Gene 517 (2013) 65–71

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Current evidence on the relationship between five polymorphisms in the matrix metalloproteinases (MMP) gene and lung cancer risk: A meta-analysis

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ARTICLE INFO

Article history:
Accepted 19 December 2012
Available online 9 January 2013

Keywords:
Matrix metalloproteinases (MMPs)
Polymorphism
Lung cancer
Risk
Meta-analysis

ABSTRACT

Purpose: Matrix metalloproteinase (MMP) 1, MMP2, MMP3 and MMP9 are important members of the MMP family. Recently, many studies have been carried out on the association between polymorphisms of MMP1-1607 1G/2G, MMP2-735 C/T, MMP2-1306 C/T, MMP3-1171 5A/6A and MMP9-1562 C/T and lung cancer risk. However the results of these studies remained inconclusive due to conflicting results from different case–control studies. To clarify these associations, we conducted a meta-analysis.
Methods: We conducted a comprehensive search in Medline, EMBASE, OVID and Chinese Biomedical Literature Database (date from Jan 2000 to Aug 2012). Overall and subgroup analysis by the ethnicity of study population was carried out. Odds ratio (OR) with 95% confidence interval (95%CI) was used to assess the strength of the association.
Results: There were 17 studies involving five polymorphic sites in four MMP genes. For MMP1-1607,increased lung cancer risk was found under dominant model (MMP1-1607 1G/2G: OR = 1.14, 95%CI = 1.03–1.26, $P = 0.01$), but not in the Caucasian population. For MMP2-1306 C/T, T polymorphism decreased lung cancer risk under dominant and recessive models (dominant, OR = 0.63, 95%CI = 0.46–0.88, $P = 0.0006$; recessive, OR = 0.61, 95%CI = 0.38–0.99, $P = 0.04$). For MMP9-1562 C/T, TT genotype decreased this risk under the recessive model (OR = 0.38, 95%CI = 0.19–0.75, $P = 0.005$), but not in the Asian population. For MMP2-735 C/T and MMP3-1171 5A/6A, there was no association between this polymorphism and lung cancer risk under the dominant and recessive models.
Conclusions: MMP1-1607 1G/2G polymorphism increased lung cancer risk in Asians. It was also found thatMMP2-1306 C/T polymorphism decreased lung cancer risk in Asians, while MMP9-1562 C/T polymorphism decreased lung cancer risk in Caucasians. No significant difference was found in any genotype of MMP2-735 C/T and MMP3-1171 5A/6A. Further studies with larger sample sizes should be carried out.

1. Introduction

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males in 2008 globally. Among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Lung cancer accounts for 13% (1.6 million) of the total cases and 18% (1.4 million) of the deaths in 2008 (Jemal et al., 2011). In addition to smoking and age which are major risk factors, genetic background also plays an important role. Matrix metalloproteases (MMPs) are a large family of proteins consisting of at least 26 human MMPs. They are zinc-dependent endopeptidases that cleave components of the extracellular matrix (ECM) and basement membrane. On the basis of their structure homology and substrate specificity, MMPs are classified into six groups: collagenases (MMP-1, -8, -13, and -18), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, and -11), matrilysins (MMP-7 and -26), transmembrane MMPs (MT-MMPs, MMP-14, -15, -16, -17, -24, and -25), and 'others' (MMP-12, -19, -20, -21, -22, -23, -27, and -28) (Visse and Nagase, 2003). Each step of tumor progression requires the remodeling of the ECM by proteases and MMPs (Rollin et al., 2007). MMPs play an important role on tumor cell behavior as a consequence of their ability to cleave growth factors, cell surface receptors, cell adhesion molecules, and chemokines/cytokines (Egeblad and Werb, 2002). MMPs may regulate angiogenesis in cancer through their ability to mobilize or activate proangiogenic factors, but they also have negative influence via generation of angiogenesis inhibitors, such as angiostatin and endostatin (Ferreras et al., 2000). Studies investigating the relationship between genetic polymorphisms and lung cancer risk are being reported with rapidly increasing frequency. Many studies have shown that there were associations between polymorphisms in the promoter regions of MMPs and lung cancer risk.

Abbreviations: MMP, matrix metalloproteinase; miRNA, microRNA; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; ECM, extracellular matrix; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; NA, not available; PCC, population-based case–control; HCC, hospital-based case–control.

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0378-1119/$ – see front matter.
http://dx.doi.org/10.1016/j.gene.2012.12.085

However the results are either inconclusive or inconsistent because the relatively small sample size of a single study might have low power to detect the effect of these polymorphisms. A previous meta-analysis (Lei et al., 2009) conducted showed that MMP2-735 C/T polymorphism could decrease lung cancer risk, but there was no association between the polymorphisms of MMP1-1607 1G/2G, MMP2-1306 C/T or MMP9-1562 C/T and lung cancer risk.

2. Materials and methods

2.1. Publication search

Using the keywords and subject terms "metalloproteinase", "MMP", "polymorphism", "variant", "risk", "susceptibility", and "lung cancer", we searched in Medline, EMBASE, OVID and the Chinese Biomedical Literature Database (CBM disk) for all articles that had been published on the association between MMP polymorphisms and cancer risk (date from Jan 2000 to Aug 2012). The reference lists of all relevant articles were also searched to identify additional studies.

2.2. Study selection

The following criteria were set to choose the studies included in the current meta-analysis: (1) published in English or in Chinese; (2) a case–control design was used to evaluate the association between any MMP polymorphism and lung cancer risk; (3) availability of genotypes or allelic frequencies; and (4) sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs). If authors reported same patient populations in two or more studies, the most recent or complete study was included in the review.

2.3. Data extraction

Information was carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data was collected from each study: first author's surname, publication date, study design (hospital-based or population-based case–control studies), ethnicity, genotyping method, the polymorphisms of MMPs and total number of cases and controls.

2.4. Statistical methods

The strength of association between MMP polymorphisms and lung cancer risk was assessed by ORs with 95% CIs. The pooled ORs were performed on the dominant (Xx + xx versus XX) and recessive model (xx versus XX + Xx) respectively (X represented major allele, x represented minor allele). The statistical heterogeneity among the studies was checked by the Q statistic. $P<0.10$ was considered statistically significant, and random effect model was used to estimate the summarized OR. Otherwise, we used the fixed effect model.

The significance of the OR was determined by the Z test with P value <0.05 considered significant. For each genetic comparison, subgroup analysis according to different ethnicity was conducted.

We plotted Begg's funnel plots and used Egger's weighted regression method to examine the underlying publication bias, and calculated P for bias. For sensitivity analysis, relatively smaller studies were excluded and the summary ORs (95% CIs) were recalculated. All analyses were conducted using Review Manager 5.1.6 (Cochrane Library Software, Oxford, England) and STATA 12.0 (STATA Corporation, College Station, Texas), using two sided P values, and all tests were two sided.

3. Results

3.1. Study characteristics

We identified 62 related articles, of which 20 studies were potentially appropriate. Two studies (Schabath et al., 2005; Su et al., 2006) did not provide sufficient data. One study (Su et al., 2005) was also excluded because the controls were the same as another one (Su et al., 2006). Thus, a total of 17 eligible studies (7983 cases and 7382 controls) met the inclusion criteria (Fig. 1). These studies were published between 2000 and 2012. Cases were histologically diagnosed and controls were matched by sex and age in almost all studies. Of those, 11 studies used healthy subjects as controls. All controls were

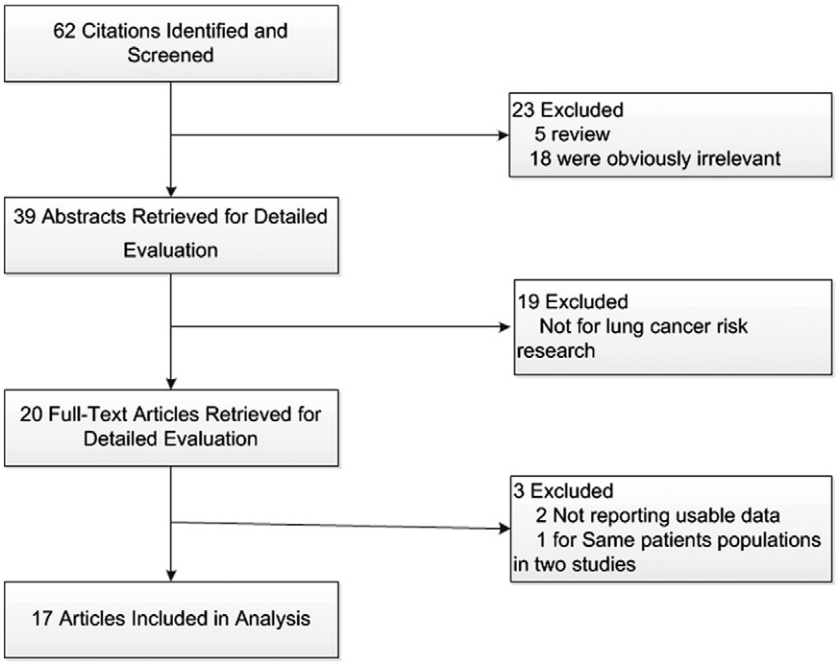

Fig. 1. Studies identified with criteria for inclusion and exclusion.