RESEARCH ARTICLE

MMP1 rs1799750 Single Nucleotide Polymorphism and Lung Cancer Risk: A Meta-analysis

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Abstract

Background: Numerous studies have investigated the association of matrix metalloproteinase 1 (MMP1) rs1799750 single nucleotide polymorphism with lung cancer susceptibility, but the findings are inconsistent. Therefore, we performed a meta-analysis to comprehensively evaluate any possible association. Methods: We searched publications from MEDLINE, EMBASE and CNKI databases which assessed links between the MMP1 rs1799750 polymorphism and lung cancer risk. We calculated the pooled odds ratio (OR) and its 95% confidence interval (95%CI) using either fixed-effects or random-effects models. Results: The meta-analysis was based on 9 publications encompassing 4,823 cases and 4,298 controls. The overall results suggested there was a significant association between the MMP1 rs1799750 polymorphism and lung cancer risk (1G vs. 2G: OR = 0.83, 95%CI = 0.73-0.94; 1G1G vs. 2G2G: OR = 0.73, 95%CI = 0.59-0.92; 1G1G vs. 1G2G/2G2G: OR = 0.87, 95%CI = 0.79-0.97; 1G1G/1G2G vs. 2G2G: OR = 0.78, 95%CI = 0.64-0.95). In the subgroup analysis by ethnicity, the association was still obvious in Asians (all P values < 0.05), but there was no association in Caucasians (all P values > 0.05). Conclusions: The MMP1 rs1799750 polymorphism is associated with decreased lung cancer risk, and a race-specific effect may exist in this association.

Keywords: MMP1 - lung cancer - single nucleotide polymorphism - meta-analysis - ethnic groups

Asian Pacific J Cancer Prev, **13 (12)**, 5981-5984

Introduction

Lung cancer was the most commonly diagnosed type of cancer as well as the leading cause of cancer death in males in 2008 (Jemal et al., 2011). Globally, lung cancer accounts for 13% (1.6 million) of the total cases and 18% (1.4 million) of the deaths (Jemal et al., 2011). Besides, the incidence and mortality rates of lung cancer have grown rapidly in developing countries (Herbst et al., 2008; Kimman et al., 2012). The average 5-year survival rate of patients with lung cancer is less than 15% because of the high incidence of metastasis (Herbst et al., 2008; Goldstraw et al., 2011). Cigarette smoking is the well known risk factor for lung cancer, which accounts for 80% of the worldwide lung cancer burden in males and at least 50% of the burden in females (Herbst et al., 2008). Tobacco smoke contains multiple carcinogens that are known to chemically modify of genomic DNA and further lead to genetic mutations. However, not all smokers develop lung cancer, but many cases are from non-smokers indicating individual genetics are also play an important role in the lung carcinogenesis (Brennan et al., 2011; Xiao et al., 2011). Matrix metalloproteinases (MMPs) is a family of zincdependent endopeptidases, which can degrade various extracellular components such as basement membranes, collagen, and fibronectin (Nelson et al., 2000). In normal physiologic conditions, Matrix metalloproteinase 1 (MMP1) is expressed constitutively at low level; however, its expression may increase markedly in pathologic conditions, such as coronary atherosclerosis, and especially cancer (Egeblad and Werb, 2002; Yamamura et al., 2002). Increased MMP-1 activity enables greater extracellular matrix (ECM) degradation, cell growth factor activation, and tumor cell immune escape, which facilitate the initiation and invasiveness of cancer (Yamamura et al., 2002). MMP1 gene is polymorphic, and a number of single nucleotide polymorphisms (SNPs) have been identified, and are potentially functional and been studied for their associations with cancer susceptibility and cancer metastasis (Zhou et al., 2011, Liu et al., 2012). A single-guanine 2G to 1G polymorphism located at the MMP-1 promoter region (SNP rs1799750) has been identified that affects the transcription level of the gene (Zhou et al., 2011). It has been demonstrated that the promoter comprising the 2G allele has significantly greater transcriptional activity compared with the 1G promoter, because the 2G allele creates a transcription factor binding site and increases transcription capacity (Su et al., 2006; Chen et al., 2012). A few studies on the association between this polymorphism and lung cancer

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susceptibility have been published, but those results were inconsistent and inconclusive (Zhu et al., 2001; Su et al., 2006; Gonzalez-Arriaga et al., 2008; Hart et al., 2011). To further evaluate the role of the MMP1 rs1799750 polymorphism in the development of lung cancer, we conducted a meta-analysis to investigate the association between this polymorphism and the occurrence of lung cancer.

Materials and Methods

Identification and eligibility of relevant studies

Studies included in this meta-analysis were to meet the following criteria: (a) evaluating the association between MMP1 rs1799750 polymorphism and lung cancer risk, (b) using a case-control design, (c) providing sufficient information to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). We searched the electronic literature MEDLINE, EMBASE and CNKI databases for all relevant articles using the search terms: "MMP1 or MMP or Matrix metalloproteinase or Matrix metalloproteinases or Matrix metalloproteinase 1 or rs1799750 or 1607 1G/2G", "variant or variation or polymorphism or polymorphisms or SNP" and "lung cancer or lung carcinoma" (last search was updated on April 30, 2012). All eligible studies were retrieved, and their bibliographies were manually checked for additional eligible studies. Additionally, abstracts and unpublished reports were not considered. If more than one article was published using the same patient population, only the latest or the largest study would be used in this meta-analysis. Two authors independently assessed the articles for compliance with the inclusion criteria, and any disagreement was resolved by discussions till consensus was reached. In addition, investigations departure from Hardy-Weinberg equilibrium (HWE) was excluded from the final analysis.

Data extraction

The following information was collected from each study: first author's surname, year of publication, ethnicity of the study population, histological types, source used for controls, total number of cases and controls, genotype methods and numbers of cases and controls with genotypes for MMP1 rs1799750 polymorphism. For those studies that included subjects of different ethnic groups, genotypes data were extracted separately for each of ethnic groups, categorized as Caucasians, Asians, or Mixed which contained more than one ethnic group.

Statistical methods

The strength of association between MMP1 rs1799750 polymorphism and lung cancer risk was assessed by calculating ORs with the corresponding 95% CIs. For MMP1 rs1799750 polymorphism, the pooled ORs were also performed for allele model (1G vs. 2G), homogenotype model (1G1G vs. 2G2G), recessive model (1G1G vs. 1G2G/2G2G), and dominant model (1G1G/1G2G vs. 2G2G). The homogeneity assumption was verified by I^2 test (Higgins et al., 2003). If the studies were found to be homogeneous (with $I^2 < 50\%$), the pooled OR estimate of all studies would be calculated by the fixed-effects model (the Mantel–Haenszel method) (Mantel and Haenszel, 1959). If homogeneity could not be assumed, a random-effects model (the DerSimonian and Laird method) would be used (DerSimonian and Laird, 1986). Subgroup analyses were performed by ethnicity including Caucasians and Asians. Funnel plot was used to verify the potential publication bias, in which a standard error of log (OR) for each study was plotted against its log (OR) (Attia et al., 2003). This meta-analysis was performed by using the software Review manager version 5.1.0. All the P values were two-sided, and a $P<0.05$ was considered statistically significant.

Results

Study characteristics

A total of 63 published records were retrieved, of which 52 were excluded after the abstract was found to be irrelevant and 11 papers was further assessed for inclusion. Two studiers were further excluded for not on the association between MMP1 rs1799750 polymorphism and lung cancer risk (Zhou et al., 2005; Sauter et al., 2008). Thus, 9 case-control studies with a total of 4823 cases and 4298 controls finally met the inclusion criteria and were included in the meta-analysis (Zhu et al., 2001; Fang et al., 2005; Su et al., 2006; Zhang et al., 2006;

Table 1. Meta-analysis of the Association Between MMP1 rs1799750 Polymorphism and Lung Cancer Risk

Comparison Model	Studies (Participants)	OR(95%CI)	P_{OR}	Model	I^2 (%)
Total studies					
1G versus 2G	9(9,121)	0.83(0.73-0.94)	0.004	Random	71%
1G1G versus 2G2G	9(9,121)	0.73(0.59-0.92)	0.006	Random	61%
1G1G versus 2G2G/2G1G	9(9,121)	0.87(0.79-0.97)	0.009	Fixed	33%
1G1G/2G1G versus 2G2G	9(9,121)	0.78(0.64-0.95)	0.012	Random	74%
Asians					
1G versus 2G	5(2,996)	0.76(0.68-0.85)	<0.001	Fixed	0%
1G1G versus 2G2G	5(2,996)	0.59(0.47-0.75)	<0.001	Fixed	0%
1G1G versus 2G2G/2G1G	5(2,996)	0.68(0.54-0.84)	0.001	Fixed	0%
1G1G/2G1G versus 2G2G	5(2,996)	0.72(0.63-0.84)	<0.001	Fixed	42%
Caucasians					
1G versus 2G	4(6,125)	0.90(0.76-1.08)	0.258	Random	79%
1G1G versus 2G2G	4(6,125)	0.86(0.66-1.14)	0.299	Random	69%
1G1G versus 2G2G/2G1G	4(6,125)	0.94(0.83-1.05)	0.257	Fixed	15%
1G1G/2G1G versus 2G2G	4(6,125)	0.86(0.64-1.17)	0.341	Random	83%

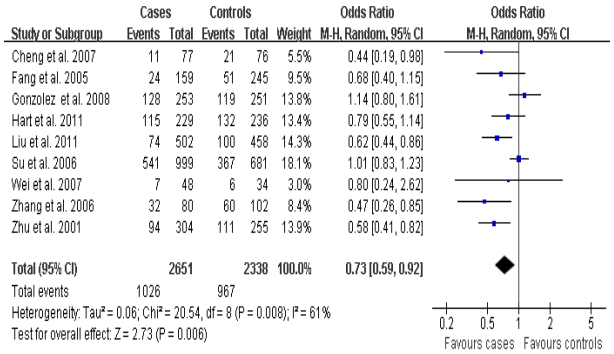

Figure 1. Meta-analysis of the Association Between MMP1 rs1799750 Polymorphism and Lung Cancer Risk Under the Homogenotype Model (1G1G vs. 2G2G)

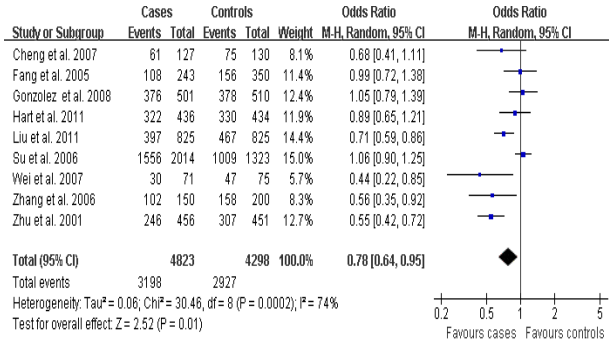

Figure 2. Meta-analysis of the Association Between MMP1 rs1799750 Polymorphism and Lung Cancer Risk Under the Dominant Model (1G1G/1G2G vs. 2G2G)

Cheng, 2007; Wei et al., 2007; Gonzalez-Arriaga et al., 2008; Hart et al., 2011; Liu et al., 2011). The distribution of genotypes for MMP1 rs1799750 polymorphism in the controls of all studies was consistent with that expected from the HWE. Of those 9 studies, sample sizes ranged from 146 to 3337, in which four studies focused on non-small cell lung cancer (NSCLC) and five ones on mixed lung cancers. There were four studies on Caucasians (Zhu et al., 2001; Su et al., 2006; Gonzalez-Arriaga et al., 2008; Hart et al., 2011), and five studies on Asians (Fang et al., 2005; Zhang et al., 2006; Cheng, 2007; Wei et al., 2007; Liu et al., 2011). Almost all of the cases were histologically confirmed, while controls were mainly matched for sex and age.

Meta-analysis results

The overall results suggested there was a significant association between MMP1 rs1799750 polymorphism and lung cancer risk (1G vs. 2G: OR = 0.83, 95%CI = 0.73-0.94; 1G1G vs. 2G2G: OR = 0.73, 95%CI = 0.59-0.92; 1G1G vs. 1G2G/2G2G: OR = 0.87, 95%CI = 0.79-0.97; 1G1G/1G2G vs. 2G2G: OR = 0.78, 95%CI = 0.64-0.95) (Table 1, Figure 1 and Figure 2). In the subgroup analysis by ethnicity, the association above was still obvious in Asians (1G vs. 2G: OR = 0.76, 95%CI = 0.68-0.85; 1G1G vs. 2G2G: OR = 0.59, 95%CI = 0.47-0.75; 1G1G vs. 1G2G/2G2G: OR = 0.68, 95%CI = 0.54-0.84; 1G1G/1G2G vs. 2G2G: OR = 0.72, 95%CI = 0.63-0.84), but there was no association between MMP1 rs1799750 polymorphism and lung cancer risk in Caucasians (All P

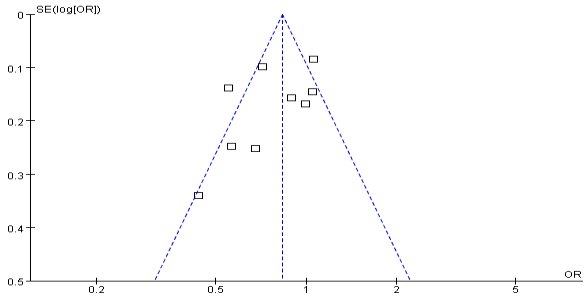

Figure 3. Funnel Plot for the Meta-analysis of the Association Between MMP1 rs1799750 Polymorphism and Lung Cancer Risk Under the Dominant Model (1G1G/1G2G vs. 2G2G)

values were more than 0.05) (Table 1).

Publication bias

Funnel plot was used to verify the potential publication bias. There was no obvious asymmetry in funnel plots under those four models, suggesting there was no potential publication bias in this meta-analysis (Figure 3).

Discussion

It is well recognized that individual susceptibility to cancer varies, even after exposure to the same environment. Therefore, it has been suggested that genetic variation, such as SNPs of genes is involved in carcinogenesis. For MMP1 gene, one single nucleotide polymorphism rs1799750 was extensively investigated for its association with cancer risk, in particular for lung cancer. Because the results from these studies were inconsistent, we performed a meta-analysis of the published reports to further evaluate the association of MMP1 rs1799750 polymorphism with the risk of lung cancer. Our meta-analysis is the first to evaluate the association between the MMP1 rs1799750 polymorphism and lung cancer risk because no such meta-analysis has been published to date. The overall results suggested there was a significant association between MMP1 rs1799750 polymorphism and lung cancer risk (1G vs. 2G: OR = 0.83, 95%CI = 0.73-0.94; 1G1G vs. 2G2G: OR = 0.73, 95%CI = 0.59-0.92; 1G1G vs. 1G2G/2G2G: OR = 0.87, 95%CI = 0.79-0.97; 1G1G/1G2G vs. 2G2G: OR = 0.78, 95%CI = 0.64-0.95) (Table 1, Figure 1 and Figure 2). In the subgroup analysis by ethnicity, the association above was still obvious in Asians (1G vs. 2G: OR = 0.76, 95%CI = 0.68-0.85; 1G1G vs. 2G2G: OR = 0.59, 95%CI = 0.47-0.75; 1G1G vs. 1G2G/2G2G: OR = 0.68, 95%CI = 0.54-0.84; 1G1G/1G2G vs. 2G2G: OR = 0.72, 95%CI = 0.63-0.84), but there was no association between MMP1 rs1799750 polymorphism and lung cancer risk in Caucasians. Thus, MMP1 rs1799750 polymorphism is associated with decreased lung cancer risk, and a race-specific effect may exist in this association.

Several studies have explored the role of the MMP1 rs1799750 polymorphism in the risk of colorectal cancer and breast cancer (Peng et al., 2010; Liu et al., 2011). Matrix metalloproteinases (MMPs) is a family of zincdependent endopeptidases, which can degrade various extracellular components such as basement membranes, collagen, and fibronectin. MMPs family is

involved in normal physiological and disease processes, including embryonic development, reproduction, and cancer. MMP1 is one of the widely expressed MMPs, which can degrade I, II, and III type collagens, and plays important roles in carcinogenesis (Egeblad and Werb, 2002; Liu et al., 2012). MMP1 rs1799750 polymorphism is a guanine insertion/deletion at −1607 base pair (bp) in the MMP1 promoter region. One allele has one guanine (1G), and the other one has two guanines (2G). The additional guanine (2G) creates an Ets-binding site, increases the transcription activity, and therefore, 2 G is associated with high level of MMP1 expression (Zhou et al., 2011). Increased MMP-1 activity enables greater ECM degradation, cell growth factor activation, and tumor cell immune escape, which facilitate the initiation and invasiveness of cancer (Yamamura et al., 2002). Thus, MMP1 rs1799750 polymorphism may affect the susceptibility to lung cancer by altering the levels of MMP1 expression. MMP1 rs1799750 1G variant is associated with decreased MMP-1 activity, and may provide a protective effect on lung cancer risk, thus decreases the risk of lung cancer.

There were several limitations to be considered in this meta-analysis. Firstly, there was lack of the original data of lung cancer histological types which limited our further evaluation of histological types and genotypes interactions. Secondly, there was lack of the original data which limited our further evaluation of potential gene-gene and gene-environment interactions. Finally, there was lack of information on disease status, genotypes, and well-documented smoking status which may also influence the results. Further studies with larger sample size and more detailed histological types are needed to evaluate potential gene-gene and gene-environment interactions in the association between the MMP1 rs1799750 polymorphism and lung cancer risk.

In conclusion, MMP1 rs1799750 polymorphism is associated with decreased lung cancer risk, and a race-specific effect may exist in this association. However, further studies are warranted to validate the association between the MMP1 rs1799750 polymorphism and lung cancer risk with larger sample size and more detailed histological types.

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