

Review Article

Association between HSD17B1 rs605059 polymorphisms and the risk of uterine diseases: a systemic review and meta-analysis

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Abstract: The aim of this study was to evaluate the HSD17B1 gene polymorphisms in the risks of endometrial cancer, endometriosis and uterine leiomyoma by meta-analysis. A comprehensive electronic search was conducted in PubMed, Medline (Ovid), Embase, Weipu, Wanfang and CNKI. The pooled ORs were performed using the Revman 5.2 software. 8 case-control studies were included: 3 were about endometrial cancer, 4 were about endometriosis and 1 was about uterine leiomyoma. The result showed no significant association between HSD17B1 rs605059 gene polymorphisms and risks of endometrial cancer (AA vs. AG+GG: OR = 1.11, 95% CI = 0.94-1.32; AA+AG vs. GG: OR = 1.79, 95% CI = 0.42-7.52; AG vs. AA+ GG: OR = 0.87, 95% CI = 0.76-1.00; AA vs. GG: OR = 1.43, 95% CI = 0.62-3.30; A vs. G: OR = 1.00, 95% CI = 0.91-1.11) or endometriosis (AA vs. AG+GG: OR = 0.99, 95% CI = 0.75-1.32; AA+AG vs. GG: OR = 1.73, 95% CI = 0.92-3.25; AG vs. AA+ GG: OR = 1.24, 95% CI = 1.00-1.53; AA vs. GG: OR = 1.54, 95% CI = 0.79-2.97; A vs. G: OR = 1.23, 95% CI = 0.90-1.68). No association was found in a subgroup analysis based on Asian ethnicity for endometriosis. This meta-analysis suggested that HSD17B1 rs605059 polymorphisms were not associated with the risks of endometrial cancer and endometriosis. Further studies are needed to validate the conclusion and clarify the relationship between HSD17B1 rs605059 polymorphisms and the risk of uterine leiomyoma.

Keywords: Endometrial cancer, endometriosis, leiomyoma, HSD17B1, polymorphism, meta-analysis

Introduction

Estrogen has been reported to be one pivotal risk factor for the development of many uterine diseases like endometrial cancer, endometriosis and uterine leiomyoma [1-3]. This is validated by the fact that women of reproductive age and postmenopausal women under estrogen replacement therapy are the most susceptible group of people for the three types of diseases [4, 5]. Therefore, it is considered that discrepancies on the process of estrogen production and metabolism should play a role in the development of endometrial cancer, endometriosis and uterine leiomyoma.

The 17 β -hydroxysteroid dehydrogenase (HSD-17B) is important in the synthesis and metabo-

lism of sex steroid hormones and 17 β -hydroxysteroid dehydrogenase type 1 (HSD17B1s) is the most common subtype [6, 7]. It is an enzyme catalyzing the conversion of estrone to the more biologically active estradiol in the final step of estrogen synthesis [8]. The encoding gene of HSD17B1 is located on chromosome 17q12-q21, and the protein is expressed in the ovaries, placenta, testis, endometrium, malignant and normal breast epithelium, and prostatic cancer cells [9-11]. Thus, it is assumed that estrogen-metabolizing gene HSD17B1 polymorphisms, which can potentially cause alterations in their biological function, should contribute to the susceptibility of individuals to hormone-related diseases. One type of HSD17B1 gene polymorphisms is rs605059. It is located in exon 6 (1954A/G) that leads to an

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amino acid change from serine to glycine at position 312 [12, 13]. Several studies have been conducted to explore the relationship between HSD17B1 rs605059 gene polymorphisms and risks of endometrial cancer, endometriosis and uterine leiomyoma. However, the results were inconclusive due to different sizes of samples and participant characteristics. Thus, we performed a meta-analysis of currently relevant studies to investigate the relationships between HSD17B1 rs605059 gene polymorphisms and risks of endometrial cancer, endometriosis and uterine leiomyoma.

Materials and methods

Literature and search strategy

A comprehensive electronic search was conducted in PubMed, Medline (Ovid), Embase, Weipu, Wanfang and CNKI for studies published from January 1995 to April 2015. The following search query was used: “uterine”, “endometrial cancer”, “endometriosis”, “leiomyoma”, “polymorphism”, “HSD17B1”, “HSD17β1”, “17β-hydroxysteroid dehydrogenase”, “variant” and “mutation”. The search was updated every week until April 10, 2015.

Inclusion and exclusion criteria

Articles fulfilling the following criteria were included: (i) analyzed HSD17B1 rs605059 polymorphisms in uterine diseases (endometrial cancer, endometriosis, leiomyoma), (ii) provided sufficient data in both case and control groups to calculate the odds ratios (ORs) and the corresponding 95% CIs, (iii) case-control studies. When duplicate data were present in different articles, only the latest one would be considered. Meanwhile, articles that didn't fulfill the criteria mentioned above were excluded.

Data extraction

Two investigators independently reviewed all potential studies. The following items were extracted: first author, year of publication, ethnicity, risk factors, diagnostic standard, features of control, target genotypes, genotyping methods, participant numbers, and genotype distributions in cases and controls. Any discrepancies were resolved by discussion with a third investigator until a consensus was reached.

Statistical analysis

Pooled ORs and corresponding 95% CIs were calculated to estimate the strength of the association between the HSD17B1 rs605059 polymorphisms and the risks of endometrial cancer, endometriosis and leiomyoma. SNPs were considered as binary variables. We estimated the risks of homozygous mutants (AA vs. AG+GG), heterozygous and homozygous mutants (AA+AG vs. GG) and heterozygous mutants (AG vs. AA+GG). We then compared the variant genotype AA with the wild type GG homozygote (AA vs. GG). We also assessed the risks of variant gene A alone. (A vs. G). Heterogeneity assumptions were checked using the Higgins I^2 test. If heterogeneity did not exist ($I^2 < 50\%$), a fixed-effects model was applied otherwise a random-effects model was used. The Z test was performed to determine the significance of the pooled ORs where $P < 0.05$ was considered statistically significant. The presence of publication bias was evaluated by visually inspecting the asymmetry in funnel plots. All analyses were performed using the Revman 5.2 software (Cochrane Collaboration, Copenhagen).

Results

Search results

92 results returned after the initial search. In our further review, 77 studies were excluded for irrelevant to 17β-hydroxysteroid dehydrogenase polymorphisms and uterine disease risks based on titles and abstracts. Among the remaining 15 articles, 2 studies were excluded for addressing HSD17B2, HSD17B3 and HSD17B4 polymorphisms instead of HSD17B1 variants [14, 15]; 2 studies reported HSD17B1 polymorphisms like rs2006200, rs2071046 and rs597255 other than rs605059 [16, 17]; 3 studies were excluded for non-case-control studies [18-20]. Therefore, we enrolled 8 articles in this meta-analysis (**Figure 1**) [21-28].

Study characteristics

Among the 8 enrolled case-control studies, 3 were about endometrial cancer, 4 were about endometriosis and 1 was about uterine leiomyoma. 7 of the total 8 studies reported the numbers of HSD17B1 rs605059 gene variants AA, AG and GG in both case and control groups separately. One study only reported the num-

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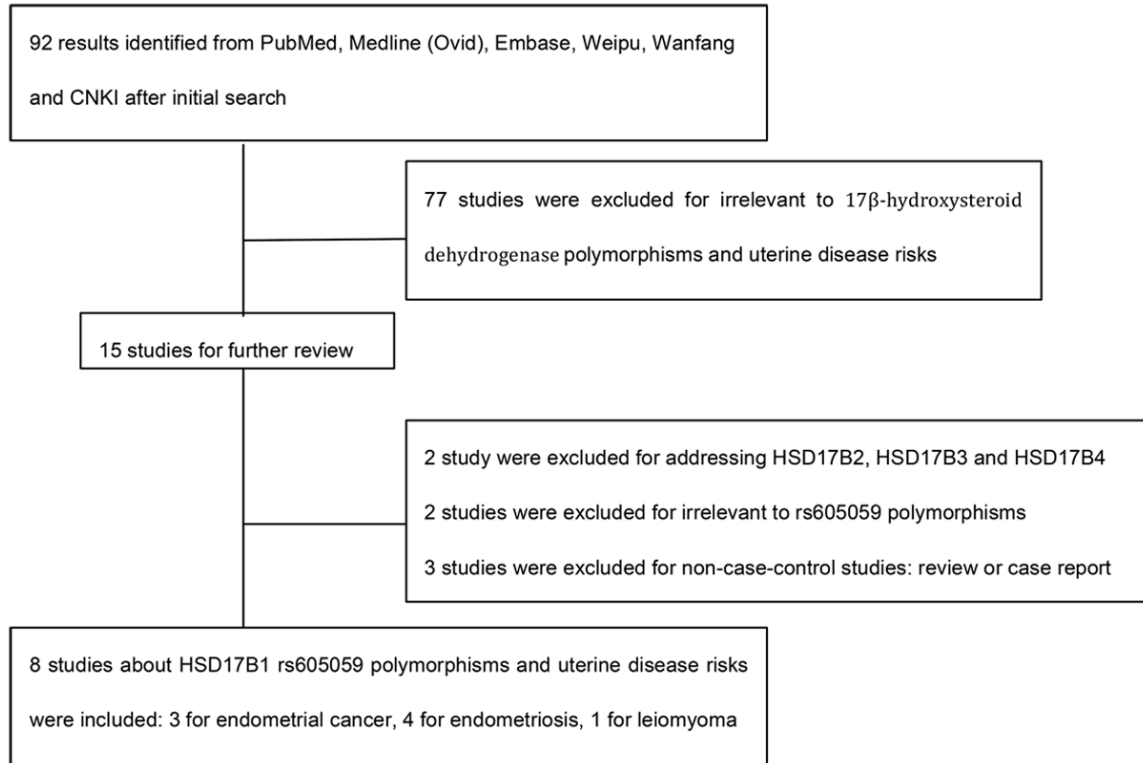


Figure 1. The flow chart of study selection.

Table 1. The characteristics and genotype distributions of included studies

First author	Year	Ethnicity	Disease type	Case number	Control number	Case			Control		
						GG	AG	AA	GG	AG	AA
Ashton	2010	Caucasian	Endometrial cancer	191	290	43	84	64	52	147	91
Dai	2006	Asian	Endometrial cancer	1031	1019	380	465	186	358	487	174
Setiawan	2003	N/A	Endometrial cancer	219	664	54	96	69	167	316	181
Wu	2012	Asian	Endometriosis	121	171	N/A	61	N/A	N/A	87	N/A
Wang	2012	Asian	Endometriosis	300	337	81	166	53	94	175	68
Tsuchiya	2005	Asian	Endometriosis	75	57	13	40	22	22	21	14
Lamp	2011	N/A	Endometriosis	150	199	23	84	43	54	93	52
Cong	2012	Asian	Leiomyoma	121	217	15	66	40	51	111	55

Table 2. Comparison of possible risk factors between cases and controls

First author	Age	BMI	Diabetes	Hypertension	Hormone therapy	Personal or relative history of cancer	Smoking	Alcohol	Menopausal statement
Ashton	NO	NO	YES	YES	YES	YES	NO	YES	N/A
Dai	NO	YES	N/A	N/A	NO	Yes	N/A	N/A	YES
Setiawan	NO	YES	NO	NO	YES	YES	YES	NO	NO
Wu	NO	NO	N/A	N/A	NO	N/A	N/A	N/A	NO
Wang	YES	NO	N/A	N/A	N/A	N/A	N/A	NA	NA
Tsuchiya	NO	N/A	N/A	N/A	N/A	N/A	N/A	N/A	NO
Lamp	YES	YES	N/A	N/A	N/A	N/A	YES	NO	YES
Cong	NO	N/A	N/A	N/A	N/A	N/A	NO	N/A	NO

NO: no difference presented between cases and controls; YES: significant difference presented between cases and controls.

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Table 3. Summary of different comparative results

Disease type	Genotypes	Overall&subgroup	Participants	OR (95% CI)	Z value	P value	I ² (%)	Effect Model
Endometrial cancer	AA vs. AG+GG	Overall	3,414	1.11 (0.94, 1.32)	1.25	0.21	0	Fixed
	AA+AG vs. GG	Overall	3,414	1.79 (0.42, 7.52)	0.79	0.43	98	Random
	AG vs. AA+GG	Overall	3,414	0.87 (0.76, 1.00)	1.97	0.05	0	Fixed
	AA vs. GG	Overall	1819	1.43 (0.62, 3.30)	0.85	0.40	93	Random
	A vs. G	Overall	6,828	1.00 (0.91, 1.11)	0.06	0.96	0	Fixed
Endometriosis	AA vs. AG+GG	Overall	1,118	0.99 (0.75, 1.32)	0.04	0.97	0	Fixed
		Asian	769	0.92 (0.65, 1.32)	0.44	0.66	0	Fixed
	AA+AG vs. GG	Overall	1,118	1.73 (0.92, 3.25)	1.71	0.09	75	Random
		Asian	769	1.66 (0.60, 4.62)	0.97	0.33	82	Random
	AG vs. AA+GG	Overall	1,410	1.24 (1.00, 1.53)	1.97	0.05	10	Fixed
		Asian	1,061	1.17 (0.92, 1.49)	1.29	0.20	24	Fixed
	AA vs. GG	Overall	539	1.54 (0.79, 2.97)	1.28	0.20	67	Random
		Asian	367	1.42 (0.50, 4.05)	0.67	0.51	75	Random
	A vs. G	Overall	2,236	1.23 (0.90, 1.68)	1.31	0.19	64	Random
Asian		1,538	1.22 (0.71, 2.09)	0.73	0.47	76	Random	

bers of heterozygous mutants AG and we failed to get any response from the corresponding authors to retrieve the numbers of homozygous mutants [24]. 6 of the total 8 studies demonstrated the patients' ethnicity as Caucasian or Asian while the other 2 failed to mention any information about the races (**Table 1**). Possible variables among participants that might affect the odds ratios were also discussed including age, body mass index, history of diabetes and hypertension, hormone therapy history, family history of cancers, smoking, alcohol consumption and menopausal status (**Table 2**).

Quantitative data analysis

Table 3 showed the pooled odds ratio of HSD17B1 rs605059 polymorphisms in the risk of endometrial cancer and endometriosis. 3,414 participants were analyzed for the HSD17B1 rs605059 polymorphisms and the risk of endometrial cancer. We found no significant association using 5 different genotype or allele comparisons: AA vs. AG+GG, AA+AG vs. GG, AG vs. AA+GG, AA vs. GG and A vs. G (AA vs. AG+GG: OR = 1.11, 95% CI = 0.94-1.32; AA+AG vs. GG: OR = 1.79, 95% CI = 0.42-7.52; AG vs. AA+GG: OR = 0.87, 95% CI = 0.76-1.00; AA vs. GG: OR = 1.43, 95% CI = 0.62-3.30; A vs. G: OR = 1.00, 95% CI = 0.91-1.11). Fixed-effects model or random-effects model was chosen according to Higgins I² test. When heterogeneity did not exist (I² < 50%), a fixed-effects model was applied otherwise a random-

effects model was used. Z values and P values were also calculated to assess the pooled ORs.

As for HSD17B1 rs605059 polymorphisms and the risk of endometriosis, 1410 participants including 646 cases and 764 controls were analyzed. The meta-analysis of the overall population failed to show any significant association between HSD17B1 rs605059 polymorphisms and the risk of endometriosis (AA vs. AG+GG: OR = 0.99, 95% CI = 0.75-1.32; AA+AG vs. GG: OR = 1.73, 95% CI = 0.92-3.25; AG vs. AA+GG: OR = 1.24, 95% CI = 1.00-1.53; AA vs. GG: OR = 1.54, 95% CI = 0.79-2.97; A vs. G: OR = 1.23, 95% CI = 0.90-1.68). A subgroup analysis based on race stratification was also performed. For Asian people, mainly Taiwanese and Japanese, no significantly increased or decreased risks of endometriosis were found for HSD17B1 rs605059 polymorphisms (AA vs. AG+GG: OR = 0.92, 95% CI = 0.65-1.32; AA+AG vs. GG: OR = 1.66, 95% CI = 0.60-4.62; AG vs. AA+GG: OR = 1.17, 95% CI = 0.92-1.49; AA vs. GG: OR = 1.42, 95% CI = 0.50-4.05; A vs. G: OR = 1.22, 95% CI = 0.71-2.09).

Only one case-control study on HSD17B1 rs605059 polymorphisms and the risk of uterine leiomyoma was available [28]. Even though the frequencies of rs605059 AA genotype and A allele were significantly increased in patients with uterine leiomyoma compared to healthy controls (GG vs. AA, OR 0.40, 95% CI 0.20-0.82; G vs. A, OR 0.68, 95% CI 0.50-0.94), we

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could still not conclude that the genotype of HSD17B1 rs605059 played a role in the leiomyoma tumorigenesis.

Publication bias

The shapes of the funnel plots appeared to be symmetrical in all comparison genetic models, suggesting the lack of publication bias for the comparisons and indicating the reliability of this meta-analysis.

Discussion

Estrogen has been reported to be one pivotal risk factor for the development of many uterine diseases like endometrial cancer, endometriosis and uterine leiomyoma. In recent years, polymorphisms of genes encoding key proteins in the pathway of estrogen synthesis and metabolism have been explored to identify possible genetic risk factors for uterine diseases [29, 30]. One importantly involved protein is the 17 β -hydroxysteroid dehydrogenase type 1 (HSD17B1), an enzyme catalyzing the conversion of estrone to the more biologically active estradiol in the final step of estrogen synthesis. Polymorphisms of HSD17B1 gene rs605059 have been investigated in some previous studies to explore their association with the risks of endometrial cancer, endometriosis and uterine leiomyoma. However, the results have been inconsistent, possibly due to limited sample sizes and variant participant characteristics. In order to address the inconsistencies of previously published studies, and to draw a more concrete conclusion, the current meta-analysis was performed.

In the present meta-analysis, 8 case-control studies were enrolled. 3 were about endometrial cancer, 4 were about endometriosis and 1 was about uterine leiomyoma. As for endometrial cancer, 3,414 participants including 1,441 cases and 1,973 controls were analyzed. No association was found between the HSD17B1 rs605059 polymorphisms and the risk of endometrial cancer using 5 different genotype or allele comparisons. Among the 4 case-control studies of endometriosis, one study reported that A allele of HSD17B1 conferred higher risk for endometriosis and another study reported that HSD17B1 SNP A allele increased overall endometriosis risk, especially for stage I-II diseases [26, 27]. In contrast, the other two stud-

ies failed to reveal any significant relationship between HSD17B1 rs605059 polymorphisms and the risk of endometriosis [24, 25]. By performing a meta-analysis, we concluded that the HSD17B1 rs605059 polymorphisms and the risk of endometriosis were not significantly associated. The pooled results of a subgroup analysis on Asian people were consistent with the overall meta-analysis. Since there was only one case-control study available to explore the HSD17B1 rs605059 polymorphisms and the risk of uterine leiomyoma, we could hardly make any concrete conclusion even though it revealed that the frequencies of rs605059 AA genotype and A allele were significantly increased in patients with uterine leiomyoma compared to healthy controls.

Despite our efforts to pool the results of currently published case-control studies, some disadvantages of the present meta-analysis should not be ignored. Firstly, the number of available studies was very limited. 3 studies were found for endometrial cancer, 4 were for endometriosis and only 1 for uterine leiomyoma. It is possible that the results of unpublished studies or further investigations might be differed from the present conclusion, thus cautions should be paid to explain the results [31]. Secondly, this meta-analysis was based on unadjusted estimations. It is known that other risk factors like age and menopausal status were also important in the development of uterine diseases [32-35]. These confounding factors might affect the validity of the results. Thirdly, available studies regarding these associations in Asian ethnicities were not sufficient. The subgroup analysis included mainly Japanese and Taiwanese Chinese people. Even though evidence for relationship between the HSD17B1 rs605059 polymorphisms and endometriosis was found in Japanese population, the overall analysis showed no significant association. Thus, studies enrolling more Asians were required.

To our knowledge, the present study was the first meta-analysis exploring the association between HSD17B1 rs605059 polymorphisms and the risks of uterine diseases. Despite all the disadvantages mentioned above, we could still conclude that HSD17B1 rs605059 polymorphisms were not associated with the risks of endometrial cancer and endometriosis. Further studies are needed to validate the con-

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clusion and clarify the association between HSD17B1 rs605059 polymorphisms and the risk of uterine leiomyoma.

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Disclosure of conflict of interest

None.

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