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Comprehensive Insights into the Genomic and Mutational Landscape of Endometriosis: Translational Perspectives for Advanced Therapeutics

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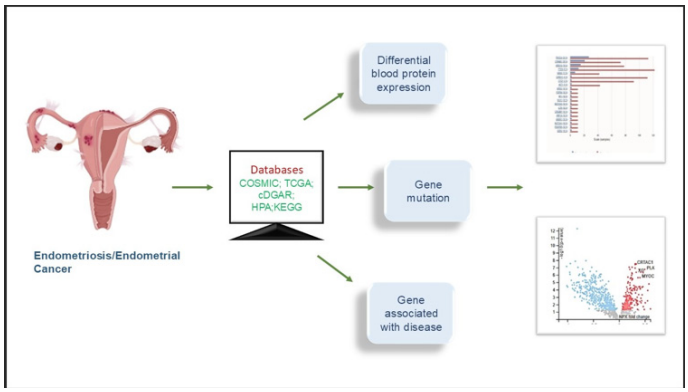
Graphical abstract



Abstract

Background: The growing incidences of endometriosis, endometrial cancer, and associated pathologies, combined with their poor prognosis and stagnant survival outcomes, point to the insufficient understanding of their aetiology and pathophysiology. This critical knowledge gap of genomic alterations and molecular subtypes has limited the development of effective targeted therapeutic strategies.

Objective: This study aims to identify potential genomic features (dysregulated genes, pathways, and non-coding RNAs) and molecular alterations (mutations, alternations, and copy number variations) that can be targeted to manage endometriosis, endometrial cancer, and associated pathologies.

Methodology: Herein, we have adopted and undertaken an integrated computational biology approach to identify mutations in *PTEN*, *PIK3CA*, *TP53*, *KRAS*, *CTNNB1,* and *ARID1A.* Furthermore, gene-to-disease association in endometrial cancer and genes related to mismatch repair were also predicted.

Results: Mutations in *PIK3CA, CTNNB1, ARID1A, PTEN, KRAS,* and *TP53* were found to be most evident. Gene-to-disease association in endometrial cancer revealed the contribution of *CDH1, MLH3, MSH3, MSH6, PTEN* and was regulated mainly by transcription factors such as *STAT3, NFKB1, RELA, AR, MTA1,* and *TFAP2A*. Genes related to mismatch repair were predicted to be significantly enriched in KEGG pathway analysis, underlining the crucial role of oxidative stress and inflammation in disease pathogenesis, which also suggests targeting ROS-mediated signaling and proinflammatory pathways could be the most relevant therapies for the treatment of suffering patients.

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Conclusion: We believe that the current work would make a significant contribution to molecular-level understanding and would provide opportunities to develop targeted therapies for managing a range of recurrent endometrial pathologies and malignancies.

Introduction

Endometriosis is a prevalent gynecological condition that affects a significant proportion (5-10%) of reproductive women [1]. The association between chronic inflammation and the development and progression of endometriosis has been extensively documented. This connection is mainly attributed to the release of proinflammatory cytokines, which stimulate the proliferation of peritoneal macrophages and mesothelial cells [2]. Moreover, numerous empirical findings have established a correlation between endometriosis and increased 17-estradiol signaling within ectopic tissue. Findings indicate that upregulation of P450 aromatase (CYP19A1) in endometriotic tissue leads to heightened synthesis of 17-estradiol locally, thereby facilitating the proliferation of ectopic lesions [3]. Endometrial Cancer (EC) is the most common gynecological malignancy worldwide [4]. Several factors, such as obesity, Polycystic Ovarian Syndrome (PCOS), anovulation, estrogen-only hormone replacement therapy, and tamoxifen use, contribute to elevated levels of unopposed estrogen exposure. These factors have been linked to the development of EC [5,6]. The exact mechanisms by which prolonged estrogen exposure leads to endometrial cancer remain unclear. However, it is hypothesized that extended estrogen stimulation may increase the expression of genes related to cell proliferation and inflammation, thereby promoting DNA damage [7]. Endometriosis has been associated with specific histological subtypes of ovarian carcinoma, specifically clear cell and endometrioid carcinoma [8]. This particular manifestation, known as Endometriosis-Associated Ovarian Cancer (EAOC), has distinct etiological features that differentiate it from other ovarian cancer subtypes. Evidence shows that women with endometriosis have roughly a threefold increased risk of developing endometrioid and clear cell subtypes [9]. Patients with these subtypes tend to have a lower cancer stage, distinct histological patterns compared to the general population, predominantly lower-grade endometriosis lesions, and significantly better overall survival rates than other ovarian carcinomas [10]. While the link between endometriosis and specific ovarian cancer subtypes is well established, the association between endometriosis and endometrial cancer is less clear than that with epithelial ovarian adenocarcinoma. Nevertheless, clinical observations suggest that the coexistence of endometrial and ovarian carcinomas is mainly associated with the endometrioid subtype [11,12]. Additionally, many such cases involve endometriosis, indicating a probable correlation between endometriosis and endometrial cancer [13].

Based on the aforementioned descriptions, endometriosis and endometrial cancer appear to exhibit similar etiological pathways, such as estrogen stimulation and chronic inflammation. Consequently, there exists a purported correlation between these two illnesses. In this study, we focused on compiling compelling evidence to establish the association between endometriosis and the likelihood of developing endometrial cancer and other pathologies in the future. This research, which is novel in its approach, aims to fill a significant gap in the current literature. Nevertheless, there is little research exploring the relationship between these two seemingly unrelated but highly relevant pathologies. Therefore, this study has been designed to examine the conjecture that endometriosis may be associated with an elevated susceptibility to the development of endometrial cancer and other pathologies. The correlation between endometriosis, other cancers and pathologies can be ascertained by exploring the gene expression profiles and studying the genomic, epigenomic and mutational landscape by publicly analyzing the datasets available using state-of-the-art machine learning and computational biology approaches.

Materials and methods

Retrieval of the highly mutated gene

The top 20 genes with the highest mutation frequency were identified and predicted using mutation data from the COSMIC (https://cancer.sanger.ac.uk/cosmic) database [14,15]. Out of endometrium tissue samples (n= 5072), the highly mutated genes were predicted from endometriosis samples (n= 72) as histological sections (accessed on 20-Aug-2023, 12:45 PM IST).

Altered blood protein profiles in endometrial cancer

Blood protein levels in the blood of patients with endometrial cancer were evaluated using the Human Disease Blood Atlas (https://www.proteinatlas.org/). A panel of proteins linked to cancer has been identified using a machine-learning-based illness prediction model. The Average Protein Expression (NPX) of all proteins in endometrial cancer relative to all other malignancies serves as the basis for identifying differentially expressed protein panels [15].

Linking genes to diseases

Genes linked to the disease were identified using eDGAR (http://edgar.biocomp.unibo.it/gene_disease_db/index.html), a database that calculates associations based on OMIM, CLINVAR, HUMSAVAR, and others. The eDGAR provides various gene/disease interactions, including enriched KEGG pathways related to disease-associated genes, transcription factors, and interacting partners.

Kaplan-Meier survival analysis

Survival is the time between the primary surgical procedure and the date of death or the most recent follow-up visit. Kaplan-Meier survival analysis was used to investigate the survival differences between the patients' groups (high and low-expressing groups) based on a log-rank p-value. P-values less than 0.05 were used to evaluate statistical significance. The proteomics, transcriptomics, and clinical follow-up data used to produce predictive survival plots were gathered from the TCGA and CPTAC [15]. Patients were divided into the top 50% to calculate Overall Survival (OS). The embedding R packages "survival", "ggplot2", and "survminer" were used to create K-M plots. For genes (*CDH1, MLH3, MSH3, MSH6*, and *PTEN*) whose protein products were discovered to be differentially elevated in endometrial cancer patients' blood samples, survival graphs were created [15].

CDH1, *MLH3*, *MSH3*, *MSH6*, and *PTEN* in Endometriosis, Endometrial Cancer and Associated Pathologies: Comparative analysis

The differential analysis of *CDH1, MLH3, MSH3, MSH6*, and *PTEN* in endometriosis, endometrial cancer, and related pathologies was conducted using proteomics data. For each gene under tumor and normal conditions, Mann-Whitney Wilcoxon

tests with box plots were generated.

Results

COSMIC datasets revealed high frequency of genetic mutations in oncogenes and others

Identification of the most significant mutated genes with considerable mutation frequency was predicted using mutation data from the COSMIC database (https://cancer.sanger.ac.uk/cosmic). Out of endometrium tissue samples (n=5072), the highly mutated genes were predicted from endometriosis samples (n=72) as histological sections (accessed on 20-Aug-2023, 12:45 PM IST). In total, there were 55,331 mutations in all genes associated with endometriosis, endometrial cancer and related pathologies. A high frequency of mutations was observed in several vital oncogenes, for instance, *PIK3CA, CTNNB1, ARID1A, PTEN*, and *KRAS*. The top-20 highly mutated genes are shown in Figure 1A.

The identified DEGs had some tumor suppressor genes, including *PTEN, PIK3R1, TP53, AIRD1A, ATR*, and some oncogenes, such as *PIK3CA, PPP2R1A*, related to the *PI3K/AKT* pathway. High gene mutations in the *RAF-ERK* or *MAPK* pathway are also found, including the *K-RAS* oncogene, *FGFR2*, a tumor suppressor gene. We also found a high percentage of *CTNNB1* gene mutations, an oncogene of the Wnt/β-catenin pathway. Other gene mutations were *CTCF*, a transcription factor acting as a tumor suppressor gene with its role in genome structure and gene regulation, *CDH4* with its role in cell adhesion, cell migration and maintaining tissue integrity, and a somatic *MED12* mutation involved in regulating gene transcription by facilitating communication between transcription factors and RNA polymerase II. Hence, all the identified mutated genes are the potential targets for therapeutics.

Proteins in blood samples of patients suffering from endometriosis, endometrial cancer and related pathologies

The Human Disease Blood Atlas has been used to assess protein levels in the blood of patients with endometrial cancer. An AI-based disease prediction model has been used to identify a panel of proteins associated with cancer. The model has identified the top 10 proteins for predicting endometrial cancer (Figure 1B). The two top proteins for endometrial cancer (PSG1) and (PLAT) are both secreted to the blood, and the origin of tissue expression is relatively heterogeneous, including urothelial and ductal cells, respectively.

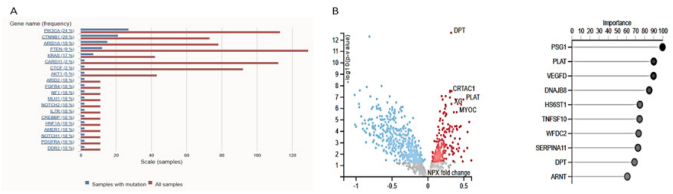

Figure 1: **(A)** Top-20 Most Mutated Genes in Endometriosis, Endometrial Cancer and Associated Pathologies. **(B)** The volcano figure illustrates the relationship between the adjusted p-value and the disparity in average protein expression (NPX) across all proteins in endometrial cancer relative to other types of cancer. The lollipop plot visually represents the ten most significant proteins derived from the cancer prediction model, displaying their respective relevance ratings on a scale of 0 to 100.

Missense non-synonymous substitutions were the most common genetic mutations/alterations in genes associated with endometriosis, endometrial cancer and related pathologies

We found that genes undergo several types of mutations, such as missense, nonsense, synonymous substitutions, in-frame, frameshift insertions, deletions, complex mutations and others, to cause pathogenesis and attain a diseased state. Regarding endometriosis, endometrial cancer, and other associated pathologies, we predicted a significant number of mutations and genetic alterations in the genes associated with these conditions. In brief, most of the alterations were of missense nature, accounting for 41% of all, followed by nonsense, frameshift insertion and deletions. In-frame deletion and insertion were the lowest of all mutations/alterations. There was a considerable percentage of synonymous substitutions as well. A pie-chart diagram that displays different categories of mutations/modifications along with their percentage stake in the genes associated with endometriosis, endometrial cancer and other associated pathologies (Figure 2).

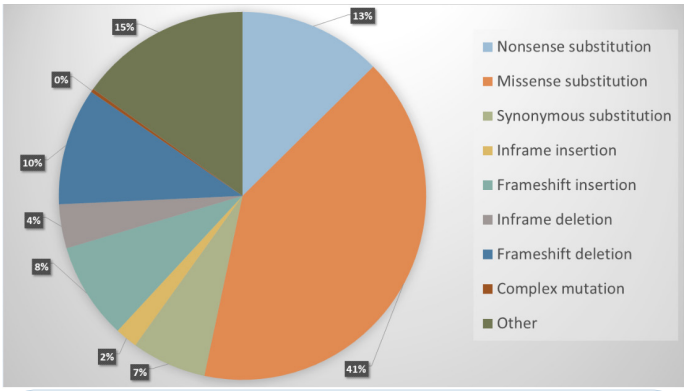

Figure 2: Quantitative description of mutations in endometriosis, Endometrial cancer and associated pathologies.

Gene-disease relationship showed a tumor-suppressor gene *pten* associated with endometriosis, endometrial cancer and related pathologies

Many diseases are thought to be related because they all share one or more genes. The goal of disorder-specific therapeutic interface approaches is to identify the genetic component of disease. Using the eDGAR database, we analyzed the association of these DEGs with specific diseases. We listed the DEGs along with their cytogenetic bands and other associated diseases in Table 1. We found that CDH1 is linked to ovarian, prostate, gastric, and breast cancer; MLH3 is associated with colorectal cancer and hereditary nonpolyposis; MSH6 is connected to mismatch repair cancer syndrome and hereditary nonpolyposis; PTEN is linked to various cancers, as well as VACTERL association with hydrocephalus, macrocephaly/autism syndrome, susceptibility to familial meningioma, Cowden disease, and Bannayan-Riley-Ruvalcaba syndrome.

Then, again, using the eDGAR database, we were able to uncover topologically credible Transcription Factors (TFs) that bind to our identified DEGs in endometriosis. We have listed the associated TFs with respective DEGs in Table 2. *PTEN* and *CDH1* were found to be related to several transcription factors such as STAT3, NF-κB, RELA, MTA1, AR, and TFAP2A. We queried the STRING database to study the interactions among identified DEGs. We found that all DEGs were interacting with each other directly. The summary of these shared interactions based on the STRING Database is listed in Table 3.

Table 1: Gene disease association of the endometrial cancer obtained from the OMIM database and others.

Gene	Reference Database	Cytogenetic Band	Other Associated Diseases
CDH1	OMIM – 608089	16q22.1	Ovarian Cancer Prostate Cancer Gastric Cancer Breast Cancer
MLH3	OMIM – 608089	14q24.3	Colorectal Cancer Hereditary Nonpolyposis
MSH3	OMIM – 608089	5q14.1	-
MSH6	OMIM – 608089	2p16.3	Mismatch Repair Cancer Syndrome Hereditary Nonpolyposis
PTEN	OMIM - 608089, HUMSAVAR	10q23.31	Vacterl Association with Hydrocephalus Head and Neck Squamous Cell Carcinoma Cutaneous Malignant Myeloma Prostate Cancer Glioma Macrocephaly/Autism Syndrome Susceptibility to Familial Meningioma Cowden Disease Bannayan-Riley-Ruvalcaba Syndrome

To clarify the functions of these DEGs, we first examined the associated biological processes and KEGG pathways in TCGA datasets. The most significantly enriched KEGG terms related to biological processes are shown in Table 4. All the DEGs were grouped into five major gene functional categories. The most enriched KEGG pathway was "mismatch repair" (p<0.000), involving three key DNA mismatch repair genes: *MSH3, MSH6, and MLH3*. Additionally, four other KEGG terms were significantly enriched with a p-value<0.05 (Table 4). KEGG enrichment analysis indicated that the identified mutated genes, such as *MSH3, MSH6, MLH3, PTEN,* and *CDH1,* are likely involved in mismatch repair, endometrial cancer, melanoma, colorectal cancer, and pathways in cancer progression (Table 4).

Table 2: Transcription factors associated with genes involved in endometrial cancer.

Transcription Factor	Genes Associated	Gene Regulated by TF
STAT3	*PTEN, CDH1*	No
NFKB1	*PTEN, CDH1*	No
RELA	*PTEN, CDH1*	No
MTA1	*PTEN, CDH1*	No
AR	*PTEN, CDH1*	No
TFAP2A	*PTEN, CDH1*	No

Table 3: Interaction among genes associated with endometrial cancer and the summary of the shared interacting partners based on the STRING database.

Gene1	Gene 2	Interaction	Interaction Mode	No. of Shared Interactions	Shared Interacting Partners
CDH1	PTEN	Direct	Activation, Binding	43	AR, FOXM1, SNAI1, VCL, SMAD4, CAV1, CDX1, EGFR, HDAC9, FOS, IGF2BP1, DLG1, NRP2, SUMO1, CCND1, PIK3CA, MTA1, SMAD3, TGFB1, TGM2, TBX3, SMARCA4, IL8, RPS6KB1, JUN, TP53, AKT1, SRC, MTA3, FOXO3, RPTOR, NOTCH1, BCL2, CDC6, IGF1R, EZH2, IGF2, PIK3R1, CDX2, UBC, LEP, PPARG, RAC3
MSH3	MLH3	Direct	Binding	15	ERCC1, POLD1, PMS2, PCNA, WRN, MSH2, ERCC4, PMS1, POLE, RPA1, EXO1, MSH6, RECQL, RAD51, MLH1
MSH3	MSH6	Direct	Binding	34	POLE4, PCNA, POLE3, FANCM, XPC, ERCC8, POLD1, RAD52, POLE, MSH2, RAD51, PMS1, SWSAP1, RECQL, CHRAC1, RAD51D, ERCC1, RAD23B, ZSWIM7, ALDH18A1, XRCC6BP1, EXO1, RAD51B, BRCA1, PMS2, WRN, XRCC4, XRCC6, ERCC4, XRCC5, OGG1, POLE2, MLH1, MLH3
MLH3	MSH6	Direct	Binding	15	ERCC1, POLD1, MSH3, PCNA, WRN, MSH2, PMS1, ERCC4, BLM, POLE, PMS2, EXO1, RECQL, MLH1, RAD51
CDH1	MSH6	No	-	2	UBC, TP53
PTEN	MSH6	No	-	3	SP1, UBC, TP53

Table 4: KEGG pathway analysis of the genes associated with endometrial cancer.

KEGG Term	KEGG Term ID	IC	p-value	Genes
Mismatch Repair	Hsa03430	8.07	0.00	*MSH3, MSH6, MLH3*
Endometrial Cancer	Hsa05213	6.81	0.033	*PTEN, CDH1*
Melanoma	Hsa05218	6.56	0.047	*PTEN, CDH1*
Colorectal Cancer	Hsa05210	6.52	0.049	*MSH3, MSH6*
Pathways in Cancer	Hsa05200	3.98	0.003	*MSH6, MSH3, PTEN, CDH1*

Comparison of DEGs in normal and endometrial tumour tissues and survival analysis

The prognostic effects of the four DEGs were evaluated. To further demonstrate the impact of gene mutations on the progression of endometriosis in cancer, we performed survival analysis on these four mutant genes. The overall survival (OS of patients with endometriosis was analyzed based on low and high expression levels of each gene. The prognostic evaluation showed that the DEGs, namely *CDH1, MSH3, MSH6,* and *PTEN*, were statistically significant in predicting endometrial cancer outcomes, with hazard ratios of 0.8846, 0.7364, 1.071, and 0.6959, respectively (Figure 3A). This indicates a low-risk association for CDH1, MSH3, and PTEN, and a high-risk association for MSH6 with endometrial cancer.

The TCGA database for endometriosis samples (n=72) as a histological section (accessed on August 20, 2023, 12:45 PM IST). The expressions of the DEGs (CDH1, MSH3, MSH6, and PTEN) in different groups were studied, and results showed that most of the DEGs were expressed significantly in metastatic tumor samples compared to normal samples (Figure 3B). We found that these four differentially expressed genes and their protein product, CDH1, MSH3, MSH6, and PTEN, explain the association of endometriosis, endometrial cancer, and other

related pathologies. Of these four, CDH1 and MSH3 are upregulated, while PTEN is downregulated; MSH6 showed no significant change in endometriosis, endometrial cancer, and related diseases.

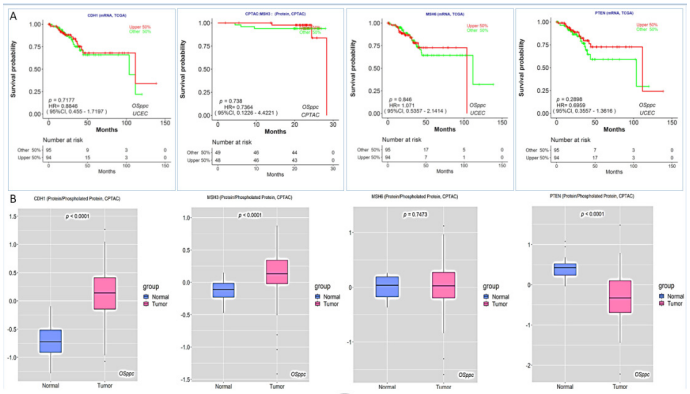

Figure 3: (A) Kaplan-Meier Survival Plots of Genes Differentially Upregulated in Blood. **(B)** Box-plot Analysis (Differential Analysis) of the Genes Associated with Endometrial Cancer. The graphs are generated by Mann-Whitney Wilcoxon test in R and R package "ggplot2".

Discussion

In this study, we identified endometriosis-related DEGs using TCGA datasets, proteins present in the blood, specific disease associations of DEGs, transcription factors linked to these genes, interactions among these DEGs, pathways, prognostic value, and validation of the identified genes. Our findings suggest that individuals diagnosed with endometriosis have an increased risk of developing endometrial cancer. Although classified as a benign disease, substantial evidence supports the idea that endometriosis might be considered a neoplastic process. This is demonstrated by research showing an increased susceptibility to certain subtypes of epithelial ovarian cancer in individuals with endometriosis, as well as molecular similarities between endometriosis and cancer. Estimates indicate that ovarian endometriosis has a malignant transformation rate of approximately 0.7% and a 4.2-fold increased risk of ovarian cancer. Additionally, a study by Zaino et al. (2013) found endometriosis in about 30% of cases with concurrent endometrioid-type endometrial and ovarian malignancies.

In recent years, bioinformatics analysis has been broadly used by researchers to explore novel biomarkers and identify molecular connections between complex diseases, e.g., PCOS, endometrial, ovarian cancers, diabetes and others [16-18]. The top-20 identified DEGs in endometriosis including *PIK3CA, CTNNB1, ARID1A, PTEN*, *KRAS, PIK3R1, TP53, ATR, PPP2R1A, FGFR2, CTCF, CDH1, MED12* are reported to be differentially mutated and shown to be interacting with each other in the development, and progression of high-grade endometrial carcinoma, endometriosis, nonendometrioid endometrial cancers, specific subgroups tumours, clear cell carcinomas of the ovary and uterine serous carcinomas, and breast cancer [19-26]. These mutations can be majorly categorised into mismatch repair gene mutations, microsatellite instability, and somatic driver mutations in endometrial carcinogenesis [27-29]. The identified top key blood proteins including PLAT, TNSF10, PSG1, ARNT, SERPINA1, VEGFD, DNAJB8, DPT, HST6ST1, WFDC2, IL-10, ST2, and DKK-4 are reported to play key roles in cell migration, tissue remodeling, inflammation, MAPK8/JNK, caspase 8, and caspase 3 activation, angiogenesis, metastasis, extracellular matrix remodeling in endometriosis, endometrial cancer and related pathologies, suggesting potential therapeutic targets and insights into their functional associations [30-34].

Our identified DEGs were associated with several cancer risks, including prostate, colorectal, gastric, breast, and ovarian cancer [35-37]. These genes were found to be interacting with each other as well in endometrial pathologies, as reported by Lee and Li [38]. The downregulation of *PTEN* was associated with the expression of *CDH1* and *CDH2* genes, and Chen, Li, Yang, Lu and Hu [39] found a positive correlation between *NDRG1* upregulation and *PTEN* down-regulation in endometrial carcinoma. We have found that the identified DEGs play a vital role in mismatch repair mechanisms and the progression of tumours in cells. Previous studies suggest that MSH3 and MSH6 may be implicated in endometrial tumorigenesis and DNA mismatch repair [40], while CDH1 could play a role in endometriosis development, with genetic polymorphisms possibly influencing endometrial carcinoma susceptibility among specific populations [41]. Finally, the DEGs (*CDH1, MSH3, MSH6,* and *PTEN*) were put to prognostic evaluation, and their differential expression was validated, indicating their therapeutic target potential. Figure 4 depicts the contribution of these genes implicated in the development and progression of endometriosis, EC, and related pathologies.

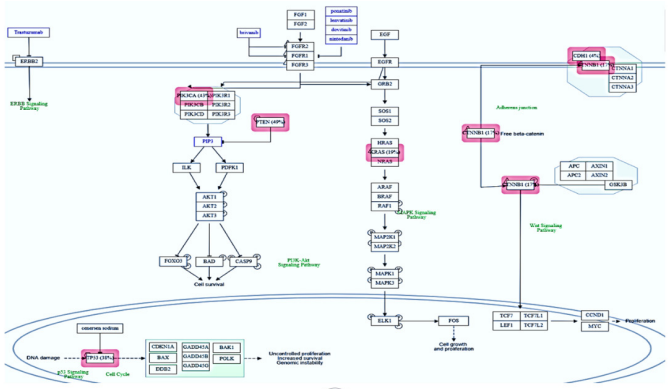

Figure 4: Model figure displaying contribution of genes explored in the current study and implicated in development of endometriosis, endometrial cancer and associated pathologies.

While there has been considerable research conducted on the relationship between endometriosis and ovarian cancer, there is a notable lack of studies investigating the correlation between endometriosis and endometrial cancer. The findings of our research diverge from the information presented in the published articles. Potential factors for these differences include underdiagnosis of endometriosis, variations in study design, and differences in ethnic groups and demographics among study populations.

The precise biological pathways behind the connection between these two illnesses remain unknown. Nonetheless, two potential processes that are believed to be common are estrogen stimulation and chronic inflammation. Endometriosis appears to be estrogen-dependent, responding to estrogen-induced signaling by increasing local estrogen production, partly due to aromatase cytochrome P450 upregulation [42,43]. Additionally, there's evidence of an abnormal overexpression of Estrogen Receptor β (ERβ) due to a methylation deficiency in the ERβ promoter, which suppresses Estrogen α (ERα) production. This altered ERβ-to-ERα ratio has been observed in endometrial carcinoma and may contribute to its progression. Furthermore, the high ERβ-to-ERα ratio in endometriosis stromal cells could lead to reduced progesterone receptor expression, potentially

causing progesterone resistance and reduced efficacy of progesterone treatments for both endometriosis and endometrial cancer. Further research is needed to fully elucidate these mechanisms [44,45].

Another potential pathway linking endometriosis and endometrial cancer involves chronic inflammation. Endometriosis tissue has been associated with elevated production of prostaglandins, cytokines, and chemokines. Both endometriosis and endometrial cancer patients exhibit increased expression of Cyclooxygenase 2 (COX-2), an enzyme crucial for the production of Prostaglandin E2 (PGE2). PGE2 is implicated in early carcinogenesis, promoting tumor growth by stimulating cell proliferation and angiogenesis while suppressing local immune responses. This chronic inflammation pathway may contribute to the development and progression of endometrial cancer in individuals with endometriosis. The potential link between estrogen stimulation and chronic inflammation is intertwined, driven by interactions involving COX-2, Estrogen Receptors (ER), and aromatase. Research has shown significant aromatase expression in endometrial cancer patients, while COX-2 is prevalent in estrogen receptor-positive cases. These findings suggest a synergistic impact, highlighting the interconnection between endometriosis and endometrial cancer, mediated through chronic inflammation and estrogen-related pathways.

The strength of our study lies in using a representative population-based database. However, it has limitations, including potential biases from ICD code-based patient selection, missing data on key factors like parity and hormone use, and the inherent constraints of retrospective cohort studies. To establish a temporal link between endometriosis and endometrial cancer, further large-scale prospective cohort studies are needed.

Conclusion

In conclusion, the results of this investigation revealed a heightened correlation between endometriosis and endometrial cancer. Through a series of comprehensive analysis of bioinformatics, we could roughly screen the mutated genes, including *CDH1, MSH3, MSH6*, and *PTEN* and pathways related to the association of endometriosis, EC. They might significantly improve the prognosis of EC. However, these key genes and pathways still need to be tested in a large quantity of clinical specimens, and need to be analyzed and validated in combination with the individual conditions of clinical patients in order to finally determine the biological targets that were most beneficial to endometrial cancer. The etiology of endometriosis and endometrial cancer is intricate, and multiple factors influence the etiopathogenesis of both conditions. However, it is possible that there is an undiscovered shared connection between the two disorders. The postulated mechanisms of linkage may encompass both the activation of estrogen and the presence of chronic inflammation. Nevertheless, further research is needed to comprehensively elucidate the precise mechanisms underlying the interplay between these two illnesses.

Author declarations

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Author contributions

The authors declare that all data were generated in-house and that no paper mill was used.

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Conflict of interest

The authors declare no potential conflict of interest that could have appeared to influence the work reported in this paper.

Availability of data and material: No data was generated during the study of the literature review.

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