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Review Article

Cytochrome P450 1B1 Leu432Val gene polymorphisms in the risks of benign uterine diseases: a systemic review and meta-analysis

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Abstract: The purpose of this meta-analysis was to evaluate the cytochrome P450 1B1 (CYP1B1) Leu432Val gene polymorphisms in the risks of benign uterine diseases. A comprehensive electronic search was performed using PubMed, Medline (Ovid), Embase, CNKI, Weipu and Wanfang. The statistical analyses of pooled odds ratios and corresponding 95% confidence intervals were undertaken using the Revman 5.2 software. 8 case-control studies including 5 uterine leiomyoma studies and 3 endometriosis/adenomyoma studies were identified. The results showed no significant association between CYP1B1 Leu432Val gene polymorphisms and the risk of uterine leiomyoma (GG *vs.* CG+CC: OR = 1.18, 95% CI = 0.66-2.11; GG+CG *vs.* CC: OR = 0.57, 95% CI = 0.25-1.33; CG *vs.* CC+GG: OR = 0.56, 95% CI = 0.29-1.07; GG *vs.* CC: OR = 0.88, 95% CI = 0.16-4.72; G *vs.* C: OR = 0.72, 95% CI = 0.38-1.37) or the risk of endometriosis/adenomyoma (GG *vs.* CG+CC: OR = 1.15, 95% CI = 0.60-2.21; GG+CG *vs.* CC: OR = 0.92, 95% CI = 0.58-1.48; CG *vs.* CC+GG: OR = 1.05, 95% CI = 0.48-1.52; GG *vs.* CC: OR = 0.95, 95% CI = 0.49-1.83; G *vs.* C: OR = 1.08, 95% CI = 0.88-1.31). No association was found in subgroup analysis stratified by Asian and Middle Eastern ethnicities. This study indicated that CYP1B1 Leu432Val polymorphisms were not correlated with the risk of benign uterine diseases.

Keywords: Leiomyoma, endometriosis, adenomyoma, CYP1B1, polymorphism, meta-analysis

Introduction

Although uterine malignancies have been widely studied due to their invasiveness and prevalence, more and more researches now focus on benign uterine diseases such as leiomyoma, endometriosis and adenomyoma. Uterine leiomyoma is characterized by high amounts of extracellular matrix components and is the leading indication for hysterectomy [1-3]. Endometriosis and adenomyoma are defined as the presence of endometrial glands and stroma outside the uterine cavity and within the myometrium, respectively [4]. Endometriosis/adenomyoma is a known cause of chronic pelvic pain and infertility [5, 6]. Uterine leiomyoma and endometriosis/adenomyoma constitute the largest part of uterine benign diseases and greatly affect women's quality of life [7]. A-l though many treatment options are now available, the possibility of infertility as well as hysterectomy raises the urgency to better understand the etiologies and risk factors. Initiating factors of benign uterine diseases are poorly understood. However, it has been well established that the disorder of enzymes involved in the metabolism of sex hormones plays a crucial role in the development of uterine diseases [8-10]. Individual differences in enzyme activities, which are related to gene polymorphisms, are one possible reason for varying disease susceptibilities. As such, it has been hypothesized that certain single nucleotide polymorphisms (SNPs) in steroid-metabolizing enzyme genes could lead to elevated risks of uterine diseases.

The P450 cytochrome system (CYP450) is an important group of enzymes involved in steroid hormone biosynthesis and CYP1B1 is one of

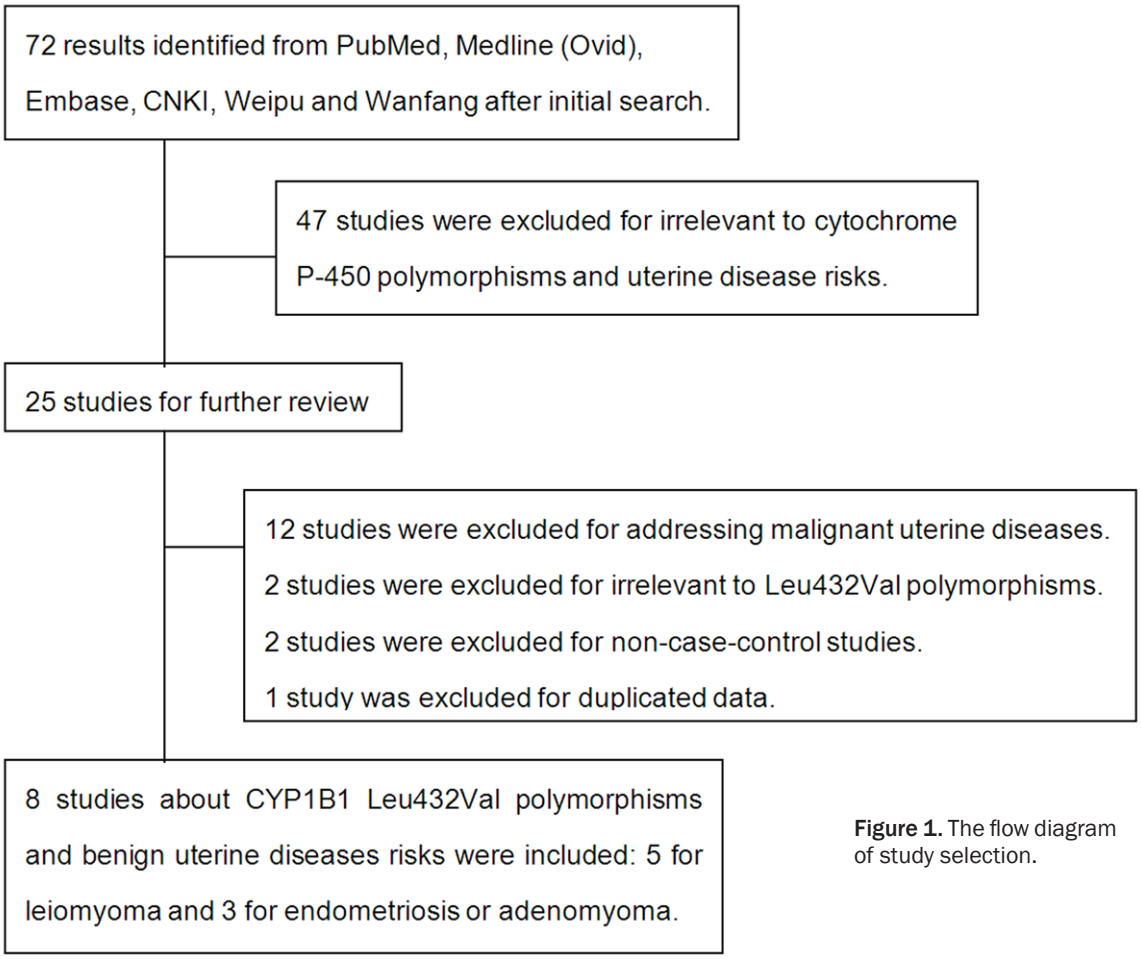

Figure 1. The flow diagram of study selection.

them. CYP1B1 specifically catalyzes the 4-hydroxylation of estradiol into 4-hydroxyestradiol (4OH), which enables the formation of free radicals that cause DNA damage through redox cycling from compounds such as hydroquinone [11, 12]. The human CYP1B1 gene is located on chromosome 2 at 2p21-22 and comprises three exons and two introns. Currently, approximately 42 common CYP1B1 allele variants have been identified, among which the Leu432Val (rs1056836) polymorphism is the most widely explored [13]. Several researches have been conducted on the association between CYP1B1 Leu432Val gene polymorphisms and risks of diseases like breast cancer, lung cancer and uterine diseases [14, 15]. One meta-analysis reported that CYP1B1 Leu432Val polymorphisms could lead to an increased risk of endometrial cancer [16]. Some studies also explored the relationship between CYP1B1 Leu432Val gene polymorphisms and risks of benign uterine diseases like leiomyoma and endometriosis/adenomyoma. 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 relationship between CYP1B1 Leu432Val gene polymorphisms and risks of leiomyoma and endometriosis/adenomyoma.

Materials and methods

Search for eligible literature

A comprehensive electronic search was performed using PubMed, Medline (Ovid), Embase, CNKI, Weipu and Wanfang for studies published from January 2006 to December 2016. The following keywords were variably combined: “uterine”, “benign”, “endometriosis”, “adenomyoma”, “leiomyoma”, “fibroid”, “polymorphism”, “CYP1B1”, “cytochrome P450 1B1”, “variant” and “mutation”. The search was updated every week until December 24, 2016.

Table 1. Characteristics and genotype distributions of included studies

First author	Year	Ethnicity	Disease type	NOS score	Case number	Control number	Case			Control		
							CC	CG	GG	CC	CG	GG
Bideau	2016	Black	Leiomyoma	6	37	52	0	4	33	1	8	43
El-Shennawy	2011	Egyptian	Leiomyoma	7	160	100	59	96	5	19	74	7
Salimi	2015	Iranian	Leiomyoma	7	105	112	42	47	16	56	45	11
Shen	2014	Chinese	Leiomyoma	8	300	300	290	10	0	250	50	0
Ye	2008	Chinese	Leiomyoma	6	100	110	71	29	0	70	40	0
Chen	2012	Chinese	Endometriosis/Adenomyoma	8	432	493	261	158	13	324	156	13
Cho	2007	Korean	Endometriosis	7	188	221	160	25	3	178	41	2
Li	2009	Chinese	Endometriosis	6	55	45	47	5	3	35	7	3

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

First author	Age	BMI	Parity	Oral Contraceptive use	Menarche age	Duration of menses	Menstrual cycle	Menopausal statement
Bideau	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A
El-Shennawy	No	No	No	N/A	N/A	N/A	N/A	N/A
Salimi	No	No	N/A	N/A	No	No	No	No
Shen	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ye	No	N/A	No	No	N/A	N/A	N/A	N/A
Chen	No	N/A	No	N/A	N/A	N/A	N/A	N/A
Cho	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Li	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A

When no difference between cases and controls existed, a "NO" would be noted; otherwise a "YES" would be noted. "N/A" means no available data presented.

Inclusion and exclusion criteria

Articles fulfilling the following criteria were included: (i) analyzed CYP1B1 Leu432Val (rs-1056836) polymorphisms in benign uterine diseases (endometriosis, adenomyoma and 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 included. Meanwhile, articles that didn't fulfill the criteria mentioned above were filtered out.

Data extraction

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

The Newcastle-Ottawa Scale (NOS) was used to investigate the quality of included studies. 3 aspects of selection, comparability, and exposure (9 scores in total) were carefully assessed. Studies that had scores higher than 5 would be included (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.).

Statistical analysis

All analyses were performed using the Revman 5.2 software (Cochrane Collaboration, Copenhagen). Briefly, the Higgins I^2 test was undertaken to calculate the pooled ORs and corresponding 95% CIs. SNPs of CYP1B1 Leu432Val were considered as binary variables. We estimated the risks of homozygous mutants (GG vs. CG+CC), homozygous and heterozygous mutants (GG+CG vs. CC) and heterozygous mutants (CG vs. CC+GG). We also compared the variant genotype GG with the wild type CC homozygote (GG vs. CC) and assessed the risks of variant gene G alone. (G vs. C). When I^2 was <50%, a fixed-effects model was applied otherwise a random-effects model was used. The *Z*

Table 3. Summary of different comparative results by pooling leiomyoma and endometriosis/adenomyoma together

Genotypes	Overall & subgroup	Participants	OR (95% CI)	Z value	*P* value	I^2 (%)	Effect Model
GG vs. CG+CC	Overall	2,810	1.17 (0.76, 1.80)	0.71	0.48	0	Fixed
	Asian	2,244	1.15 (0.60, 2.21)	0.42	0.67	0	Fixed
	Middle Eastern	477	0.90 (0.24, 3.35)	0.16	0.88	71	Random
GG+CG vs. CC	Overall	2,810	0.81 (0.43, 1.56)	0.62	0.54	86	Random
	Asian	2,244	0.61 (0.31, 1.18)	1.48	0.14	86	Random
	Middle Eastern	477	0.78 (0.21, 2.84)	0.38	0.71	90	Random
CG vs. CC+GG	Overall	2,810	0.65 (0.41, 1.04)	1.81	0.07	79	Random
	Asian	2,244	0.59 (0.30, 1.16)	1.53	0.13	86	Random
	Middle Eastern	477	0.80 (0.35, 1.80)	0.54	0.59	78	Random
GG vs. CC	Overall	2,115	0.99 (0.62, 1.58)	0.04	0.97	39	Fixed
	Asian	1,823	0.95 (0.49, 1.83)	0.15	0.88	0	Fixed
	Middle Eastern	215	0.70 (0.09, 5.67)	0.33	0.74	87	Random
G vs. C	Overall	5,620	0.78 (0.53, 1.16)	1.22	0.22	81	Random
	Asian	4,488	0.65 (0.36, 1.15)	1.48	0.14	85	Random
	Middle Eastern	954	0.94 (0.43, 1.29)	0.15	0.88	88	Random

test was performed to determine the significance of the pooled ORs where $P<0.05$ was considered statistically significant [17]. The presence of publication bias was evaluated by visually inspecting the asymmetry in funnel plots.

Results

Search results

The initial search identified 72 publications according to the search strategy. In our further screening, 47 studies were excluded for they were notrelevant to CYP polymorphisms and uterine disease risks based on titles and abstracts. Among the 25 articles remained, 12 studies were filtered out for addressing malignant uterine diseases, namely endometrial cancer and uterine sarcoma; 2 studies reported CYP1B1 polymorphisms other than rs1056836 (C/G); 2 studies were excluded for non-case-control studies; 2 studies were published by the same author with partially duplicated data hence the earlier one was excluded [18]. Moreover, all of the remaining 8 studies had NOS scores higher than 5 and thus were enrolled in this meta-analysis (**Figure 1** and **Table 1**) [19-26].

Study characteristics

Among the 8 enrolled case-control studies, 5 were about uterine leiomyoma and 3 were about endometriosis or adenomyoma. 1 study focused on black population, 2 studies analyzed Middle Eastern population (Egyptian and Iranian) while the remaining 5 were about Asian participants. All studies reported the numbers of CYP1B1 Leu432Val gene variants CC, CG and GG in both case and control groups separately (**Table 1**). Possible variables among participants that might affect the odds ratios were also displayed including age, body mass index (BMI), parity, oral contraceptive use, menarche age, duration of menses, menstrual cycle and menopausal statement (**Table 2**).

Quantitative data analysis

Table 3 showed the odds ratios of CYP1B1 Leu432Val polymorphisms in the risk of uterine benign diseases by pooling leiomyoma and endometriosis/adenomyoma together. 2,810 participants were analyzed while 2,244 Asian and 477 Middle Eastern individuals were stratified. No significant association was found in 5 different genotype or allele comparisons: GG *vs.* CG+CC: OR = 1.17, 95% CI = 0.76-1.80; GG+CG *vs.* CC: OR = 0.81, 95% CI = 0.43-1.56; CG *vs.* CC+GG: OR = 0.65, 95% CI = 0.41-1.04; GG *vs.* CC: OR = 0.99, 95% CI = 0.62-1.58; G *vs.* C: OR = 0.78, 95% CI = 0.53-1.16. These overall results were in line with subgroup analysis in Asian population (GG *vs.* CG+CC: OR = 1.15, 95% CI = 0.60-2.21; GG+CG *vs.* CC: OR = 0.61,

Table 4. Summary of different comparative results based on disease types

Disease type	Genotypes	Overall & subgroup	Participants	OR (95% CI)	Z value	*P* value	I^2 (%)	Effect Model
Leiomyoma	GG vs. CG+CC	Overall	1,376	1.18 (0.66, 2.11)	0.57	0.57	48	Fixed
		Asian	810	Not estimated				
		Middle Eastern	477	0.90 (0.24, 3.35)	0.16	0.88	71	Random
	GG+CG vs. CC	Overall	1,376	0.57 (0.25, 1.33)	1.30	0.20	85	Random
		Asian	810	0.36 (0.09, 1.45)	1.44	0.15	90	Random
		Middle Eastern	477	0.78 (0.21, 2.84)	0.38	0.71	90	Random
	CG vs. CC+GG	Overall	1,376	0.56 (0.29, 1.07)	1.75	0.08	79	Random
		Asian	810	0.36 (0.09, 1.45)	1.44	0.15	90	Random
		Middle Eastern	477	0.80 (0.35, 1.80)	0.54	0.59	78	Random
	GG vs. CC	Overall	963	0.88 (0.16, 4.72)	0.15	0.88	74	Random
		Asian	681	Not estimated				
		Middle Eastern	215	0.70 (0.09, 5.67)	0.33	0.74	87	Random
	G vs. C	Overall	2,752	0.72 (0.38, 1.37)	1.00	0.32	86	Random
		Asian	1,620	0.38 (0.10, 1.55)	1.35	0.18	90	Random
		Middle Eastern	954	0.94 (0.43, 1.29)	0.15	0.88	88	Random
Endometriosis/Adenomyoma	GG vs. CG+CC	Overall	1, 434	1.15 (0.60, 2.21)	0.42	0.67	0	Fixed
	GG+CG vs. CC	Overall	1,434	0.92 (0.58, 1.48)	0.32	0.75	58	Random
	CG vs. CC+GG	Overall	1,434	1.05 (0.48, 1.52)	0.53	0.59	67	Random
	GG vs. CC	Overall	1,142	0.95 (0.49, 1.83)	0.15	0.88	0	Fixed
	G vs. C	Overall	2,868	1.08 (0.88, 1.31)	0.71	0.48	45	Fixed

95% CI = 0.31-1.18; CG *vs*. CC+GG: OR = 0.59, 95% CI = 0.30-1.16; GG *vs*. CC: OR = 0.95, 95% CI = 0.49-1.83; G *vs*. C: OR = 0.65, 95% CI = 0.36-1.15.) and Middle Eastern population (GG *vs*. CG+CC: OR = 0.90, 95% CI = 0.24-3.35; GG+CG *vs*. CC: OR = 0.78, 95% CI = 0.21-2.84; CG *vs*. CC+GG: OR = 0.80, 95% CI = 0.35-1.80; GG *vs*. CC: OR = 0.70, 95% CI = 0.09-5.67; G *vs*. C: OR = 0.94, 95% CI = 0.43-1.29). Fixed-effects model or random-effects model was chosen according to Higgins I^2 test. Briefly, when heterogeneity did not exist (I^2<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.

In consideration of the intriguing difference between uterine leiomyoma and endometriosis/adenomyoma, meta-analysis was conducted separately based on disease types (**Table 4**). As for CYP1B1 Leu432Val polymorphisms and the risk of leiomyoma, 1,376 participants including 810 Asians and 477 Middle Eastern individuals were analyzed. The meta-analysis of the overall population failed to show any significant association between CYP1B1 Leu432-Val polymorphisms and the risk of leiomyoma (GG *vs*. CG+CC: OR = 1.18, 95% CI = 0.66-2.11; GG+CG *vs*. CC: OR = 0.57, 95% CI = 0.25-1.33; CG *vs*. CC+ GG: OR = 0.56, 95% CI = 0.29-1.07; GG *vs*. CC: OR = 0.88, 95% CI = 0.16-4.72; G *vs*. C: OR = 0.72, 95% CI = 0.38-1.37). Similarly, for 1,434 participants in the 3 endometriosis/adenomyoma studies, no significant association was presented between CYP1B1 Leu432Val polymorphisms and the risk of endometriosis/adenomyoma (GG *vs*. CG+CC: OR = 1.15, 95% CI = 0.60-2.21; GG+CG *vs*. CC: OR = 0.92, 95% CI = 0.58-1.48; CG *vs*. CC+GG: OR = 1.05, 95% CI = 0.48-1.52; GG *vs*. CC: OR = 0.95, 95% CI = 0.49-1.83; G *vs*. C: OR = 1.08, 95% CI = 0.88-1.31). Stratified calculation based on ethnicities revealed same tendency. Notably, 2 studies had no participants with GG genotype, resulting 2 subgroups unable to be calculated.

Publication bias

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

Discussion

Uterine benign diseases like leiomyoma and endometriosis/adenomyoma are complicated and are related to an interaction between multiple genes, hormone, growth factor, cytokines, and the environment [27-29]. Some researches

revealed the amelioration of the symptoms of leiomyoma and endometriosis/adenomyoma after menopause, indicating that hormone metabolization could play a crucial role in the development of these diseases [30, 31]. Thus, it is conjectured that any discrepancies in the hormone-metabolizing genes could affect the risks of leiomyoma and endometriosis/adenomyoma. CYP1B1 takes part in estrogen metabolism, which catalyzes the conversion of 17b-estradiol (E2) to the catechol estrogens, 4-hydroxyestradiol (4-OH-E2) and 2-hydroxyestradiol (2-OH-E2) and is involved in the activation of polycyclic aromatic hydrocarbons [32]. Previous studies found a significant association of the CYP1B1 Val432Leu polymorphisms with an increased risk of breast cancer and endometrial cancer but no solid conclusions were drawn to benign uterine diseases like leiomyoma and endometriosis/adenomyoma due to limited sample sizes and different characteristics of the participants. Thus, we performed a meta-analysis in the aim of exploring the association of CYP1B1 Val432Leu polymorphisms and the risks of leiomyoma and endometriosis/adenomyoma.

In the present meta-analysis, 8 case-control studies were enrolled including 5 leiomyoma studies and 3 endometriosis/adenomyoma studies. By performing a meta-analysis, we concluded that CYP1B1 Leu432Val polymorphisms were not significantly correlated with risks of benign uterine diseases combining leiomyoma and endometriosis/adenomyoma together. Meanwhile, CYP1B1 Leu432Val polymorphisms and the risks of leiomyoma and endometriosis/adenomyoma were not significantly associated based on disease types. These findings were also consistent with the stratified assessment based on ethnicities.

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 publications was very limited. 5 studies were yielded for uterine leiomyoma and 3 were for endometriosis/adenomyoma. It is possible that the results of further investigations or unpublished studies might be differed from the present conclusion, thus cautions should be paid to explain the results. Secondly, this meta-analysis was based on unadjusted estimations. Risk factors like BMI and menstruation status were also known to be important in the development of uterine diseases. These confounding factors might affect the validity of the results. Thirdly, available studies regarding to these associations in Asian and Middle Eastern ethnicities were not sufficient. The subgroup analysis for Asian participants included mainly Chinese and Korean people, while only Iranian and Egyptian people were assessed for Middle Eastern individuals. Thus, studies with wider-ranged enrollment were suggested.

To our knowledge, the present study was the first meta-analysis exploring the correlation between CYP1B1 Leu432Val polymorphisms and benign uterine diseases risks. Despite all the disadvantages mentioned above, we might still conclude that CYP1B1 Leu432Val polymorphisms were not associated with the risks of leiomyoma and endometriosis/adenomyoma either separately or in pooled perspective. Further studies are needed to validate the conclusion and clarify the association between CYP1B1 Leu432Val polymorphisms and the risk of benign uterine diseases in different ethnicities.

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Disclosure of conflict of interest

None.

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