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# Role of cytochrome P450 *2C19* polymorphisms and body mass index in endometriosis: A case–control study

Jéssica Vilarinho Cardoso[a,b], Maurício Simões Abrão[c,d], Plínio Tostes Berardo[e], Renato Ferrari[f], Luiz Eurico Nasciutti[g], Daniel Escorsim Machado[b,g], Jamila Alessandra Perini[a,b,*]

[a] Program of Post-graduation in Public Health and Environment, National School of Public Health, Oswald Cruz Foundation, Rio de Janeiro, RJ, Brazil
[b] Research Laboratory of Pharmaceutical Sciences, West Zone State University, Rio de Janeiro, Brazil
[c] Endometriosis Section, Gynecologic Division, Hospital das Clinicas, HCFMUSP, Faculty of Medicine, University of São Paulo, São Paulo, SP, Brazil
[d] Gynecologic Division, BP - The Portuguese Beneficence of São Paulo, São Paulo, SP, Brazil
[e] Gynecology Service, Hospital Federal dos Servidores do Estado, Rio de Janeiro, RJ, Brazil
[f] Gynecology Institute, Hospital Moncorvo Filho, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[g] Biomedical Sciences Institute, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

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ABSTRACT

*Objective:* To investigate the contribution of *CYP2C19* polymorphisms and body mass index (BMI) in the development of endometriosis.
*Study design:* This is a case-control study that includes 356 women (187 cases and 169 controls) recruited from two hospitals in the Brazilian public health system. The genotyping analyses of the *CYP2C19*2* and *CYP2C19*17* polymorphisms were performed using TaqMan allelic discrimination assays, and the association of the studied polymorphisms with endometriosis was evaluated by multivariate logistic regression. Pearson correlation coefficients were used to investigate the interaction between BMI and *CYP2C19* polymorphisms.
*Results:* The variant allele frequencies of *CYP2C19*2* were significantly different between cases and controls, and after adjusting for confounding factors, the CYP2C19*2 polymorphism was more frequent in women with endometriosis, considering all cases (*CYP2C19*2*: OR = 1.83; 95% CI = 1.17–2.85) and only deeply infiltrating endometriosis (DIE) cases (*CYP2C19*2*: OR = 2.32; 95% CI = 1.42–3.77). BMI was significantly lower in endometriosis patients (26.5 ± 4.68) than in controls (27.8 ± 5.65, $P < 0.02$). Among obese women (BMI 30–40), the *CYP2C19*2* polymorphism had a greater association with endometriosis (*CYP2C19*2*: OR = 3.27; 95% CI = 1.55–6.89). There was a positive correlation between *CYP2C19*2* and BMI 30–40 ($P = 0.004$).
*Conclusions:* The findings of our study suggest that *CYP2C19*2* is positively associated with endometriosis and that BMI may have a significant interaction with *CYP2C19*2* and the risk of endometriosis.


## Introduction

Endometriosis is a relevant public health problem that affects approximately 10% of reproductive-age women [1]. Endometriosis is an estrogen dependent condition characterized by the presence of functional endometrial tissue outside the uterine cavity and is currently one of the most important causes of female infertility [2]. Although its etiology remains unclear, several studies have suggested an association with various demographic/personal factors (e.g., BMI, educational attainment and smoke), menstruation (e.g., early menarche and irregular menstrual cycles), reproductive factors (e.g., parity reduction) and genetic factors [3–9].

The growth of endometrial tissue is mediated by aromatase P450, which is a key component of estrogen biosynthesis that promotes the conversion of testosterone into estradiol and androstenedione into outshone [10]. The cytochrome P450 family 2, subfamily C, 19 (CYP2C19), a member of the CYP supergene family, is an important candidate that is present in the estrogen conversion process of estradiol to outshone and in the production of estradiol and outshone 2α- and 16α-hydroxylation metabolites.

* Corresponding author at: West Zone State University - UEZO, Research Laboratory of Pharmaceutical Sciences, Av. Manuel Caldeira de Alvarenga, 1.203, Campo Grande, Zip code 23070-200, Rio de Janeiro, RJ, Brazil.
*E-mail address:* jamilaperini@yahoo.com.br (J.A. Perini).

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[11,12]. In addition to its involvement in the biosynthesis of hormones [13], the CYP2C19 enzyme is also involved in the metabolism of many drugs [14], the detoxification of potential carcinogens [15,16], and the bioactivation of some environmental procarcinogens [16]. A series of polymorphisms related to *CYP2C19* have been found to play a role in the pathogenesis of endometriosis [17–21]. Among the known allelic variants of *CYP2C19*, *CYP2C19*2* (G681A – splice site mutation) and *CYP2C19*17* (C806T – increased gene expression) stand out and are classified as slow and ultra-fast metabolizers, respectively, resulting in decreased or increased metabolic capacity of the enzyme [10,22]. These polymorphisms were selected for this study based on their high frequencies in the Brazilian population, corresponding to 13% for the *CYP2C19*2* allele and 17% for the *CYP2C19*17* allele [23].

Several studies have shown a significant association between endometriosis and low BMI, but the precise mechanism remains uncertain [4,5,8]. A recent a genome-wide association study (GWAS), with 3194 endometriosis cases and 7060 controls, described locus 7p15.2 as being associated with endometriosis and fat distribution, suggesting that both conditions may have a shared genetic basis [6]. In this context, the aim of this study was to investigate the association of *CYP2C19* polymorphisms with BMI in women with endometriosis.

## Materials and methods

### *Study design*

The study protocol was approved by the Ethics Committees of the Brazilian *Hospital Federal dos Servidores do Estado* (414/2011) and of the *Hospital Moncorvo Filho* of Federal University of Rio de Janeiro (1.244.294/2015). This case-control study included 356 women recruited from two Brazilian public hospitals that are reference institutions for the diagnosis and treatment of endometriosis in Rio de Janeiro, Brazil, from 2011 through 2016. All participants provided informed consent and completed a demographics questionnaire by interviews during preoperative appointments in the two hospitals of the Brazilian public health system.

A total of 187 patients with endometriosis, diagnosed by laparoscopy (n = 96) or laparotomy (n = 33) with histological confirmation of the disease or those diagnosed by magnetic resonance imaging (MRI) (n = 58), were selected as the case group. According to the disease stages of the patients with surgical diagnosis, stratified by the revised American Fertility Society classification [24], 41 (31.8%) were diagnosed as minimal or mild (Stages I–II), 81 (62.8%) were diagnosed as moderate or severe (Stages III–IV), and 7 (5.4%) had this information missing. According to Nisolle and Donnez, [25] endometriosis may be classified as superficial endometriosis (SUP), ovarian endometrioma (OMA) or deeply infiltrating endometriosis (DIE). According to this classification, 27 (14.4%) endometriotic patients were classified as SUP, 51 (27.3%) as OMA, and 102 (54.6%) as DIE, and 7 (3.7%) had this information missing. Both superficial peritoneal and ovarian endometrioma may be found in association with deep endometriosis, and such cases were considered DIE [26].

The control group consisted of 169 women with a negative diagnosis of endometriosis by laparoscopy (n = 140) or laparotomy (n = 29) who had undergone surgery to treat benign diseases, such as ovarian cysts (n = 30), myoma (n = 52), hydrosalpinx (n = 5), tubal ligation (n = 48) or other reasons (n = 34). The exclusion criteria were women who had been diagnosed with adenomyosis, a previous history or current diagnosis of cancer, hypertension-related chronic kidney disease or rheumatoid arthritis.

BMI was calculated as the weight (kg) divided by the square of height ($m^2$). According to WHO's expert committee [27], the women were classified as underweight ($BMI < 18.5$), normal weight ($18.5 \leq BMI \leq 24.9$), overweight ($25 \leq BMI \leq 29.9$), obese ($30 \leq BMI < 40$) or morbidly obese ($BMI \geq 40$). As described in our previous study [8], only severe and incapacitating symptoms of pain were considered in this study. Infertility was defined as a couple not being able to conceive after one year of regular, contraceptive-free intercourse (primary or secondary) [8].

### *CYP2C19 genotyping*

DNA was extracted using a genomic DNA extraction kit (Genomic DNA Extraction, Real Biotech Corporation, Banqiao City, Taiwan) following the procedures recommended by the manufacturer. The genotyping analyses of the *CYP2C19*2* (rs4244285) and *CYP2C19*17* (rs12248560) polymorphisms were performed using a TaqMan allelic discrimination assay kit obtained from Applied Biosystems (C_25986767_70 and C_25986767_70, respectively). For all polymorphisms, real-time polymerase chain reaction (PCR) was performed using a 7500 Real-Time System (Applied Biosystems, Foster City, CA, USA), and the genotypes were then directly determined.

### *Statistical analysis*

Student's *t*-test was used to compare continuous variables between endometriosis patients and controls, and results are expressed as the mean ± standard deviation (SD). Chi-square ($\chi 2$) test or Fisher's exact test, when applicable, was applied to compare differences in age, BMI, marital status, education level, and endometriosis clinical symptoms and for the statistical analysis of the distribution frequencies of genotypes and alleles between the two groups. Additionally, the Hardy-Weinberg equilibrium (HWE) was calculated by the chi-square test for goodness-of-fit. *CYP2C19*1* is the default allele, calculated as *CYP2C19*1* = 1 – (*CYP2C19*2* + *CYP2C19*17*). Multivariate logistic regression analyses were performed to identify possible confounding factors in the associations between the polymorphisms and endometriosis or between the polymorphisms and endometriosis features, which was estimated by the odds ratio (OR) with a 95% confidence interval (95% CI). Pearson's correlation test was used to evaluate the strength of the relationship between the polymorphisms and endometriosis-related BMI. Difference were considered statistically significant when $P < 0.05$. All analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 20.0.

## Results

There were significant differences between the cases and controls regarding mean age (35.9 ± 7.29 and 37.7 ± 8.59, respectively, $P = 0.03$), education level ($P < 0.001$) and all endometriosis clinical symptoms (dysmenorrhea, non-cyclic chronic pelvic pain, deep dyspareunia, infertility, cyclical urinary and intestinal symptoms, $P < 0.001$). With regards to the characteristics of the menstrual cycle including menarche age (12.5 ± 1.72 versus 12.5 ± 1.99, respectively, $P = 0.98$), average duration of menstrual bleeding (6.9 ± 4.52 versus 6.5 ± 6.01 days, respectively, $P = 0.41$) and average time interval between menstruations (25.3 ± 8.95 versus 26.9 ± 11.48 days, respectively, $P = 0.22$), there were no significant differences between the two groups. There was a significant difference between the two groups in mean BMI (26.5 ± 4.68 cases and 27.8 ± 5.65 controls, $P = 0.02$). The control group (43.2%) exhibited a higher BMI (obese and morbidly obese) than the endometriosis group (25.7%).

All polymorphisms were in Hardy–Weinberg equilibrium. Patients with endometriosis showed a higher frequency of the variant allele *CYP2C19*2* than the controls. Conversely, no

significant differences were detected in the allele or genotype distribution of the *CYP2C19*17* polymorphisms between the two groups. Table 1 shows the association analysis of the *CYPC219*2* and *CYP2C19*17* polymorphisms between control and endometriosis cases, either considering all cases or only DIE patients. Because endometriosis is also affected by clinical and demographic variables, such characteristics should to be analyzed in parallel with genetic variations. Such variables were evaluated in multivariate logistic regression models, with only age and BMI remained significant co-factors for endometriosis susceptibility. After adjusting for confounding factors, variant allele and genotypes of the *CYP2C19*2* polymorphism were associated with a higher risk (approximate 2-fold) of endometriosis, either considering all cases or DIE cases (Table 1). In addition, we also observed that the *CYP2C19*2* polymorphism was positively associated with disease susceptibility, considering only stages III–IV of endometriosis (OR = 1.94; 95% CI = 1.14–3.30) (data not shown). No significant association was found for the *CYP2C19*17* polymorphism in endometriosis development considering all cases or DIE cases (Table 1).

Combined analyses of the polymorphisms studied and BMI in endometriosis development were used to evaluate gene-environment interactions. Endometriosis cases had a higher frequency of the *CYP2C19*2* polymorphism for all categories of BMI (<18.5 = 3.7%; 18.5–24.9 = 29.4%; 25–29.9 = 41.2%; 30–40 = 22.5%; >40 = 3.2%) than controls (BMI < 18.5 = 1.8%; 18.5–24.9 = 27.2%; 25–29.9 = 27.8%; 30–40 = 35.5%; >40 = 7.7%). Among women with a BMI 30–40, the variant allele *CYP2C19*2* was associated with a higher risk of endometriosis susceptibility (*CYP2C19*2:* OR = 3.27; 95% CI = 1.55–6.89 and **1/*2 + *2/*2*: OR = 4.24; 95% CI = 1.68–10.7). There was a relationship between the *CYP2C19*2* polymorphism and obese women (BMI 30–40), which was related to endometriosis (correlation coefficient $r^2 = 0.280$, $P = 0.004$). However, no significant association was observed for the C*YP2C19*17* polymorphism (data not shown).

In addition, we investigated the association of the *CYPC219*2* and *CYP2C19*17* polymorphisms with the absence or presence of dysmenorrhea, pelvic pain, dyspareunia, infertility, and urinary and intestinal problems in the endometriosis patients, but no significant differences were found (data not shown).

## Comment

Estrogen is highly expressed in endometriotic lesions compared with the normal endometrium [28,29]. A recent meta-analysis of 11 genome-wide studies identified five novel loci that were significantly associated with endometriosis risk, implicating genes involved in steroid hormone pathways, such as the estrogen receptor (*ESR1*), and thus reinforcing the important role of this hormone in endometriosis susceptibility [30].

The *CYP2C19*17* polymorphism was not significantly associated with endometriosis risk in our study, in agreement with Painter et al. [19]. However, a lower endometriosis risk was previously observed for carriers of the *CYP2C19*17* allele in only one study [20]. The *CYP2C19*17* variant (in the 5′-flanking region of the gene) may confer a rapid metabolism of CYP2C19 substrates, which may decrease estrogen levels and, therefore, reduce endometriosis risk [31].

We found that allelic and genotypic variants of *CYP2C19*2* were associated with increased risk of susceptibility to endometriosis. Only four studies have evaluated the association of this polymorphism with the development of endometriosis. Çayan, et al. [17] and Painter et al. [20] proposed that the *CYP2C19*2* polymorphism increased endometriosis risk, corroborating our findings. However, the other two studies did not observe an association of the *CYP2C19*2* polymorphism with the disease [18,19]. This synonymous polymorphism located in exon 5 causes no change to the amino acid sequence, but creates an alternative splice site downstream resulting in a truncated, non-functional protein [32] and a poor metabolizer phenotype [10].

Estrogens are also produced in adipocytes, and the increased production of estrogen is associated with increased adiposity [33]. Reduced or increased estrogen expression has been associated with the prevalence of certain aspects of the metabolic syndrome [34–36], and polymorphisms in estrogen-related genes have been associated with abnormal adiposity [35,37]. We hypothesized that CYP2C19 could alter circulating estrogen levels and modify the risk of endometriosis influenced by BMI status. Thus, we observed that *CYP2C19*2* is positively associated with endometriosis in women with BMI between 30 and 40. These findings suggest a gene-environment interaction in the susceptibility to endometriosis.

**Table 1**
Association analysis of the *CYPC219*2* and *CYP2C19*17* polymorphisms between control and cases (all endometriosis patients or DIE cases).

| Polymosphisms | Controls (n = 169) | Endometriosis (n = 187) | *P* value[a] | OR $_{adjusted}$ (95% CI) [b,c] | DIE (n = 102) | *P* value[a] | OR $_{adjusted}$ (95% CI) [b,d] |
|---|---|---|---|---|---|---|---|
| *CYP2C19*2* | N (%) | | | | N (%) | | |
| Genotypes | | | | | | | |
| **1/*1* | 131 (77.5) | 122 (65.3) | | 1 [e] | 61 (59.8) | | 1 [e] |
| **1/*2* | 36 (21.3) | 58 (31.0) | 0.02 | 1.83 (1.10–3.06) | 35 (34.3) | 0.01 | 2.13 (1.18 – 3.83) |
| **2/*2* | 2 (1.2) | 7 (3.7) | 0.14 | 3.49 (0.67 – 18.1) | 6 (5.9) | 0.02 | 6.80 (1.31 – 35.4) |
| **1/*2 + *2/*2* | 38 (22.5) | 65 (34.7) | 0.01 | 1.92 (1.17 – 3.17) | 41 (40.2) | 0.003 | 2.39 (1.36 – 4.20) |
| Alleles | | | | | | | |
| **1* | 298 (88.2) | 302 (80.7) | | | 157 (77.0) | 0.001 | |
| **2* | 40 (11.8) | 72 (19.3) | 0.008 | 1.83 (1.17 – 2.85) | 47 (23.0) | | 2.32 (1.42 – 3.77) |
| *CYP2C19*17* | | | | | | | |
| Genotypes | | | | | | | |
| **1/*1* | 104 (61.5) | 124 (66.3) | | 1 [e] | 63 (61.8) | | 1 [e] |
| **1/*17* | 51 (30.2) | 55 (29.4) | 0.97 | 0.99 (0.61 – 1.60) | 32 (31.4) | 0.94 | 0.97 (0.51 – 1.87) |
| **17/*17* | 14 (8.3) | 8 (4.3) | 0.07 | 0.40 (0.15 – 1.06) | 7 (6.8) | 0.53 | 0.72 (0.26 – 2.00) |
| **1/*17 + *17/*17* | 65 (38.5) | 63 (33.7) | 0.52 | 0.86 (0.55 – 1.36) | 39 (38.2) | 0.82 | 1.06 (0.63 – 1.80) |
| Alleles | | | | | | | |
| **1* | 259 (76.6) | 303 (81.0) | | | 158 (67.5) | | |
| **17* | 79 (23.4) | 71 (19.0) | 0.19 | 0.98 (0.96 – 1.01) | 46 (32.5) | 0.88 | 0.99 (0.97 – 1.03) |

Default allele, calculated as *CYP2C19*1* = 1 – (*CYP2C19*2* + *CYP2C19*17*). OR: odds ratio; CI: confidence interval; DIE: deep infiltrating endometriosis. [a] Chi-square test or Fisher's exact test.[b] Adjusted by age and BMI. [c] Controls vs. all endometriosis patients. [d] Controls vs DIE. [e] Reference group.

Recent advances in gene technology have led to the discovery of new genes for obesity and infertility susceptibility, as family history and genetic factors play roles in both conditions [38]. Although epidemiological data can be used to better understand endometriosis, further studies are needed to investigate the genetic, environmental, and pathophysiology of BMI decline in women with endometriosis. This is the first study to link *CYP2C19* polymorphisms with endometriosis-related BMI. In addition, all of our controls were surgically evaluated to detect endometriosis, excluding the presence of asymptomatic endometriosis. However, this was a hospital-based study conducted in two Brazilian public hospitals over a period of almost 5 years. In addition, the sample size is relatively small, which may be due to the long time required to diagnose endometriosis. Due to the variety in the presentation and severity of clinical symptoms of endometriosis, approximately 5–8 years elapse from the onset of symptoms to the definitive diagnosis of the disease [8,39,40].

In summary, the findings of our preliminary study demonstrate that variants of *CYP2C19*2* are positively associated with endometriosis and that BMI may have a significant interaction with *CYP2C19*2* and risk of endometriosis.

## Conflict of interest

None of the authors declare any conflicts of interest.

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