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REVIEW

Association between oestrogen receptor alpha (ESR1) gene polymorphisms and endometriosis: a meta-analysis of 24 case-control studies

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Abstract The PvuII (C > T), XbaI (A > G) and $(TA)_n$ polymorphisms of ESR1 gene are potentially associated with susceptibility to endometriosis. A meta-analysis was conducted to evaluate comprehensively the associations between endometriosis and ESR1 polymorphisms. Twenty-four studies, including 2740 cases and 3208 controls, were retrieved through searches of PubMed, EMBASE, Web of Science, CBM and CNKI. Meta-analyses showed that PvuII was associated with endometriosis only for stage I–III, only under a recessive model (OR = 1.53, 95% CI 1.05 to 2.21; P = 0.025). The short allele and TA_{13} of $(TA)_n$ were associated with a higher risk of endometriosis (OR_S = 1.71, 95% CI 1.01 to 2.81, P = 0.046; OR_{TA13} = 1.45, 95% CI 1.06 to 1.97, P_{TA13} = 0.019); TA_{20} repeats was associated with a lower risk (OR = 0.36, 95% CI 0.16 to 0.80; P = 0.012). No statistically significant association was found in the XbaI polymorphism. This meta-analysis indicated that the PvuII and XbaI polymorphisms were not associated with the risk of endometriosis, whereas stage classification of endometriosis was likely to influence the association of PvuII polymorphism. The $(TA)_n$ polymorphisms might play roles in the susceptibility to, or protection against, the pathogenesis of endometriosis.

KEYWORDS: endometriosis, estrogen receptor α, meta-analysis

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Introduction

Endometriosis is a common and highly investigated gynaecologic disease affecting 6–10% women of reproductive age. It is characterized by the presence of endometrial tissue, including endometrial glandular and stromal cells, outside the uterine cavity, mainly on the pelvic peritoneum, ovaries and in the rectovaginal septum (Giudice and Kao, 2004). Despite the high prevalence of this disease, its cause and pathophysiology remain obscure. Previous evidence has shown that endometriosis is a complex hormone-dependent disorder influenced by multiple environmental and genetic factors (Falconer et al., 2007; Rizner, 2009). Oestrogen receptor alpha, as the predominant form of oestrogen receptors in the normal endometrium, is encoded by the oestrogen receptor 1 (ESR1) gene. Therefore, genetic mutations in ESR1 may lead to aberrant gene expression and may be involved in pathogenesis and development of endometriosis.

A number of ESR1 polymorphisms, such as rs2234693, rs9340799, rs3138774, rs1884052, rs3020348, and rs1159327, have been investigated for their potential associations with endometriosis. Among these variants, two of the most studied are defined by the restriction enzymes PvuII (rs2234693, C > T) and XbaI (rs9340799, A > G) in intron 1 of ESR1, which have been evaluated in 25 studies (Chen et al., 2011; Ding et al., 2005; Dong et al., 2005; Fu et al., 2001, 2002; Georgiou et al., 1999; Govindan et al., 2009; Gu et al., 2012; Hsieh et al., 2007; Huang et al., 2005; Kim et al., 2005; Kitawaki et al., 2001; Lamp et al., 2011; Luisi et al., 2006; Matsuzaka et al., 2012; Paskulin et al., 2013; Renner et al., 2006; Shan et al., 2006; Song et al., 2005; Sun et al., 2010; Trabert et al., 2011; Wang et al., 2004; Xie et al., 2009; Zhang et al., 2007; Zhao et al., 2011) and 17 studies (Chen et al., 2011; Ding et al., 2005; Dong et al., 2005; Fu et al., 2002; Gu et al., 2012; Hsieh et al., 2007; Huang et al., 2005; Kim et al., 2005; Matsuzaka et al., 2012; Paskulin et al., 2013; Renner et al., 2006; Shan et al., 2006; Song et al., 2005; Sun et al., 2010; Trabert et al., 2011; Wang et al., 2004; Xie et al., 2009), respectively. The third most investigated polymorphism is the $(TA)_n$ dinucleotide repeat in the promoter region of ESR1, which has been evaluated in six studies (Georgiou et al., 1999; Hsieh et al., 2005; Kim et al., 2005; Lamp et al., 2011; Matsuzaka et al., 2012; Shan et al., 2006).

So far, the roles of these three variants in the pathogenesis of endometriosis remain controversial; the outcomes of the previously reported articles were inconsistent, and the three published meta-analyses (Guo, 2006; Hu et al., 2012; Li et al., 2012) have some limitations. The previous meta-analyses considered a relatively small sample size because some qualified studies were not included owing to limitations of search criteria and publication date. Meanwhile, the subgroup analyses were insufficient. Many factors that can cause heterogeneity were not fully considered. These limitations are likely to affect the accuracy of their results.

Moreover, it is also worth mentioning that several genome-wide association studies focusing on patients with endometriosis have been published to date. A number of susceptible polymorphisms in several related genes, such as CDKN2BAS, NFE2L3, WNT4, ID4 and GREB1, have been revealed (Adachi et al., 2010; Albertsen et al., 2013; Nyholt et al., 2012; Painter et al., 2011; Uno et al., 2010). To the best of our knowledge, no polymorphism in or near ESR1 gene associated with endometriosis has been detected. Most genome-wide association studies, however, were conducted in white people, whereas limited studies were conducted in other populations till now. In addition, genome-wide association studies of endometriosis are still ongoing, which indicates that endometriosis has not been adequately studied and many candidate genes have not yet been revealed.

On the basis of the above reasons, an updated meta-analysis of 24 detailed studies was conducted to further evaluate the association between ESR1 polymorphisms and endometriosis susceptibility.

Materials and methods

Literature search

Relevant papers published before October 2015 were searched in several electronic databases, particularly, PubMed, EMBASE, Web of Science, CBM (Chinese Biomedical Literature Database), and CNKI (China National Knowledge Infrastructure). No restrictions on language, population, or sample size were set in this meta-analysis. The search strategies were based on the combinations of the following keywords: ("estradiol receptor alpha" or "ER alpha" or "estrogen receptor 1" or "ESR1") and ("polymorphism" or "variant" or "mutation") and "endometriosis". Additional relevant literatures were obtained from the reference lists of the prospective articles.

Inclusion and exclusion criteria

Studies were included on the basis of the following criteria: full-text articles; original case-control or cohort study evaluating at least one of the three ESR1 polymorphisms linked with the risk of endometriosis; sufficient data to estimate an odds ratio (OR) and 95% confidence interval (CI); Chinese articles published in Chinese core periodicals; and no overlapping data. For the studies with the same authors, only those with the largest sample sizes or the most recent publication dates were selected to avoid overlapping patients and controls. Studies were excluded on the basis of the following criteria: meta-analyses, letters, reviews, or editorial articles; studies with no control cases; studies based on incomplete or sufficient data, such as deficiency of specific genotype distribution in cases and controls.

Data extraction

Two investigators (LZ and CG) independently extracted useful data from each study. Discrepancies were resolved through discussion. The following information was collected from each included study: name of the first author, year of publication, country of origin, ethnicity of descent, number of participants, source of control, detected sample, genotype method, genotype distribution in cases and controls, minor allele frequency, disease stage, outcomes, and probability