

## RESEARCH ARTICLE

# Matrix Metalloproteinase-2 -1306 C>T Gene Polymorphism is Associated with Reduced Risk of Cancer: a Meta-analysis

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### Abstract

Matrix metalloproteinase-2 (MMP2) is an endopeptidase, mainly responsible for degradation of extracellular matrix components, which plays an important role in cancer disease. A single nucleotide polymorphism (SNP) at -1306 disrupts a Sp1-type promoter site. The results from the published studies on the association between MMP2 -1306 C>T polymorphism and cancer risk are contradictory and inconclusive. In the present study, a meta-analysis was therefore performed to evaluate the strength of any association between the MMP2 -1306 C>T polymorphism and risk of cancer. We searched all eligible studies published on association between MMP2 -1306 C>T polymorphism and cancer risk in PubMed (Medline), EMBASE and Google Scholar online web databases until December 2013. Genotype distribution data were collected to calculate the pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) to examine the strength of the association. A total of 8,590 cancer cases and 9,601 controls were included from twenty nine eligible case control studies. Overall pooled analysis suggested significantly reduced risk associated with heterozygous genotype (CT vs CC: OR=0.758, 95% CI=0.637 to 0.902,  $p=0.002$ ) and dominant model (TT+CT vs CC: OR=0.816, 95% CI=0.678 to 0.982,  $p=0.032$ ) genetic models. However, allelic (T vs C: OR=0.882, 95% CI=0.738 to 1.055,  $p=0.169$ ), homozygous (TT vs CC: OR=1.185, 95% CI=0.825 to 1.700,  $p=0.358$ ) and recessive (TT vs CC+CT: OR=1.268, 95% CI=0.897 to 1.793,  $p=0.179$ ) models did not show any risk. No evidence of publication bias was detected during the analysis. The results of present meta-analysis suggest that the MMP2 -1306 C>T polymorphism is significantly associated with reduced risk of cancer. However, further studies with consideration of different populations will be required to evaluate this relationship in more detail.

**Keywords:** Meta-analysis - MMP2 - cancer - susceptibility - polymorphism

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### Introduction

Cancer is a dreadful disease and shown major impact on human health associated with high morbidity and mortality worldwide (Jemal et al., 2011). It is now established that cancer is a multistep process, which results from complex interactions between environmental and genetic factors (Pharoah et al., 2000). Its increasing incidence and mortality rate during the last two decades posed a big challenge to clinicians and scientists. The precise etiology of this fatal disease is still unclear, it has been suggested that low penetrance gene interplay with environmental factors is a major cause of increasing risk of cancer (Lichtenstein et al., 2000). Thus, it is anticipated that the detection of host genetic factors for susceptibility to cancer would significantly help the therapeutic strategies and global control of this deadly disease.

Matrix metalloproteinase (MMPs) are a superfamily

of zinc-dependent endopeptidases, which are involved in degradation of extracellular matrix and basement membrane, required for tumor cell migration and dissemination (Wagenaar et al., 2004; Curran and Murray, 1999). MMPs also contribute to epithelial-mesenchymal transition, angiogenesis, autophagy, and apoptosis and mainly produced by infiltrating inflammatory cells and stromal cells, which can be stimulated by molecules on the surface of cancer cells (Nabeshima et al., 2002; Deryugina and Quigley, 2006).

MMP2 (gelatinase A, localized on 16q13) is a member of the MMP family that primarily hydrolyzes type IV collagen and known to play a key role in tumor invasion and metastasis (Bjorklund and Koivunen, 2005). On the other hand, MMP2 is also involved in growth factor-binding proteins and receptors, which are main factors for cell proliferation and inhibition of apoptosis (Sternlicht and Werb, 1999). The higher expression of MMP2

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protein or mRNA has been observed in several human cancers (Bonomi, 2002; Lebeau et al., 2004). Functional SNPs in MMP2 gene's promoter regions may modify the production of proteolytic enzymes, and in turn modify the risk for carcinogenesis. At the genetic level, many single nucleotide polymorphisms (SNPs) have been identified throughout the coding and non-coding regions. A C→T (rs243865) transition which is found in promoter region -1306 reported to abolish the Sp1 transcriptional factor binding site (CCACC box) and display lower promoter activity and reduction in transcriptional activity of MMP2 gene (Price et al., 2001). Sp1 is a ubiquitously expressed transcription factor that binds to GC/GT-rich elements to regulate a variety of genes. The CCACC box has been shown to be essential for Sp1 binding and promoter function in several genes by invariably activating transcription (Kang et al., 1996; Qin et al., 1999).

Numbers of molecular epidemiological case-control studies have been carried out to interpret the possible association between the MMP2 -1306 C>T polymorphism and human malignancy in different populations (Xu et al., 1999; Yu et al., 2002; 2004; Miao et al., 2003; Li et al., 2004; Zhou et al., 2004; 2005; Elander et al., 2006; Kader et al., 2006; O-Charoenrat and Khanatapura, 2006; Hettiaratchi et al., 2007; Roehe et al., 2007; Rollin et al., 2007; Lei et al., 2007; Zhai et al., 2007; Baltazar et al., 2008; Delgado et al., 2008; Dos et al., 2009; Ohtani et al., 2009; Li et al., 2010; Aysegul et al., 2011; Chaudhary et al., 2011; Kumar et al., 2011; Satpute et al., 2012; Saeed et al., 2013; Srivastava et al., 2013a; 2013b; Wiczorek et al., 2013; Yaykasli et al., 2013; Shalaby, et al., 2014), but results are always inconsistent. Inconsistency in results could be attributed to small sample size and low statistical power. Recently, Burton et al. (2009) suggested that large enough sample size is good to study the genetic associations with complex disease. Therefore these results prompted us to perform the meta-analysis from pooled all published studies to determine the more precise association and understanding the role of MMP2 -1306 C>T polymorphism in cancer. Meta-analysis is a powerful tool because it employs quantitative method to combine the data from individual studies where individual sample sizes are smaller and have lower statistical power, and provides robust conclusion (Cohn and Becker, 2003; Mandal et al., 2013).

## Materials and Methods

### Identification and evaluation of pertinent studies

We searched electronic research literature from PubMed (Medline) and EMBASE, last search updated on December 2013 with the combination of following keywords: 'MMP2 promoter (polymorphism OR mutation OR variant) AND cancer susceptibility. The search was focused on studies that had been conducted in humans. All retrieved articles were evaluated by reading the titles and abstracts, and all published studies matching with the eligible criteria were retrieved for this meta-analysis. We also did manual search of reference lists from the retrieved articles for other eligible articles.

### Inclusion and exclusion criteria

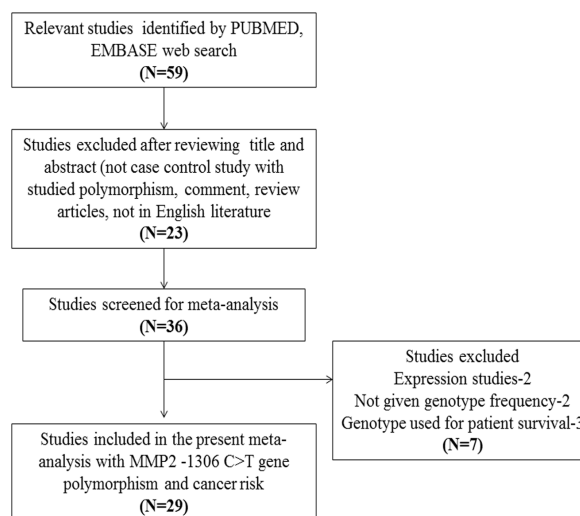
Articles included in the current meta-analysis had to meet all the following criteria: a) must evaluated the association between MMP2 polymorphism and cancer risk, b) used a case-control design, c) recruited histologically confirmed cancer patients and healthy controls, d) have available all genotype frequency in case and control, e) published in the English language. In addition to above, when the same patient populations appeared in several publications, only the most recent or complete study was included in this meta-analysis. The major reasons for study exclusion were, overlapping of the data, case-only studies, review articles, and genotype frequencies or number not reported. The selection procedure of most pertinent studies has been depicted as a flow diagram in Figure 1.

### Data extraction and quality assessment of the studies

For each retrieved publication, the methodological quality assessment and data extraction were independently abstracted in duplicate by two independent investigators using a standard protocol. Data-collection form was used to ensure the accuracy of the collected data by strictly following the inclusion criteria mentioned above. The major characteristic abstracted from the retrieved studies included the name of the first author, year of publication year, the country of origin, the number of cases and controls, type of cancer, genotype frequencies for cases and controls and source of genotyping. Cases related with disagreement on any item of the data from the collected studies were fully discussed with investigators to reach a final consensus.

### Statistical analysis

In order to estimate the strength of association between MMP2 -1306 C>T polymorphism and cancer risk was measured by pooled ORs and their corresponding 95% CIs were calculated (Woolf, 1995). Heterogeneity assumption between studies across the eligible comparison was performed by the chi-square-based Q-test (Wu and Li, 1999). Heterogeneity was considered significant at p-value <0.05 to avoid underestimation of the presence



**Figure 1. Flow Chart Showing the Identification and Selection of the Studies for the Present Meta-analysis**

of heterogeneity. A fixed effect model (if  $p > 0.05$ ) (Mantel and Haenszel, 1959) or a random effect model (if  $p < 0.05$ ) (DerSimonian and Laird, 1986) was used for pooling the results. Furthermore,  $I^2$  statistics was also employed to efficiently test for the heterogeneity (Higgins et al., 2003). Hardy-Weinberg equilibrium (HWE) in the controls was measured via chi-square test. Funnel plot asymmetry was estimated by Egger's linear regression test which is a type of linear regression approach to measure the funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the t-test ( $p$ -value  $< 0.05$  was considered as representation of statistically significant publication bias) (Egger et al., 1997). All the statistical evaluations were performed by Comprehensive Meta-Analysis (CMA) Version 2 software program (Biostat, USA). All  $p$ -values were two sided and statistical significance was considered as  $p$ -value  $< 0.05$  for this meta-analysis.

## Results

### Literature search and meta-analysis databases

According to the selection (inclusion and exclusion) criteria, total twenty nine research articles were finally included through literature search from the PubMed (Medline), EMBASE and Google web search. All retrieved articles were examined carefully by reading the titles and abstracts, and the full texts for the potentially relevant publications were further checked for their

suitability for this meta-analysis. Studies either showing MMP2 polymorphism to predict survival in cancer patients or considering MMP2 variants as an indicators for response to therapy were excluded straightaway. Similarly, studies investigating the levels of MMP2 mRNA or protein expression or relevant review articles were also excluded. We included only case-control or cohort design studies having frequency of all three genotype. Besides the database search, the references available in the retrieved articles were also checked for other potential articles (Table 1). Characteristic of included studies and distributions of genotypes, minor allele frequency (MAF) in the controls and cases have been shown in Tables 1 and 2.

### Publication bias

The Begg's funnel plot and Egger's test were performed to evaluate the publication bias among the included studies for this meta-analysis. The appearance of the shape of funnel plots and the results of Egger's test have shown no evidence of publication bias in all the genetic models (Table 3).

### Evaluation of heterogeneity

Q-test and  $I^2$  statistics were employed to test heterogeneity among the selected studies. Heterogeneity was observed in all the studied genetic models. Thus, random effects model was used to synthesize the data (Table 3).

**Table 1. Main Characteristics of MMP2-1306 C>T Studies Included in the Meta-analysis**

First author and year	Cancer	Country	Study design	Genotyping method	Control	Cases
Yaykasli et al. 2013	Prostate	Turkey	HB	PCR-RFLP	46	61
Saeed et al. 2013	Colorectal	Saudi Arabia	HB	TaqMan	122	95
Srivastava et al. 2013	Bladder	India	HB	PCR-RFLP	200	200
Wieczorek et al. 2013	Bladder	Poland	HB	TaqMan	199	241
Srivastava et al. 2012	Prostate	India	HB	PCR-RFLP	200	190
Satpute et al. 2012	OSCC	India	HB	PCR-RFLP	20	40
Chaudhary et al. 2011	HNSCC	India	HB	PCR-RFLP	422	426
Kumar et al. 2011	Glioblastoma	India	HB	PCR-RFLP	150	110
Aysegul et al. 2011	Lung	Turkey	HB	PCR-RFLP	100	200
Li et al. 2010	ESCC, GCA	China	HB	PCR-RFLP	624	592
Dos Reis et al. 2009	Prostate	Brazil	HB	RT-PCR	147	100
Ohtani et al. 2009	Colorectal	Japan	HB	PCR-RFLP	67	47
Delgado-Enciso et al. 2008	Breast	Mexican	HB	PCR-RFLP	90	90
Baltazar et al. 2008	Cervical	Mexican	HB	PCR-RFLP	126	54
Zhai et al. 2007	HNCC	China	HB	Sequencing	480	434
Lei et al. 2007	Breast	Germany	PB	TaqMan	952	959
Rollin et al. 2007	NSCLC	France	HB	DHPLC	90	90
Roehe et al. 2007	Breast	Brazil	HB	DNA sequencing	100	89
Hettiaratchi et al. 2007	Colorectal	Australia	HB	RT-PCR	471	503
Kader et al. 2006	Bladder	USA	HB	TaqMan	560	560
Ocharoenrat et al. 2006	HNCC	Thailand	HB	ARMS-PCR	250	239
Elander et al. 2006	Colorectal	Sweden	HB	DHPLC	208	127
Zhou et al. 2005	Lung	China	HB	DHPLC	777	770
Zhou et al. 2004	Breast	China	HB	DHPLC	509	462
Xu et al. 2004	Colorectal	China	HB	DHPLC	126	126
Yu et al. 2004	Esophageal	China	HB	DHPLC	777	527
Lin et al. 2004	OSCC	China	HB	DHPLC	147	121
Miao et al. 2003	GCA	China	HB	DHPLC	789	356
Yu et al. 2002	Lung	China	HB	DHPLC	852	781

\*HB: Hospital based; PB: Population based; GCA: Gastric cardia adenocarcinoma; NSCLC: non-small cell lung cancer; DHPLC: Denaturing high performance liquid chromatography

### Association of MMP2 -1306 C>T polymorphism and overall cancer susceptibility

We pooled all twenty nine studies together and it resulted into 8590 cancer cases and 9601 controls,

examining the overall association between MMP2 -1306 C>T polymorphism and cancer risk. The pooled OR from overall studies indicated reduced risk between MMP2 -1306 C>T polymorphism and cancer risk in

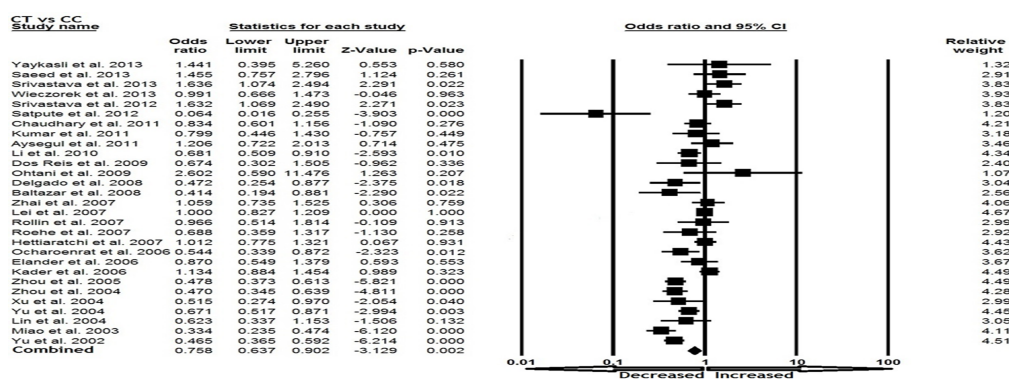
**Table 2. Genotypic distribution of MMP2 -1306 C>T gene polymorphism included in the meta-analysis**

Authors and year	Controls				Cancer cases				HWE
	Genotype			Minor allele MAF	Genotype			Minor allele MAF	p-value
	CC	CT	TT		CC	CT	TT		
Yaykasli et al. 2013	42	4	0	0.04	51	7	3	0.10	0.75
Saeed et al. 2013	92	23	1	0.10	66	24	5	0.17	0.73
Srivastava et al. 2013	131	62	7	0.19	102	79	19	0.29	0.91
Wieczorek et al. 2013	120	72	7	0.21	143	85	13	0.23	0.33
Srivastava et al. 2012	131	62	7	0.19	101	78	11	0.26	0.91
Satpute et al. 2012	4	15	1	0.42	29	7	4	0.18	0.01
Chaudhary et al. 2011	298	104	20	0.17	299	87	40	0.19	0.007
Kumar et al. 2011	109	39	2	0.14	84	24	2	0.12	0.47
Aysegul et al. 2011	65	32	3	0.19	123	73	4	0.20	0.69
Li et al. 2010	487	137	6	0.11	491	94	80	0.19	0.28
Dos Reis et al. 2009	59	21	20	0.30	50	12	38	0.44	<0.0001
Ohtani et al. 2009	64	3	0	0.02	41	5	1	0.07	0.85
Delgado et al. 2008	50	42	4	0.26	63	25	2	0.16	0.18
Baltazar et al. 2008	76	47	3	0.21	43	11	0	0.10	0.16
Zhai et al. 2007	402	70	1	0.07	358	66	3	0.08	0.25
Lei et al. 2007	520	359	69	0.26	520	359	70	0.26	0.51
Rollin et al. 2007	60	29	1	0.17	60	28	2	0.17	0.21
Roehe et al. 2007	66	32	2	0.18	63	21	5	0.17	0.4
Hettiaratchi et al. 2007	274	169	28	0.23	290	181	32	0.24	0.77
Ocharoenrat et al. 2006	190	56	4	0.12	206	33	0	0.06	0.95
Elander et al. 2006	109	89	10	0.26	69	49	9	0.26	0.12
Kader et al. 2006	312	202	31	0.24	297	218	28	0.25	0.82
Zhou et al. 2005	539	220	18	0.16	635	124	11	0.09	0.42
Zhou et al. 2004	349	154	6	0.16	381	79	2	0.08	0.01
Xu et al. 2004	92	32	2	0.14	106	19	1	0.08	0.67
Yu et al. 2004	539	220	18	0.16	409	112	6	0.11	0.42
Lin et al. 2004	107	34	6	0.15	101	20	0	0.08	0.13
Miao et al. 2003	542	229	18	0.16	312	44	0	0.06	0.27
Yu et al. 2002	585	248	19	0.16	644	127	10	0.09	0.21

\*MAF, Minor allele frequency, HWE, Hardy Weinberg equilibrium

**Table 3. Statistics to Test Publication Bias and Heterogeneity in the Present Meta-analysis**

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% Confidence Interval	p-value	Q-value	Pheterogeneity	I <sup>2</sup> (%)	
T vs C	-0.20	-2.75-2.34	0.87	236.25	<0.0001	88.14	Random
TT vs CC	-0.21	-1.47-0.92	0.64	85.32	<0.0001	67.18	Random
CT vs CC	-0.07	-2.12-1.97	0.94	146.36	<0.0001	80.87	Random
TT+CT vs CC	-0.05	-2.26-2.37	0.95	186.05	<0.0001	84.95	Random
TT vs CC+CT	-0.12	-1.28-1.03	0.82	80.14	<0.0001	65.06	Random



**Figure 2. Forest Plot with ORs on Overall Cancer Risk Associated with MMP2 -1306 C>T Gene Polymorphism (CT vs CC; Heterozygous Model)**



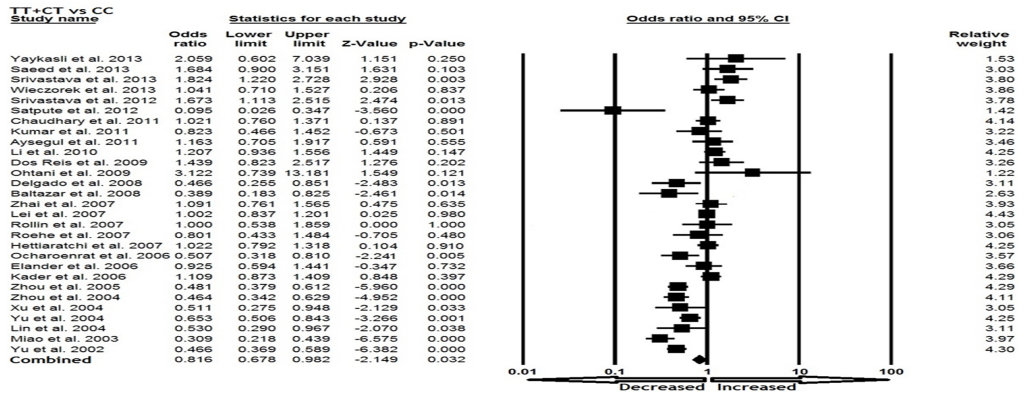


Figure 3. Forest Plot with ORs on Overall Cancer Risk Associated with MMP2 -1306 C>T Gene Polymorphism (TT+CT vs CC; Dominant Model)

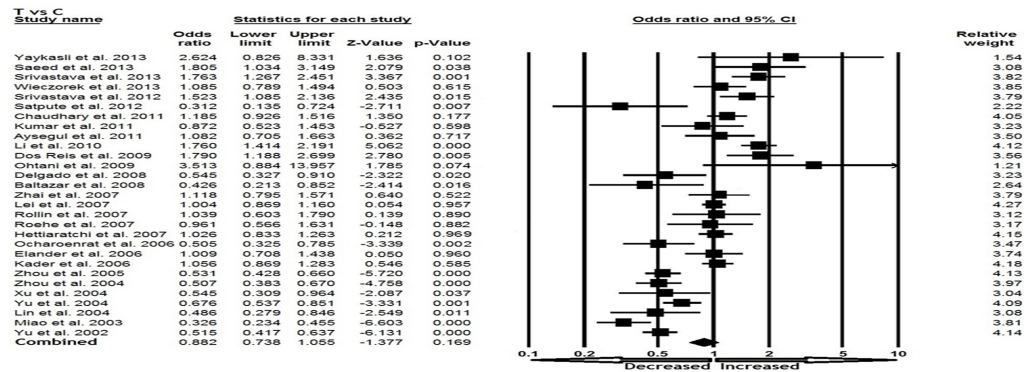


Figure 4. Forest Plot with ORs on Overall Cancer Risk Associated with MMP2 -1306 C>T Gene Polymorphism (T vs C; Allelic Model)

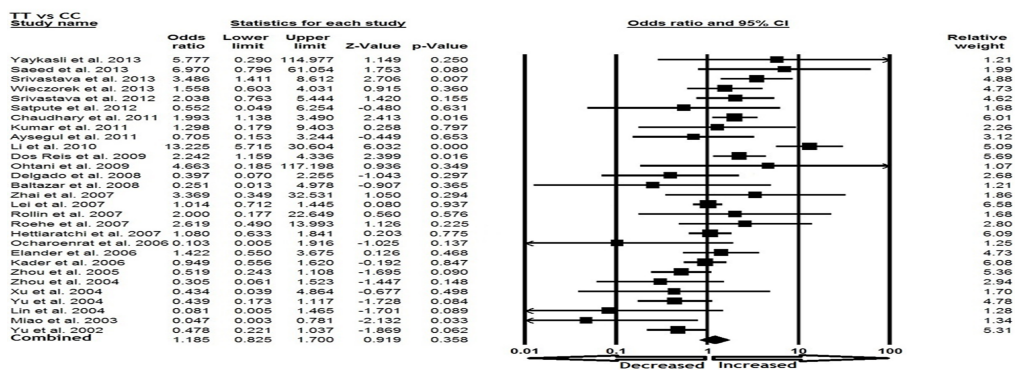


Figure 5. Forest Plot with ORs on Overall Cancer Risk Associated with MMP2 -1306 C>T Gene Polymorphism (TT vs CC; Homozygous Model)

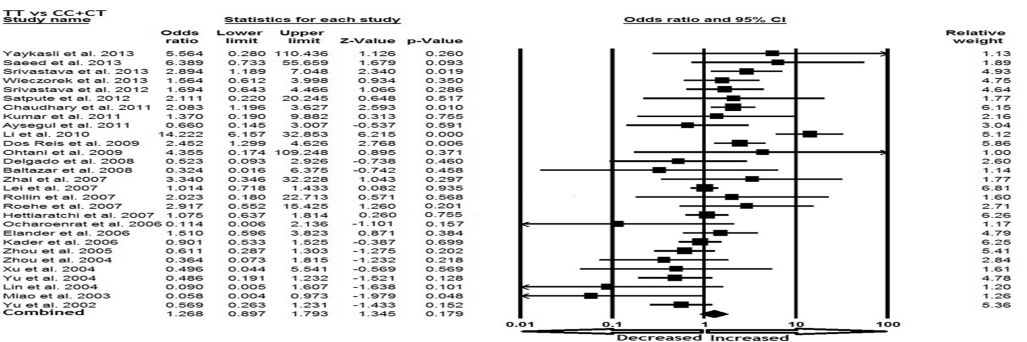


Figure 6. Forest Plot with ORs on Overall Cancer Risk Associated with MMP2 -1306 C>T Gene Polymorphism (TT vs CC+CT; Recessive Model)

two genetic models, heterozygous (CT vs CC:  $p=0.002$ ;  $OR=0.758$ ,  $95\%CI=0.637$  to  $0.902$ ; Figure 2) and dominant model (TT+CT vs CC:  $p=0.032$ ;  $OR=0.816$ ,

$95\%CI=0.678$  to  $0.982$ ; Figure 3). However, allelic (T vs C:  $p=0.169$ ;  $OR=0.882$ ,  $95\%CI=0.738$  to  $1.055$ ; Figure 4), homozygous (TT vs CC:  $p=0.358$ ;  $OR=1.185$ ,

95%CI=0.825 to 1.700; Figure 5) and recessive (TT vs CC+CT:  $p=0.179$ ; OR=1.268, 95%CI=0.897 to 1.793; Figure 6) models did not show any increased or decreased risk of cancer.

## Discussion

Cancer remains the most lethal disease worldwide, despite improvements in diagnostic and therapeutic techniques. It has been widely accepted that host genetic factors including genetic polymorphism, had garnered interest with regard to the study of the carcinogenesis. Microenvironment of tumor cells composed of numerous interdependent cell types, including fibroblast, endothelial and lymphatic cells; bone marrow derived cells and embedded with extracellular matrix (ECM). ECM of tumor has a unique composition and recognized as a major regulator of carcinogenesis (Hanahan and Weinberg, 2011). Disruption to such control mechanisms deregulates and disorganizes the ECM, leading to abnormal behaviors of cells residing in the niche and ultimately failure of organ homeostasis and function, permitting invasion into surrounding connective tissues, entry and exit from blood vessels, and metastasis to distant organs (Cox and Erler, 2011). MMPs are able to degrade virtually all ECM components and viewed as essential for tumor progression (Van Kempen et al., 2006). Expression of MMP2 is elevated in carcinomas in association with low differentiation grade and accelerated tumor progression (Vihinen and Kahari, 2002). Having known the important roles of MMPs in carcinogenesis, it is reasonable to speculate that host genomic polymorphism of MMP2 gene may affect the tumor occurrence. Recently, genetic variants of the MMP2 -1306 C>T gene polymorphism and its role in the etiology of several cancers have been studied extensively, but the results are inconclusive. As it is known that, individual studies with a small sample size may not have enough statistical power to detect a small risk factor. Our main focus was to estimate the more precise results to understand the contribution of MMP2 -1306 C>T gene polymorphism in overall cancer risk. Therefore, we performed the current meta-analysis to appraise whether MMP2 -1306 C>T gene polymorphism could have an impact on susceptibility to overall cancer.

This meta-analysis was based on the accumulation of all eligible data to analyze overall cancer susceptibility. The associations for the allele contrast, dominant and recessive model of MMP2 -1306 C>T were examined. We found that the MMP2 -1306 C>T polymorphism were associated with a significantly reduced risk in heterozygous and dominant genetic models. The same trend of associations was also reported in meta-analysis of digestive and lung cancer as well as in metastasis of cancer (Li et al., Hu et al., 2013; Liu et al., 2012). However, a recent meta-analysis suggests that MMP-2 C735T and C1306T polymorphisms influence susceptibility to lung cancer in Asians (Guo et al., 2012). The results of another meta-analysis suggest that MMP-2 -1306C>T polymorphism is not associated with breast cancer susceptibility, although the association among Latin-Americans in the dominant model was found significant (Yang et al., 2014). MMP2

-1306 disrupt sp1 binding site and a previous study has demonstrated that a reduction in Sp1 DNA binding activity or phosphorylation by nonsteroidal anti-inflammatory drugs suppresses MMP2 expression (Pan et al., 2002). This observation clearly recommend that absence of the Sp1 sequence in the MMP2 gene would produce a lower level of MMP2 protein in individuals carrying -1306 T allele than those carrying the C allele. Reduced expression would be expected to be associated with a reduced risk of cancer. An animal study also shown that lower expression level of MMP2 is associated with reduced risk of tumor formation (Bergers et al., 2000; Itoh et al., 1998). MMPs are not always involved in development of cancer, they have also shown anti-tumor effects, as illustrated by the inhibiting effects on angiogenesis (Martin and Matrisian, 2007). However, cancer etiology is polygenic and role of different MMP polymorphisms in the risk of developing cancer is diverse. Hence, a single genetic variant is usually insufficient to predict risk of this complex disease.

Despite the current findings, our results have some limitations. Heterogeneity is an important issue when interpreting the results of meta-analysis. In present study we found inter-study heterogeneity. The source of heterogeneity may arise from many aspects, such as the region of study, the sample size the case and the control group, clinical characteristic of different tumor, and the genotyping method. Due to the limited number of studies, subgroup analysis was not performed and this study was based on unadjusted estimates, while a more precise analysis could be performed if individual data were available.

In spite of this, our current study has some advantage. Publication bias is a well-known problem that was not detected by funnel plot and Egger linear regression in the present meta-analysis indicating that the results are statistically robust. In this study we used explicit criteria for a study's inclusion and performed strict data extraction and analysis to make satisfactory and reliable conclusion.

In conclusion, a meta-analysis is an important tool of statistical data-analysis and pools both statistically significant and non-significant data from individual studies and suggests a precise and absolute conclusion. The overall results of this meta-analysis suggested that MMP2 -1306 C>T gene polymorphism is associated with decreased cancer risk. In the present study we only analyzed the MMP2 -1306 C>T variant, without considering the interaction between several other SNPs. In our future study, we will try to further explore the other pertinent interactions to facilitate the discovery of cancer development. In addition to the targeted research to further clarify a potential role of MMP2 -1306 C>T gene variant in cancer risk, future well designed large-scale studies with the consideration of gene-gene and gene-environment interactions should be warranted to evaluate the possible association.

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