted by two independent investigators according to the inclusion criteria. In case of conflicts, the disagreements were discussed and resolved with consensus. The following data were extracted from each study: first author’s name, publication year, ethnicity, total numbers of cases and controls, cancer type, source

of controls (population-based controls and hospital-based controls), genotyping method, and Hardy-Weinberg equilibrium (HWE) of controls.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to estimate the strength of association between MMP-12-82A>G polymorphism and cancer risk for each study. Five different comparison models were calculated for each polymorphism: allele model, homozygote model, heterozygote model, recessive model, and dominant model. The Cochran’s chi-square *Q* statistic test and *I*² statistics test were utilized to measure the potential heterogeneity among the studies. An *I*² that represents the percentage value of less than 25% indicates “low”, value of 25% to 50% indicates “moderate”, and value of more than 50% indicates “high”. If *P* value for heterogeneity test was less than 0.05, ORs were calculated according to

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Table 1. Characteristics of included studies in the meta-analysis

First author [Ref.]	Year	Ethnicity	Cases/Controls	Cancer type	Source of control	Genotyping method	HWE
Shin [20]	2005	Asian	1118/1223	Breast cancer	PB	Taqman	0.98
Kader [21]	2006	European	557/557	Hepatocellular cancer	HB	Taqman	0.06
Su [22]	2006	European	2014/1323	Lung cancer	HB	Taqman	0.32
Woo [23]	2007	Asian	185/304	Colorectal cancer	PB	PCR-RFLP	0.79
Zhai [24]	2007	Asian	433/480	Hepatocellular cancer	HB	AS-PCR	0.51
Zhang-a [25]	2008	Asian	316/609	Esophageal cancer	PB	PCR-RFLP	0.45
Zhang-b [25]	2008	Asian	243/609	Gastric cancer	PB	PCR-RFLP	0.45
Li [26]	2009	Asian	256/329	Ovarian cancer	HB	PCR-RFLP	0.76
Li-a [28]	2010	Asian	257/624	Gastric cancer	HB	PCR-RFLP	0.46
Li-b [28]	2010	Asian	335/624	Esophageal cancer	HB	PCR-RFLP	0.46
Jia I [29]	2010	Asian	300/300	Ovarian cancer	HB	PCR-RFLP	0.75
Cheung [30]	2012	European	309/279	Esophageal cancer	HB	PCR	0.90
VAN [31]	2013	European	385/619	Colorectal cancer	HB	Taqman	0.48
Grudny [32]	2013	European	53/54	Lung cancer	HB	PCR-RFLP	0.57
Wieczorek [34]	2013	European	241/199	Bladder cancer	HB	PCR-RFLP	0.35
Wang [35]	2013	Asian	300/300	Lung cancer	HB	PCR-RFLP	0.70
Yang [36]	2014	Asian	148/148	Laryngeal carcinoma	HB	PCR-LDR	0.87

the random-effect model [16]. Otherwise, the fixed-effect model was used [17]. Sensitivity analyses were conducted by omitting each study to find potential outliers. The potential publication bias was assessed by Begg's funnel plot and Egger's test [18, 19]. All statistical analyses were performed using the software STATA version 12.0 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of eligible studies

According to the search strategy, a total of seventeen relevant case-control studies [20-34] 7,450 cases and 7,348 controls were included in our meta-analysis. The search strategy was illustrated in **Figure 1**. The detailed characteristics of the included studies were shown in **Table 1**. Among the twenty studies, eleven studies were conducted in Asian populations and six studies were in European population. In the subgroup analysis by source of control, thirteen studies were performed in hospital-based controls and four were in population-based controls. There were three studies concerning lung cancer, three studies concerning esophageal cancer, two studies concerning colorectal cancer, two studies concerning gastric cancer, two studies concerning ovarian cancer, two studies

concerning hepatocellular carcinoma, and the other studies concerning breast cancer, laryngeal carcinoma and bladder cancer. In addition, all the included studies met HWE.

Quantitative data synthesis

The results of the meta-analysis were listed in detail in **Table 2**. By pooling all eligible studies, MMP-12-82A>G polymorphism was not associated with increased cancer risk under all the five genetic models (allele model: OR=1.09, 95% CI=0.93-1.28, P=0.30; homozygous model: OR=1.14, 95% CI=0.78-1.67, P=0.48; heterozygous model: OR=1.06, 95% CI=0.89-1.26, P=0.54; recessive model: OR=1.15, 95% CI=0.79-1.68, P=0.46; dominant model: OR=1.08, 95% CI=0.91-1.28, P=0.41) (**Figure 2**). Even after stratified analyses based on ethnicity, we could not find significant relationship between MMP-12-82A>G polymorphism and increased cancer risk among Asian populations (allele model: OR=1.15, 95% CI=0.85-1.56, P=0.38; homozygous model: OR=1.98, 95% CI=0.32-12.09, P=0.46; heterozygous model: OR=1.15, 95% CI=0.83-1.60, P=0.40; recessive model: OR=1.99, 95% CI=0.33-12.16, P=0.46; dominant model: OR=1.15, 95% CI=0.84-1.59, P=0.38) and European populations (allele model: OR=1.00, 95% CI=0.90-1.11, P=0.98; homozygous model: OR=1.12,

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Table 2. Stratified analysis of MMP-12-82A/G polymorphism and cancer risk

MMP-12-82A/G	G vs. A		GG vs. AA		GA vs. AA		GG vs. GA+AA		GG+GA vs. AA	
	OR (95% CI)	<i>P</i> ^a	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Overall	1.09 (0.93-1.28)	0.30	1.14 (0.78-1.67)	0.48	1.06 (0.89-1.26)	0.54	1.15 (0.79-1.68)	0.46	1.08 (0.91-1.28)	0.41
Ethnicity										
Asian	1.15 (0.85-1.56)	0.38	1.98 (0.32-12.09)	0.46	1.15 (0.83-1.60)	0.40	1.99 (0.33-12.16)	0.46	1.15 (0.84-1.59)	0.38
European	1.00 (0.90-1.11)	0.98	1.12 (0.76-1.64)	0.58	0.97 (0.87-1.10)	0.66	1.12 (0.76-1.65)	0.55	0.99 (0.88-1.11)	0.81
Source of control										
HB	1.16 (0.96-1.41)	0.13	1.10 (0.75-1.61)	0.63	1.13 (0.92-1.40)	0.24	1.11 (0.75-1.62)	0.61	1.16 (0.94-1.42)	0.17
PB	0.89 (0.68-1.17)	0.40	4.34 (0.48-38.88)	0.19	0.83 (0.63-1.10)	0.19	4.39 (0.49-39.32)	0.19	0.86 (0.65-1.13)	0.28
Cancer type										
Lung cancer	1.21 (0.64-2.27)	0.56	1.64 (0.17-15.48)	0.66	1.03 (0.88-1.21)	0.71	1.47 (0.19-11.32)	0.72	1.16 (0.66-2.02)	0.61
Colorectal cancer	0.90 (0.71-1.15)	0.41	1.18 (0.51-2.74)	0.69	0.83 (0.63-1.11)	0.21	1.24 (0.54-2.86)	0.61	0.86 (0.65-1.13)	0.28
Esophageal cancer	0.87 (0.53-1.43)	0.58	1.90 (0.47-7.69)	0.37	0.85 (0.53-1.37)	0.51	1.82 (0.45-7.35)	0.40	0.86 (0.52-1.42)	0.55
Gastric cancer	1.10 (0.72-1.68)	0.66	-	-	1.10 (0.72-1.70)	0.66	-	-	1.10 (0.72-1.70)	0.66
Ovarian cancer	2.44 (1.45-4.08)	<0.01	-	-	2.50 (1.48-4.22)	<0.01	-	-	2.50 (1.48-4.22)	<0.01
Hepatocellular carcinoma	0.92 (0.73-1.15)	0.46	1.75 (0.57-5.30)	0.33	0.85 (0.66-1.10)	0.20	1.83 (0.60-5.54)	0.29	0.88 (0.68-1.12)	0.29
other cancer	1.38 (0.75-2.53)	0.30	3.08 (0.84-11.29)	0.09	1.34 (0.66-2.73)	0.42	3.06 (0.83-11.20)	0.09	1.38 (0.70-2.72)	0.35

OR odds ratio, CI confidence interval, ^aRandom-effect model was used when *P*-value of Q-test for heterogeneity <0.05, otherwise fixed-effect model was used.

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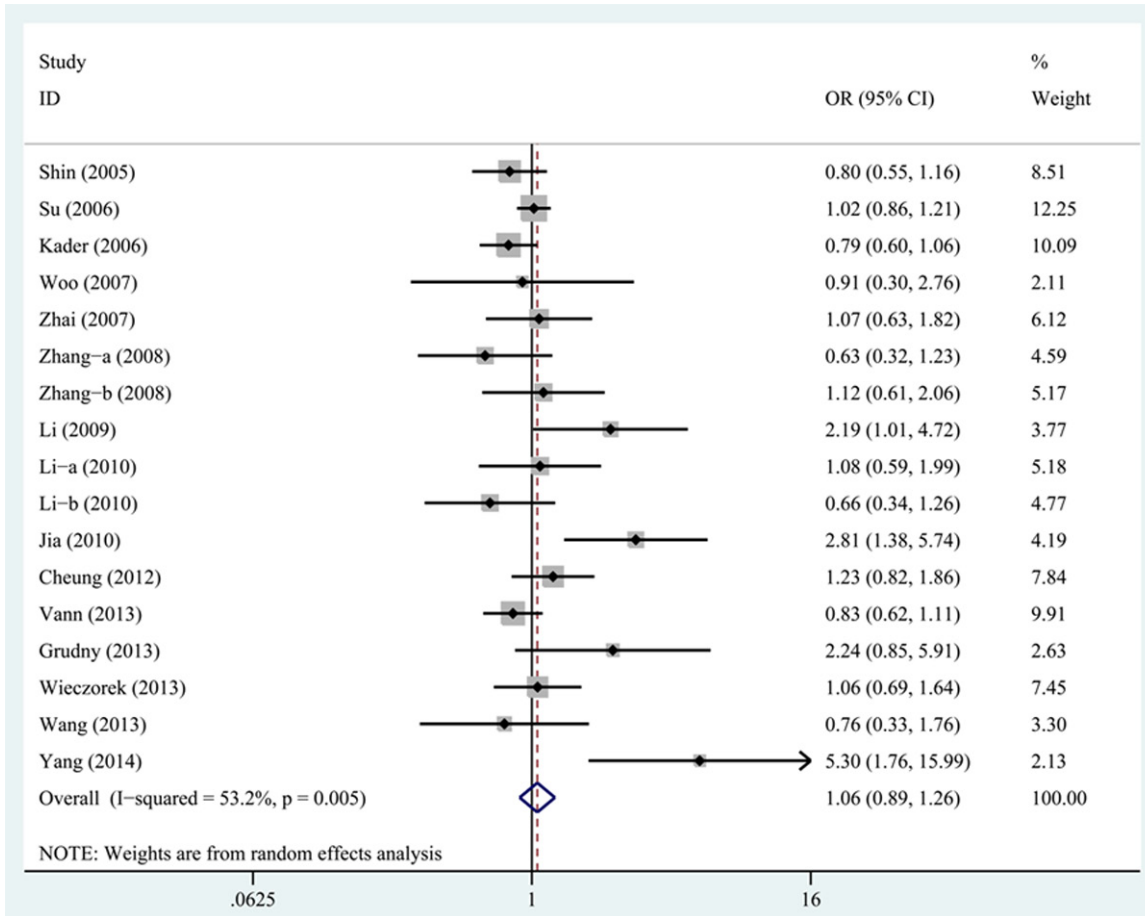


Figure 2. Forest plot of ORs for the association of MMP-12-82A>G polymorphism with cancer risk under heterozygous model (GA vs. AA).

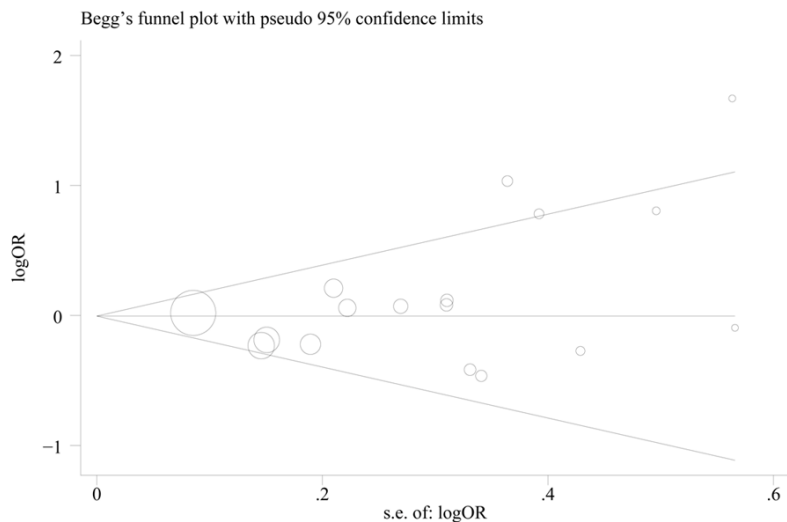


Figure 3. Begg's funnel plot of the association between MMP-12-82A>G polymorphism and cancer risk under heterozygous model (GA vs. AA). Circles represent the weight of studies.

recessive model: OR=1.12, 95% CI=0.76-1.65, P=0.55; dominant model: OR=0.99, 95% CI=0.88-1.11, P=0.81) (Table 2). Furthermore, in the subgroup analyses based on source of control, we found no significant association between MMP-12-82A>G polymorphism and increased cancer risk in hospital-based (allele model: OR=1.16, 95% CI=0.96-1.41, P=0.13; homozygous model: OR=1.10, 95% CI=0.75-1.61, P=0.63; heterozygous model: OR=1.13, 95% CI=0.92-1.40, P=0.24; recessive model: OR=1.11, 95% CI=0.75-1.62, P=0.61; dominant model: OR=1.16, 95% CI=0.94-1.42, P=0.17) or population-based studies (allele model: OR=0.89, 95% CI=0.68-1.17,

95% CI=0.76-1.64, P=0.58; heterozygous model: OR=0.97, 95% CI=0.87-1.10, P=0.66;

$P=0.40$; homozygous model: $OR=4.34$, 95% $CI=0.48-38.88$, $P=0.19$; heterozygous model: $OR=0.83$, 95% $CI=0.63-1.10$, $P=0.19$; recessive model: $OR=4.39$, 95% $CI=0.49-39.32$, $P=0.19$; dominant model: $OR=0.86$, 95% $CI=0.65-1.13$, $P=0.28$) (Table 2). However, when we stratified analysis by cancer type, strong association was observed in ovarian cancer (allele model: $OR=2.44$, 95% $CI=1.45-4.08$, $P<0.01$; heterozygous model: $OR=2.50$, 95% $CI=1.48-4.22$, $P<0.01$; dominant model: $OR=2.50$, 95% $CI=1.48-4.22$, $P<0.01$), but not in lung cancer, colorectal cancer, esophageal cancer, gastric cancer, hepatocellular carcinoma and other types of cancer (all $P>0.05$) (Table 2).

Sensitivity analysis

The sensitivity analysis indicated that no individual study influenced the OR value of MMP-12-82A>G polymorphism. Thus, the results of our meta-analysis are statistically robust.

Publication bias

Begg's funnel plot was performed to assess the publication bias of the selected articles. For MMP-12-82A>G polymorphism, the results of Begg's funnel plot did not reveal any evidence of obvious asymmetry (Figure 3). Egger's test also showed no significant evidence of publication bias (homozygous model: $P=0.132$).

Discussion

In this meta-analysis, we retrieved seventeen case-control studies with 7,450 cases and 7,348 controls and systematically evaluated the association between -82A>G polymorphism in promoter region of MMP-12 and the risk of cancer. Overall, we observed that MMP-12-82A>G polymorphism was not significantly associated with increased risk of cancer under all genetic models. In addition, no matter when we stratified analysis by ethnicity or source of control, there was no strong relationship in any genetic models. However, when we stratified analysis by cancer type, significant association was identified in ovarian cancer, not in other types of cancer. Collectively, these data suggest that MMP-12-82A>G polymorphism is a genetic risk factor for developing ovarian cancer.

MMP-12 is a member of MMP family that is mainly produced by macrophages and inflammatory cells and is involved in tissue regeneration, wound repair, and the regulation of immune surveillance [35-37]. MMP-12 could cleave plasminogen and collagen XVIII, resulting in the generation of angiostatin and endostatin that exert angiostatic effects [38, 39]. On the other side, MMP-12 could promote angiogenesis through cleaving diverse components of the extracellular matrix including collagen type IV and fibrin [40]. It has been suggested that MMP-12 is implicated in the processes of pro-tumorigenesis by inhibiting cancer cells apoptosis and promoting cancer cells invasion and migration [41, 42]. Considering that the SNP of MMP-12-82A>G could affect the expression of MMP-12 and increase the risk of cancer, the association between MMP-12 promoter gene polymorphism and the risk of cancer has been a focus of recent studies.

Shin et al. reported no association between MMP-12-82A>G polymorphism and breast cancer risk [20]. Similarly, no association between MMP-12-82A>G polymorphism and cancer risk was reported in other types of cancer [21-24]. Nevertheless, Li et al. demonstrated that MMP-12-82A>G polymorphism was related to the risk of ovarian cancer [26]. Therefore, the relationship between MMP-12-82A>G polymorphism and cancer risk remains controversial. To the best of our knowledge, this is the first meta-analysis that comprehensively evaluated the effect of MMP-12-82A>G polymorphism on cancer risk. Our results showed that there was no significant association between MMP-12-82A>G polymorphism and cancer risk whether by stratified analysis based on ethnicity or the source of control, or by general analysis under all genetic models. Interestingly, in the stratified analysis based on cancer type, MMP-12-82A>G polymorphism might contribute to an increased susceptibility to ovarian cancer but not lung cancer, colorectal cancer, esophageal cancer, gastric cancer, hepatocellular carcinoma and other types of cancer. To a large extent, this discrepancy may be explained by the fact that different types of cancer have diverse mechanism of carcinogenesis. Another reason may be that the pathways of carcinogen metabolism are complicated and can be affected by a variety of lifestyle-related factors and environmental factors. Additionally, the size of cancer

types is small, thus we are unable to detect a significant association in other types of cancer. Therefore, further studies with larger sample sizes in diverse cancers are needed to evaluate the association between MMP-12-82A>G polymorphism and cancer risk based on cancer types.

In our meta-analysis, no significant evidence of publication bias was observed, suggesting that our results are reliable. However, several limitations should be considered. First of all, the available data about MMP-12-82A>G consist of twenty case-control studies involving 7,450 cases and 7,348 controls, which may not provide sufficient power to explore the exact correlation. Hence, studies with larger sample sizes and representative population are warranted to validate the current findings. Second, our results were based on single-factor estimates, thus the association of MMP-12-82A>G polymorphism with cancer risk might be affected by other factors, such as the age, gender, family history and environmental factors. Third, only the published studies were included in this meta-analysis, the possible effect of unpublished studies should be considered.

In conclusion, the current meta-analysis suggests that MMP-12-82A>G polymorphism may not alter the risk of overall cancer, but contribute to an increased risk of ovarian cancer. However, comprehensive studies with larger sample sizes, especially involving many types of cancer, are necessary to confirm our findings.

Acknowledgements

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Disclosure of conflict of interest

None.

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