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Original Article

Association between matrix metalloproteinase 1 -1607 1G>2G polymorphism and cancer risk: a meta-analysis including 19706 subjects

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Abstract: The association between *MMP1* -1607 1G>2G polymorphism and cancer risk has been reported, but results remained controversial and ambiguous. To assess the association between *MMP1* -1607 1G>2G polymorphism and cancer risk, a meta-analysis was performed. Based on comprehensive searches of the PubMed, Elsevier Science Direct, Excerpta Medica Database (Embase), and Chinese Biomedical Literature Database (CBM), we identified outcome data from all articles estimating the association between *MMP1* -1607 1G>2G polymorphism and cancer risk. The pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated. Thirty-eight studies involving 10178 cases and 9528 controls were included. Overall, significant association between *MMP1* -1607 1G>2G polymorphism and cancer susceptibility was observed for additive model (OR = 1.21, 95% CI 1.09-1.35), for codominant model (OR = 1.34, 95% CI 1.10-1.63), for dominant model (OR = 1.17, 95% CI 1.01-1.34), for recessive model (OR = 1.31, 95% CI 1.14-1.52). In the subgroup analysis by ethnicity, the significant association was found among Asians but not among Caucasians. In the subgroup analysis by site of cancer, significant associations were found among lung cancer, colorectal cancer, head and neck cancer and bladder cancer. This meta-analysis demonstrated that the *MMP1* -1607 1G>2G polymorphism was significantly associated with cancer risk.

Keywords: Cancer, MMP1, meta-analysis, genetics

Introduction

Cancer is a disease resulting from complex interactions between environmental and genetic factors [1, 2]. Genetic factors, including the sequence alterations and organization aberrations of the cellular genome that range from single-nucleotide substitutions to gross chromosome, could modulate several important biological progress and alert susceptibility to cancer consequently.

Matrix metalloproteinase (MMP) is a family of zinc-dependent endopeptidases that are able to degrade essentially all extracellular matrix (ECM) components, such as basement membranes, collagen, and fibronectin [3, 4]. The human MMPs family, which consists of at least 26 proteases, can be divided into several subgroups according to their structure and substrate specificity [5]. Among the MMPs, MMP1 is the most highly expressed interstitial collagenase degrading fibrillar collagens, which are major constituents of the extracellular matrix. The level of MMP1 expression can be affected by single nucleotide polymorphism (SNP). An SNP of the MMP1 gene occurs at position 1607 bp upstream of the transcriptional initiation site. An insertion of a guanine base (G) creates the sequence 5'-GGAT-3', the core binding site for members of the EST family of transcription factors [6]. *MMP1* -1607 2G allele has been associated with higher transcriptional activity of the gene [6].

To identify whether the *MMP1* -1607 1G>2G polymorphism is involved in the pathogenesis of tumors in vivo, many case-control studies concerning this allelic variation and cancer risk have been broadly performed [7-44]. However, there is still uncertainty about the level of risk for a variety of cancers in a number of studies investigating the effect of -1607 1G>2G polymorphism on different types of cancers and ethnic populations. Therefore, we performed a meta-analysis to identify statistical evidence

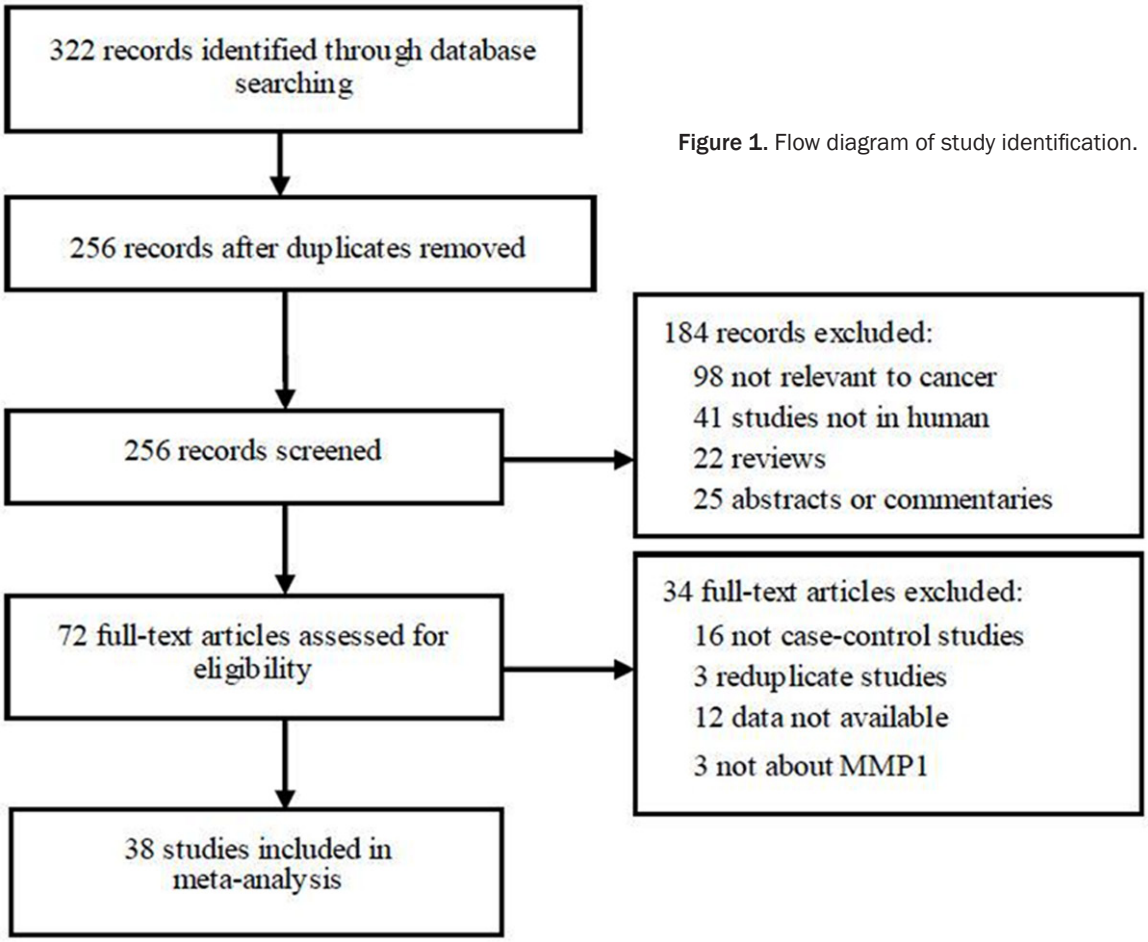

Figure 1. Flow diagram of study identification.

for an association between the *MMP1* -1607 1G>2G polymorphism and cancer risk using all published data to date.

Methods

Publication search and inclusion criteria

Data were collected from the following electronic databases: PubMed, Elsevier Science Direct, Excerpta Medica Database (Embase), and Chinese Biomedical Literature Database (CBM). We searched the articles using the search terms "matrix metalloproteinase 1 or MMP1", "polymorphism or SNP", "cancer or neoplasm or carcinoma". Additional studies were identified by a hand search of references of original studies and review articles. No language restrictions were applied. A study was included in the current meta-analysis if (1) it was published up to June, 2014; (2) it was a case-control study of the *MMP1* -1607 1G>2G polymorphism and cancer risk. We excluded the study in which family members were studied. When there were multiple studies from the same population, only the largest study was included.

Data extraction

Two investigators independently extracted data from the included studies. Data extracted from eligible studies included the first author's name, publication date, country origin, ethnicity, site of tumor, total numbers of cases and controls. The two investigators checked the data extraction results and reached consensus on all of the data extracted. If different results were generated, they would check the data and have a discussion to come to an agreement.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) in controls in each study was calculated by chi-squared test. P value < 0.05 was considered a departure from HWE. The association between *MMP1* -1607 1G>2G polymorphism and cancer risk

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

First author	Year	Country	Race	Site	Case	Control	HWE
Ye	2001	UK	Caucasian	Mixed	142	139	Yes
Hinoda	2002	Japan	Asian	Colorectal	127	101	Yes
Ghilardi	2002	Italy	Caucasian	Mixed	110	86	Yes
Hirata	2003	Japan	Asian	Mixed	210	119	Yes
Hashimoto	2004	Japan	Asian	Head and neck	568	140	Yes
Zinzindohoue	2004	France	Caucasian	Head and neck	249	129	Yes
Lin	2004	China	Asian	Head and neck	147	121	Yes
Matsumura	2004	Japan	Asian	Mixed	166	215	Yes
Ju	2005	Korea	Asian	Mixed	332	232	Yes
Su	2005	USA	Caucasian	Lung	1323	2014	Yes
Kondo	2005	Japan	Asian	Head and neck	82	83	Yes
McCready	2005	USA	Caucasian	Head and neck	57	81	Yes
Lai	2005	China	Asian	Mixed	197	197	Yes
Cao	2006	China	Asian	Head and neck	120	96	Yes
Zhang	2006	China	Asian	Lung	200	150	Yes
O-charoenrat	2006	Thailand	Asian	Head and neck	300	300	Yes
Elander	2006	Sweden	Caucasian	Colorectal	208	127	Yes
Woo	2006	Korea	Asian	Colorectal	304	185	Yes
Przybylowska	2006	Poland	Caucasian	Mixed	129	141	Yes
Kader	2006	USA	Caucasian	Bladder	555	556	Yes
Cheng	2007	China	Asian	Lung	130	127	Yes
Ju	2007	Korea	Asian	Mixed	332	133	Yes
Wei	2007	China	Asian	Lung	75	71	Yes
Vairaktaris	2007	Greece	Caucasian	Head and neck	141	156	Yes
Tasci	2007	Turkey	Asian	Bladder	94	102	Yes
Shimizu	2008	Japan	Asian	Head and neck	91	69	Yes
Patricia	2008	Spain	Asian	Lung	510	501	Yes
Kouhkan	2008	Iran	Asian	Colorectal	100	150	Yes
Penelope	2009	USA	Caucasian	Head and neck	455	313	Yes
Dos Reis	2009	Brazil	Caucasian	Mixed	100	100	Yes
Vairaktaris	2009	Greece	Caucasian	Head and neck	168	162	Yes
Srivastava	2010	India	Asian	Bladder	200	200	Yes
Chaudhary	2010	India	Asian	Head and neck	426	422	Yes
Liu	2011	China	Asian	Lung	825	825	Yes
Hart	2011	Norway	Caucasian	Lung	434	436	Yes
Cheung	2012	Canada	Caucasian	Head and neck	279	309	Yes
Fakhoury	2012	USA	Asian	Lung	51	41	Yes
Wieczorek	2013	Poland	Caucasian	Bladder	241	199	Yes

HWE, Hardy-Weinberg equilibrium.

was estimated by the odds ratio (OR), together with the 95% confidence interval (95% CI). The significance of the pooled OR was determined by the Z test, with $P < 0.05$ considered significant. Stratified analysis was also performed by ethnicity and cancer site. We estimated the ORs in the dominant model, recessive model, codominant model, and additive model.

Heterogeneity between studies was assessed by Q test. If $P < 0.1$, the heterogeneity was considered statistically significant. The I^2 values were used to quantify the percentage of the total variation among studies when heterogeneity was assessed. When $I^2 < 50\%$, a fixed effects model was applied to estimate the pooled results. Otherwise, the random-effect model was used. Sensitivity analysis was car-

Table 2. Main results of meta-analysis

	No. of study	Case/control	2G vs. 1G		2G2G vs. 1G1G		2G2G+1G2G vs. 1G1G		2G2G vs. 2G1G+1G1G	
			OR (95% CI)	$P_{heterogeneity}$	OR (95% CI)	$P_{heterogeneity}$	OR (95% CI)	$P_{heterogeneity}$	OR (95% CI)	$P_{heterogeneity}$
Overall	38	10178/9528	1.21 (1.09-1.35)	< 0.001	1.34 (1.10-1.63)	< 0.001	1.17 (1.01-1.34)	< 0.001	1.31 (1.14-1.52)	< 0.001
Site										
Head and neck cancer	13	3083/2381	1.20 (1.03-1.31)	< 0.001	1.27 (0.80-2.00)	< 0.001	1.07 (0.77-1.50)	< 0.001	1.34 (1.02-1.67)	< 0.001
Lung cancer	8	3548/4165	1.16 (1.01-1.34)	0.004	1.28 (1.00-1.63)	0.027	1.12 (1.00-1.25)	0.189	1.22 (1.01-1.49)	0.004
Bladder cancer	4	1103/1053	1.59 (0.88-2.86)	< 0.001	2.18 (0.77-6.16)	< 0.001	1.62 (0.74-3.57)	< 0.001	1.44 (1.05-1.97)	< 0.001
Colorectal cancer	4	739/563	1.59 (1.34-1.88)	0.812	2.22 (1.52-3.24)	0.902	1.67 (1.19-2.34)	0.965	1.85 (1.46-2.34)	0.784
Race										
Caucasian	15	5101/5449	1.04 (0.90-1.19)	< 0.001	1.09 (0.84-1.41)	< 0.001	1.08 (0.91-1.28)	0.001	1.03 (0.84-1.26)	< 0.001
Asian	22	5077/4079	1.36 (1.17-1.58)	< 0.001	1.59 (1.19-2.13)	< 0.001	1.27 (1.01-1.61)	< 0.001	1.56 (1.30-1.87)	< 0.001

ried out by removing each study at a time to evaluate the stability of the results. Publication bias was analyzed by performing Egger's test quantitatively [45]. All statistical analysis was conducted using STATA software (version 11.0; STATA Corporation, College Station, TX). Two sided *P*-values < 0.05 were considered statistically significant.

Results

Characteristics of the included studies

A total of 322 articles were retrieved after first search in PubMed, Elsevier Science Direct, Embase, and CBM. As shown in **Figure 1**, after our selection, 38 case-control studies fulfilled the inclusion criteria [7-44]. Characteristics of included studies are summarized in **Table 1**. There were 16 studies used Caucasians and 22 studies used Asians. Thirteen studies investigated head and neck cancer, four studies investigated bladder cancer, four studies investigated colorectal cancer, and eight studies investigated lung cancer.

Results of meta-analysis

The overall OR for 2G versus 1G (additive model) was 1.21 (95% CI 1.09-1.35). This result suggested that individuals who carry the 2G allele may have a 21% increased cancer risk compared with 1G allele carrier. When all the studies were pooled into meta-analysis using other genetic models (**Table 2**), there was also significant association between *MMP1* -1607 1G>2G polymorphism and cancer risk (for codominant model: OR = 1.34, 95% CI 1.10-1.63; for dominant model: OR = 1.17, 95% CI 1.01-1.34; for recessive model: OR = 1.31, 95% CI 1.14-1.52).

In the subgroup analyses by ethnicity, the significant association was found among Asians (OR = 1.36, 95% CI 1.17-1.58) but not among Caucasians (OR = 1.04, 95% CI 0.90-1.19) in additive model (2G vs. 1G). In the subgroup analysis by site of cancer, *MMP1* -1607 1G>2G polymorphism was significantly associated with lung cancer and colorectal cancer in each genetic models. In addition, this polymorphism increased bladder cancer risk in the recessive model (OR = 1.44, 95% CI 1.05-1.97) and head and neck cancer risk in the recessive model and additive model (**Table 2**).

Every single study involved in this meta-analysis was deleted each time to examine the influence of the individual data set to the pooled ORs. Elimination of each study made no qualitative difference on the pooled OR values, which indicated that the final results of the meta-analysis were stable (data not shown). Egger's test further confirmed the absence of publication bias in this meta-analysis (*P* > 0.05).

Discussion

This current meta-analysis of 38 studies including 10178 cases and 9528 controls systematically evaluated the association between *MMP1* -1607 1G>2G polymorphism and cancer risk. The results indicated that -1607 1G>2G polymorphism was a conspicuous high risk factor for developing cancer in the overall study populations. In the subgroup analysis by ethnicity, no significant association was found in Caucasians. However, cancer risk was increased in Asians who carried 2G allele, suggesting a possible influence among environmental exposures and different genetic backgrounds. After stratification by site, this association remained significant in lung cancer, colorectal cancer, head and neck cancer and bladder cancer. This result indicated that *MMP1* -1607 1G>2G polymorphism might play a same role in the etiology of different cancers.

Functional analyses have shown that the expression level of MMP1 depends on the genetic variation within the promoter of the *MMP1* gene. The -1607 2G allele is thought to form the core of a consensus DNA element recognized by the Ets transcription factor, which up-regulates MMP1 transcription [6]. Further investigations of association of -1607 1G>2G with allelic expression imbalance suggest that this polymorphism does not account for all differences in allelic expression observed [46]. Transcription of a gene is more likely to be influenced by multiple polymorphisms, and these are hypothesized by some authors to be located in the promoter of that gene, which acts in concert to exert a haplotype effect [47]. Pearce et al. [48] investigated the promoter region in detail and found that the -1607 1G>2G deletion alone cannot fully segregate the various MMP1 haplotypes that differ in promoter activity.

Thus, the mechanism was still unclear and this issue should be investigated in the future studies.

Some limitations should be addressed. First, in this meta-analysis, we found obvious heterogeneity across studies. Importantly, it should be acknowledged that potential heterogeneity and bias may distort the results. Therefore, results from this meta-analysis should be interpreted with caution. Second, due to lacking of the original data of the eligible studies, we could not perform other subgroup analyses based on age, smoking, and so on. Third, cancer is a multifactorial disease and potential interactions among gene-gene and gene-environment should be considered.

In conclusion, a significant association was detected between the *MMP1* -1607 1G>2G polymorphism and cancer risk. Moreover, further studies with large sample size of different ethnic populations and cancer types will be necessary to validate this result.

Disclosure of conflict of interest

None.

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