

Epidemiologic Factors Associated with Endometriosis in East Asia

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Abstract

Aim: With a perplexing pathogenesis and an incidence rate of approximately 10% among women of reproductive age, endometriosis affects more women in Asia than in any other continent in the world. This paper reviews the available data on the epidemiology and risk factors associated with endometriosis in East Asia.

Methods: Included studies were published between January 2000 and December 2016. Articles were required to include East Asian patients with a diagnosis of endometriosis and to study epidemiology, such as the prevalence and/or incidence, associated with inherited, environmental, and/or lifestyle factors. A total of 65 candidate articles were retrieved and 22 were included in the final review.

Results: Only one study provided an estimate of prevalence (6.8%). Short menstrual cycle, family history of endometriosis, and some genetic polymorphisms are associated with the risk of developing endometriosis. Smoking, lower body mass index, and lower parity associated with increased risk of endometriosis were suggested as modifiable factors. Limitations of this study include the poor quality of data identified, and the language barriers behind the study retrieval.

Conclusions: Data on the epidemiology of endometriosis in the East Asian populations are limited. The available data that examine potential genetic factors do not unveil whether such factors directly contribute to the increased risk of endometriosis. Further extensive studies on endometriosis in Asian women are required to improve the management of this disease.

Keywords: Asia, endometriosis, epidemiology

INTRODUCTION

Endometriosis is a disease characterized by the presence of ectopic endometrial tissue outside the uterine cavity, with clinical presentations of dysmenorrhea, dyspareunia, dyschezia, and sometimes diarrhea.^[1,2] Endometriosis is an estrogen-dependent disease strongly influenced by the cyclic change of steroid hormones and it causes inflammatory conditions in the pelvic cavity^[3,4] and may present with subfertility, ongoing pelvic pain, and/or pelvic mass despite treatment with oral contraceptives and analgesics.^[5-8] While the incidence of malignant change was rare,^[9,10] endometriosis

remains an important cause of morbidity impeding quality of life in women of reproductive age.^[11] Although the exact etiology and pathogenesis of endometriosis are unclear,^[12] environmental and genetic factors which induce complex immunological interactions within the pelvic cavity have been implicated in the disease.^[13]

In the Western populations, endometriosis is estimated to occur in 5% to 10% of the population; however, the prevalence of endometriosis is suspected to be higher in

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Asian women, affecting approximately 15% of women.^[5,14,15] Indeed, compared to women in the United States of America, women from Southeast Asia and Japan have a higher prevalence of endometriosis although this may be confounded by socioeconomic status, and the fact that the studies upon which these estimates were based were of poor quality and in some cases were over 40 years old.^[11] Despite this, the suggestion that prevalence rates might be higher in Asian populations and the fact that these populations are numerically significantly larger than elsewhere implies that endometriosis is a significantly larger problem for Asian countries than elsewhere in the world. Furthermore, given the plethora of ethnic variations that exist among Asian populations, the epidemiological data and trends from Western countries may not always be relevant to populations in Asia. Combined, this suggested that an updated approach to determining the epidemiology of endometriosis in Asian populations is required.

Understanding the epidemiology and risk factors for endometriosis in the Asian context is important to guide

patient care. This includes both the diagnosis and treatment of this debilitating condition. As the clinical impact of the lifestyle and environmental factors on the development of endometriosis is a frequently asked question by the patients and the researchers, the objective of this review was to describe the epidemiology, including the associated inherited, lifestyle, and/or environmental factors with the incidence of endometriosis in the East Asian populations.

METHODS

We undertook a search of English literature from Medline, PubMed, and the Cochrane Library (including the Cochrane Database of Systematic Reviews) for all articles relate to human endometriosis published between January 2000 and December 2016. The MeSH terms included all subheadings, and keywords included “endometriosis risk,” “endometriosis association,” “endometriosis epidemiology,” “endometriosis gene,” and “endometriosis environment.” All published works were included from the electronic database searches

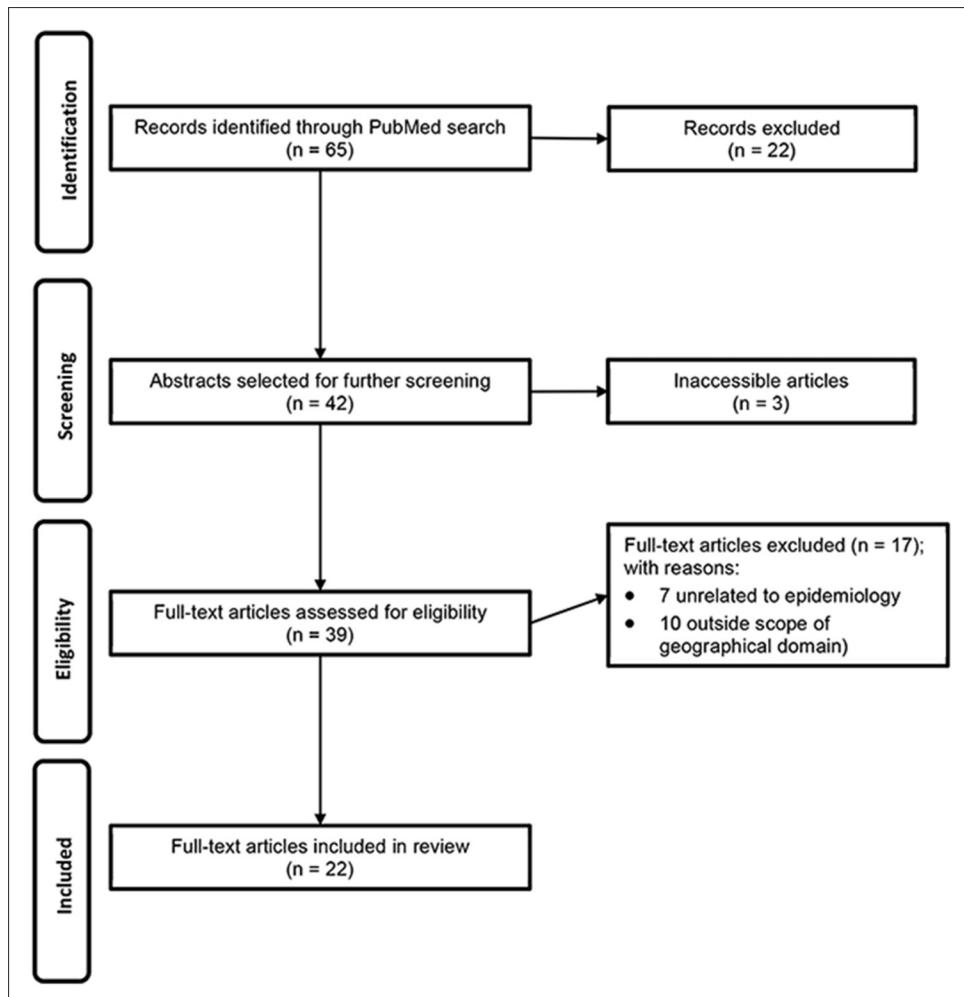


Figure 1: Flow diagram of article selection process

Table 1: Studies of demographic or environmental parameters

Reference	Sample Size	Involved factors	Population	Summary
Yasui <i>et al.</i> , 2015 ^[20]	Cohort: 330	Menstrual cycle Infertility Cigarette smoking	Japanese	Surgically confirmed endometriosis (Group A, $n=210$), imaging diagnosed endometriosis without a surgical procedure (Group B, $n=120$). A short menstrual cycle at 18-22 years of age and cigarette smoking at 30 years of age were associated with significantly increased risk of endometriosis (Group A + Group B) In women with a history of infertility, a short menstrual cycle was associated with a significantly increased risk of endometriosis in both Group A and Group B, but risk profiles of endometriosis were different between Group A and Group B in women without a history of infertility
Yi <i>et al.</i> , 2009 ^[21]	Cohort: 481	BMI	Korean	Women in stages III or IV endometriosis had a significantly lower BMI than those in stages I or II disease
Itoh <i>et al.</i> , 2008 ^[22]	Case: 54 Control: 74	Cadmium	Japanese	No association between higher urinary cadmium concentration and the risk of endometriosis
Tsukino <i>et al.</i> , 2005 ^[23]	Case: 58 Control: 81	Organochlorine	Japanese	No association between higher serum levels of these organochlorine compounds and an increased risk of endometriosis among infertile Japanese women
Kashima <i>et al.</i> , 2004 ^[24]	Case: 339 Control: 284	Family history	Japanese	Heritable genetic factors contribute to the development of endometriosis

BMI: Body mass index

and cross-references pick-up was also performed during the review search if the article was not initially found. Each article was assessed on the abstract for its relevance and only those focusing on epidemiologic information, such as prevalence, incidence, and correlating risk factors, were included. Adenomyosis, which is the endometriotic disorder of the uterus,^[16-18] was not included in this review as it is a disease different from the peritoneal or ovarian endometriosis.^[19] Laboratory studies of disease mechanism were also excluded. In consideration of the ethnic similarity, only studies developed from East Asia (including ethnic groups of Chinese, Taiwanese, Japanese, and Koreans peoples) were included; however, those derived from Northern Asia (such as ethnic groups of Siberia), Central Asia (such as ethnic groups Turkic, Iranian, and Russians peoples), South Asia (including ethnic groups of India, Indochinese Peninsula, and Filipino peoples), and West Asia (such as ethnic groups of Arab peoples and Jews) were not included.

RESULTS

A total of 65 candidate articles were identified fitting the scope of the current review, and finally, 22 eligible articles included for review [Figure 1]. We found five studies of demographic and/or environmental parameters related to endometriosis [Table 1], 12 studies showed positive findings for an association of a genetic polymorphism with endometriosis [Table 2], and another 5 studies found negative results for a correlation of genotypes with endometriosis [Table 3].

Epidemiology

The majority of included studies were either retrospective cohort studies or case-control studies, neither of which is

able to produce reliable incidence nor prevalence estimates. Indeed, there was only one study from which an estimate of prevalence was obtainable. This was a large survey of nurses from Japan, in which 1025 of 15,019 (6.8%) self-reported endometriosis.^[20] The authors of this study found that 89% of women with self-reported endometriosis had a diagnosis confirmed by laparoscopy.^[20]

Body mass index

Only one study reported the effect of body mass index (BMI) on the severity of endometriosis. Korean women with early or mild endometriosis have a significantly higher BMI compared to those with advanced disease even after adjusting for age, parity, and menstrual factors.^[21]

Parity

Only one study reported the effect of parity on the development of endometriosis. Korean women with only one child experience a more severe disease than those with more than one child.^[21]

Environmental exposure

Environmental exposure includes cigarette smoking and exposure to industrial chemicals. One study reported that cigarette smoking is associated with an increased risk of endometriosis in women with surgically confirmed endometriosis from Japan.^[20]

A number of industrial chemicals and environmental pollutants are known to either mimic or antagonize endogenous hormones.^[41] Of particular interest are the organochlorides, found in pesticides, and heavy metals. However, in two studies of infertile women from Japan, there was very little difference in the levels of these compounds in women with or without

Table 2: Summary of Genetic polymorphism studies with significant differences

Reference	Sample size	Involved genes	Population	Summary
Lee, <i>et al.</i> , 2014 ^[25]	Case: 673 Control: 500	CDKN2B-AS gene WNT4 gene	Korean	The CC genotype of the rs10965235 SNP in the CDKN2B-AS gene and the GG genotype of the rs16826658 SNP near the WNT4 gene were significantly associated with endometriosis in Korean population
Cho <i>et al.</i> , 2013 ^[26]	Case: 201 Control: 183	MMP-2 gene TIMP-2 gene	Korean	In MMP-2, G/A haplotype of 9082A>G and 9152A>G in intron 2 was associated with a reduced risk of endometriosis (OR 0.7, 95% CI 0.5-1.0, <i>P</i> =0.04) In TIMP-2, the CC genotype of 42196430T>C and C/C haplotype of 42196041G>C/42196430T>C in the promoter region showed an increased risk of endometriosis (OR 3.0, 95% CI 1.2-8.0, <i>P</i> =0.02; OR 1.6, 95% CI 1.1-2.4, <i>P</i> =0.02) In TIMP-2, the CC genotype of 42183387T>C and the C/G/C haplotype of 42175617C>T/42181597G>A/42183387T>C in intron 1 were associated with a reduced risk (OR 0.5, 95% CI 0.3-0.97, <i>P</i> =0.04; OR 0.6, 95% CI 0.4-0.95, <i>P</i> =0.03)
Wang <i>et al.</i> , 2012 ^[27]	Case: 300 Control: 337	HSD17B3 FSHR CYP19	Taiwanese	These 4 nsSNPs reside (rs6165, rs6166, rs2066479, rs700519) in 3 genes related to estrogen synthesis (HSD17B3, FSHR, and CYP19) increases endogenous production of more estrogens may be more strongly associated with the risk of endometriosis
Kim <i>et al.</i> , 2012 ^[28]	Case: 268 Control: 242	COX-2 gene	Korean	The C allele for -765G/C of the COX-2 gene was associated with significantly lower risk of advanced-stage endometriosis (OR, 0.14; 95% CI, 0.06-0.30) The -765C allele may be protective against the development of the disease in Korean women
Wang <i>et al.</i> 2011 ^[29]	Case: 300 Control: 337	FSH receptor gene	Taiwanese	The mutant alleles of FSH receptor gene at the position 680 of amino acid (Asn680Ser) (GG genotype, 680Ser/Ser and GA genotype, 680Ser/Asn) may have a protective effect on the development of endometriosis in Taiwanese Chinese women
Kang <i>et al.</i> , 2010 ^[30]	Case: 421 Control: 421	FGF2 gene	North Chinese	FGF2 754C/G polymorphism may be associated with a risk of developing endometriosis. The G allele in the FGF2 gene may potentially protect against the disease.
Lee <i>et al.</i> , 2008 ^[31]	Case: 246 Control: 248	TNF- α a gene	Korean	This difference at the TNF: g.[-1031T >C] tends to increase in Stage IV endometriosis (<i>P</i> =0.01). The genotype frequencies at the TNF: g.[-1031T >C] and the TNF: g.[-863C >A] sites may be associated with advanced stage endometriosis
Kang <i>et al.</i> , 2008 ^[32]	Case: 298 Control: 324	TIMP-2 gene MMP-2 gene	North Chinese	The frequency of the TIMP-2 -418C/C homozygote was significantly low in patients with endometriosis (0.7%), the C/C genotype may significantly decrease the risk of endometriosis development, with an odds ratio OR of 0.18 (95% CI confidence interval, 0.04-0.79). TIMP-2-418C/C homozygote may be a protective factor against the development of endometriosis No significant difference in genotype and allelotype distributions of the MMP-2-1306C→T was found between patients and control
Shan <i>et al.</i> , 2007 ^[33]	Case: 152 Control: 189	E-cadherin gene	North Chinese	There was a significant difference in the frequency of the E-cadherin 3'-UTR C --> T genotypes between endometriosis and controls (<i>P</i> =0.01) When compared with the T/T+T/C genotypes, the C/C genotype had a significantly increased susceptibility to endometriosis, with an adjusted odds ratio OR of 1.79 (95% confidence interval CI=1.17-2.76) E-cadherin 3'-UTR C --> T polymorphism, the -160 A/-347 GA haplotype of two promoter polymorphisms suggesting a potential role in endometriosis development
Kitawaki <i>et al.</i> , 2006 ^[34]	Case: 202 Control: 236	IL-6 gene ICAM-1 gene	Japanese	The IL-6-634C/G and ICAM-1 469K/E polymorphisms synergistically affect the susceptibility for endometriosis. The frequency of ICAM-1 EE homozygotes who concomitantly carried the IL-6-634G allele was significantly higher in patients with endometriosis (<i>P</i> =0.0396, d.f. 2) No differences in the IL-6-634C/G genotypes and allele frequencies or the ICAM-1 469K/E polymorphisms between patients and control
Tsuchiya <i>et al.</i> , 2005 ^[35]	Case: 79 Control: 59	HSD17B1 gene CYP19 gene	Japanese	Individuals having at least one A-allele (A/G or A/A genotype) of HSD17B1 showed a significantly increased risk of endometriosis (A/G genotype: adjusted OR, 3.06; 95%CI 1.21-0.74; A/A genotype: adjusted OR, 3.02; 95%CI 1.08-8.43) There was a significant trend associating A/G + A/A genotypes with severity of endometriosis (<i>P</i> for trend <0.01) No statistically significant association was found for the CYP19 polymorphism
Kitawaki <i>et al.</i> , 2004 ^[13]	Case: 185 Control: 176	IFNG gene IL4 gene	Japanese	The IFNG CA-repeat polymorphism is associated with susceptibility to endometriosis No differences in IL-4-590C/T genotypes and allele frequencies between control women and patients with endometriosis

SNP: Single -nucleotide polymorphism, TNF-: Tumor necrosis factor- alpha, GST: Glutathione-S-transferases, CI: Confidence interval, OR: Odds ratio

endometriosis.^[22,23] Yet, given these women were infertile, the influence of such environmental toxins in an unselected group of women with endometriosis remains unclear.

Infertility

Infertility is significantly associated with increased risk of endometriosis in women with surgically confirmed

Table 3: Summary of genetic polymorphism studies with no association or significance

Reference	Sample size	Involved genes	Population	Summary
Matsuzaka et al., 2012 ^[36]	Case: 100 Control: 143	ESR1 gene	Japanese	No statistically significant differences were noted in the SNP allele frequencies and genotypes between the cases and controls in ESR1 gene. ESR1 gene polymorphisms are not significantly associated with the development of endometriosis
Chae et al., 2010 ^[37]	Case: 390 Control: 351	ICAM-1 gene IL-6 gene	Korean	The K469E and G241R polymorphisms in the ICAM-1 gene and the C-634G polymorphism in the IL-6 gene may not be genetic factors related to susceptibility to advanced-stage endometriosis
Lee et al., 2009 ^[38]	Case: 237 Control: 164	IL-2R β gene	Korean	The C627T polymorphism of the IL-2R β gene is not associated with advanced stage endometriosis in a Korean population
Kim et al., 2008 ^[39]	Case: 105 Control: 101	VEGF genes	Korean	Endostatin G (4349) A and VEGF C (936) T polymorphisms was not associated with endometriosis Serum endostatin levels (but not VEGF levels) were negatively correlated with the development of endometriosis, specifically in early-stage endometriosis patients
Hur et al., 2005 ^[40]	Case: 194 Control: 259	GSTM1 gene GSTT1 gene GSTP1 gene	Korean	No association was noted between the genetic polymorphisms of GSTM1, GSTT1, and GSTP1 with the development of endometriosis in Korean women

SNP: Single- nucleotide polymorphism, TNF-: Tumor necrosis factor- alpha, GST: Glutathione-S-transferases

endometriosis from Japan although whether endometriosis is the causal factor for infertility remains a possibility.^[20] Unsurprisingly then, there appears to be an association of a diagnosis of infertility in women who are subsequently diagnosed with endometriosis.

Menstrual cycle length

A short menstrual cycle length, at age 18–22 years of age, was significantly associated with an increased risk of endometriosis in women surgically confirmed endometriosis from Japan.^[20] However, in Korean women, no association between menstrual cycle length and disease severity was found.^[21]

Family history and genetics

In a Japanese study, the prevalence of endometriosis in siblings of women diagnosed with endometriosis was 8.8% compared to 1.5% of controls, suggesting that there is a familial tendency for endometriosis.^[24] There may therefore be a genetic link between specific polymorphisms and the development of endometriosis.

Several genes have been studied [Tables 2 and 3]. An increased risk of endometriosis has been reported in women with *CDKN2B-AS/rs10965253* and *WNT4/rs16826658* single-nucleotide polymorphisms (SNPs);^[25] *TIMP-2* promoter region;^[26] estrogen synthesis and metabolism genes (nonsynonymous SNPs rs6165, rs6166, rs2066479, and rs700519);^[27] *FGF2 754C/C* polymorphism;^[30] -C805 or -1031T/C *TNFA* gene polymorphism;^[31] A264C *HSD17B1* polymorphisms in cytochrome P450 CYP19;^[34] a13 allele in interferon gamma (*IFN- γ*); and *IFN- γ* CA repeat polymorphisms;^[34] A264C *HSD17B1* polymorphisms in cytochrome P450 CYP19;^[35] and a13 allele in *IFN- γ* and *IFN- γ* CA repeat polymorphisms.^[13]

Table 4: Factors associated with increased risk of endometriosis

Modifiable risk factors	Non-modifiable risk factors
Parity	Genetics
BMI	Family history
	Early menarche
	Infertility
Factors of unknown significance	
Smoking	Menstrual cycle length
Heavy metals	
Organochlorines	

BMI: Body mass index

In contrast, alterations in the *TIMP-2* intron 1 region and *MMP-2*,^[26] -765C allele of *COX-2* gene,^[29] SNPs in the follicle-stimulating hormone receptor *FSHR* gene,^[29] *FGF2 754C/G* or *G/G*,^[30] -863C/A *TNFA* gene polymorphism,^[31] 418C/C *TIMP-2* polymorphism,^[32] and appear to be protective. Increased serum endostatin levels (but not *VEGF* levels) are negatively correlated with development of endometriosis.^[39]

Other genetic alterations have been reported to have no association with the development of endometriosis. These include *ESR1* gene polymorphisms (although the authors speculated this may be due to low sample size),^[36] K469E and G241R polymorphisms in *ICAM-1*;^[37] C627T in *IL-2R β* gene;^[38] G (4349) A, C (936) T, 405G,-406C>T *VEGF* polymorphisms;^[39] and *GSTM1*, *GSTT1*, and *GSTP1*.^[40]

The role of the E-cadherin gene is controversial, with several studies reporting a significant association with endometriosis risk, particularly with 160C/-347 GA and 30-UTR C/T polymorphisms,^[33] while other polymorphisms are not associated with increased risk (-160C/A and -347 G/GA).^[33]

Risk factors

One study^[20] proposed an idea that some inherited or constitutional factors which increased the risk of endometriosis could hardly be changed, while some others which correlated to lifestyle or environmental factors could be modifiable. Collectively, for the current review, nonmodifiable risk factors include infertility, menstrual cycle length, early menarche, family history, and genetics; however, factors include diet, BMI, length of breastfeeding, physical activity, and exposure to heavy metals and pesticides could be modifiable to the development of endometriosis [Table 4].

DISCUSSION

In contrast to the abundant articles focused on the molecular biologic studies,^[4,12,42] there was limited data on the epidemiology of endometriosis in the East Asian populations despite earlier reports suggesting that endometriosis is more common in women from Asia than from Western countries.^[5,11,14,15] In the present review, it appears that the best characterized risk factors in the East Asian populations are the various genetic polymorphisms that have been studied. In contrast to the genetic or familial factors which are nonmodifiable, factors such as parity, smoking, and probably the BMI could be the modifiable factors for the development of endometriosis. Regrettably, almost all these found articles were limited by their low strength of evidence and lack of the strong support of causal relationship, so these factors finally could only conclude an association or correlation with endometriosis.

Endometriosis is a dynamic and complex disorder, involving the interplay of genetic and environmental factors. The current review revealed a number of risk factors for endometriosis, including early menarche,^[43] increased BMI,^[44-46] environmental factors (including cigarette smoking),^[47] and genetic factors.^[48,49] It seems some of our findings were consistent with other studies that early menarche, shorter menstrual length, duration of infertility, and family history of endometriosis are strongly associated with endometriosis,^[8,50,51] while higher parity and higher BMI are associated with decreased risk.^[8] However, some associations have not yet been proven or disproven, such as smoking and the influence of diet.^[8,50,52,53] A Japanese study in the current review found cigarette smoking significantly increased the risk of endometriosis, while another study from Boston, USA, found smoking was associated with decreased risk,^[8] and a study from Sweden found no significant association between smoking and endometriosis.^[50] The same study from Sweden also found no significant associations with level of education, BMI, oral contraceptive use, coffee consumption, or alcohol intake.

BMI is significantly associated with disease severity in one Korean study,^[21] those with lower BMI being more likely to

have more severe disease compared to those with higher BMI. Other studies have also suggested that women with a low BMI are at greater risk of endometriosis.^[8,44-46] This might explain the difference in the prevalence in Asian women compared to women from the United States,^[11] given that average BMIs are much higher in the US population. However, a critical question is whether the low BMI is the cause or the consequence of developing endometriosis even though these studies suggested a correlation. Besides, if BMI is a potential predisposing factor of endometriosis, it is still unknown if there are any BMI-related genetic or environmental factors which could be involved.

Factors contributing toward or against endometriosis development are far from clearly understood, and the interaction between genetic susceptibility and environmental factors is inadequately studied, despite over 50 years of hypothesis-driven research.^[3] The epidemiological data reviewed in the current study suggested that the development of endometriosis in the East Asian populations is strongly driven by genetic factors; however, almost all these studies were focused on the genetic SNPs. It is still unclear the exact biological significance of these SNPs or the mechanisms of subsequent signaling.

There are several limitations to the current review. First, we only included articles that were published in English, which may lead to bias considering this review is specifically focused on the East Asian populations. Second, as with all reviews, there is possible publication bias and we have not formally assessed this. Third, the retrieved publications were from only several countries within East Asia (Japan, Taiwan, Korea, and China). Although we also found some available data from India^[54-59] (South Asia), epidemiology-related researches from other Asian countries remains sparse. Fourth, probably because of the difficulties of epidemiologic studies, the level of evidence for lifestyle research may not be strong enough. Although these data are still worthy as a reference of an East Asian population, surely, there was no strong evidence to support if those proposed “modifiable” risk factors could really change the development of endometriosis. Fifth, links between the genetic and mechanistic studies of the development of endometriosis were lacking. From a cohort viewpoint, the clinical impact of the genetic polymorphism in a woman’s life is unclear, and it is not clear whether those revelations would be altered after conception or not, as the incidence of endometriosis significantly declines after successful pregnancy. Obviously, there are many questions yet to be answered.

Data on the epidemiologic factors of endometriosis in the Asian populations are limited. The available data that examine potential genetic factors, however, do not reveal whether such factors directly contribute to increased risk

of endometriosis. Smoking, low parity, and probably BMI could be modifiable risk factors associated with endometriosis among East Asian women. Further extensive studies on endometriosis in Asian women are required to identify other risk factors for the management of this condition.^[60]

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Conflicts of interest

There are no conflicts of interest.

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