Archives of Current Medical Research
Arch Curr Med Res 2026; 7(1): 244-254

Received: 28 November 2025
Revised: 12 January 2026
Accepted: 15 January 2026
DOI: 10.47482/acmr.1831809

ORIGINAL ARTICLE

Comparison of Molecular Alterations and Survival Analysis in Uterine Endometrioid Carcinomas and Serous Carcinomas: An *In Silico* Study

Zeynep Sağnak Yılmaz[1,2]

1 Karadeniz Technical University, Faculty of Medicine, Department of Pathology, Trabzon, Türkiye
2 Dokuz Eylul University, Graduate School of Health Sciences, Department of Molecular Pathology, Izmir, Türkiye

Abstract

Background: Endometrioid and serous endometrial carcinomas exhibit distinct molecular, epigenetic, and clinical characteristics. This study aimed to compare mutations, survival, and biological pathway analysis between these two subtypes using an *in silico* approach.

Methods: Endometrioid (n=399) and serous (n=109) carcinomas from The Cancer Genome Atlas Uterine Corpus Endometrial Carcinoma (PanCancer Atlas) dataset were analyzed via cBioPortal. Genomic mutations, mRNA expression levels, MSI (microsatellite instability) sensor scores and overall survival were compared. Differentially mutated genes were identified. P< 0.0.5 and q< 0.05 were considered statistically significant. Pathway enrichment analyses were performed using g:Profiler and WebGestalt.

Results: 662 genomic mutations and 10757 mRNA expression levels showed significant differences. In endometrioid carcinomas, *PTEN, ARID1A, CTNNB1, CTCF, KMT2B, KRAS*, *NEB*, and *RNF43* were the most significantly mutated genes; whereas in serous carcinomas, *TP53* and *PPP2R1A* were the predominantly mutated genes (p<0.001 and q<0.001). The MSI-High rate was higher in endometrioid tumors (31.6% vs. 0.9%, p = 7.215e-3). The median survival was 102.83 months in endometrioid tumors and 63.91 months in serous tumors (p=5.28e-8). Pathway analyses revealed enrichments in proteasome, mismatch repair, DNA replication, spliceosome, base excision repair, as well as developmental and metabolic pathways.

Conclusion: It was observed that endometrioid tumors develop through gradual genetic disruptions within the PI3K–PTEN–AKT–mTOR and WNT/β-catenin axes, whereas serous tumors develop through high genomic instability driven by *TP53* mutations, and DNA repair pathway defects. This molecular distinction explains the more aggressive clinical behavior and lower survival rates of serous carcinomas, emphasizing the importance of specific diagnostic and therapeutic strategies.

Keywords: Endometrial carcinoma, bioinformatics, differentially expressed genes, pathway enrichment analysis.

Corresponding Author:
Zeynep Sağnak Yılmaz, MD, PhD, Karadeniz Technical University Faculty of Medicine, Pathology Department
Kalkinma Mah Farabi Hastanesi Tıbbi Patoloji AD 61080 Trabzon/ Türkiye
Dokuz Eylül University Graduate School of Health Sciences, Department of Molecular Pathology, İnciraltı, 35330, Balçova/ İzmir/ Türkiye
Email: zeynep.sagnak@hotmail.com.tr

INTRODUCTION

Endometrial cancer is the most common neoplasm among gynecological malignancies (1). According to The Cancer Genome Atlas (TCGA), endometrial carcinomas are molecularly classified into four subgroups: *POLE* mutant (ultramutated), microsatellite instability (MSI) (hypermutated), copy number low (endometrioid), and copy number high (serous-like) (2). Endometrioid carcinomas constitute approximately 85% of endometrial carcinomas, while serous carcinomas account for approximately 3-10% (3). *PTEN* inactivation is the primary molecular alteration effective in the development of endometrioid carcinomas, whereas *TP53* inactivation has been identified as a key driver in the development of most serous carcinomas and some high-grade endometrioid carcinomas. In contrast to grade 1 and 2 endometrioid tumors where *TP53* mutations are rare, approximately 50% of grade 3 tumors exhibit *TP53* mutations (4). Uterine serous carcinomas exhibited frequent *TP53* mutations, extensive copy number alterations, and minimal DNA methylation changes. In contrast, most uterine endometrioid carcinomas exhibited frequent mutations in *PTEN, CTNNB1, PIK3CA, PIK3R1, ARID1A*, and *KRAS*, with minimal copy number alterations or *TP53* mutations.

Generally, the endometrioid histotype is characterized by mutations in the PI3K–PTEN–AKT–mTOR, RAS–MEK–ERK, and canonical WNT–β-catenin pathways, as well as MSI and *POLE* mutations (1). MSI is present in approximately 30% of endometrioid carcinomas and is associated with a hypermutated phenotype (5). Serous carcinomas are relatively mutation-silent compared to most endometrioid carcinomas but have higher rates of copy number alterations (6). Other molecular changes involved in the pathogenesis of serous carcinoma include somatic mutations in *PPP2R1A, FBXW7, SPOP, CHD4*, and *TAF1*, as well as amplification of *ERBB2*, *MYC*, and *CCNE1* (1). The aim of our study is to reveal *in silico* the pathways associated with molecular alterations in the development of endometrioid and serous carcinomas, which exhibit different genetic profiles, and to provide a new perspective regarding targeted therapy.

MATERIALS AND METHODS

Data Set

The molecular data in the study were obtained from the public bioinformatics database CbioPortal for Cancer genomics (CbioPortal) website (https://www.cbioportal.org/ accessed on 27 November 2025) (7). TCGA, Uterine Corpus Endometrial Carcinoma (PanCancer Atlas) dataset, including uterine endometriod carcinoma cases (n=399) and uterine serous carcinoma cases (n=109) was used.

Identification of Differentially Mutated Genes

Genomic differences between the two groups (endometriod carcinoma and serous carcinoma) were analysed in terms of 'genomic alterations' and 'mRNA expression' using the Cbioportal database. All statistical analyses were performed through the CbioPortal. The threshold for statistical significance was set at $p < 0.05$ and $q < 0.05$. Differentially mutated genes and differentially expressed genes (DEGs) between groups were identified.

MSIsensor Score and Survival Analysis

MSIsensor scores were examined using the cBioPortal database, and a comparison was made between the two groups. Values of $p < 0.05$ and $q < 0.05$ were considered statistically significant. The MSIsensor Score is a numerical score that bioinformatically measures the MSI level of a tumor. A score close to 0 indicates stability, while a high score indicates MSI-High (MSI-H), implying genomic instability due to mismatch repair (MMR) deficiency. In cBioPortal, based on the MSISensor Score, cases are divided into three groups: "MSISensor>10 = MSI-H, <4 = Microsatellite Stable (MSS), >4-10 = MSI-Low (MSI-L)". Additionally, we investigated survival analysis for endometrioid and serous carcinoma groups and performed comparisons between the groups through cBioPortal.

Pathway Analysis

G:Profiler, a public bioinformatics database, was utilized to identify pathways associated with the 662 differentially mutated genes between the two groups (https://biit.cs.ut.ee/gprofiler/gost / accessed on 27 November 2025) (8). Pathways associated with mRNA DEGs were accessed through the WEB-based Gene SeT Analysis Toolkit (WebGestalt) (https://www.webgestalt.org / accessed on 27 November 2025), a public bioinformatics database (9). Over-representation analysis (ORA) was used for enrichment analysis. Biological Process (BP) pathways were

accessed through Gene Ontology (GO). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was also performed. 'Genome' was selected as the reference set. Results with $p < 0.05$ and a false discovery rate (FDR) ≤ 0.05 were considered statistically significant.

RESULTS

The Most Common Mutations

The most frequently detected mutations in any group and their rates are shown in Table 1. *PTEN, ARID1A, PIK3CA, TTN, PIK3R1, CTNNB1, KMT2D*, and *CTCF* mutations were found most frequently in the endometrioid carcinomas (*PTEN*: 82%, *ARID1A*: 54.4%, *PIK3CA*: 53.6%, *TTN*: 43.8%, *PIK3R*1: 36.3%, *CTNNB*1: 33.5%, *KMT2D*: 32%, *CTCF*: 31.4%). *TP53* and *PPP2R1A* mutations were most frequently observed in the serous carcinomas (*TP53*: 88%, *PPP2R1A*: 38%). There was a statistically significant difference in these genes (except *PIK3CA*) between the two groups ($p < 0.05$, $q < 0.05$).

Differentially Mutated Genes

Significant genomic mutations were detected in 662 genes between uterine endometrioid carcinomas and serous carcinomas (Supplementary Table S1). 660 genes were enriched in endometrioid carcinomas, and 2 genes were enriched in serous carcinomas. The 10 most significant genes were as follows: Genes were enriched in endometrioid carcinomas: *PTEN* (p= 4.18e-44, q= 7.99e-40), *ARID1A* (p= 1.36e-19, q= 8.65e-16), *CTNNB1* (p= 2.06e-15, q= 9.82e-12), *CTCF* (p= 5.33e-13, q= 2.04e-9, *KMT2B* (p= 1.18e-8, q= 3,228E-02), *KRAS* (p= 1.79e-8, q= 4,272E-02), *NEB* (p= 6.55e-8, q= 1,391E-01), *RNF43* (p= 7.90e-8, q= 1,509E-01), and genes were enriched in serous carcinomas: *TP53* (p= 2.04e-37, q= 1.95e-33), *PPP2R1A* (p= 1.02e-9, q= 3,263E-03) (Table 2).

Differentially Expressed mRNAs

10757 DEGs showed significant difference between endometrioid carcinomas and serous carcinomas (4693 genes

Table 1. The most common gene mutations in uterine endometrioid carcinomas and serous carcinomas

Gene	Endometrioid carcinoma (Number and percentage of mutant cases)	Serous carcinoma (Number and percentage of mutant cases)	*p* value	*q* value
Most commmonly mutated genes in endometrioid carcinomas				
PTEN	318 (82%)	11 (10.2%)	4.18e-44	7.99e-40
ARID1A	211 (54.4%)	9 (8.3%)	1.36e-19	8.65e-16
PIK3CA	208 (53.6%)	40 (37%)	3.193e-3	0.0634
TTN	170 (43.8%)	25 (23.2%)	8.840e-5	0.0137
PIK3R1	141 (36.3%)	12 (11.1%)	1.37e-7	2.377e-4
CTNNB1	130 (33.5%)	1 (0.9%)	2.06e-15	9.82e-12
KMT2D	124 (32%)	11 (10.2%)	2.443e-6	1.944e-3
CTCF	122 (31.4%)	2 (1.9%)	5.33e-13	2.04e-9
Most commonly mutated genes in serous carcinomas				
TP53	83 (21.4%)	95 (88%)	2.04e-37	1.95e-33
PPP2R1A	43 (11.1%)	41 (38%)	1.02e-9	3.263e-03

Table 2. The top 10 differentially expressed genomic alterations between uterine endometrioid carcinomas and serous carcinomas

Gene	Endometrioid carcinoma (Number and percentage of mutant cases)	Serous carcinoma (Number and percentage of mutant cases)	Log2 Ratio	*p* value	*q* value	Enriched in
PTEN	318 (82%)	11 (10.2%)	3.01	4.18e-44	7.99e-40	Endometrioid Carcinoma
TP53	83 (21.4%)	95 (88%)	-2.04	2.04e-37	1.95e-33	Serous Carcinoma
ARID1A	211 (54.4%)	9 (8.3%)	2.71	1.36e-19	8.65e-16	Endometrioid Carcinoma
CTNNB1	130 (33.6%)	1 (0.9%)	5.18	2.06e-15	9.82e-12	Endometrioid Carcinoma
CTCF	122 (31.4%)	2 (1.9%)	4.09	5.33e-13	2.04e-9	Endometrioid Carcinoma
PPP2R1A	43 (11.1%)	41 (38%)	-1.78	1.02e-9	3.263e-03	Serous Carcinoma
KMT2B	104 (26.8%)	4 (3.7%)	2.86	1.18e-8	3.228e-02	Endometrioid Carcinoma
KRAS	95 (24.5%)	3 (2.8%)	3.14	1.79e-8	4.272e-02	Endometrioid Carcinoma
NEB	98 (25.3%)	4 (3.7%)	2.77	6.55e-8	1.391e-01	Endometrioid Carcinoma
RNF43	73 (18.8%)	1 (0.9%)	4.34	7.90e-8	1.509w-01	Endometrioid Carcinoma

with higher expression levels in endometrioid carcinomas, 6064 genes with higher expression levels in serous carcinomas) (Supplementary Table S2). The 10 most significant genes are as follows: *SRARP* (p= 3.30e-57, q= 6.59e-53), *LINC02418* (p= 8.11e-49, q= 8.09e-45), *ELAPOR1* (p= 3.94e-48, q= 2.62e-44), *ERMN* (p= 8.66e-46, q= 2.88e-42), *TFF3* (p= 4.25e-42, q= 9.42e-39) genes had higher expression in endometrioid carcinomas and *WNT7A* (p= 9.12e-47, q= 4.26e-43), *L1CAM* (p= 1.07e-46, q= 4.26e-43), *SLC6A12* (p= 4.55e-45, q= 1.30e-41), *FIGNL2* (p= 3.92e-42, q= 9.42e-39), *LINC0026* (p= 4.75e-42, q= 9.47e-39) genes had higher expression in serous carcinomas.

MSIsensor Score

The MSIsensor score was higher in endometrioid carcinoma cases and lower in serous carcinomas, and a significant difference was detected between the two groups (p = 7.215e-3, q = 0.0147) (Figure 1). Consequently, MSI status differs between subtypes. Among endometrioid carcinomas with an available MSIsensor score (n=398), 247 cases (62.1%) were MSS, 25 (6.3%) were MSI-L, and 126 (31.6%) were MSI-H. In serous carcinomas (n=109), 105 cases (96.3%) were MSS, 3 (2.8%) were MSI-L, and 1 (0.9%) was MSI-H.

Survival

The median survival time was 63.91 months in the serous carcinoma group and 102.83 months in the endometrioid carcinoma group. Overall survival was higher in endometrioid carcinomas (p= 5.28e-8, q= 1.06e-7) (Figure 2). Upon examination of the graph, it is observed that the probability of survival in patients with endometrioid carcinoma remains higher throughout the follow-up period, with the curve remaining quite stable

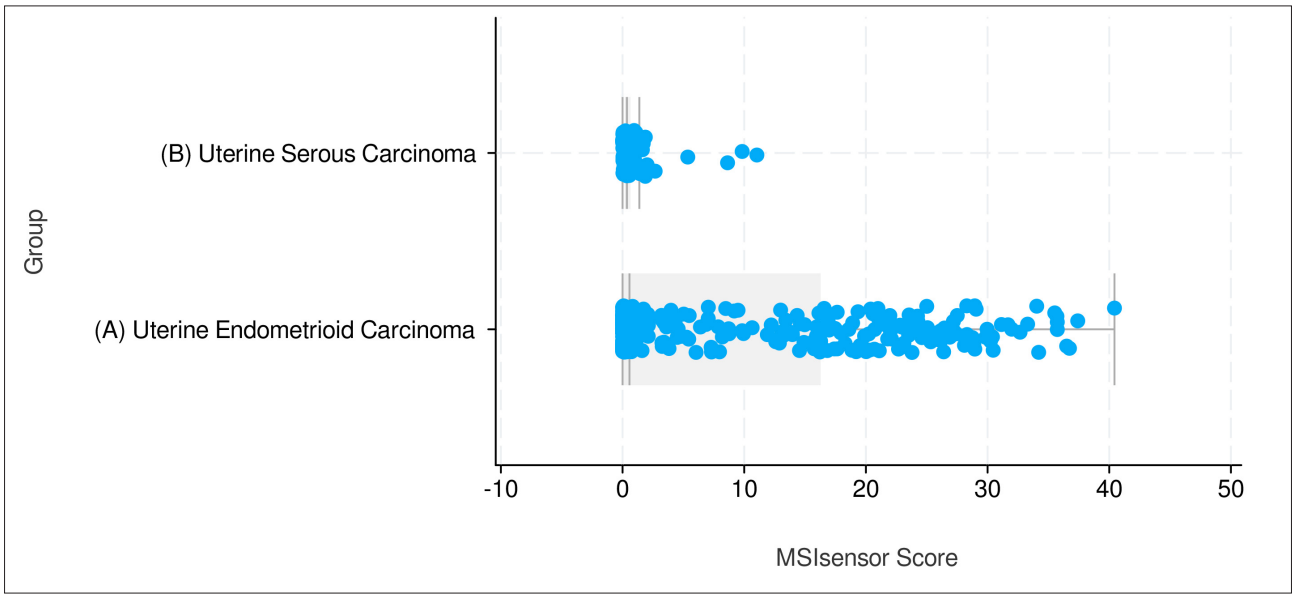


Figure 1: MSIsensor score range in endometrioid carcinoma and serous carcinoma

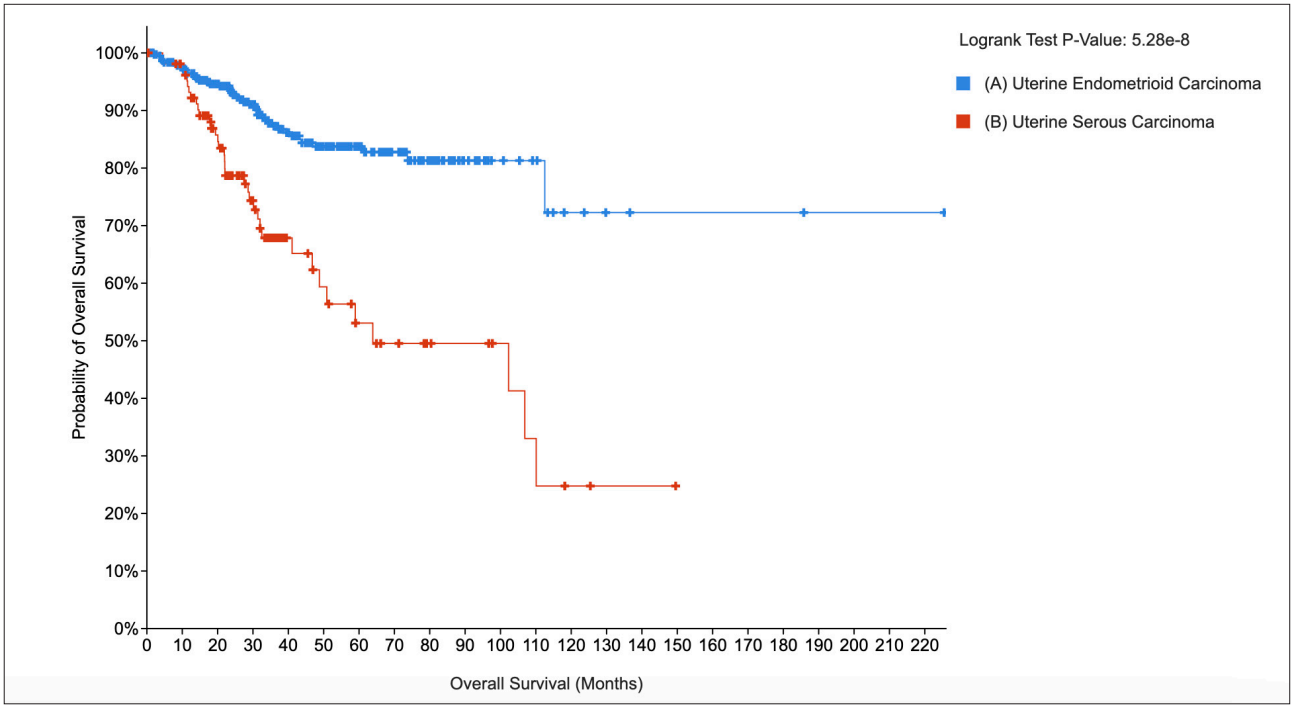
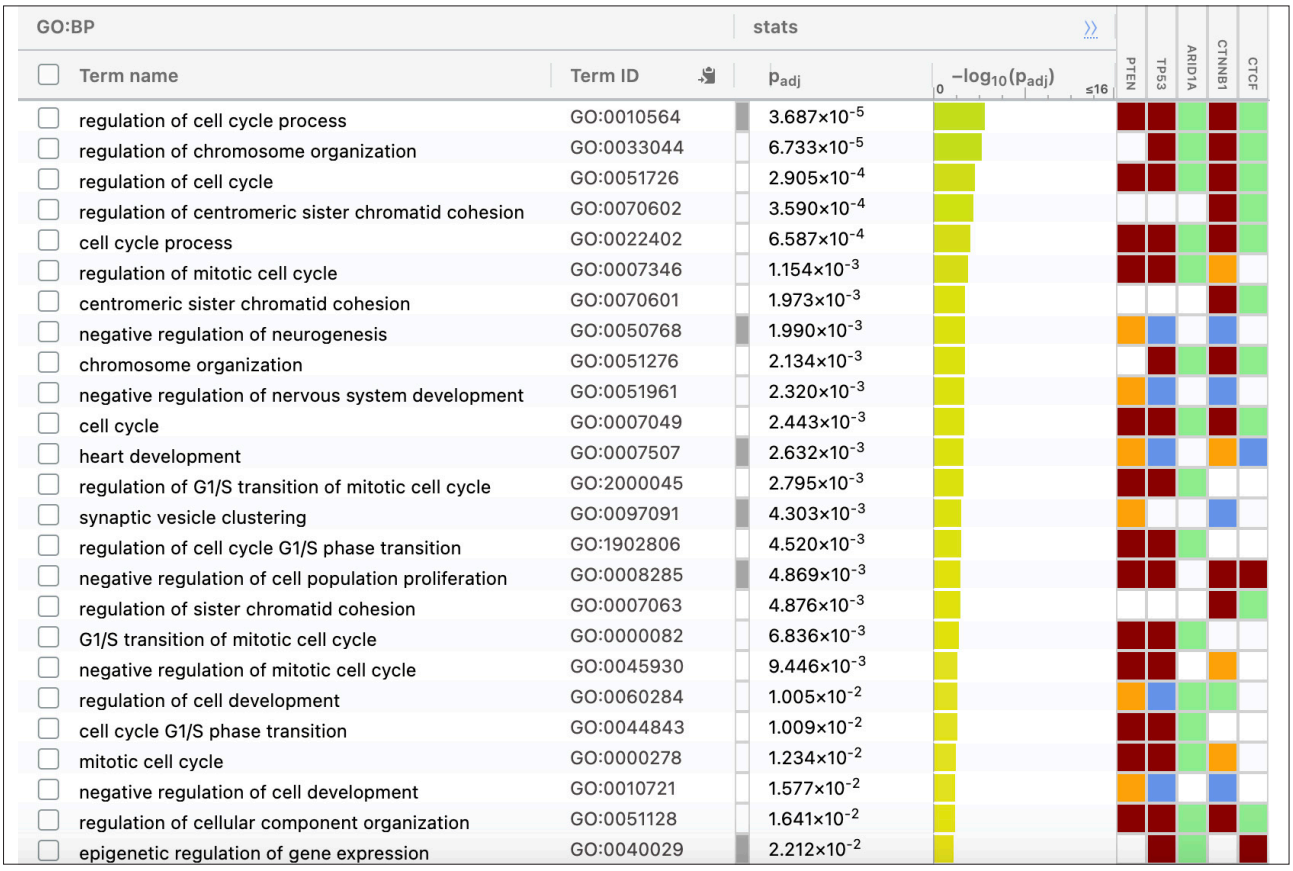


Figure 2: Overall survival (months)

even after the 80th month. In contrast, the overall survival curve for patients with serous carcinoma showed a rapid decline within the first 20–40 months, and the survival probability dropped below 40% after approximately the 60th month. The log-rank test demonstrated that this separation is statistically highly significant.

Pathways

Figure 3 shows the BP in which the differentially mutated genes between endometrioid and serous endometrial carcinomas are enriched. The pathways associated with these genes include regulation of cell cycle, mitotic cell cycle, chromosome organization, regulation of cell



GO:BP		stats	PTEN	TP53	ARID1A	CTNNB1	CTCF
Term name	Term ID	p_{adj}	$-\log_{10}(p_{adj})$ 0 ≤16				
regulation of cell cycle process	GO:0010564	3.687×10^{-5}					
regulation of chromosome organization	GO:0033044	6.733×10^{-5}					
regulation of cell cycle	GO:0051726	2.905×10^{-4}					
regulation of centromeric sister chromatid cohesion	GO:0070602	3.590×10^{-4}					
cell cycle process	GO:0022402	6.587×10^{-4}					
regulation of mitotic cell cycle	GO:0007346	1.154×10^{-3}					
centromeric sister chromatid cohesion	GO:0070601	1.973×10^{-3}					
negative regulation of neurogenesis	GO:0050768	1.990×10^{-3}					
chromosome organization	GO:0051276	2.134×10^{-3}					
negative regulation of nervous system development	GO:0051961	2.320×10^{-3}					
cell cycle	GO:0007049	2.443×10^{-3}					
heart development	GO:0007507	2.632×10^{-3}					
regulation of G1/S transition of mitotic cell cycle	GO:2000045	2.795×10^{-3}					
synaptic vesicle clustering	GO:0097091	4.303×10^{-3}					
regulation of cell cycle G1/S phase transition	GO:1902806	4.520×10^{-3}					
negative regulation of cell population proliferation	GO:0008285	4.869×10^{-3}					
regulation of sister chromatid cohesion	GO:0007063	4.876×10^{-3}					
G1/S transition of mitotic cell cycle	GO:0000082	6.836×10^{-3}					
negative regulation of mitotic cell cycle	GO:0045930	9.446×10^{-3}					
regulation of cell development	GO:0060284	1.005×10^{-2}					
cell cycle G1/S phase transition	GO:0044843	1.009×10^{-2}					
mitotic cell cycle	GO:0000278	1.234×10^{-2}					
negative regulation of cell development	GO:0010721	1.577×10^{-2}					
regulation of cellular component organization	GO:0051128	1.641×10^{-2}					
epigenetic regulation of gene expression	GO:0040029	2.212×10^{-2}					

Figure 3: Gene pathways associated with differentially mutated genes from g:Profiler.

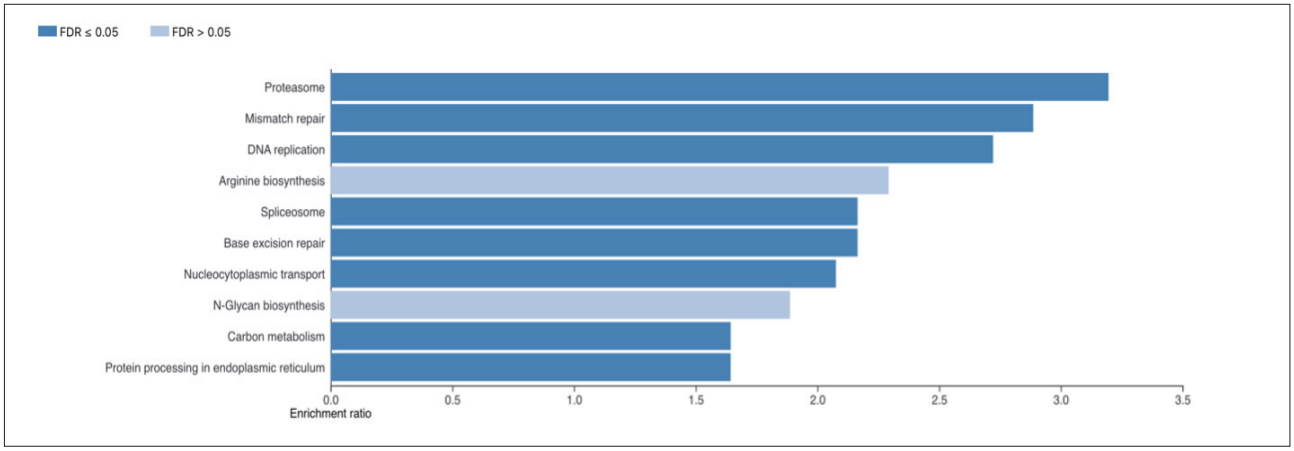


Figure 4: KEGG pathways analysis for mRNA DEGs between endometrioid and serous carcinomas.

development, and cellular component organization. Analysis results reveal that the most dominantly affected pathways in both subtypes are processes directly related to cellular proliferation and genomic stability, such as cell cycle regulation, chromosome organization, centromeric sister chromatid cohesion, and G1/S and mitotic transition control. Overall, these findings indicate that the transcriptomic differences arising in endometrioid and serous carcinomas are concentrated in biological pathways critical for tumor progression, such as cell cycle control, chromosomal integrity, epigenetic regulation, and developmental processes.

KEGG enrichment analysis indicates that DEGs between endometrioid and serous endometrial carcinomas are significantly enriched in pathways associated with essential cellular maintenance mechanisms. According to Figure 4, the highest enrichment rate was observed in the proteasome pathway, followed by mismatch repair and DNA replication. These findings reveal distinct transcriptomic differences between the two subtypes, particularly in protein degradation, DNA repair, and replication processes. Furthermore, pathways related to cellular integrity and metabolic functions, such as the spliceosome, base excision repair, nucleocytoplasmic transport, N-glycan biosynthesis, carbon metabolism, and protein processing in the endoplasmic reticulum, also showed significant enrichment. The results indicate that endometrioid and serous carcinomas exhibit substantial differences not only in gene expression but also in biological pathways.

DISCUSSION

In our *in silico* study, *TP53* and *PPP2R1A* gene mutations were more frequent in serous carcinomas, whereas *PTEN, ARID1A, PIK3CA, TTN, PIK3R1, CTNNB1, CTCF, KMT2B, KRAS, NEB*, and *RNF43* genes were observed at higher rates in endometrioid carcinomas. Our *in silico* analysis correlates with the finding that serous carcinomas generally have a lower mutation load compared to endometrioid carcinomas (10).

The most striking molecular mechanism in these tumors is mutations in the *TP53* gene, with over 85% of serous carcinomas exhibiting *TP53* mutations (1). In endometrioid carcinomas, however, it is seen at a much lower rate (10%) compared to serous carcinomas (11). Consistent with our study, *PPP2R1A* mutation has been reported in the literature at higher rates in serous carcinomas compared to the endometrioid type (19-43% vs. 7-13%) (11,12). In our study, *TP53* and *PPP2R1A* showed expression differences, predominantly in serous carcinomas. (*TP53*: 88% vs. 21.4%, p= 2.04e-37, q= 1.95e-33; *PPP2R1A*: 38% vs. 11.1%, p= 1.02e-9, q= 3.263e-03).

A significantly altered PI3K signaling pathway exists in serous carcinomas. While an increase in *PIK3CA* mutations is most frequently seen in these tumors (17-43%), *PTEN* and *PIK3R1* mutations have been reported at lower rates (1). In the literature, *PIK3CA* mutation has been reported in both serous and endometrioid carcinomas. However, unlike other mutations, there is no sginificant difference between the two groups (*PIK3CA* mutation 40-50% in endometrioid type, 20-40% in serous type) (11). Consistent with the literature, our *in silico* study found *PIK3CA* mutation at a higher rate in the endometrioid type (53.6% vs. 37%), but it was not a gene with a significant difference between the two groups ($q > 0.05$). *PIK3R1* mutation is frequently seen in endometrioid carcinoma with rates of 20-43% (6,13,14). Its incidence in serous carcinomas is low (5-8%) (12). Consistent with the literature, *PIK3R1* mutation was observed at a lower rate in serous carcinomas in our study (11.1% in serous vs. 36.3% in endometrioid).

The *ARID1A* tumor suppressor gene is frequently mutated in endometrioid carcinoma (15). While it is mutant in 39-60% of endometrioid carcinoma cases, this rate is 7-11% in serous carcinomas (12). In our study, *ARID1A* mutation was common in endometrioid carcinomas, and a significant difference was detected between the two groups (54.4% vs. 8.3%; p= 1.36e-19, q= 8.65e-16). *PTEN* acts as a tumor suppressor by inhibiting the activation of the PI3K pathway. Somatic mutation of *PTEN* occurs in 69-80% of endometrioid tumors and is the most common genomic alteration in this subtype (1). In serous carcinomas, the rate is 2-3% (12). In our study, the *PTEN* gene also showed significant enrichment in endometrioid carcinomas (82% vs. 10.2%; p= 4.18e-44, q= 7.99e-40).

The *KRAS* gene, frequently mutated in endometrial carcinomas (20-40%), whereas its mutation rate is lower in serous carcinomas (2-6%) (11,12). In our study, the *KRAS* gene showed enrichment in endometrioid carcinomas (24.5% vs. 2.8%; p= 1.79e-8, q= 4.272e-02). *CTNNB1* mutation is generally seen in 19-37% of endometrioid carcinomas, whereas it is at a low rate like 1%

in serous carcinomas (1,11). In our *in silico* study, we found that *CTNNB1* mutation rates were significantly higher in endometrioid carcinomas (33.6% vs. 0.9%; p= 2.06e-15, q= 9.82e-12).

RNF43 negatively regulates WNT-β-catenin signaling (1). In the literature, *RNF43* is somatically mutated in 18-27% of endometrioid carcinomas (16). Recent studies have identified *ATR, CTCF, JAK1, RNF43*, and *RPL22* genes as driver genes sustaining pathogenic frameshift mutations in mononucleotide repeats in MSI-positive endometrioid carcinomas (1,16). We also detected significantly high mutation rates in *RNF43* as well as *ATR, CTCF, JAK1*, and *RPL22* genes in endometrioid carcinomas in our *in silico* data (*RNF43*: p= 7.90e-8, q= 1.509w-01, *CTCF*: p= 5.33e-13, q= 2.04e-9, *ATR*: p= 1.380e-3, q= 0.0452, *JAK1*: p= 1.154e-5, q= 5.250e-3, *RPL22*: p= 3.06e-7, q= 4.118e-4).

MSI is more associated with endometrioid carcinomas than serous carcinomas in endometrial cancers. According to the literature, 34-44% of endometrioid carcinomas are associated with MSI, whereas this rate drops to 0-3% in serous carcinomas (12). Consistent with the literature, our *in silico* results showed that endometrioid carcinoma cases were associated with MSI at a higher rate compared to serous carcinoma (31.6% vs. 0.9%; p = 7.215e-3, q = 0.0147).

Studies on *KMT2B* gene mutation in endometrial carcinomas are limited in the literature; Cuevas et al. (17) detected this mutation at a rate of 43.7% in endometrioid carcinomas, while it was not detected at all in serous carcinomas. In our study, *KMT2B* mutation was found at a significantly higher rate in endometrial carcinomas with a significant difference (26.8% vs. 3.7%; p= 1.18e-8, q= 3.228e-02). *NEB* is a gene associated with myopathy in the literature, and there is only one study on the mutation of this gene in endometrial carcinomas (18,19). Lopez-Ozuna et al. (19) showed that the *NEB* gene is more highly expressed in obese patients diagnosed with endometrial cancer showing lymph node involvement compared to those without involvement. According to our *in silico* data, the mutation rate in the *NEB* gene is significantly higher in endometrioid carcinomas (25.3% vs. 3.7%; p= 6.55e-8, q= 1.391e-01). New studies are needed to compare the mutation of this gene between endometrioid and serous carcinomas.

The mutation profile obtained in this study clearly demonstrates the distinct molecular divergence between endometrioid and serous endometrial carcinomas. The high prevalence of *PTEN, ARID1A, CTNNB1, CTCF, KRAS*, and *RNF43* mutations in endometrioid tumors is consistent with previous studies emphasizing that the PI3K/AKT signaling pathway, chromatin remodeling mechanisms, and Wnt/β-catenin pathways are fundamental determinants in endometrioid carcinogenesis (1,20). These molecular alterations support the perspective that endometrioid tumors develop through gradual genetic disruptions targeting regulatory and epigenetic networks. In contrast, the predominance of *TP53* and *PPP2R1A* mutations in serous carcinomas indicates that this subtype possesses a distinct molecular pathway.

It is known that serous carcinomas are characterized by a worse prognosis compared to the endometrioid type (21). In the study by Sait et al. (22), the overall survival of endometrioid carcinomas was found to be 118.7 months, while the overall survival of papillary serous carcinomas was lower at 44.1 months. Consistent with the literature, serous carcinomas had lower survival in our study as well (median months for endometrioid carcinomas: 102.83 months, serous carcinomas: 63.91 months).

While the interpretation of individual genes often provides a limited biological insight, pathway analysis helps to explain the underlying biology of the disease more holistically by revealing which signaling networks, metabolic pathways, or cellular processes these genes collectively affect. This approach offers a significant advantage in elucidating the molecular programs underlying fundamental cancer-related phenotypes such as cell cycle, apoptosis, immune evasion, and metastatic behavior (23). DEG-based pathway analyses have become indispensable tools in bioinformatics-based molecular studies for understanding pathogenesis mechanisms, identifying new therapeutic targets, predicting drug response, and classifying molecular subtypes (24,25).

The pathway differences between endometrioid and serous carcinomas indicate that the molecular mechanisms driving tumor development are different. In this analysis, it was observed that differentially expressed mutations were significantly enriched in biological processes such as cell cycle control, tissue development,

regulation of signal transduction, stress response, and neurogenesis. These findings are consistent with previous studies showing that deregulation in pathways associated with the cell cycle is a fundamental finding in endometrial carcinogenesis and contributes to biological behavior differences between subtypes (1,6).

KEGG pathway analyses revealed that DEGs are linked to essential cellular maintenance mechanisms such as proteasome activity, mismatch repair, and DNA replication. Additionally, processes such as regulation of the cell cycle, mitotic cell cycle, chromosome organization, control of cellular development, and cellular component organization were determined to be among the pathways with which DEGs are significantly associated. Mismatch repair defects and associated DNA replication abnormalities have been demonstrated in endometrial tumors, particularly in the context of genomic instability and oncogenic mutation accumulation (26).

Serous carcinomas, characterized by extensive copy number alterations and marked chromosomal instability, frequently show disruptions in pathways associated with mitotic activity and chromosome organization (6). The enrichment of proteasome-related pathways in our *in silico* data is also noteworthy. Since the proteasome plays a role in DNA repair, proteasome dysfunction is known to have effects on the DNA damage response and tumor aggressiveness (27). The strong enrichment of pathways such as proteasome, DNA replication, spliceosome, and base excision repair in serous carcinomas is consistent with the aggressive biology of this subtype defined by high genomic instability and *TP53* disruption (20). Genomic analyses reporting *TP53* mutations in serous tumors have revealed that the early disruption of this gene triggers the distinct chromosomal instability of serous carcinoma (20). Furthermore, considering that *PPP2R1A* mutations enriched in serous carcinoma in our study have significant effects on cell cycle control and mitotic supervision, the detection of these pathways in the analysis is an expected situation (28). Detection of a significant difference between the two groups in terms of MSIsensor scores *in silico* shows a correlation with the mismatch repair pathway being effective in the pathway analysis.

This *in silico* analysis demonstrates that uterine endometrioid and serous carcinomas diverge significantly at the molecular, epigenetic, and biological pathway levels. While endometrioid tumors have a more stable genomic structure, MSI, pathway enrichment associated with metabolic and developmental processes, and better survival outcomes; serous tumors are characterized by high genomic instability, MSS, severe DNA repair defects, significant disruptions in proteasome and replication pathways, and a parallel poor survival profile.

These fundamental biological differences explain the aggressive clinical behavior of the serous subtype and emphasize the importance of earlier diagnosis anda molecularly targeted therapies. Our findings underscore the importance of subtype-specific strategies in the clinical management of endometrioid and serous carcinomas and provide a molecular basis for future targeted treatment approaches.

REFERENCES

1. Bell DW, Ellenson LH. Molecular Genetics of Endometrial Carcinoma. Annu Rev Pathol Mech Dis. 2019;14(1):339–67.
2. Jamieson A, McAlpine JN. Molecular Profiling of Endometrial Cancer From TCGA to Clinical Practice. J Natl Compr Cancer Netw. 2023;21(2):210–6.
3. Dedes KJ, Wetterskog D, Ashworth A, Kaye SB, Reis-Filho JS. Emerging therapeutic targets in endometrial cancer. Nat Rev Clin Oncol. 2011;8(5):261–71
4. Lax SF, Kendall B, Tashiro H, Slebos RJC, Ellenson LH. The frequency of p53, k-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma. Cancer. 2000;88(4):814–24.
5. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. Mutational landscape and significance across 12 major cancer types. Nature. 2013;502(7471):333–9.
6. Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73.
7. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4.
8. Kolberg L, Raudvere U, Kuzmin I, Adler P, Vilo J, Peterson H. g:Profiler—interoperable web service for functional enrichment analysis and gene identifier mapping (2023 update). Nucleic Acids Res. 2023;51(W1):W207–12.
9. Liao Y, Wang J, Jaehnig EJ, Shi Z, Zhang B. WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs. Nucleic Acids Res. 2019;47(W1):W199-W205.
10. Getz G, Gabriel SB, Cibulskis K, Lander E, Sivachenko A, Sougnez C, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
11. Bogani G, Ray-Coquard I, Concin N, Ngoi NYL, Morice P, Enomoto T, et al. Uterine serous carcinoma. Gynecol Oncol. 2021;162(1):226–34.
12. Urick ME, Bell DW. Clinical actionability of molecular targets in endometrial cancer. Nat Rev Cancer. 2019;19(9):510–21.
13. Urick ME, Rudd ML, Godwin AK, Sgroi D, Merino M, Bell DW. PIK3R1 (p85α) Is Somatically Mutated at High Frequency in Primary Endometrial Cancer. Cancer Res. 2011;71(12):4061–7.
14. Correction: High Frequency of PIK3R1 and PIK3R2 Mutations in Endometrial Cancer Elucidates a Novel Mechanism for Regulation of PTEN Protein Stability. Cancer Discov. 2021;11(10):2658–2658.
15. Wiegand KC, Hennessy BT, Leung S, Wang Y, Ju Z, McGahren M, et al. A functional proteogenomic analysis of endometrioid and clear cell carcinomas using reverse phase protein array and mutation analysis: protein expression is histotype-specific and loss of ARID1A/BAF250a is associated with AKT phosphorylation. BMC Cancer. 2014;14(1):120.
16. Giannakis M, Hodis E, Jasmine Mu X, Yamauchi M, Rosenbluh J, Cibulskis K, et al. RNF43 is frequently mutated in colorectal and endometrial cancers. Nat Genet. 2014;46(12):1264–6.
17. Cuevas D, Valls J, Gatius S, Roman-Canal B, Estaran E, Dorca E, et al. Targeted sequencing with a customized panel to assess histological typing in endometrial carcinoma. Virchows Arch. 2019;474(5):585–98
18. Savarese M, Sarparanta J, Vihola A, Jonson PH, Johari M, Rusanen S et al. Panorama of the distal myopathies. Acta Myologica. 2020;39(4):245-265.
19. López-Ozuna VM, Kogan L, Hachim MY, Matanes E, Hachim IY, Mitric C, et al. Identification of Predictive Biomarkers for Lymph Node Involvement in Obese Women With Endometrial Cancer. Front Oncol. 2021;11:695404.
20. Molefi T, Mabonga L, Hull R, Sebitloane M, Dlamini Z. From Genes to Clinical Practice: Exploring the Genomic Underpinnings of Endometrial Cancer. Cancers (Basel). 2025;17(2):320.
21. Boruta DM, Gehrig PA, Groben PA, Bae-Jump V, Boggess JF, Fowler WC, et al. Uterine serous and grade 3 endometrioid carcinomas. Cancer. 2004;101(10):2214–21.
22. Sait KH, Anfinan N, Sait H, Shamrani H, Sait M. Overall and progression-free survival in endometrial carcinoma: A single-center retrospective study of patients treated between 2000-2018. Ann Saudi Med. 2023;43(5):315–28.
23. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci. 2005;102(43):15545–50.
24. Pham M, Wilson S, Govindarajan H, Lin C-H, Lichtarge O. Discovery of disease- and drug-specific pathways through community structures of a literature network. Wren J, editor. Bioinformatics. 2020;36(6):1881–8.
25. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer Genome Landscapes. Science. 2013;339(6127):1546–58.
26. Jumaah AS, Al-Haddad HS, Salem MM, McAllister KA, Yasseen AA. Mismatch repair deficiency and clinicopathological characteristics in endometrial carcinoma: a systematic review and meta-analysis. J Pathol Transl Med. 2021;55(3):202–11.
27. Jacquemont C, Taniguchi T. Proteasome Function Is Required for DNA Damage Response and Fanconi Anemia Pathway Activation. Cancer Res. 2007;67(15):7395–405.
28. Perl AL, O'Connor CM, Fa P, Mayca Pozo F, Zhang J, Zhang Y, et al. Protein phosphatase 2A controls ongoing DNA replication by binding to and regulating cell division cycle 45 (CDC45). J Biol Chem. 2019;294(45):17043–59.

Abbreviations List

CbioPortal for Cancer genomics: CbioPortal
Differentially expressed genes: DEGs
False discovery rate: FDR
Gene Ontology: GO
Kyoto Encyclopedia of Genes and Genomes: KEGG
Microsatellite instability: MSI
Microsatellite stable: MSS
Mismatch repair: MMR
MSI-Low: MSI-L
MSI-High: MSI-H
Over-representation analysis: ORA
The Cancer Genome Atlas: TCGA
WEB-based Gene SeT Analysis Toolkit: WebGestalt.

Ethics Approval and Consent to Participate

The study did not require ethical approval.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data supporting the conclusions described here are presented in figures and supplementary materials. The TCGA, Uterine Corpus Endometrial Carcinoma (PanCancer Atlas) dataset in cbioportal can be accessed at CbioPortal website (https://www.cbioportal.org/study/summary?id=ucec_tcga_pan_can_atlas_2018 / accessed on 27 November 2025).

Competing Interests

The author declares that no conflicts of interest.

Funding

The author declared that this study has received no financial support. This research received no external funding.

Author Contributions

The author was responsible for the idea and concept, study design, supervision, literature review, writing of the article, and critical revision.

Acknowledgements

There are no acknowledgements.