

Original Article

The association between MMP-12 82 A/G polymorphism and susceptibility to various malignant tumors: a meta-analysis

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Abstract: Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases responsible for degrading essentially all components of the extracellular matrix (ECM). Accumulating evidence suggests that MMPs might play a critical role in growth, invasion, and metastasis of malignant tumors. A single nucleotide polymorphism (SNP) in the promoter region of MMP-12, MMP-12 82 A/G (rs2276109), has been recognized to play a critical role in regulating the expression of MMP-12, however, its correlation with tumor susceptibility remains controversial. To address this issue, we performed meta-analysis to investigate the association MMP-12 82 A/G polymorphism and susceptibility of nine malignant tumors from 11 studies, including 6153 cancer patients and 6838 controls. Two reviewers independently screened studies for eligibility and extracted data for included studies. While overall no evident association between MMP-12 82 A/G and tumor susceptibility was observed, subgroup analysis revealed a specific role of G allele in increasing the susceptibility for epithelial ovarian carcinoma (EOC) using the allele model (fixed effects OR = 2.45, 95% CI = 1.46-4.10, P = 0.001) and the dominant model (fixed effects OR = 2.52, 95% CI = 1.49-4.24, P = 0.001). We thus suggest that G allele of MMP-12 82 A/G polymorphism is a genetic risk factor for EOC.

Keywords: MMP-12, single nucleotide polymorphism, tumor susceptibility

Introduction

MMPs are a pivotal family of zinc enzymes that are playing critical roles in degradation of ECM components during normal development and disease processes. Based on their structure and substrate specificity, MMPs can be divided into five groups: collagenases, gelatinases, stromelysins, matrilysins and membrane type MMPs (MT-MMPs) [1]. Accumulating evidence MMPs are common characteristics of carcinoma progression and are associated with tumor growth, invasion, and metastasis through regulating remodeling of ECM and modulating tumor microenvironment [2-6].

Matrix Metalloproteinase 12 (MMP-12), also known as macrophage elastase, belongs to the stromelysin-like MMPs subgroup and is predominantly expressed in macrophages. The function of MMP-12 involves elastin degradation and macrophage migration as well as angi-

ostatin production, which could prevent tumour angiogenesis. Previous studies showed that a functional SNP in MMP-12 gene are playing a critical role in regulating MMP-12 expression by affecting the binding site of the transcription factor activator protein 1 (AP1). A allele of MMP-12 82 A/G has a greater affinity for the transcription factor and results in higher MMP-12 promoter activity [7]. Recently, several studies reported that reduced that abnormal expression of MMP-12 are associated with both reduced tumor growth and increased overall survival [8, 9]. It has also been shown that G allele of MMP-12 82 A/G increases the risk of bladder cancer [10], epithelial ovarian carcinoma [11] and colorectal cancer [12] studies. In contrast, no significant association was observed between MMP-12 82 A/G polymorphism and non-small cell lung cancer or breast cancer [13]. Accordingly, the association between MMP-12 82 A/G polymorphism and cancer risk remains controversial. To address

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Table 1. Main characteristics and methodological quality of all eligible studies

First author	Year	Country	Ethnicity	Source	Number		Gender (M/F)		Age (years)		Disease	Sample	Method
					Case	Control	Case	Control	Case	Control			
Aesun Shin [19]	2005	China	Asians	PB	1129	1229	0/1129	0/1229	47.6±8.0	47.2±8.7	BRC	blood	Sequencing
A.K Kader [20]	2006	US	Caucasians	PB	560	560	433/127	431/129	65 (21-88)	64 (24-89)	BC	blood	TaqMan
Li Su [21]	2006	US	Caucasians	HB	2014	1323	1041/973	584/739	67 (26-91)	59 (19-96)	LC	blood	TaqMan
MJ Woo [22]	2007	Korea	Asians	HB	185	304	95/90	NR	54 (23-81)	NR	CRC	blood	PCR-RFLP
Yun Zhai [23]	2007	China	Asians	HB	433	480	NR	NR	NR	NR	HCC	blood	Sequencing
Bradbury [24]	2009	US	Mixed	PB	313	455	279/34	396/59	64 (21-91)	64 (19-96)	EA	blood	TaqMan
Yan Li [11]	2009	China	Asians	HB	256	329	0/256	0/329	53 (20-79)	51 (20-75)	EOC	blood	PCR-RFLP
Yan Li [26]	2010	China	Asians	HB	335	624	225/110	400/224	60.1±9.3	60.4±8.4	ESCC	blood	PCR-RFLP
Yan Li [26]	2010	China	Asians	HB	257	624	168/89	400/224	60.5±8.3	60.4±8.4	GCA	blood	PCR-RFLP
Jia J [25]	2010	China	Asians	HB	300	300	0/300	0/300	53 (20-79)	52 (20-76)	EOC	blood	PCR-RFLP

Note: HB, hospital-based; PB, population-based; NR, not reported; RFLP, restriction fragment length polymorphism. PCR-RFLP polymerase chain reaction-restriction fragment length polymorphism. BRC, breast cancer; BC, bladder cancer; LC, lung cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; EA, esophageal adenocarcinoma; EOC, epithelial ovarian carcinoma; ESCC, esophageal squamous cell carcinoma; GCA, gastric cardia adenocarcinoma.

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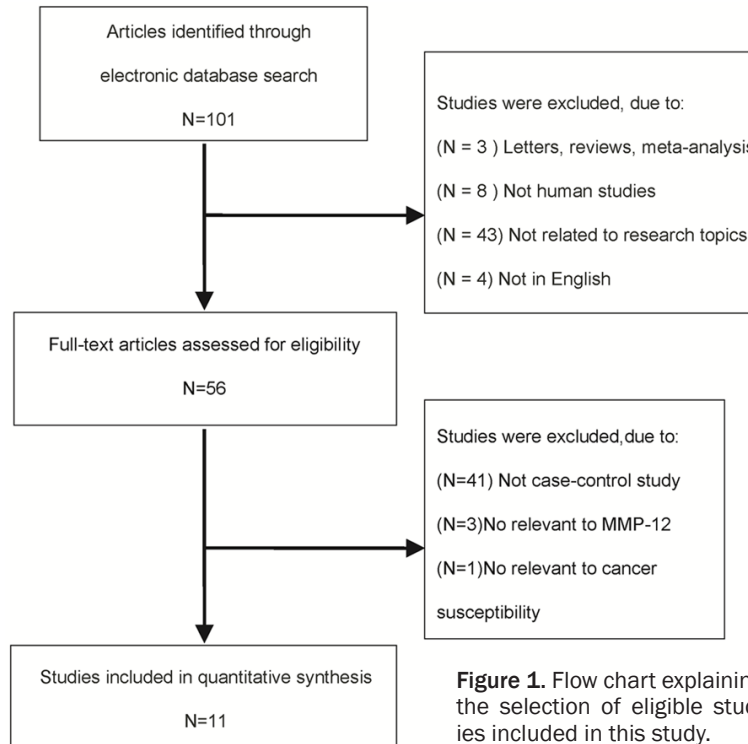


Figure 1. Flow chart explaining the selection of eligible studies included in this study.

Selection criteria

All eligible studies should meet the following criteria: (1) independent case-control studies that evaluated about MMP-12-82 A-G polymorphism and cancer risk; (2) all patients diagnosed with cancers were confirmed; (3) containing information about available genotype frequency; (4) study published in English; (5) *P* value on Hardy-Weinberg equilibrium (HWE) of controls must be more than 0.05; (6) only full-text manuscripts were included. Major exclusion criteria included: (1) no control population; (2) duplication of previous publications; (3) no available genotype frequency. The data sources are summarized in **Table 1**.

Data extraction

From each eligible article, two investigators extracted information according to the selection criteria independently and arrived at a final agreement on all the items through discussion and reexamination. Data were collected on the first author's name, year of publication, country of origin, ethnicity, source of control, genotyping methods, cancer type, sample size in cases and controls and so on.

Statistical analysis

Odds ratios (ORs) corresponding to 95% confidence interval (CI) were applied to measure the strength of the association based on the genotype frequencies in cases and controls. We examined the association between MMP-12-82-A/G polymorphism and cancer risk using five genetic contrasts: allelic contrast (G-allele vs A-allele), homozygote comparison (GG vs AA), heterozygote comparison (A/G vs AA), dominant genetic model (GG+A/G vs AA) and recessive genetic model (GG vs A/G+AA). Different variables were adjusted for different studies, and thereby, only crude ORs were pooled in the meta-analysis. 95% CI was calculated for the summary OR using the Z test. A fixed or random effect model was applied in this meta-analysis. The heterogeneity across

this issue, we conducted a comprehensive meta-analysis based on 11 studies containing 6153 cancer patients and 6838 control subjects to evaluate the association between MMP-12 82 A/G genetic polymorphism and susceptibility of various malignant tumors, including breast cancer (BRC), bladder cancer (BC), colorectal cancer (CRC), lung cancer (LC), epithelial ovarian carcinoma (EOC), esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EA), gastric cardia adenocarcinoma (GCA), hepatocellular carcinoma (HCC).

Materials and methods

Search strategy

We searched for all articles that had been published on the association between MMP-12 polymorphisms and cancer risk in Pubmed, Embase, the Cochrane Library, CBM, and CNKI Electronic databases, by using the following keywords: 'MMP-12' or 'metalloproteinase-12', 'polymorphism' and 'cancer' (before Nov 20, 2014). The reference lists of all relevant articles were also searched to identify additional studies. Database searching and data extraction were performed by two independent reviewers.

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Table 2. The genotype distribution of studies included in this study

First author	Year	Case			Control			HWE
		AA	AG	GG	AA	AG	GG	
Aesun Shin [19]	2005	1063	51	4	1153	69	1	0.975
A.K Kader [20]	2006	438	110	9	420	133	4	0.059
Li Su [21]	2006	1535	449	30	1008	289	26	0.324
MJ Woo [22]	2007	180	5	0	295	9	0	0.793
Yun Zhai [23]	2007	404	29	0	449	30	1	0.508
Bradbury [24]	2009	241	69	3	373	77	5	0.648
Yan Li [11]	2009	238	18	0	318	11	0	0.758
Yan Li [26]	2010	322	13	0	588	36	0	0.458
Yan Li [26]	2010	241	16	0	588	36	0	0.458
Jia J [25]	2010	271	29	0	289	11	0	0.746

the enrolled studies was evaluated by the Cochran's Q-statistic ($P < 0.05$ was considered as statistically significant) and I^2 test (ranges from 0 to 100%). The random effect model was used when a significant Q test with $P < 0.05$ or $I^2 > 50\%$, which indicates heterogeneity among studies. When there was no statistical heterogeneity, we used a fixed effects model [14-16]. We plotted Begg's funnel plots and used Egger's weighted regression method to examine the underlying publication bias, and calculated P for bias [17, 18]. For sensitivity analysis, relatively smaller studies were excluded and the summary ORs (95% CIs) were recalculated. All statistical analysis were done with Review Manager 5.0 version and STATA software (version 12.0; Stata Corporation, College Station, TX, USA), using two-sided P values ($P \leq 0.05$ was considered significant).

Results

Baseline characteristics of included studies

A total of 101 abstracts that met the inclusion criteria were retrieved by two independent reviewers. After reading the full articles, a total of 11 eligible studies that described the association between the MMP-12 polymorphism and cancer were included in this study, which included 6153 cases and 6838 controls (**Figure 1**). Baseline characteristics of the studies included in our analysis are shown in **Table 1**. Studies included in this meta-analysis involve breast cancer (BRC) [19], bladder cancer (BC) [20], lung cancer (LC) [21], colorectal cancer (CRC) [12, 22], hepatocellular carcinoma (HCC) [23], esophageal adenocarcinoma (EA) [24], epithelial ovarian carcinoma (EOC) [11, 25],

esophageal squamous cell carcinoma (ESCC) [26] and gastric cardia adenocarcinoma (GCA) [26]. A total of seven studies were performed in Asians, three studies were in Caucasians descendants, and one was categorized as mixed population. Blood samples were used to determine genetic polymorphisms in all the included studies by various genotyping methods including PCR-RFLP, TaqMan Assay and direct DNA sequencing. No genotype distribution in the

control groups deviating from Hardy-Weinberg equilibrium (HWE) was observed in any of the studies included (**Table 2**), supporting the reliability of our analysis.

Overall effect of MMP-12 82 A/G polymorphism on cancer risk

We first evaluated the association between MMP-12 82 A/G polymorphism and cancer risk when all the eligible studies were pooled in the overall population. As shown in **Table 3** and **Figure 2A-E**, however, no overall effect was observed when the allele model (G allele vs A allele, fixed-effects OR = 1.00, 95% CI = 0.91-1.10, P -heterogeneity = 0.067, $P = 0.994$, $I^2 = 42.3\%$) or the dominant model (GG+AG vs AA, random-effects OR = 1.04, 95% CI = 0.87-1.24, P -heterogeneity = 0.028, $P = 0.699$, $I^2 = 50.4\%$) were used. As there was no G/G genotype in some studies, only six case-control studies were included to analysis the other genetic model. No association was found using the recessive model (GG vs AG+AA, fixed-effects OR = 1.03, 95% CI = 0.70-1.52, P -heterogeneity = 0.373, $P = 0.877$, $I^2 = 6.8\%$), the homozygote model (GG vs AA, fixed-effects OR = 1.02, 95% CI = 0.69-1.50, P -heterogeneity = 0.424, $P = 0.916$, $I^2 = 0.0\%$), or the heterozygote model (GG vs AG, fixed-effects OR = 1.06, 95% CI = 0.72-1.58, P -heterogeneity = 0.195, $P = 0.754$, $I^2 = 32.0\%$).

G allele of MMP-12 82 A/G polymorphism is associated with enhanced risk for EOC

In the subgroup analysis stratified by ethnicity, no significant association between MMP-12 82 A/G polymorphism and cancer risk was

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Table 3. Meta-analysis of the association between MMP-12 82A/G polymorphism and cancer risk

Subgroup analysis	G allele vs A (Allele model)			GG+A/G vs AA (Dominant model)			GG vs A/G+AA (Recessive model)			GG vs AA (Homozygous model)			GG vs A/G (Heterozygous model)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Number of studies	11			11			6			6			6		
A>G	1	0.91-1.10	0.99	1.04	0.87-1.24	0.69	1.03	0.70-1.52	0.87	1.02	0.69-1.50	0.91	1.06	0.72-1.58	0.75
<i>Ethnicity</i>															
Caucasians	0.94	0.84-1.06	0.32	0.93	0.82-1.06	0.28	0.99	0.66-1.51	0.98	0.98	0.64-1.48	0.91	1.05	0.68-1.60	0.83
Asians	1.09	0.89-1.35	0.41	1.16	0.81-1.66	0.42	1.98	0.42-9.32	0.38	1.97	0.42-9.28	0.21	2.19	0.47-10.29	0.17
Mixed	1.29	0.93-1.79	0.13	1.36	0.95-1.94	0.09	0.87	0.21-3.67	0.85	0.93	0.22-3.92	0.92	0.67	0.15-2.91	0.59
<i>Genotype methods</i>															
PCR-RFLP	1.33	0.76-2.33	0.32	1.33	0.76-2.31	0.317		NA			NA			NA	
Non-PCR-RFLP	0.96	0.85-1.09	0.55	0.96	0.85-1.09	0.554	1.03	0.70-1.52	0.88	1.02	0.69-1.50	0.92	1.06	0.72-1.58	0.75
<i>Tumor type</i>															
CRC	0.9	0.70-1.15	0.41	0.86	0.65-1.13	0.275	1.24	0.54-2.86	0.61	1.18	0.51-2.74	0.69	1.43	0.60-3.39	0.42
LC	0.98	0.84-1.13	0.76	1	0.85-1.18	0.99	0.75	0.44-1.28	0.3	0.76	0.45-1.29	0.31		0.43-1.28	0.29
EOC	2.45	1.46-4.10	0.001	2.52	1.49-4.24	0.001		NA			NA	0.74		NA	
ESCC	0.67	0.35-1.26	0.21	0.66	0.34-1.26	0.21		NA			NA			NA	
EA	1.29	0.93-1.79	0.13	1.36	0.95-1.94	0.09	0.87	0.21-3.67	0.85	0.93	0.22-3.92	0.92	0.67	0.15-2.91	0.59
GCA	1.08	0.59-1.97	0.79	1.08	0.59-1.99	0.79		NA			NA			NA	
HCC	1	0.60-1.68	0.99	1.04	0.62-1.76	0.88	0.37	0.02-9.08	0.54	0.37	0.02-9.12	0.54	0.35	0.01-8.80	0.51
BC	0.87	0.67-1.51	0.34	0.83	0.63-1.10	0.21	2.27	0.70-7.41	0.17	2.15	0.66-7.06	0.23	2.72	0.82-9.07	0.1
BRC	0.86	0.60-1.23	0.42	0.85	0.59-1.23	0.39	4.38	0.49-39.31	0.18	4.34	0.48-38.88	0.19	5.4	0.58-49.88	0.14

Note: W, wild allele; M, mutant allele; WW, wild homozygote; WM, heterozygote; MM, mutant homozygote; SNP, single-nucleotide polymorphism.

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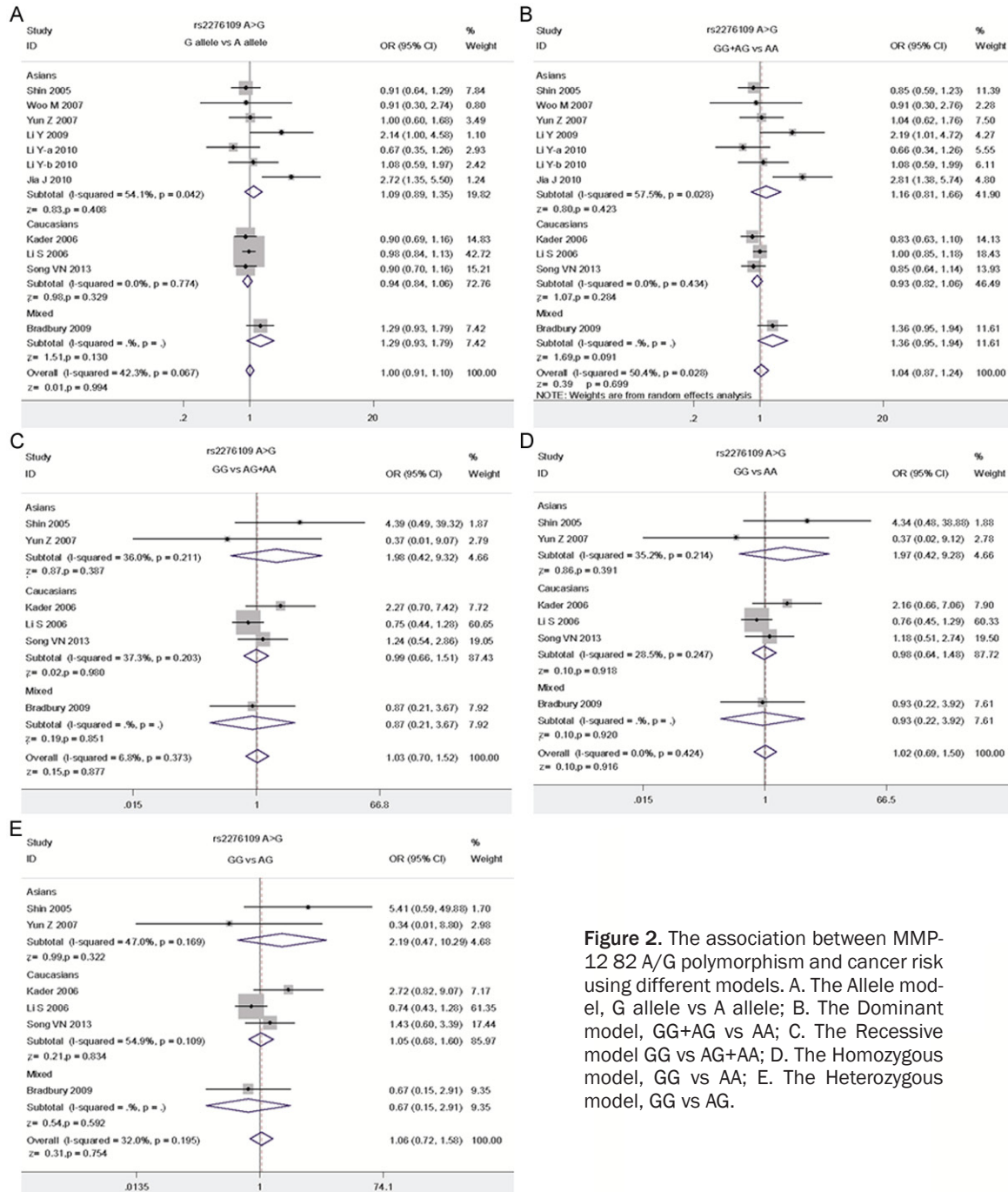


Figure 2. The association between MMP-12 82 A/G polymorphism and cancer risk using different models. A. The Allele model, G allele vs A allele; B. The Dominant model, GG+AG vs AA; C. The Recessive model GG vs AG+AA; D. The Homozygous model, GG vs AA; E. The Heterozygous model, GG vs AG.

observed in either Asians or Caucasians. Similar results were observed when Non-PCR-RFLP or PCR-RFLP genotype methods were used (Table 3). When stratified by disease types, however, we observed that G allele of MMP-12 82 A/G significantly enhances the risk of epithelial ovarian carcinoma (EOC) using allele model (G allele vs A allele) (fixed effects OR = 2.45, 95% CI = 1.46-4.10, P = 0.001) and dominant model (fixed effects OR = 2.52, 95% CI = 1.49-4.24, P = 0.001) (Table 3 and Figure

3). No significant association could be observed between MMP-12 82 A/G and the risk of other cancers (Table 3, P > 0.05), indicating that the effect is specific to EOC.

Publication bias

Begg's test and a funnel plot were performed to evaluate the publication bias of the literature used in this analysis. As shown in Figure 3A-E, No significant bias was observed by using any

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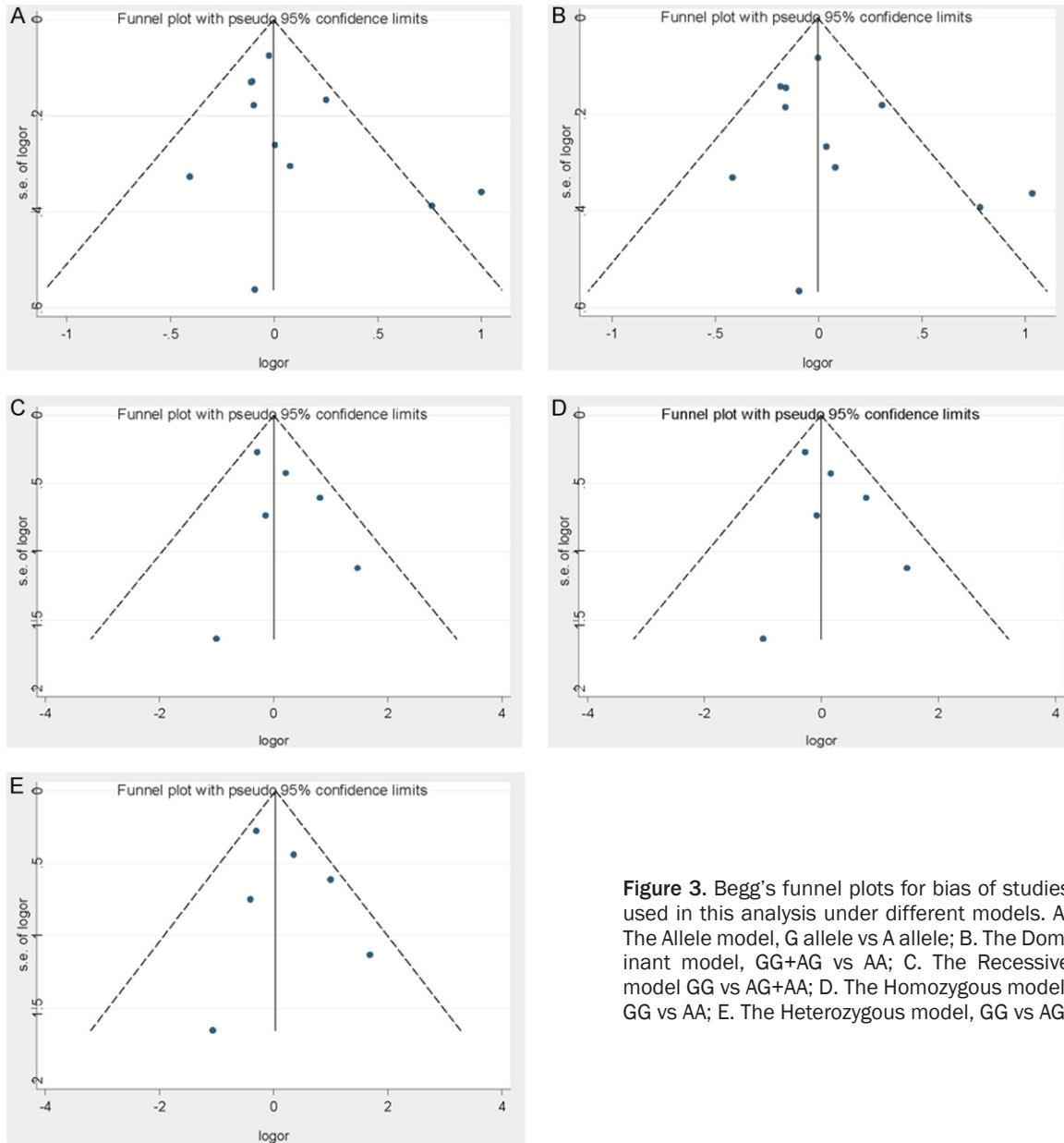


Figure 3. Begg's funnel plots for bias of studies used in this analysis under different models. A. The Allele model, G allele vs A allele; B. The Dominant model, GG+AG vs AA; C. The Recessive model GG vs AG+AA; D. The Homozygous model, GG vs AA; E. The Heterozygous model, GG vs AG.

of the models (the Allele model, G allele vs A allele, $t = 1.25$, $P = 0.241$; the Dominant model, GG+A/G vs AA, $t = 1.09$, $P = 0.304$; the Recessive model, GG vs A/G+AA, $t = 1.01$, $P = 0.369$; the Homozygous model, GG vs AA, $t = 1.06$, $P = 0.348$; the Heterozygous model, GG vs A/G, $t = 0.86$, $P = 0.441$).

Discussion

Meta-analysis is a useful method for investigating the associations of diseases with genetic variations via integrative analysis of different studies on the same topic, thus possibly

enhance statistic power and provide more conclusive results. A major advantage of meta-analysis is that it minimises publication bias. Many studies have demonstrated that genetic factors play important roles in the pathogenesis of various tumors. In this study, we performed a meta-analysis was to estimate the relevance of rs2276109 (-82A>G) polymorphism in the MMP-12 gene with cancer susceptibility. With the large number of cases and controls extracted from different studies, overall we did not observed any evidence that MMP-12 82 A/G polymorphism may affect cancer risk. However, based on subgroup analysis based on

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the type of disease in our finding, it suggested that MMP-12 82 A/G polymorphism may be closely related to increase the risk of EOC (in allelic contrast and dominant model), however, such association was not observed in other cancer types, including CRC, LC, EA, ESCC, GCA, HCC, and BC.

We acknowledge some limitations to our meta-analysis. Firstly, it has been widely accepted that cancer is caused by multitudinous factors, such as, interactions of gene-environment and gene-gene, even various polymorphism loci in the same chromosome (eg.1082A>G variant) could affect the gene expression [27], Sun [28] and Su [21] et al reported that multiple cancer-associated genetic variants suggested that the MMP1-MMP3-MMP12 gene cluster plays important roles in lung cancer progression. Accordingly, the effect of MMP-12 82 A/G polymorphism alone might be compromised without considering the influence of other genetic variations. On the hand, almost all of the studies we included were conducted in Asians and Caucasians ethnic groups, additional studies are needed to be investigated the influence in other populations. In addition, as the selection criteria outlined above, all studies were published in English. Papers published in languages such as Chinese were not included, which might also bring bias to our analysis. Moreover, as cancer is caused by multiple genetic and environmental factors, lacking of environment data limited our further evaluation of gene-environment interaction and whether these SNPs are causal remained uncertain. As gene expression is regulated at multiple levels [6, 29-35], further studies are also required to investigate the roles of these SNPs in regulating the expression of MMP-12 gene in vivo.

In conclusion, G allele of MMP-12 82 A/G polymorphism may significantly increase the risk of EOC, while such relationship was not evident for other cancer types. Further association studies with larger sample sizes and functional characterization of are required to reveal the role of MMP-12 82 A/G polymorphism in EOC pathogenesis.

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Disclosure of conflict of interest

None.

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