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Review Article

Meta-analysis of association of the matrix metalloproteinase 2 (-735 C/T) polymorphism with cancer risk

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Abstract: The association between matrix metalloproteinase 2 (*MMP2*) gene polymorphisms and cancer risk has been investigated in many published studies; however, the currently available results are inconclusive. Therefore, we performed a meta-analysis to provide conclusive evidence for an association between the *MMP2* polymorphism (-735 C/T) and cancer risk. Sixteen case-control studies with 11792 individuals were included in this meta-analysis. The odds ratio (OR) and 95% confidence interval (95% CI) were used to investigate the strength of the association. Overall, the *MMP2* polymorphism (-735 C/T) was not associated with cancer risk in any of the models. However, the subgroup analysis revealed that dominant model (C/T+T/T *vs*. C/C: OR=1.24, 95% CI=1.01-1.53) and codominant 1 model (C/T *vs*. C/C: OR=1.30, 95% CI=1.05-1.62) were significantly associated with cancer risk in the Caucasian population. In conclusion, our meta-analysis indicated that the *MMP2* polymorphism (-735 C/T) might be genetic risk factor for the carcinogenesis in Caucasians. However, more studies with a larger sample size are needed to provide more precise evidence.

Keywords: Matrix metalloproteinase 2, polymorphism, cancer, meta-analysis

Introduction

Cancer is a broad group of diseases characterized by unregulated cell growth and invade healthy cells in human. The cancer may invade or spread to other parts of the body. Cancer invasion and metastasis involve the detachment of tumor cells from the primary tumor, invasion through the basement membrane, intravasation into the circulatory system, extravasation at a distant site, and outgrowth of a secondary tumor [1]. The remodeling of extracellular matrix by matrix metalloproteinase (MMPs) is important for each step of cancer progression [2].

MMPs are a family of Zn^{2+}-dependent endopeptidases. They are essential for tumor growth, angiogenesis, and metastatic processes [3-5]. Among secreted MMPs, MMP2 plays a significant role in cancer invasion and metastasis by degrading extracellular matrix. In addition, it plays an important role in cell proliferation, apoptosis and immune surveillance [2, 6-8]. MMP2 is expressed in normal healthy tissues. Expanding studies have shown that the expression of MMP2 is up-regulated in several types of cancers [9-11]. It suggested that MMP2 may play a significant role in the development and progression of cancers.

The *MMP2* gene is located on the long arm of chromosome 16 between positions 13 and 21. Several single nucleotide polymorphisms (SNP) in the promoter region of *MMP2* gene have recently been identified. Especially, *MMP2* polymorphism (-735 C/T) in the promoter region has been characterized functionally [12, 13].

Up to now, number of studies have been conducted to evaluate the association between *MMP2* promoter polymorphism and risk of dif-

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

Study	Cancer type	Country	Ethnicity	Year	Genotyping method	Case/ control	Case			Control			HWE
							CC	CT	TT	CC	CT	TT	
Rollin et al. [16]	Lung cancer	French	Caucasian	2007	PCR-RFLP	89/90	69	18	2	67	21	2	0.82
Zhou et al. [17]	Lung cancer	China	Asian	2004	PCR-RFLP	770/777	506	230	34	425	313	39	0.05
Zhou et al. [18]	Head & neck cancer	China	Asian	2007	Sequencing	580/478	397	159	24	281	167	30	0.44
Ozgen et al. [19]	Head & neck cancer	Turkey	Caucasian	2008	PCR-RFLP	42/147	23	19	0	99	51	7	0.89
Yu et al. [20]	Esophageal cancer	China	Asian	2004	PCR-RFLP	527/777	323	179	25	425	313	39	0.05
Sun et al. [21]	Esophageal cancer	China	Asian	2009	PCR-RFLP	335/624	222	100	13	408	187	29	0.21
Zhai et al. [22]	Hepatocellular carcinoma	China	Asian	2007	Sequencing	431/478	229	167	35	281	167	30	0.44
Sun et al. [15]	Gastric cancer	China	Asian	2009	PCR-RFLP	257/624	185	63	9	408	187	29	0.21
Li et al. [23]	Ovarian cancer	China	Asian	2008	PCR-RFLP	246/324	164	69	13	181	127	16	0.29
Park et al. [24]	Colorectcal cancer	Korea	Asian	2010	PCR-RFLP	333/318	180	128	25	189	110	19	0.58
Sharma et al. [25]	Gallbladder cancer	India	Asian	2012	PCR-RFLP	410/230	290	112	8	188	40	2	0.94
Gonzalez et al. [26]	Lung cancer	Spain	Caucasian	2012	PCR-RFLP	879/803	596	206	14	465	125	20	0.002
Srivastava et al. [27]	Prostate cancer	India	Asian	2012	PCR-RFLP	190/200	132	50	8	135	60	5	0.58
Srivastava et al. [28]	Bladder cancer	India	Asian	2013	PCR-RFLP	200/200	122	69	9	135	60	5	0.58
Yari et al. [29]	Breast cancer	Iran	Asian	2014	PCR-RFLP	98/135	70	28	0	80	52	3	0.09
Mahmoud et al. [14]	Lymphoma	Egypt	Caucasian	2014	PCR-RFLP	100/100	70	23	7	85	15	0	0.42

ferent types of cancers in diverse populations including breast cancer, bladder cancer, esophageal cancer, lung cancer, hepatocellular carcinoma, prostate cancer and etc. However, the results from the published studies remain conflicting rather than conclusive. Therefore, we performed a meta-analysis on all eligible case-control studies to clarify the association between *MMP2* polymorphism (-735 C/T) and susceptibility to cancer.

Materials and methods

Search strategy

Case and control studies were identified by searching in PubMed, Medline, and Google, up to January 2015 without language restrictions. Relevant studies were identified using the terms: "matrix metalloproteinase2 or MMP2 AND "polymorphism or polymorphisms or variant" AND-735 AND "cancer or carcinoma". The study was restricted to human. Additional studies were searched by hand search of original or review articles references. If data or data subsets were published in more than one article, only the genetic data from the larger sample size were included.

Inclusion criteria

Studies were included if they met the following criteria: (1) evaluated the association between the MMP2 polymorphism (-735 C/T) and cancer; (2) used a case-control study design; (3) contained sufficient published data for the estimation of an odds ratio (OR) with a 95% confidence interval (CI).

Data extraction

The two investigators independently extracted data and reached consensus on all of the items. If the two investigators generated different results, they would check the data again and had a discussion to come to an agreement. Data extracted from the selected articles including the first author's name, year of publication, country of origin, ethnicity of study population, number of cases and controls and genotype frequency of *MMP2* polymorphism (-735 C/T). The ethnicity was divided into Asian and Caucasian population.

Statistical analysis

The chi-square test was used to calculate the Hardy-Weinberg equilibrium (HWE) in the control group. And meta-analysis was performed using the comprehensive meta-analysis software (Corporation, NJ, USA). The pooled *p* value, OR and 95% CI were used to investigate association between risk of cancer and *MMP2* polymorphism (-735 C/T). The random effects model or the fixed effects model was used. OR with the corresponding 95% CI was calculated for the codominant 1 model (C/C *vs*. C/T), codominant 2 model (C/C *vs*. T/T), dominant model (C/C *vs*. C/T+T/T), recessive model (C/C+C/T *vs*. T/T), and allele (C *vs*. T), respectively [14, 15]. The *P*-value less than 0.05 was regarded as statistically significant. A χ^2-test-based Q

Table 2. Overall analysis between *MMP2* polymorphism (-735 C/T) and susceptibility of cancer

Genetic comparison	Population	OR (95% CI)	*P*	Heterogeneity		Model
				P	I^2	
C *vs*. T	All	0.98 (0.85-1.14)	0.80	<0.001	76.74	Random
	Asian	0.93 (0.79-1.09)	0.37	<0.001	77.89	Random
	Caucasian	1.26 (0.83-1.91)	0.27	0.03	65.60	Random
C/C+C/T *vs*. T/T	All	0.95 (0.79-1.14)	0.58	0.29	14.40	Fixed
	Asian	0.99 (0.81-1.20)	0.91	0.56	<0.001	Fixed
	Caucasian	0.62 (0.34-1.16)	0.14	0.12	48.90	Fixed
C/C *vs*. C/T+T/T	All	0.97 (0.81-1.16)	0.71	<0.001	78.20	Random
	Asian	0.90 (0.74-1.09)	0.28	<0.001	79.26	Random
	Caucasian	1.24 (1.01-1.53)	**0.040**	0.17	40.72	Fixed
C/C vs. C/T	All	0.99 (0.80-1.15)	0.63	<0.001	76.41	Random
	Asian	0.89 (0.73-1.07)	0.22	<0.001	76.84	Random
	Caucasian	1.30 (1.05-1.62)	**0.015**	0.42	<0.001	Fixed
C/C vs. T/T	All	0.90 (0.75-1.09)	0.29	0.12	30.71	Fixed
	Asian	0.93 (0.76-1.14)	0.48	0.20	25.38	Fixed
	Caucasian	0.66 (0.35-1.23)	0.19	0.12	48.76	Fixed

OR, odds ratio; Bold numbers indicant significant association with risk of cancer.

statistic test was performed to assess heterogeneity of the study. We also determined the effect of heterogeneity using I^2 test. The random-effects Mantel-Haenszel method was adopted if the result of the Q test was a *P*-value less than 0.05 or a I^2 statistic was larger than 50%, which indicated the statistically significant heterogeneity between the studies. Otherwise, the fixed-effects Mantel-Haenszel method was adopted. To test for publication bias, the Egger's regression was applied.

Results

Study characteristics

Our meta-analysis of present study included sixteen studies, as shown in **Table 1**, comprising 16 articles including 5487 cancer patients and 6305 control subjects were ultimately selected [16-31]. The characteristics of the selected studies in terms of *MMP2*-735 C/T polymorphism and cancer type are summarized in **Table 1**. The types of various cancers included were; lung cancer (3), head and neck cancer (2), esophageal cancer (2), hepatocellular carcinoma (1), gastric cancer (1), ovarian cancer (1), colorectal cancer. (1), gallbladder cancer (1), prostate cancer (1), bladder cancer (1), breast cancer (1), and lymphoma (1).

Quantitative synthesis

Table 2 shows the results from the overall meta-analysis. The sixteen studies were analyzed in meta-analysis. And **Figure 1** shows OR and 95% CI of individual and pooled data for the *MMP2*-735 C/T polymorphism and susceptibility of cancer.

The T allele and genotypes including T allele of the *MMP2*-735 C/T polymorphism was not associated with susceptibility for cancer when compared with the C allele and genotype including C allele in the overall population (*P*>0.05, **Table 2** and **Figure 1A-C**).

When stratified for ethnicity, T/T and/or C/T genotypes, and T allele did not show any significant association with cancer in the Asian population (*P*>0.05). However, there was significant association with risk of cancer in the Caucasian population. When the C/T genotype+T/T genotype of *MMP2*-735 C/T polymorphism was compared with C/C genotype (dominant model), there was a significant association with risk of cancers in the Caucasian population (fixed model, OR=1.24, 95% CI=1.01-1.53, *P*=0.040, heterogeneity=40.72, **Table 2**). And in the codominant 1 model, frequency of C/T genotype in the Caucasian population also showed significant association compared C/C genotype (fixed model, OR=1.30, 95% CI=1.05-1.62, *P*= 0.015, heterogeneity <0.001). Although the study by Gonzalez, et al. 2012 was observed that HWE in the control group was not consistent (*P*=0.002), a publication bias was not observed (Egger's regression *P*=0.87 in the codominant 1 model and Egger's regression *P*=0.65 in the dominant model).

Discussion

MMP2 is involved in the proteolysis of the extracellular matrix, making it a key enzyme in cancer initiation and progression. MMP2 can regulate the tumor microenvironment and thus, plays a critical role in both tumor invasion and

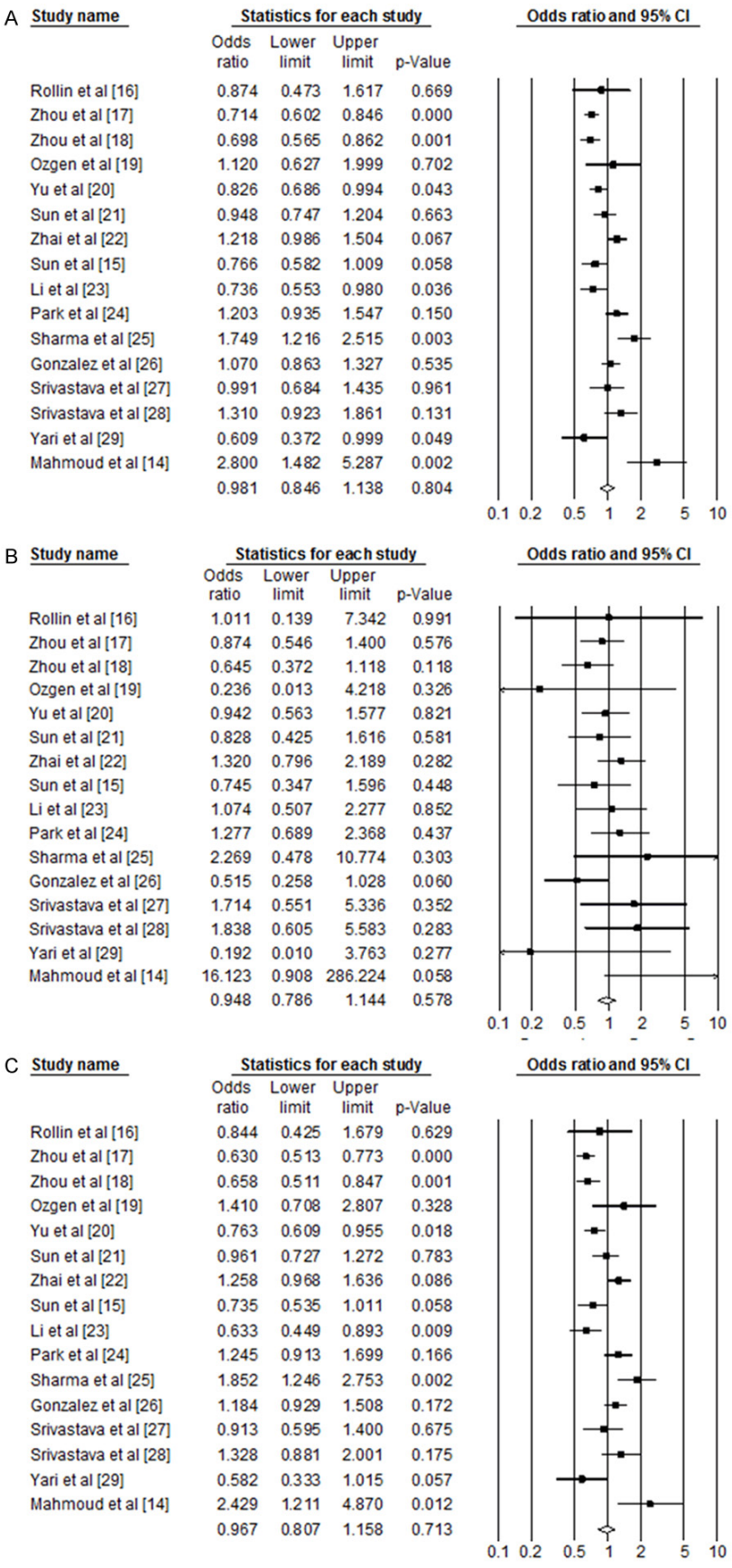

Figure 1. Odds ratio and 95% CI of individual and pooled data for the *MMP2* polymorphism (-735 C/T) and susceptibility of cancer. A: C allele *vs*. T allele; B: C/C genotype + C/T genotype *vs*. T/T genotype; C: C/C genotype *vs*. C/T genotype + T/T genotype.

metastasis. Also, numerous studies have shown poor prognosis in tumors overexpressing MMP2 [10, 11].

The *MMP2*-735 C/T polymorphism is located in the promoter region, appears to be closely associated with expression of MMP2, and is involved in the process of tumor progression. The association between *MMP2*-735 C/T polymorphism and cancer risk has been investigated in a broad range of studies with either a relatively small or larger sample size for the different populations. In previous meta-analysis studies, the *MMP2*-735 C/T polymorphism was reported to be associated with increased cancer risk [32]. Also, it was reported that *MMP2*-735 C/T polymorphism was associated with lung cancer risk, and patients with high MMP2 expression levels have poor overall survival compared with those with low MMP2 expression levels [33]. However, because of the difference in the number of participants and genetic background, the evidence provided by each study is not sufficient enough to draw a convincing conclusion.

We conducted an up-dated meta-analysis including with 5487 cases and 6305 controls from 16 case-control studies to evaluate the association between *MMP2*-735 C/T polymorphism and the cancer risk.

In our study, we examined the association of *MMP2*-735 C/T polymorphism with the risk for cancer by meta-analysis. We found that this polymorphism was related with the increased risk of cancer. Subgroup analysis by ethnicity demonstrated that the *MMP2*-735 C/T polymorphisms were associated with increased cancer risk among the Caucasian population under the dominant and co-dominant 1 model.

We also have to mention the importance of heterogeneity. The heterogeneity was found in some comparisons in our meta-analysis. To get more full and accurate detail of the precious date, we used random-effects model or fixed model. The results were stable with the sensitivity analysis which did not change the results of the meta-analysis.

This meta-analysis still had some limitations and the results should be evaluated with caution. First, this meta-analysis is a type of secondary and retrospective study, it was limited by the quality of primary studies, and our meta-analysis was so, too. Second, we could not perform the analysis of gene-gene and gene-environment interactions.

In conclusion, this present study investigated the relationship between *MMP2*-735 C/T polymorphism and the susceptibility to cancer. We found that *MMP2*-735 C/T polymorphism may contribute to an increase in susceptibility to cancer in the Caucasian population. Further a lager study considering gene-gene and gene-environment interactions is needed to provide more evidence supporting the association of *MMP2*-735 C/T polymorphism with cancer risk.

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Disclosure of conflict of interest

None.

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