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Endometriosis Is Associated With The ESR1 Gene Polymorphisms Rs9340799 And Rs2234693 And The Serum Levels Of Estradiol And CA19-9 Endometriosis Is Associated With ESR1 Polymorphisms

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ABSTRACT
Endometriosis is a complex, estrogen-dependent disorder characterized by the abnormal growth of endometrial tissue outside the uterus. Although the condition is believed to have a hereditary component, its exact causes are still not fully understood. Various genetic factors have been proposed, and differences linked to ethnicity have also been noted. At the same time, there is a strong need for less invasive methods of diagnosing this disease. In this study, we examined the potential link between endometriosis and two polymorphisms in the Estrogen Receptor 1 (ESR1) gene–rs9340799 and rs2234693 among women in Babylon province, Iraq. Additionally, we assessed the serum levels of estradiol (E2) and the tumor marker CA19-9 to explore their diagnostic value alongside the genetic variations. The study was designed as a case-control analysis, including 50 women diagnosed with endometriosis and 50 healthy, unrelated women as controls. Genotyping for the ESR1 polymorphisms was carried out using polymerase chain reaction (PCR) followed by gene sequencing, while electrochemiluminescence assays measured serum concentrations of E2 and CA19-9. Statistical analysis involved calculating odds ratios and using Chi-squared tests to explore associations, while ROC (Receiver Operating Characteristic) analysis was employed to evaluate the diagnostic performance of the markers. Findings revealed that both the rs9340799 X allele and the rs2234693 P allele were significantly more frequent in the endometriosis group compared to controls ($p<0.0001$ for both). Furthermore, patients exhibited higher serum levels of estradiol and CA19-9 ($p<0.001$), and these elevations were correlated with the presence of the ESR1 polymorphisms ($p<0.01$). ROC analysis indicated that combining the two genetic markers with serum E2 and CA19-9 levels could distinguish endometriosis cases from controls with 91% accuracy (sensitivity 92%, 95% CI: 80%-98%; specificity 74%, 95% CI: 60%-85%). Overall, the study highlights a strong association between endometriosis and the ESR1 gene polymorphisms rs9340799 and rs2234693, as well as elevated serum levels of estradiol and CA19-These findings suggest that this combination of genetic and biochemical markers holds promise for the development of improved diagnostic approaches, although further research is needed to validate these results.
Keywords: *Endometriosis, estrogen, rs9340799, rs2234693, estradiol, CA19-9.*

INTRODUCTION
Endometriosis is a chronic, estrogen-dependent inflammatory condition of the pelvis, marked by the implantation and growth of endometrial tissue outside the uterus (Wykes et al., 2004). This aberrant tissue growth can result in the formation of adhesions and scarring, leading to symptoms such as pelvic pain, dysmenorrhea, dyspareunia, dysuria, and infertility (Ochoa Bernal & Fazleabas, 2024). Affecting approximately 5–10% of women of reproductive age (Giudice, 2010), endometriosis presents a significant burden, both economically and on healthcare systems worldwide (Al-Hendy & Salama, 2006). Although the precise cause of endometriosis remains unclear, it is widely believed that numerous genetic factors, each contributing a modest effect, play a role in its development (Vassilopoulou et al., 2019). Among the early genetic candidates investigated was the Estrogen Receptor 1 (ESR1) gene, which encodes estrogen receptor alpha, the main estrogen receptor found in healthy endometrial tissue (Zhang et al., 2007). Two polymorphisms in this gene, characterized by the restriction enzymes PvuII (rs2234693, T>C) and XbaI (rs9340799, A>G), have received particular attention. However, past studies examining the relationship between these variants and endometriosis have reported inconsistent findings (Georgiou et al., 1999, Kitawaki et al., 2001, Wang et al., 2004, Kim et al., 2005, Renner et al., 2006, Luisi et al., 2006, Hsieh et

al., 2007, Govindan et al., 2009, Xie et al., 2009 and Zhao et al., 2016). Such inconsistencies align well with the idea of a polygenic model for endometriosis, where many small genetic influences accumulate to affect disease risk, necessitating replication studies across different populations. Notably, while these polymorphisms have been explored in Caucasian and East Asian cohorts, there has been little to no investigation in Arab West Asian women.

At the same time, diagnosing endometriosis largely relies on the surgical excision and histological examination of lesions obtained through laparoscopy, a procedure that is invasive, costly, and often results in diagnostic delays. Identifying serum biomarkers could offer a less invasive and more accessible diagnostic approach. Two promising candidates are the estrogen hormone estradiol (E2) and the tumor marker CA19-9 (cancer antigen 19-9). CA19-9 is normally produced by pancreatic and biliary ductal cells, as well as by gastric, colonic, endometrial, and salivary epithelial tissues. While detectable at low levels in the serum under normal conditions, CA19-9 levels can rise in a range of benign gastrointestinal diseases (S. Kim et al., 2020). Elevated serum CA19-9 levels have been reported in endometriosis (Socolov et al., 2017) and in patients with both benign and malignant ovarian tumors (Lertkhachonsuk et al., 2020), with significant decreases observed following treatment (Matalliotakis et al., 1998). Endometriosis is also associated with increased production of estradiol (E2), largely synthesized locally within the endometriosis lesions (Chantalat et al., 2020).

In this study, we conducted a case-control investigation to explore the association between endometriosis, the ESR1 gene polymorphisms rs9340799 and rs2234693, and serum levels of E2 and CA19-9 among women in the Babylon province of Iraq. Our findings demonstrate a strong link between the two ESR1 polymorphisms and the presence of endometriosis (X. Zhao et al., 2011), with the frequency of these genetic variants rising alongside increasing levels of serum E2, and to a lesser extent, CA19-9. ROC analysis further suggests that combining these four markers could enhance the diagnostic process for endometriosis (Altmäe et al., 2007).

MATERIALS AND METHODS

This case-control study was carried out between January and August 2024 at the Department of Biochemistry, College of Medicine, University of Babylon, in collaboration with the Babel Teaching Hospital for Maternity and Children in Hilla city, Iraq. A total of 100 women participated, including 50 patients diagnosed with endometriosis via laparoscopy (mean age: 39.3 ± 4.1 years) and 50 control subjects without endometriosis (mean age: 41.6 ± 3.5 years). The control group comprised women attending the hospital for routine check-ups or unrelated medical concerns who showed no clinical signs or symptoms suggestive of endometriosis. To minimize confounding factors, individuals with a history of any type of cancer, diabetes, or renal or liver diseases were excluded from participation. The study was conducted following the ethical guidelines outlined in the Declaration of Helsinki and received approval from the local ethics committee of the College of Medicine, University of Babylon, on January 8, 2024. Informed consent was obtained from all participants before any sample collection.

Measurements

Serum E2 and CA19-9

From each subject three ml venous blood was withdrawn in a serum separation gel tube (AFCO, Jordan), centrifuged at 3000 rpm for 20 min, and the separated sera were divided in 2 aliquots that were kept at -20 °C until further analysis. Serum levels of estradiol (E2) and CA19-9 were measured by electrochemiluminescence (Cobas 6000, Roche, Switzerland).

SNP

The SNP analysis for this study was carried out at the ASCo Learning Center in Baghdad, Iraq. Unless otherwise specified, all reagents and materials used for the SNP procedures were sourced from Promega, USA. For each participant, two milliliters of venous blood were collected into EDTA tubes (AFCO, Jordan), gently mixed on a shaker at room temperature for ten minutes, and subsequently stored at -20 °C until further processing. Before analysis, the frozen blood samples were thawed and mixed again at room temperature for 15 minutes. Genomic DNA was extracted from the thawed samples using the ReliaPrep™ Blood gDNA Miniprep System, following the manufacturer's instructions. DNA concentrations were measured using a Quantus Fluorometer (Promega, USA).

To amplify the target region of the ESR1 gene encompassing the rs9340799 (XbaI) and rs2234693 (PvuII) polymorphisms (Chen FuQiang et al., 2011), a 966 bp fragment was generated via PCR. The primers used for amplification were ESR1-F (CCTTTCTGTGTTCCTCTTCTC) and ESR1-R (GATGCAGCAGATCCACTTTA), synthesized by Macrogen, Korea. PCR reactions were prepared in 20 µl volumes containing 10 µl of GoTaq® Green Master Mix (2X), 1 µl of each primer (10 pmol), 6 µl of nuclease-free water, and 2 µl of template DNA. Amplification was conducted using a PCR Express Thermal Cycler (Veriti, USA) under the following conditions: an initial denaturation at 94 °C for 4 minutes, followed by 30 cycles of denaturation at 94 °C for 30 seconds, annealing at 55 °C for 30 seconds, and extension at 72 °C for 45 seconds. A final extension step was performed at 72 °C for 7 minutes, with a final hold at 4 °C to terminate the reactions (Sun et al., 2010).

One-fifth of each PCR product was separated on an agarose gel and visualized through ethidium bromide staining to confirm successful amplification. The remaining PCR products were subjected to sequencing using the Applied Biosystems 3730XL DNA Analyzer (Macrogen Corporation, Korea). Throughout the analysis, the rs9340799 variant (mutant) allele is referred to as X, while the rs2234693 variant (mutant) allele is designated as P.

Statistical Analysis

Statistical analyses for this study were performed using a range of specialized software tools. Odds ratios (ORs), chi-squared tests for trends, and comparisons of the areas under the ROC curves (AUCs) were calculated using MedCalc software (https://www.medcalc.org/index.php). Hardy-Weinberg equilibrium (HWE) assessments and 2x3 Fisher's exact tests were conducted via the online resource provided by COG Genomics (https://www.cog-genomics.org/software/stats). Receiver operating characteristic (ROC) curve analyses, crucial for evaluating the diagnostic performance of the genetic markers and serum biomarkers, were carried out using StatsDirect software. Scatter plots illustrating relationships between serum levels and genotypes were generated using SRplot, an accessible platform designed for robust statistical graphics (Tang et al., 2023). Differences in mean serum levels of estradiol (E2) and CA19-9 between the patient and control groups were assessed using Student's t-test. Throughout the study, a two-tailed p-value of less than 0.05 was considered indicative of statistical significance (Proestling et al., 2024).

These methods were selected to rigorously evaluate the association between endometriosis, ESR1 gene polymorphisms (rs9340799 and rs2234693), and serum biomarkers, aligning with the study's objective to explore both genetic and biochemical contributions to the disease and their potential diagnostic value (Al-Hendy & Salama, 2006).

RESULTS & DISCUSSION

ESR1 gene polymorphisms

A 966 base pair fragment of the ESR1 gene, covering both the rs9340799 and rs2234693 polymorphisms, was successfully amplified using PCR. Following confirmation of amplification through agarose gel electrophoresis (Fig. 1), the PCR products were sequenced using an ABI3730XL DNA analyzer (Macrogen Corporation, Korea).

The allelic and genotypic distributions of the two polymorphisms in the control and endometriosis groups are summarized in Table 1. The control group was hospital-based and consisted of women who attended routine check-ups or presented with non-specific gynecological issues but had no symptoms suggestive of endometriosis and no history of cancer. For rs2234693, the pp, Pp, and PP genotypes were observed in 31, 15, and 4 control individuals, respectively. These distributions conformed to Hardy-Weinberg Equilibrium (HWE) (p=0.25).

In contrast, for rs9340799, the xx, Xx, and XX genotypes were detected in 33, 10, and 7 control samples, respectively. However, these genotypes deviated significantly from HWE (p=0.003), likely reflecting the high rates of consanguinity typical in Middle Eastern populations (Yang et al., 2014). Despite this deviation, rs9340799 was retained for further analysis as its findings mirrored those of rs2234693, which remained within HWE.

In the endometriosis group, the distribution of rs9340799 genotypes shifted notably: the wild-type homozygous genotype (xx) was detected in only 10 cases, compared to 14 heterozygous (Xx) and 26 homozygous variant (XX) cases (Table 1). Statistically, the xx genotype was significantly underrepresented

among patients (OR=0.13, 95% CI: 0.05–0.32, p<0.0001), while the XX genotype was significantly more frequent (OR=6.65, 95% CI: 2.516–17.601, p=0.0001). At the allelic level, the variant X allele frequency was 0.66 in endometriosis patients compared to 0.24 in controls (p<0.0001), indicating a strong association between the X allele and endometriosis (Eldafira et al., 2021).

A similar trend was seen with rs2234693. Only 5 endometriosis patients carried the homozygous wild-type pp genotype, compared to 31 controls (OR=0.07, 95% CI=0.023–0.202, p<0.0001). In contrast, the heterozygous Pp genotype was more common among patients (29 cases vs. 15 controls; OR=3.22, 95% CI=1.412–7.356, p=0.0055), as was the homozygous variant PP genotype (16 cases vs. 4 controls; OR=5.41, 95% CI=1.660–17.646, p=0.0051). At the allelic level, the frequency of the P allele was significantly higher in the endometriosis group (0.61) compared to controls (0.23) (OR=5.24, 95% CI=2.831–9.687, p<0.0001). Collectively, these findings demonstrate that endometriosis is associated with a higher prevalence of the rs2234693 P allele (p<0.0001).

Serum blood markers

Serum concentrations of CA19-9 and estradiol (E2) were measured using chemiluminescence techniques. In the control group (n=50), the mean serum CA19-9 level was 9.03 ± 0.9 U/ml, whereas in the endometriosis group (n=50), it was significantly elevated at 16.74 ± 1.6 U/ml. Likewise, the mean serum E2 concentration in the control group was 25.99 ± 4.0 pg/ml, compared to 73.34 ± 10.0 pg/ml in the endometriosis group (n=49, with one outlier excluded) (Fig. 2). These findings demonstrate that patients with endometriosis had significantly higher serum levels of both CA19-9 and E2 compared to controls (p<0.001).

To further explore the possible influence of ESR1 polymorphisms on serum biomarker levels, we stratified the samples into four quartiles based on ascending concentrations of E2 or CA19-9. For each quartile, we calculated odds ratios using five genetic models: allelic (variant vs. wild-type allele), homozygous (variant homozygotes vs. wild-type homozygotes), heterozygous (heterozygotes vs. wild-type homozygotes), dominant (variant homozygotes + heterozygotes vs. wild-type homozygotes), and recessive (variant homozygotes vs. wild-type homozygotes + heterozygotes). The summarized data in Table 2 reveal a consistent pattern: the frequency of both ESR1 variants increased progressively across higher E2 and CA19-9 quartiles.

For instance, focusing on the allelic model and relative to the lowest E2 quartile, the odds ratio for the rs9340799 X variant allele was 1.56 (95% CI: 0.680–3.561, p=0.299) in the second quartile, 2.15 (95% CI: 0.948–4.894, p=0.067) in the third quartile, and 3.89 (95% CI: 1.677–9.017, p=0.002) in the highest quartile. This upward trend in X allele frequency with increasing E2 levels was statistically significant (p for trend=0.001). Similarly, the odds ratio for the rs2234693 P variant rose from 1.71 (95% CI: 0.742–3.961, p=0.207) in the second E2 quartile, to 2.37 (95% CI: 1.035–5.444, p=0.041) in the third, and 3.31 (95% CI: 1.427–7.662, p=0.005) in the fourth quartile, with a significant p for trend of 0.003.

Comparable trends were observed when quartiles were based on CA19-9 levels. Overall, these associations were strongest under the allelic and homozygous models and comparatively weaker under the heterozygous model.

ROC analysis

The findings from this study suggest a clear association between endometriosis and both the ESR1 gene polymorphisms rs2234693 and rs9340799, as well as elevated serum levels of E2 and CA19-9. These biomarkers, when considered together, hold potential as diagnostic tools for endometriosis. To explore this further, we conducted an ROC analysis. The results, summarized in Table 3 and Figure 3, show that each polymorphism and serum marker can predict endometriosis with an average accuracy of 77% (95% CI: 0.67-0.86), achieving a sensitivity of 0.79 (95% CI: 0.65-0.89) and a specificity of 0.71 (95% CI: 0.56-0.82). When two of the four markers (genetic and biochemical) were combined, the AUC increased to an average of 83% (95% CI: 0.75-0.91), with a sensitivity of 0.77 (95% CI: 0.63-0.88) and a specificity of 0.81 (95% CI: 0.68-0.90) (Li et al., 2012). A combination of three markers raised the AUC to an average of 88% (95% CI: 0.81-0.95), with a sensitivity of 0.80 (95% CI: 0.66-0.90) and specificity of 0.84 (95% CI: 0.71-0.92). The optimal combination, incorporating all four markers, achieved an AUC of 91% (95% CI: 0.86-0.97), with a sensitivity of 0.92 (95% CI: 0.80-0.98) and a specificity of 0.74 (95% CI: 0.60-0.85). These results

suggest that the combination of these genetic and biochemical markers could be highly effective for diagnosing endometriosis.

DISCUSSION

Endometriosis is a complex, hereditary, steroid-dependent condition that significantly impacts many women (Christian et al., 2022). Unfortunately, the detection and initiation of treatment for endometriosis are often delayed by several years, mainly because the disease can remain asymptomatic for long periods (Huang et al., 2005). Additionally, the current diagnostic approach, which relies on surgical examination, is costly and can sometimes fail to detect the disease altogether. In regions with limited healthcare infrastructure, such as those affected by conflict or natural disasters, performing such procedures may not be feasible (Lee et al., 2020). Consequently, there is a growing demand for simpler, non-invasive diagnostic methods that could enable earlier detection and prompt treatment.

In this study, we aimed to explore the potential of using a combination of genetic and biochemical markers to detect endometriosis (Lamp et al., 2011). To achieve this, we first assessed the association between the disease and two frequently studied polymorphisms in the first intron of the human ESR1 gene—rs9340799 (T>C) and rs2234693 (A>G). We then examined the correlation between these polymorphisms and serum levels of estrogen (E2) and the inflammatory marker CA19-9. Both of these polymorphisms are believed to affect the transcriptional regulation of the ESR1 gene, potentially altering the levels and activity of estrogen receptors (S. H. Kim et al., 2005). Our findings indicate a significant association between endometriosis and both the rs9340799 and rs2234693 polymorphisms. Among the 50 endometriosis samples in this study, 26 were homozygous for the rs9340799 XX genotype (OR=6.65, 95% CI=2.5-17.6, p=0.0001), 16 were homozygous for rs2234693 PP (OR=5.41, 95% CI=1.66-17.646, p=0.0051), and 29 were heterozygous for rs2234693 Pp (OR=3.22, 95% CI=1.412-7.356, p=0.0055).

Studies investigating the link between ESR1 polymorphisms and endometriosis have yielded mixed results. Some studies, like ours, have shown a clear association (Georgiou et al., 1999), (Kitawaki et al., 2001), (Luisi et al., 2006), (Hsieh et al., 2007), (Govindan et al., 2009) and (Xie et al., 2009), while others have not found such a relationship (Wang et al., 2004), (S. H. Kim et al., 2005) and(Renner et al., 2006). These inconsistencies may stem from ethnic differences, which could influence both the prevalence of endometriosis and the frequency of these polymorphisms (Bougie et al., 2019). Therefore, it is important to investigate these polymorphisms in diverse populations. Most research on the association between endometriosis and the ESR1 polymorphisms rs9340799 and rs2234693 has been conducted in East Asia (e.g., China, Japan, Korea, India, and Indonesia), Europe (e.g., Greece, Italy, Germany, Estonia, and Austria), the USA (Trabert et al., 2011), and Brazil (Paskulin et al., 2013). To our knowledge, this is the first study to examine this association in West Asian Arabic women. Given the small sample size in this study, further research with larger cohorts is necessary to confirm these findings.

Endometriosis lesions are often characterized by elevated local estrogen levels, which contribute to a positive feedback loop involving steroid hormone-driven inflammation (Reis et al., 2013). Previous research has shown that CA19-9 levels are elevated in endometriosis, particularly in more advanced stages and (Kurdoglu et al., 2009). This increase is likely due to the inflammatory response and tissue damage, similar to other benign conditions that cause elevated CA19-9 levels (S. Kim et al., 2020). However, since CA19-9 is related to the Lewis blood group antigens, only patients in certain blood groups (Le α-β+ or Le α+β-) will express the antigen, limiting its universal applicability as a biomarker. Nevertheless, elevated CA19-9 levels in the serum of endometriosis patients may help rule out other conditions (Socolov et al., 2017).

In our study, we observed significantly higher serum levels of E2 and CA19-9 in endometriosis patients compared to the control group. We further showed that these elevated levels were associated with higher frequencies of the variant alleles for both rs9340799 and rs2234693 polymorphisms. Our findings align with previous studies by Schuit et al. (2005), who found a correlation between plasma E2 levels and the ESR1 rs2234693-rs9340799 haplotype in postmenopausal women and men. In women, plasma E2 levels increased with the number of copies of the haplotype containing both polymorphisms, and a similar trend, though not statistically significant, was observed in men. Additionally, a study of 1538 women from the SWAN study (Sowers et al., 2006) found that serum E2 levels were consistently higher in

individuals with the rs2234693 CC and rs9340799 GG genotypes compared to those with the rs2234693 TT and/or TC and rs9340799 AA and/or AG genotypes. More recently, Grub et al. (2024) showed that ESR1 gene polymorphisms modulate the effect of E2 fluctuations on the trajectory of menopausal symptoms.

Finally, our study demonstrates that combining the two ESR1 polymorphisms with the blood markers E2 and CA19-9 allows for differentiation between endometriosis and control samples with a sensitivity of 0.92 (95% CI=0.80-0.98) and specificity of 0.74 (95% CI=0.60-0.85). These figures are comparable to the sensitivity and specificity of surgical diagnosis for endometriosis (Gu et al., 2012) and (Taylor et al., 2018). The slightly lower specificity could be attributed to the fact that the control group consisted of hospital-based women, some of whom were uncharacterized gynecological patients. Larger studies are needed to validate these findings, but if confirmed, this approach could greatly enhance early diagnosis and treatment initiation, at a much lower cost than current methods.

CONCLUSION

This study provides compelling evidence supporting the association of endometriosis with both genetic and biochemical markers, specifically the ESR1 polymorphisms rs9340799 and rs2234693, as well as elevated serum levels of E2 and CA19-9. Our findings show that these two ESR1 variants are significantly more frequent in women with endometriosis and correlate strongly with higher levels of E2 and CA19-9, suggesting a combined genetic and inflammatory contribution to disease development. These results are consistent with previous studies in other populations and highlight the importance of considering ethnic background in genetic association studies. Importantly, the combination of genetic polymorphisms and serum markers demonstrated a high diagnostic performance, with sensitivity and specificity comparable to surgical diagnosis, offering a promising, non-invasive alternative for early detection of endometriosis.

Given the small sample size and hospital-based control group in this initial investigation, further large-scale studies are needed to validate these findings. If confirmed, the implementation of such a diagnostic approach could dramatically improve the timely identification and management of endometriosis, particularly in regions with limited access to specialized surgical diagnostics.

DECLARATIONS

Author contributions

Dr. MF Smaism and Dr. NM Sulaiman participated in developing the concept and design of the study, informed the participants, performed the diagnosis, collected the samples, and reviewed and edited the manuscript. TH Farhood participated in developing the concept and design of the study, collected the samples, performed the analysis, and drafted the manuscript. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of interest

The authors declare that they have no competing financial or non-financial interests about the work described.

Author's approval:

All authors have seen and approved this study for publication.

Data availability

Data are available at request from the corresponding author.

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Legends

Table 1: Genetic and allelic frequencies of the rs9340799 and rs2234693 polymorphisms. OR: odds ratio. 95%CI: 95% confidence interval. *p**: *p* value of test of significance calculated according to (Sheskin, 2003).
Table 2: Association between allelic or genotypic frequency and the level of E2 or CA19-9. *p* for trend is from a chi-squared test (Cochran, 1954) and (Armitage, 1955) for the difference between the distributions of allelic or genotypic frequencies in the different quartiles. E2 levels (mean ± SD): 8.19±3.1 Pg/ml in Q1, 19.31±4.8 Pg/ml in Q2, 46.78±12.6 Pg/ml in Q3, and 126.50±70.2 Pg/ml in Q4. CA19-9 levels (mean ± SD): 3.32±2.5 U/ml in Q1, 8.56±1.0 U/ml in Q2, 13.84±1.9 U/ml in Q3, and 25.82±9. U/ml 1 in Q4.

Table 3: Summary of the different ROC curves obtained with each dataset. The difference of AUC, relative to CA19-9, is calculated with MedCalc according to (Hanley & McNeil, 1983)
Figure 1: The PCR-amplified 966 bp ESR1 gene fragment separated on 1.5% agarose-gel and stained with ethidium bromide. M: 100bp ladder. Lanes marked 6-24: 966bp PCR product in corresponding sample.

Figure 2: Serum levels of CA19-9 (upper panels) and E2 (lower panels) in control (C) vs. endometriosis (E), and in the presence (_var) or absence (_wt) of rs9340799 (left panels) or rs2234693 (right panels). Decimal numbers depict the p value from a student's t-test.

Figure 3: Summary ROC plot for CA19-9, E2, rs9340799, rs2234693, and combinations thereof (i.e. the product of the separate values) for detection of endometriosis. Each point represents the sensitivity and specificity (plotted as 1-specificity) for each evaluation. The bars represent the 95% confidence intervals. A combination of two factors is the product of their values. The polymorphisms are represented by a value of 1 in the absence, 2 in the presence of 1 copy, and 3 in the presence of two copies of the variant allele.

Tables and Figures
Table 1

rs9340799					
	E (N=50)	C (N=50)	OR	95 % CI	*p* *
xx	10	33	0.13	0.05-0.32	<0.0001
Xx	14	10	1.56	0.62-3.94	0.35
XX	26	7	6.65	2.52-17.60	0.0001
x	34	76	0.16	0.09-0.30	< 0.0001
X	66	24	6.15	3.31-11.40	< 0.0001
rs2234693					
	E (N=50)	C (N=50)	OR	95 % CI	*p* *
pp	5	31	0.07	0.02-0.20	<0.0001
Pp	29	15	3.22	1.41-7.36	0.0055
PP	16	4	5.41	1.66-17.65	0.0051
p	39	77	0.19	0.10-0.35	< 0.0001
P	61	23	5.24	2.83-9.69	< 0.0001

Table

			rs9340799						rs2234693					
			x	X	OR	95%CI	*p*	*p* for trend	p	P	OR	95%CI	*p*	*p* for trend
Allele (wt vs var)	E2	Q1	35	15	ref	ref	ref	0.001	36	14	ref	ref	ref	0.003
		Q2	30	20	1.56	0.680-3.561	0.299		30	20	1.71	0.742-3.961	0.207	
		Q3	26	24	2.15	0.948-4.894	0.067		26	24	2.37	1.035-5.444	0.041	
		Q4	18	30	3.89	1.677-9.017	0.002		21	27	3.31	1.427-7.662	0.005	
	CA19.9	Q1	32	18	ref	ref	ref	0.001	32	18	ref	ref	ref	0.021
		Q2	36	13	0.89	0.368-2.146	0.793		35	15	0.76	0.330-1.758	0.524	
		Q3	22	28	2.26	1.013-5.052	0.046		26	24	1.64	0.737-3.655	0.225	
		Q4	20	30	2.67	1.188-5.985	0.017		23	27	2.09	0.936-4.653	0.072	
			xx	XX	OR	95%CI	*p*	*p* for trend	pp	PP	OR	95%CI	*p*	*p* for trend
Homozygous (wt/wt vs var/var)	E2	Q1	16	6	ref	ref	ref	0.010	14	1	ref	ref	ref	0.002
		Q2	11	6	1.45	0.371-5.710	0.591		10	5	7.00	0.705-69.493	0.097	
		Q3	10	9	2.40	0.654-8.811	0.187		7	6	12.00	1.199-120.083	0.035	
		Q4	6	12	5.33	1.373-20.712	0.016		5	8	22.40	2.210-227.058	0.009	
	CA19.9	Q1	13	6	ref	ref	ref	0.009	11	4	ref	ref	ref	0.032
		Q2	15	4	0.58	0.133-2.506	0.464		12	2	0.46	0.070-3.017	0.417	
		Q3	9	12	2.89	0.790-10.571	0.109		7	6	2.36	0.485-11.452	0.288	
		Q4	6	11	3.98	0.992-15.909	0.051		6	8	3.67	0.771-17.430	0.102	
			xx	Xx	OR	95%CI	*p*	*p* for trend	pp	Pp	OR	95%CI	*p*	*p* for trend
Heterozygous (wt/wt vs wt/var)	E2	Q1	16	3	ref	ref	ref	0.065	14	10	ref	ref	ref	0.059
		Q2	11	8	3.88	0.837-17.967	0.083		10	10	1.40	0.424-4.623	0.581	
		Q3	10	6	3.20	0.649-15.776	0.153		7	12	2.40	0.697-8.260	0.165	
		Q4	6	6	5.33	1.000-28.436	0.050		5	11	3.08	0.812-11.677	0.098	
	CA19.9	Q1	13	6	ref	ref	ref	0.156	11	10	ref	ref	ref	0.187
		Q2	15	6	0.87	0.224-3.355	0.836		12	11	1.01	0.309-3.296	0.989	
		Q3	9	4	0.96	0.210-4.421	0.961		7	12	1.89	0.532-6.687	0.326	
		Q4	6	8	2.89	0.689-12.120	0.147		6	11	2.02	0.543-7.494	0.295	
			xx	XX+Xx	OR	95%CI	*p*	*p* for trend	pp	PP+Pp	OR	95%CI	*p*	*p* for trend
Dominant (wt/wt vs var/var+wt/var)	E2	Q1	16	9	ref	ref	ref	0.007	14	11	ref	ref	ref	0.007
		Q2	11	14	2.26	0.727-7.047	0.159		10	15	1.91	0.620-5.876	0.260	
		Q3	10	15	2.67	0.850-8.366	0.093		7	18	3.27	1.008-10.621	0.048	
		Q4	6	18	5.33	1.554-18.304	0.008		5	19	4.84	1.368-17.095	0.014	
	CA19.9	Q1	13	12	ref	ref	ref	0.015	11	14	ref	ref	ref	0.062
		Q2	15	10	0.72	0.236-2.215	0.564		12	13	0.85	0.280-2.591	0.777	
		Q3	9	16	1.93	0.621-5.977	0.257		7	18	2.02	0.623-6.557	0.242	
		Q4	6	19	3.43	1.026-11.476	0.045		6	19	2.49	0.741-8.351	0.140	
			xx+Xx	XX	OR	95%CI	*p*	*p* for trend	pp+Pp	PP	OR	95%CI	*p*	*p* for trend
Recessive (wt/wt+wt/var vs var/var)	E2	Q1	19	6	ref	ref	ref	0.035	24	1	ref	ref	ref	0.011
		Q2	19	6	1.00	0.273-3.662	1.000		20	5	6.00	0.647-55.664	0.115	
		Q3	16	9	1.78	0.521-6.085	0.357		19	6	7.58	0.839-68.464	0.071	
		Q4	12	12	3.17	0.937-10.701	0.065		16	8	12.00	1.366-105.416	0.025	
	CA19.9	Q1	19	6	ref	ref	ref	0.029	21	4	ref	ref	ref	0.074
		Q2	21	4	0.60	0.147-2.469	0.482		23	2	0.46	0.076-2.755	0.393	
		Q3	13	12	2.92	0.874-9.778	0.082		19	6	1.66	0.405-6.785	0.482	
		Q4	14	11	2.49	0.741-8.351	0.140		17	8	2.47	0.634-9.626	0.192	

Table 3

ROC	AUC	SE	95%CI	Sensitivity	95%CI	Specificity	95%CI	Difference AUC	SE	*p*
CA19-9	0.740	0.05	0.642-0.839	0.714	0.567-0.834	0.76	0.618-0.869	Ref	Ref	Ref
E2	0.778	0.05	0.684-0.872	0.735	0.589-0.851	0.78	0.640-0.885	0.04	0.07	0.594
rs9340799	0.759	0.05	0.669-0.849	0.796	0.657-0.898	0.66	0.512-0.788	0.02	0.07	0.786
rs2234693	0.785	0.04	0.701-0.869	0.898	0.778-0.966	0.62	0.472-0.753	0.04	0.07	0.500
CA19-9*rs9340799	0.812	0.04	0.726-0.899	0.796	0.657-0.898	0.78	0.640-0.885	0.07	0.07	0.283
CA19-9*rs2234693	0.829	0.04	0.745-0.913	0.694	0.546-0.817	0.90	0.782-0.967	0.09	0.07	0.180
rs9340799*rs2234693	0.819	0.04	0.734-0.904	0.816	0.680-0.912	0.76	0.618-0.870	0.08	0.07	0.235
E2*rs9340799	0.836	0.04	0.756-0.915	0.776	0.634-0.882	0.78	0.640-0.885	0.10	0.06	0.140
E2*rs2234693	0.840	0.04	0.763-0.917	0.816	0.680-0.912	0.74	0.597-0.854	0.10	0.06	0.120
CA19-9*E2	0.849	0.04	0.772-0.926	0.714	0.567-0.834	0.90	0.782-0.967	0.11	0.06	0.089
CA19-9*rs9340799*rs2234693	0.856	0.04	0.780-0.931	0.837	0.703-0.927	0.82	0.686-0.914	0.12	0.06	0.070
E2*rs9340799*rs2234693	0.876	0.03	0.808-0.943	0.816	0.680-0.912	0.80	0.663-0.900	0.14	0.06	0.027
CA19-9*E2*rs9340799	0.890	0.03	0.829-0.951	0.837	0.703-0.927	0.78	0.640-0.885	0.15	0.06	0.012
CA19-9*E2*rs2234693	0.895	0.03	0.835-0.955	0.714	0.567-0.834	0.94	0.835-0.987	0.15	0.06	0.009
E2*CA19-9*rs9340799*rs2234693	0.913	0.03	0.861-0.966	0.918	0.804-0.977	0.74	0.597-0.854	0.17	0.06	0.002

Figure 1

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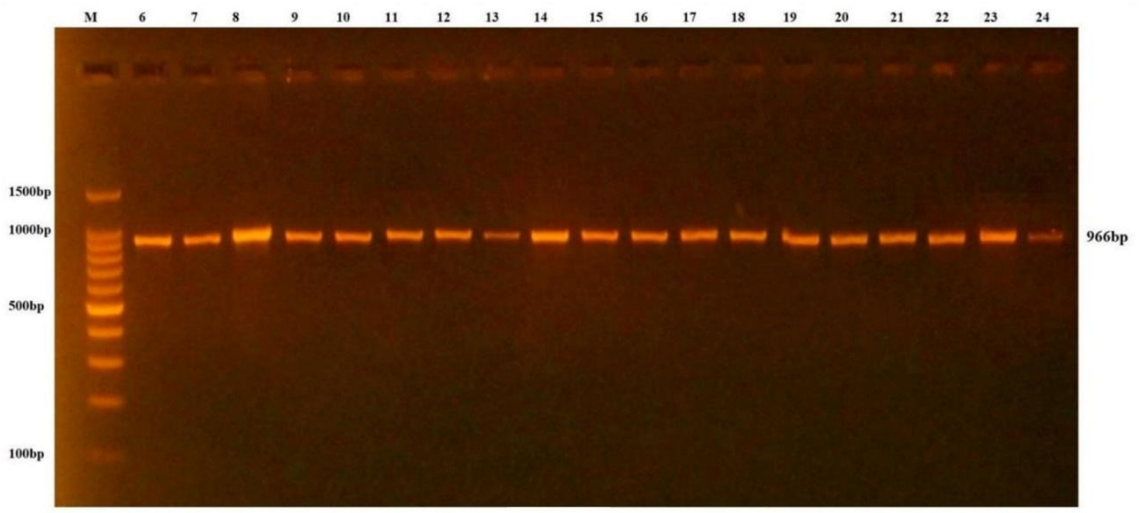

Figure 2

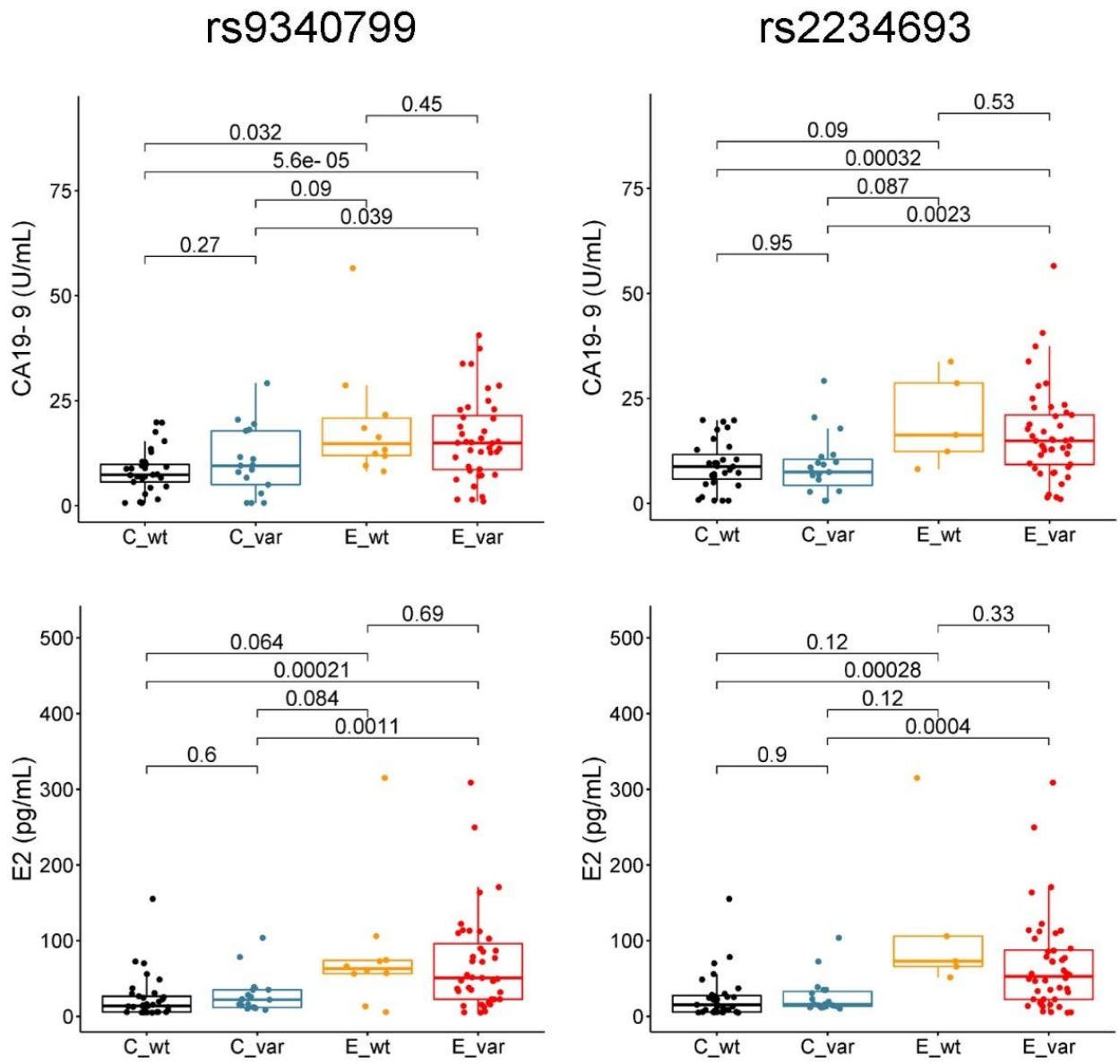

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Figure 3