Associations between various possible promoter polymorphisms of MMPs genes and endometriosis risk: a meta-analysis

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ABSTRACT

Background: Endometriosis is a common, benign gynecological disorder affecting life quality of reproductive-aged women. Several polymorphisms in the promoter regions of the MMPs genes have been reported that were related to endometriosis risk. However, there are many contradictory conclusions, and no meta-analysis focused on this association systematically.

Objectives: To evaluate the associations between various possible polymorphisms of MMPs genes and endometriosis risk, and confirm which kinds of MMPs genetic polymorphisms are associated with endometriosis risk, in order to identify the etiology and pathogenesis of endometriosis and the potential effective markers for predicting the predisposition to endometriosis.

Search strategy: An exhaustive electronic literature search was conducted, using keywords MMP, endometriosis and SNP, in English and Chinese.

Selection criteria: All eligible case-control studies by written in English or Chinese of the associations of MMPs polymorphisms with endometriosis risk, which had sufficient data for examining an odds ratio (OR) with 95% confidence interval (CI), were identified up to March 1, 2015.

Data collection and analysis: A total of 1833 patients and 2190 controls from 12 studies were included. Allele frequency differences between cases and controls were performed with the use of odds ratios (ORs) and their respective 95% confidence intervals (CIs) for five genetic models.

Main results: For MMP-1 -1607 1G>2G (rs1799750) polymorphism, significant associations were observed both in overall comparison and subgroup analyses based on the stage of endometriosis, ethnicity of each study population and method of genotyping under four genetic models. In contrast, for MMP-2 15918 T>C (rs243847), MMP-2 -753 C>T (rs2285053), MMP-7 -181 A>G (rs11568818), MMP-9 -1562 C>T (rs3918242) and MMP-9 R279Q (rs17576) polymorphisms, no association was found in overall comparison, but in subgroup analyses based on source of control, stage of endometriosis, or ethnicity.

Conclusions: MMP-1 -1607 1G>2G polymorphism might modulate risk of endometriosis, so does the MMP-2 15918 T>C, MMP-2 -753 C>T, MMP-7 -181 A>G, MMP-9 -1562 C>T and MMP-9 R279Q polymorphisms in some subgroups.

Introduction

Endometriosis is a common, benign gynecological disorder associated with non-cyclic pelvic pain and infertility in women of reproductive age, which is characterized histologically by the presence of uterine endometrial glands and stroma outside of the normal location – the uterine cavity. This disease greatly deteriorates quality of life in approximately 6–10% of reproductive-aged women and 20–50% of infertile women [1]. Although many theories have been presented to explain the occurrence of endometriosis, the etiology and pathogenesis remain enigmatic to date. The most widely accepted theory is the retrograde menstruation proposed by J. Sampson, which is based on the assumption that endometriosis is caused by the implantation of

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endometrial cells via trans-tubal regurgitation during menstruation [2]. However, this theory still fails to explain the fact that almost 90% of women have a menstrual reflux [3], whereas only 10% have endometriosis. A growing body of evidence indicates that genetic factors influence susceptibility to the disease [4,5]. Endometriosis is inherited as a complex genetic trait that multiple gene loci interact with each other and with the environment to produce the phenotypic disease [6]. This implies that genetic susceptibility to endometriosis varies among individuals in the general population.

Similar to the process of malignant tumor invasion, the invasion and extracellular matrix (ECM) remodeling of endometrial cells may be necessary in forming endometriotic lesions. Completeremodeling of ECM is necessary for the ectopic growth of endometrial implants. Invasion indice of cells from peritoneal endometriosis lesions was higher compared with that from normal endometrium cells [7]. An altered remodeling of extracellular matrix due to an increased local concentration of matrix metalloproteinases (MMPs) has been claimed to contribute to an increased adherence and invasiveness of retrogradely menstruated endometrial fragments [8]. MMPs, are an important family of extracellular zinc-containing proteases in several organs including female reproductive system, that are responsible for hydrolyzing ECM components and components of the basement membrane, and the development of endometriosis [9]. Furthermore, endometrial stromal cells also secrete several MMPs, which are under the regulation of ovarian steroid hormones [10,11]. It is well known that single nucleotide polymorphisms (SNPs) in metalloproteinase genes can lead to changes in their gene transcription and expression and thus influence the enzyme activity [12].

Several polymorphisms in the promoter regions of the MMPs genes have been well described. The first study certified the relationship between MMPs polymorphism and endometriosis was conducted by Shan et al. [13]. They found a significant association between MMP-1 -1607 1G>2G (rs1799750) polymorphism and endometriosis. However, the MMP-3 -1171 5A>6A (rs35068180) polymorphism is unlikely to be associated with endometriosis in the population of North China. Since then, several epidemiologic studies of the association of various MMPs polymorphisms with endometriosis risk have been carried out, but the results remain inconclusive and complicated [13–25]. In addition, the sample size was small in individual studies, conclusions were drawn with a lack of statistical power. Therefore, a meta-analysis was conducted to derive a more precise evaluation of the association between all MMPs genetic polymorphisms and the risk of endometriosis by pooling all the available data, to maximize the power to detect the association, and identify the etiology and pathogenesis of endometriosis and the potential effective markers for predicting the predisposition to endometriosis. Moreover, no comprehensive meta-analysis focused on the association between all MMPs genetic polymorphisms had been reported and the risk of endometriosis had been published. Hence, we performed a meta-analysis of 12 publications covering 1833 cases and 2190 controls to get a clearer overall picture of the effect of MMPs genetic polymorphisms on the risk of endometriosis.

Materials and methods

Search strategy

Two authors (Liu and Yang) independently conducted a systematic literature search in the PubMed, Web of Science, Science Director, Springer Link, China National Knowledge Infrastructure (CNKI), Wanfang Data and CQVIP electronic databases in English and Chinese, to identify all eligible case-control studies about the associations of MMPs polymorphisms with endometriosis risk (up to March 1, 2015). The search terms and keywords used were as follows: "MMP", "matrix metalloproteinase", "collagenase", "gelatinase", "matrilysin" or "PUMP" and "endometriosis", and "polymorphism", "variant", "genotype" or "SNP". For example, we used search formula "(MMP OR matrix metalloproteinase OR collagenase OR gelatinase OR matrilysin OR PUMP) AND endometriosis AND (polymorphism OR variant OR genotype OR SNP) AND (english[Language] OR chinese[Language])" searching in the PubMed, and limited the date of publication up to March 1, 2015. After performing the electronic key word searches, we manually reviewed the references of the search results to identify additional evaluable studies. We contacted authors directly for important data that were not reported in original articles. We selected studies using PRISMA. Studies included in our meta-analysis have to meet the following criteria: (1) use a case–control design and (2) sufficient data for examining an odds ratio (OR) with 95% confidence interval (CI). However, abstracts, unpublished reports, studies without control population and articles not written in English or Chinese were excluded.

Inclusion and exclusion criteria

Studies were included if they: (1) were case-control studies; (2) referred to Asian or Caucasian women with endometriosis; (3) were diagnosed histologically; (4) analyzed allelic variations of MMPs carrying by PCR, RFLP or Tagman; (5) assessed the associations between MMPs polymorphisms and endometriosis risk; (6) had sufficient available data to calculate an odds ratio (OR) with a 95% confidence interval (CI) and P-value; and (7) were published in English or Chinese.

Studies were excluded if they: (1) had insufficient information about genotype frequency or number, (2) if the same population was evaluated in two or more studies, only the most recent or the one with the largest study population was included in this meta analysis.

Data extraction

The following details were extracted from each article included in the meta-analysis using Excel: first author, publication year, ethnicity of the study population (categorized as Asian and Caucasian), stage of endometriosis (categorized as stage I, II, III and IV), the source of controls (categorized as hospital-based and population-based), the number of cases and controls, and genotype distribution, allele frequency, genotyping methods, and Hardy–Weinberg equilibrium (HWE). To minimize bias and improve reliability, two investigators (Liu and Yang) extracted the data independently, and any discrepancies were addressed by a joint re-evaluation of the article with the third author (Fan) and discussed to reach a consensus on all items (the details of each study).

Statistical analysis

We evaluated the association of MMPs polymorphisms and endometriosis risk using ORs and 95% CIs. The significance of pooled ORs was estimated via a Z-test ($P < 0.05$ was considered statistically significant). Heterogeneity between studies was assessed via Cochran's chi-square Q statistic test. A random effects model was used when the P value for heterogeneity was less than 0.1, which indicated obvious heterogeneity of the data; otherwise, a fixed-effects model was used. Heterogeneity across studies was also detected using an I^2 test. As a guide, I^2 values of 0% to 40% might not be important, I^2 values of 30% to 60% may represent moderate heterogeneity, I^2 values of 50% to 90% may represent substantial