A/G polymorphism of matrix metalloproteinase 7 gene promoter region and cancer risk: A meta-analysis

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Abstract. This meta-analysis was conducted to evaluate the effect of the matrix metalloproteinase 7 (MMP7)-181A/G polymorphism on cancer risk. Twenty-seven case-control studies were identified via a literature search through PubMed, Web of Science and China National Knowledge Infrastructure databases. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were applied to assess the strength of the association between MMP7-181A/G polymorphism and cancer risk. The 27 studies were further assessed according to Hardy-Weinberg equilibrium (HWE) and Hardy-Weinberg disequilibrium (HWD), with 24 case-control studies found to be under HWE. A significant association was observed between MMP7-181A/G polymorphism and increased cancer risk (cervical and other types of cancer) in Asian, but not in European populations.

Introduction

The processes of tumorigenesis and metastasis involve cancer cell migration and penetration through the extracellular matrix (ECM) (1). Matrix metalloproteinases (MMPs) are a family of highly conserved zinc-dependent proteolytic enzymes that are able to degrade essentially all ECM components and regulate diverse cell behaviors (2). MMPs play pivotal roles in physiological ECM remodeling, such as tissue regeneration in pregnancy, wound healing and angiogenesis (3). MMPs are also involved in pathological conditions, such as cancer, arthritis, autoimmune diseases and atherosclerosis (4).

Matrix metalloproteinase 7 (MMP7) (punctuated metalloproteinase-1, PUMP-1, matrilysin) is coded by a gene localized on chromosome 11q21-q22. MMP7 is capable of degrading elastin, fibronectin, proteogylcans and type IV collagen (5) and of cleaving non-matrix substrates of the cell surface, such as E-cadherin, pro-tumor necrosis factor and Fas ligand. MMP7 is predominantly expressed in the epithelium of various organs under physiological conditions and may be overexpressed in a variety of cancers, such as cancers of the colorectum, esophagus, stomach, kidney and breast (6,7).

Numerous molecular epidemiological studies on the association of MMP7 polymorphisms with cancer susceptibility have been conducted. However, the association between MMP7-81A/G polymorphism and cancer risk has not been elucidated. Therefore, a system review and meta-analysis was performed.

Materials and methods

Search strategy and eligibility criteria. Two investigators (J. Wu and X. Guan) independently conducted key word searches in PubMed, Web of Science and the China National Knowledge Infrastructure databases to identify all eligible studies between 2000 and 2013. The following terms were used: 'MMP7' or 'matrix matalloproteinase 7' and 'polymorphism' and 'cancer', 'tumor', 'neoplasm' or 'carcinoma' (last search update, February 20th, 2013). References cited in the publications were also screened by hand. The following criteria were required to be met: i) the publication was a case-control study; ii) the study evaluated the association between MMP7-181A/G polymorphism and cancer; iii) odds ratios (ORs) or available data for their calculation were reported; and iv) the study was published in English or Chinese.

Data extraction. The following basic data were collected: first author, publication year, cancer type and ethnicity of study populations. Two investigators conducted data extraction independently and discrepancies were resolved through discussions.

Statistical analysis. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the association between MMP7-181A/G polymorphism and cancer risk (8). Stratified analyses were also performed by cancer type (if one cancer type was contained in less than three single

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

Author	Year	Country	Ethnicity	Cancer type	Sample size (case/control)	P_{HWE}	Refs.
Ghilardi *et al*	2003	Italy	European	Colorectal	58/111	0.129	(27)
Li *et al*	2008	China	Asian	Gastric	338/380	0.999	(30)
Ohtani *et al*	2009	Japan	Asian	Colorectal	119/67	0.421	(24)
Wu *et al*	2011	China	Asian	Cervical	217/190	0.010	(36)
Kubben *et al*	2006	The Netherlands	European	Gastric	79/169	0.000	(34)
Vairaktaris *et al*	2007	Germany/Greece	European	Oral	159/120	0.018	(35)
Li *et al*	2006	China	Asian	Ovarian	138/160	0.714	(29)
Woo *et al*	2007	Korea	Asian	Colorectal	185/304	0.232	(25)
Fang *et al*	2010	China	Asian	Colorectal	237/252	0.315	(18)
Lu *et al*	2006	China	Asian	Adult astrocytoma	221/366	0.319	(6)
de Lima *et al*	2009	Brazil	other	Colorectal	108/113	0.488	(28)
Dziki *et al*	2011	Poland	European	Colorectal	184/205	0.295	(17)
Lievre *et al*	2006	France	European	Colorectal	596/565	0.098	(20)
Singh *et al*	2008	India	Asian	Cervical	150/162	0.750	(22)
Srivastava *et al*	2010	India	Asian	Bladder	200/200	0.810	(19)
Sugimoto *et al*	2008	Japan	Asian	Gastric	160/156	0.332	(16)
Yi *et al*	2010	Taiwan	Asian	Endometrial	118/229	0.931	(21)
Qiu *et al*	2008	China	Asian	Hepatocellular	425/475	0.338	(23)
Beeghly-Fadiel *et al*	2008	China	Asian	Breast	1079/1082	0.236	(7)
Tao *et al*	2010	China	Asian	Cervical	225/170	0.169	(31)
Yao	2011	China	Asian	Cervical	95/120	0.326	(33)
Zhang *et al*	2010	China	Asian	Epithelial ovarian	130/159	0.713	(32)
Malik *et al*	2011	India	Asian	Gastric	108/195	0.547	(14)
Malik *et al*	2011	India	Asian	Esophageal	135/195	0.547	(15)
Zhang *et al*	2005	China	Asian	Gastric	201/350	0.888	(26)
				NSCLC	243/350	0.888	
				ESCC	258/350	0.888	

HWE, Hardy-Weinberg equilibrium; NSCLC, non-small-cell lung cancer; ESCC, esophageal squamous cell carcinoma.

studies, it was classified in the 'other' group) and smoking status. Two methods were utilized: the dominant genetic model (GG/GA vs. AA) and allelic contrast (G allele vs. A allele).

The between-study heterogeneity was assessed through Chi-square-based Q test (Cochran's Q statistic) and I^2 statistic (9,10). A fixed-effects model (the Mantel-Haenszel method) was used when P>0.05 and I^2<50% (11). Otherwise, the random-effects model [the DerSimonian and Laird (12) method] was used. Additionally, meta-regression and sensitivity analyses were performed to investigate the sources of heterogeneity and assess the stability of the results, respectively. The Hardy-Weinberg equilibrium (HWE) in controls was recalculated and P<0.05 was considered to indicate a statistically significant difference. The Begg's rank correlation method (13) was used to investigate publication bias. All analyses were performed with Stata software version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Study characteristics. After comprehensive searching, 25 eligible publications (6,7,14-36) including 27 studies

with a total of 6,166 cases and 7,195 controls, were included in this meta-analysis. Among these, Malik *et al* published 2 studies (14,15) involving 2 different cancer types, using the same control populations. Additionally, Zhang *et al* (26) investigated 3 types of cancer in one publication. The genotype distribution of the controls in all the studies was consistent with Hardy-Weinberg equilibrium, except for 3 studies (34-36). Twenty studies used the polymerase chain reaction-restriction fragment length polymorphism method to analyse genotypes. The cases were histopathologically diagnosed in the majority of the studies and the controls were free from cancer. The characteristics of studies on MMP7-181A/G polymorphism are provided in Table I and the flow diagram of the literature search is shown in Fig. 1.

Quantitative synthesis. The MMP7-181G allele frequency varied widely among the control subjects of the 27 case-control studies, ranging from 0.028 in Asian to 0.57 in European populations.

For the overall analysis of the 27 case-control studies, a significantly increased cancer risk was found to be associated with the G allele compared to the A allele (OR=1.34,

Table II. Stratified analyses of the effect of metalloproteinase 7-181A/G polymorphism on cancer risk (HWE/HWD groups).

Variables	No.[a]	Cases/controls	GG/GA vs. AA		G vs. A	
			OR (95% CI)	P-value[b]	OR (95% CI)	P-value[b]
Total	27	6166/7195	1.33 (1.15-1.54)	<0.001	1.34 (1.17-1.53)	<0.001
Cancer type						
Gastric	5	886/1250	1.34 (0.82-2.20)	0.002	1.41 (0.97-2.03)	0.007
Colorectal	7	1487/1617	1.02 (0.76-1.36)	0.042	1.05 (0.85-1.32)	0.036
Cervical	4	687/642	1.28 (1.02-1.59)	0.666	1.38 (1.16-1.63)	0.799
Other	11	3106/3686	1.56 (1.25-1.96)	0.006	1.56 (1.21-2.01)	<0.001
Quality assessment						
Low	12	2071/2409	1.14 (0.85-1.54)	<0.001	1.18 (0.89-1.56)	<0.001
High	15	4095/4786	1.42 (1.23-1.65)	0.059	1.34 (1.17-1.53)	0.011
Ethnicity						
European	5	1076/1170	1.03 (0.71-1.51)	0.013	1.00 (0.74-1.34)	0.001
Asian	21	4982/5912	1.42 (1.21-1.67)	0.001	1.47 (1.28-1.69)	0.001
Source of control						
HB	16	3190/3975	1.27 (1.03-1.57)	<0.001	1.35 (1.13-1.61)	<0.001
PB	10	2976/3220	1.40 (1.14-1.73)	0.028	1.32 (1.05-1.65)	<0.001
Smoking status						
Smoking	7	651/498	1.66 (1.21-2.28)	0.204	1.56 (1.23-1.99)	0.243
Non-smoking	6	742/929	1.57 (1.15-2.14)	0.399	1.59 (1.25-2.00)	0.895

HWE/HWD, Hardy-Weinberg equilibrium/Hardy-Weinberg disequilibrium; OR, odds ratio; CI, confidence interval; HB, hospital-based; PB, population-based; [a]number of comparisons; [b]P-value of Q-test for heterogeneity.
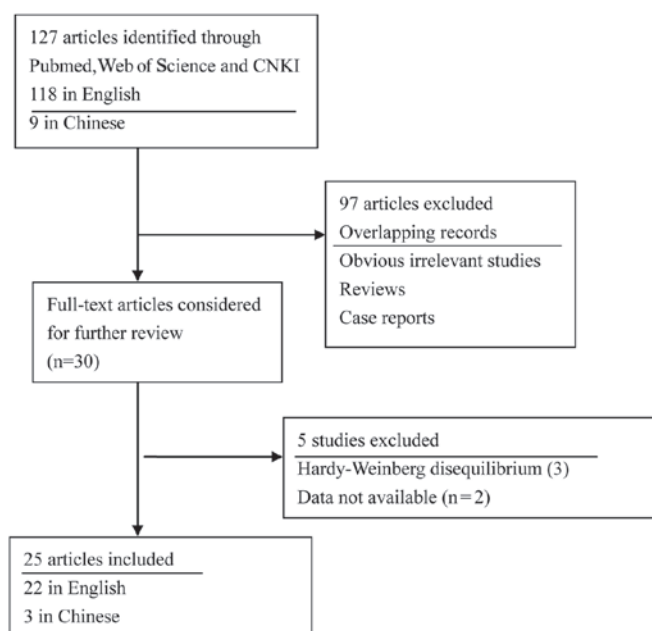

Figure 1. Flow diagram of the literature search in this meta-analysis. CNKI, China National Knowledge Infrastructure.

95% CI: 1.17-1.53). A significantly increased cancer risk was also found to be associated with the G allele carriers (GG/GA genotypes) compared to the AA genotype in a dominant model (OR=1.33, 95% CI: 1.15-1.54). Similarly, an increased

cancer risk was identified in the 24 case-control studies under HWE [G vs. A: OR=1.43, 95% CI: 1.26-1.62 (Table III); GG/GA vs. AA: OR=1.42, 95% CI: 1.23-1.63)].

Data were stratified according to the ethnicity of the participants into European, Asian and other. A statistically significant association was observed with the Asian but not the European ethnicity, regardless of whether studies under Hardy-Weinberg disequilibrium (HWD) were excluded (Tables II and III).

Data were stratified according to cancer type into gastric, cervical, colorectal and other types of cancer (Tables II and III). A significant association was observed between MMP7-181A/G polymorphism and cervical and other types of cancer, regardless of whether studies under HWD were excluded. Of note, certain inconsistencies were oserved in the HWE and HWE/HWD groups. In the former, a significantly elevated risk for gastric cancer was observed (OR=1.72, 95% CI: 1.33-2.23 for GG/GA vs. AA; OR=1.67, 95% CI: 1.35-2.08 for G vs. A), whereas no significant association with gastric cancer was observed in the latter (OR=1.34, 95% CI: 0.82-2.20 for GG/GA vs. AA; OR=1.41, 95% CI: 0.97-2.03 for G vs. A). Additionally, no increased colorectal cancer risk was found to be associated with the G allele or G allele carriers in the HWE or the HWE/HWD group.

When smoking status was considered, a significantly increased cancer risk was found to be associated with the G allele and G allele carriers in the smoking as well as the

Table III. Stratified analyses of the effect of metalloproteinase 7-181A/G polymorphism on cancer risk (Hardy-Weinberg equilibrium group).

Variables	No.[a]	Cases/controls	GG/GA vs. AA		G vs. A	
			OR (95% CI)	P[b]	OR (95% CI)	P[b]
Total	24	5711/6716	1.42 (1.23-1.63)	0.001	1.43 (1.26-1.62)	<0.001
Cancer type						
Gastric	4	807/1081	1.72 (1.33-2.23)	0.691	1.67 (1.35-2.08)	0.925
Colorectal	7	1487/1617	1.02 (0.76-1.36)	0.042	1.05 (0.85-1.32)	0.036
Cervical	3	470/452	1.40 (1.07-1.84)	0.961	1.45 (1.18-1.77)	0.913
Other	10	2947/3566	1.64 (1.30-2.07)	0.007	1.68 (1.36-2.08)	0.003
Quality assessment						
Low	9	1616/1930	1.31 (0.94-1.84)	0.001	1.37 (1.01-1.86)	0.001
High	15	4095/4786	1.42 (1.23-1.65)	0.059	1.41 (1.24-1.61)	0.011
Ethnicity						
European	3	838/881	1.30 (0.91-1.86)	0.135	1.24 (0.97-1.59)	0.091
Asian	20	4765/5722	1.45 (1.23-1.71)	0.001	1.49 (1.29-1.72)	0.001
Source of control						
HB	15	3111/3806	1.35 (1.11-1.64)	0.003	1.41 (1.19-1.67)	<0.001
PB	8	2542/2799	1.54 (1.21-1.98)	0.031	1.45 (1.18-1.79)	0.029
Smoking status						
Smoking	7	651/498	1.66 (1.21-2.28)	0.204	1.56 (1.23-1.99)	0.243
Non-smoking	6	742/929	1.57 (1.15-2.14)	0.399	1.59 (1.25-2.00)	0.895

OR, odds ratio; CI, confidence interval; HB, hospital-based; PB, population-based; [a]number of comparisons; [b]P-value of Q-test for heterogeneity.

non-smoking groups. The stratified analyses of the eligible studies are summarized in Tables II and III.

Evaluation of heterogeneity. In the 27 case-control studies, it was observed that variable ethnicity could explain 34.82% (G vs. A) and 13.54% (GG/GA vs. AA) of the I^2, whereas HWE could explain 43.93% (G vs. A) and 35.28% (GG/GA vs. AA) of the I^2. In the 24 case-control studies under HWE, none of these variables contributed significantly to heterogeneity.

Sensitivity analysis. A sensitivity analysis was conducted to evaluate the effect of each individual study on the pooled OR and removal of any individual study imparted no significant difference in the HWE or the HWE/HWD group.

Publication bias analysis. No evidence of publication bias for the association of MMP7-181A/G polymorphism with cancer risk was identified in our meta-analysis (HWE group, P=0.90 for GG/GA vs. AA and P=0.07 for G vs. A; HWE/HWD group, P=0.97 for GG/GA vs. AA and P=0.09 for G vs. A).

Discussion

Our meta-analysis was a systematic review of the association between the MMP7-181A/G polymorphism and cancer suscep-tibility, which provided evidence that the G allele and G allele carriers were significantly associated with an increased cancer

risk (also in Asian ethnicity when race was considered). Data were then stratified by cancer type. A significantly increased risk of cervical and other types of cancer were observed in the HWE and HWE/HWD groups (GG/GA vs. AA; G vs. A) and an increased risk of gastric cancer was observed in the HWE group (GG/GA vs. AA; G vs. A). However, we failed to identify any significant association between MMP7-181A/G polymor-phism and gastric cancer in the HWE/HWD group. Therefore, we hypothesized that the results of the 24 case-control studies under HWE were reliable. However, further studies on the effect of MMP7-181A/G polymorphism on cancer risk are required to support this hypothesis.

Data were also stratified according to European and Asian ethnicity. A statistically significant association was observed in the Asian but not in the European populations. Although the reason for this discrepancy is unclear, it may be attributed to differences in genetic traits among different ethnic groups and a potential reporting bias.

Tobacco is a well-known carcinogen, exposure to which may lead to smoking-related cancers. Increased cancer susceptibility was found to be associated with the G allele and G allele carriers in the smoking as well as the non-smoking groups. These findings indicate that MMP7-181A/G polymor-phism may play a pivotal role in cancer development.

Several limitations should be considered in our meta-anal-ysis. First, the majority of the eligible studies only addressed the association of MMP7-181A/G polymorphism with cancer risk.

However, we believe that further studies assessing the effect of gene-gene or gene-environment interactions may eventually achieve a more comprehensive understanding. Second, publication bias is likely to exist, despite the publication bias of low significance or lack thereof in our meta-analysis. Third, significant heterogeneity was detected in the overall comparisons and some of the subgroup analyses. Therefore, a meta-regression analysis was performed to identify the sources of heterogeneity and it was observed that HWE and ethnicity could explain the heterogeneity across studies, whereas other variables, such as cancer type and source of controls could not, possibly due to the heterogeneity resulting from other factors.

In conclusion, the MMP7-181A/G polymorphism is a risk factor for cancer development, particularly cervical and other types of cancer, in Asian populations. Further case-control studies (including HWE or HWE/HWD) estimating the effect of gene-gene and gene-environment interactions may eventually achieve a more comprehensive understanding.

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