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Expression and Prognostic Potential of *ESR1* in Breast Cancer

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Abstract: This study aims to explore the potential of *ESR1* as a biomarker in breast cancer (BRCA) using bioinformatics analysis tools. The up-regulation of *ESR1* expression in BRCA was investigated using UALCAN and GEPIA2, illustrating its role in BRCA progression. Furthermore, analyses based on various variables such as gender, age, race, and pathological stages of BRCA patients revealed a consistent up-regulation of ESR1, emphasizing its role in the development and progression of BRCA. Additionally, an analysis of *ESR1* promoter methylation levels across various parameters revealed hypomethylation, affirming the inverse correlation between methylation and *ESR1* expression. Prognostic analysis further indicated that overexpression of *ESR1* is associated with poor overall survival, highlighting its potential as a prognostic biomarker in BRCA. Moreover, genetic mutation analysis using cBioPortal disclosed a minor role of *ESR1* genetic mutations in BRCA, with only 2.5% of genetic alterations observed. The STRING and DAVID tools were utilized to conduct pathway enrichment analysis, revealing diverse biological functions of *ESR1* and its 10 interconnected genes. Altogether, these results underscore the significance of understanding *ESR1* up-regulation in BRCA and demonstrate its potential as a therapeutic, diagnostic, and prognostic biomarker.

Keywords: Breast cancer; *ESR1*; Biomarker; Bioinformatics analysis

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1. Introduction

Cancer is a predominant medical problem worldwide. In 2022, approximately 20 million new cases and 9.7 million cancer-related deaths were reported globally. Among the numerous types of cancer, breast cancer (BRCA) is the second most common, accounting for 2.3 million cases and representing the leading cause of cancer-related mortality in women worldwide [1-3]. The incidence of breast cancer continues to rise, with the majority of cases occurring in developed and industrialized nations [4,5]. Major risk factors associated with breast cancer include alcohol consumption, aging, hormonal status, family history, nutrition, obesity, and genetic mutations [6]. The World Health Organization (WHO) recognizes 18 histological types of BRCA, with invasive breast cancer being the most prevalent, comprising 40%–80% of cases [6,7]. Additionally, four molecular subtypes of BRCA have been identified: Luminal, HER2-enriched, Basal-like, and Normal Breast-like [8,9]. Common treatments

for BRCA include surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy [10]. However, a 30% recurrence rate in early-stage BRCA, along with treatment resistance and medication side effects, remains a significant obstacle to successful treatment [11]. Metastatic BRCA, in particular, has a poor prognosis, with a 5-year tumor-specific survival rate of only 29% [12,13]. Given these challenges, the identification of effective diagnostic, therapeutic, and prognostic biomarkers for BRCA is crucial.

The estrogen receptor 1 (*ESR1*) gene encodes the estrogen receptor-α (ERα), a ligand-activated transcription factor. ERα is expressed in BRCA, and 75% of tumors are estrogen receptor-positive (ER^+), which is associated with high mortality. The Luminal A and Luminal B subtypes of BRCA are ER^+, with Luminal B being a highly metastatic and recurrent subtype [14-17]. Endocrine therapy (ET) is highly recommended and effective for treating ER^+ BRCA. However, a significant number of early-stage tumors relapse even after ET, with 15%–20% of metastatic BRCA cases showing resistance to this therapy [18]. The transcriptional activity of ERα is regulated by specific domains within *ESR1*. Various mechanisms alter ER expression, such as when ligands bind to the receptor, allowing ER to regulate critical tumorigenesis genes by interacting with specific DNA sequences and coregulatory proteins. Signaling pathways are activated when ER interacts with tyrosine kinase receptors and signaling proteins, with growth factors further stimulating ER's transcriptional function. Alterations in these pathways contribute to ET resistance [19-23]. Furthermore, mutations in ESR1 are associated with a worse prognosis [24].

Given the potential of *ESR1* in BRCA, extensive research has been conducted globally. However, to date, bioinformatics analysis of *ESR1* as a diagnostic, therapeutic, and prognostic biomarker in BRCA has not been fully explored. Therefore, this study aims to conduct a comprehensive bioinformatics analysis of *ESR1* in BRCA.

2. Methodology

2.1. UALCAN

UALCAN is an accessible and effective online database based on TCGA data, widely employed to analyze gene expression in cancer [25]. In this study, UALCAN was used to elucidate *ESR1* expression in BRCA. Additionally, UALCAN contributed significantly to analyzing the promoter methylation levels of *ESR1* in BRCA. This database allowed for the investigation of *ESR1* methylation and expression across various variables.

2.2. Kaplan-Meier plotter

Kaplan-Meier (KM) Plotter is a web-based tool that plays a pivotal role in determining the impact of genes on the overall survival (OS) of cancer patients [26]. In this study, KM Plotter was used to perform a survival analysis of *ESR1* in BRCA. The hazard ratio was calculated with a 95% confidence interval, and the *P*-value was set at 0.05.

2.3. GEPIA2

Gene Expression Profiling Interactive Analysis 2 (GEPIA2) is an online tool based on TCGA and GTEx datasets, which enables comprehensive analysis of gene expression and survival data [27]. In this study, GEPIA2 was utilized to assess the survival analysis of *ESR1* in BRCA. GEPIA2 was also used to evaluate *ESR1* expression in BRCA samples and across different cancer stages.

2.4. cBioPortal

cBioPortal is a user-friendly and robust web-based tool widely used to evaluate genetic mutations in various cancers [28]. This study employed cBioPortal to analyze genetic alterations of *ESR1* in BRCA.

2.5. STRING

The Search Tool for the Retrieval of Interacting Genes (STRING) is a web-based tool used to construct Protein-Protein Interaction (PPI) networks of genes [29]. In this study, STRING was used to construct a PPI network for *ESR1* and to reveal interactions with related genes.

2.6. DAVID

To examine the enrichment analysis of specific genes and their interlinked counterparts, the bioinformatics tool DAVID was employed [30]. In this study, DAVID was used to perform pathway enrichment analysis, evaluating the biological significance of *ESR1* and its interconnected genes.

3. Results

3.1. Analysis of ESR1 expression in BRCA and normal samples

The UALCAN database was employed to analyze *ESR1* expression in BRCA and normal control samples. An increase in *ESR1* expression was observed in BRCA samples compared to normal samples (**Figure 1**). Previous studies have suggested that significantly upregulated genes are involved in the progression of cancers [31,32]. The significant overexpression of *ESR1* in primary tumor samples indicates that ESR1 plays a role in the progression and development of BRCA.

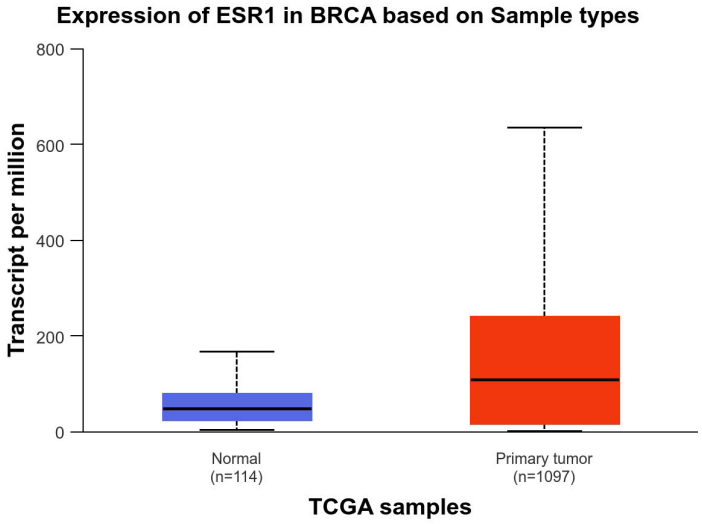

Figure 1. Expression analysis of *ESR1* in BRCA and normal samples using UALCAN

3.2. Analysis of ESR1 expression in BRCA categorized by various parameters

Further investigation was conducted to assess *ESR1* expression in BRCA across various parameters. First, *ESR1* expression was analyzed based on individual cancer stages, showing a significant upregulation across all stages of BRCA (**Figure 2A**). Next, *ESR1* expression was assessed by age group, revealing upregulation with variation between groups; the highest expression was observed in patients aged 81–100 years compared to those aged 21–40 years (**Figure 2B**). *ESR1* expression was then analyzed based on race, showing upregulation in Caucasians and dysregulation in African-Americans and Asians (**Figure 2C**). Gender-based analysis revealed upregulation in both male and female BRCA patients, with higher expression in males (**Figure 2D**). Overall, the observed variation, dysregulation, and upregulation of *ESR1* expression suggest its involvement in the progression and development of BRCA.

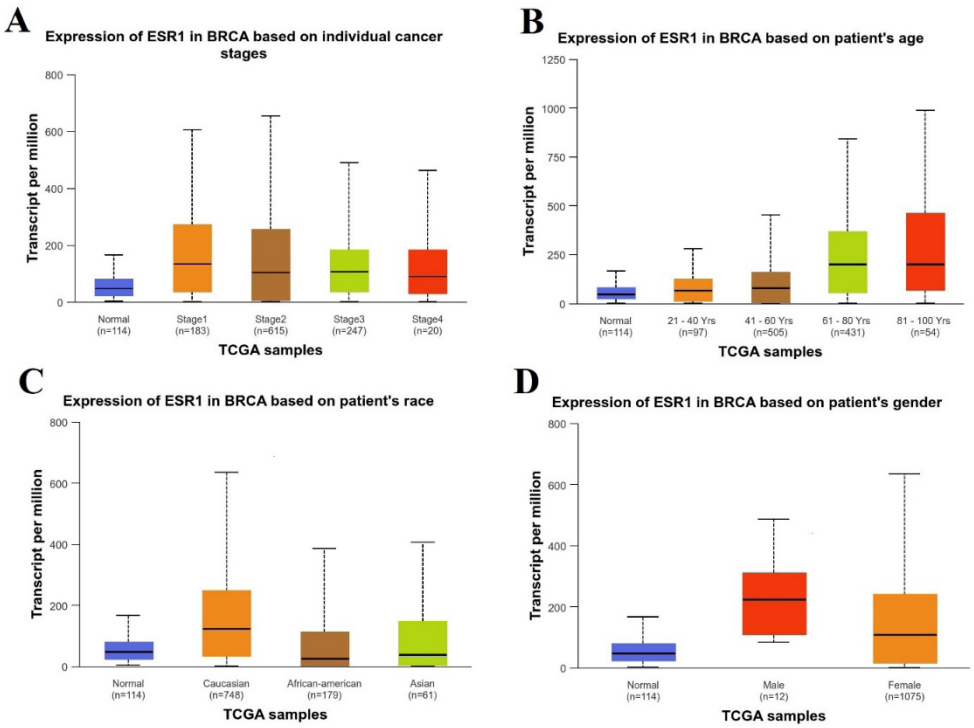

Figure 2. *ESR1* expression in various parameters. **(A)** Analysis of *ESR1* expression in BRCA based on pathological stages; **(B)** Analysis of *ESR1* expression in BRCA based on patients' age; **(C)** Analysis of *ESR1* expression in BRCA based on patients' race; **(D)** Analysis of *ESR1* expression in BRCA based on patients' gender

3.3. Analysis of promoter methylation of ESR1 in BRCA and normal samples

To further the research, the promoter methylation level of *ESR1* in BRCA and normal control samples was analyzed using UALCAN. Significant hypomethylation of *ESR1* was observed in BRCA samples compared to normal samples (**Figure 3**). Previous research has indicated an inverse relationship between gene methylation and gene expression [33]. Thus, the hypomethylation of *ESR1* suggests its overexpression and role in BRCA progression.

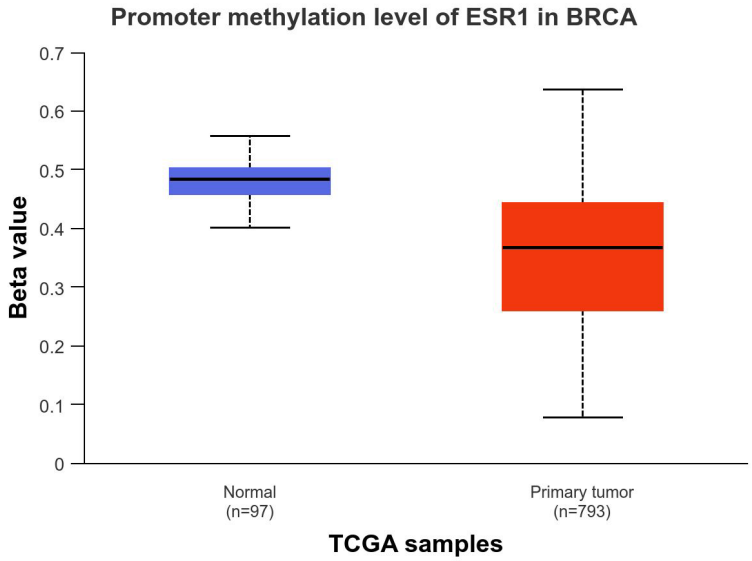

Figure 3. Analysis of promoter methylation level of *ESR1* in BRCA using UALCAN

3.4. Analysis of promoter methylation levels of ESR1 in BRCA categorized by various parameters

Next, promoter methylation levels of *ESR1* in BRCA were analyzed across various parameters, including patient age, gender, race, and cancer stage. First, hypomethylation of *ESR1* was observed across all individual cancer stages (**Figure 4A**). *ESR1* was also hypomethylated in BRCA patients of different races (**Figure 4B**). Further analysis revealed variation in *ESR1* methylation levels across age groups, with the highest hypomethylation observed in patients aged 81–100 years, compared to those aged 21–40 years (**Figure 4C**). Similarly, gender-based analysis showed that *ESR1* was more highly hypomethylated in male patients than in female patients (**Figure 4D**). Collectively, these results suggest that *ESR1* hypomethylation contributes to BRCA progression across different demographic parameters.

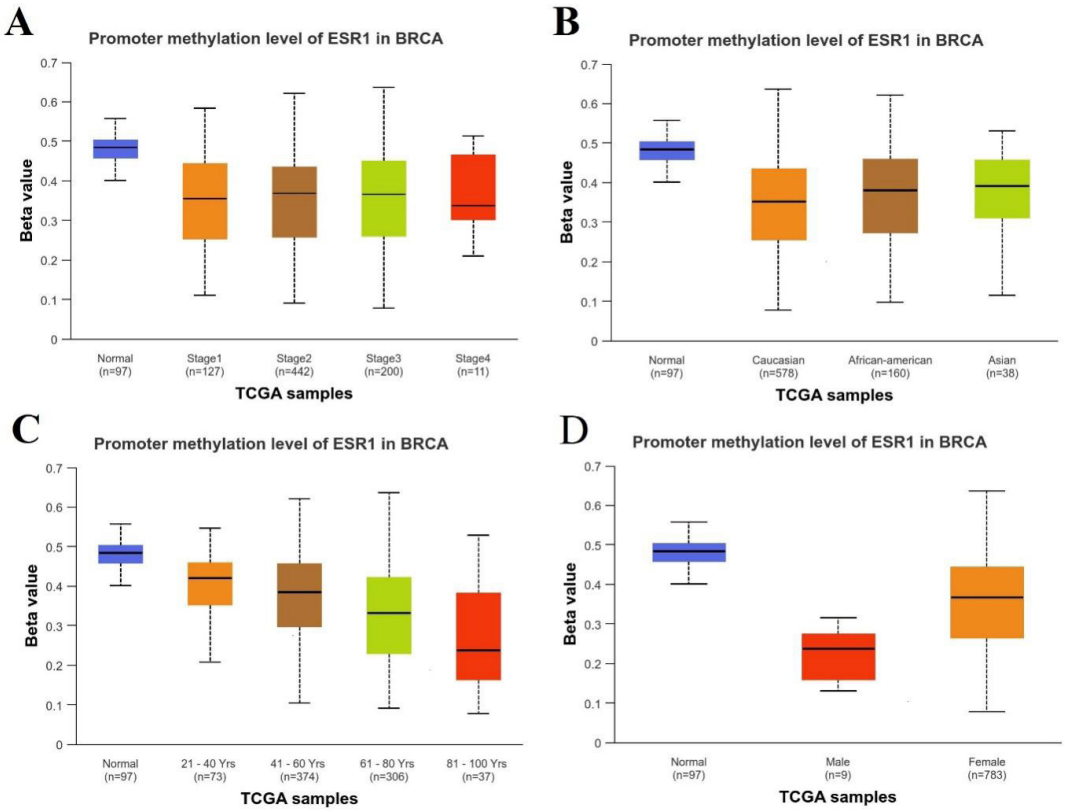

Figure 4. Promoter methylation levels of *ESR1* in various parameters. **(A)** Analysis of *ESR1* promoter methylation levels in BRCA based on pathological stages; **(B)** Analysis of *ESR1* promoter methylation levels in BRCA based on patients' race; **(C)** Analysis of *ESR1* promoter methylation levels in BRCA based on patients' age; **(D)** Analysis of *ESR1* promoter methylation levels in BRCA based on patients' gender

3.5. Prognostic analysis of ESR1 in BRCA

The KM plotter was employed to examine the role of *ESR1* in the OS of BRCA patients. It was found that BRCA patients with overexpression of *ESR1* had lower OS, whereas those with lower expression showed better OS (**Figure 5**). However, the difference was not statistically significant, as the *P*-value was 0.1. These results suggest that *ESR1* expression impacts the OS of BRCA patients. The observed overexpression of *ESR1* in BRCA samples correlates with a higher mortality rate, highlighting its potential as a prognostic biomarker in BRCA.

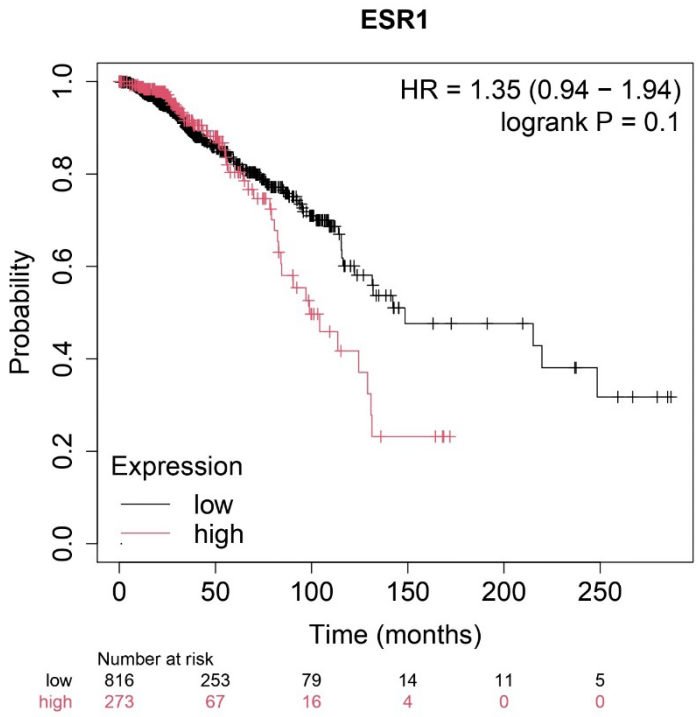

Figure 5. Prognostic analysis of ESR1 in BRCA using KM plotter

3.6. Verification of survival analysis and ESR1 expression in BRCA

To validate the findings related to *ESR1* expression and its effect on the OS of BRCA patients, GEPIA2 was utilized. *ESR1* expression in BRCA samples was first compared to normal samples, revealing that *ESR1* was upregulated in BRCA, consistent with previous findings (**Figure 6A**). Subsequently, the stage plot module of GEPIA2 was used to analyze *ESR1* expression in individual cancer stages, showing that *ESR1* was upregulated across all stages of BRCA (**Figure 6B**). These results confirm the earlier conclusion that *ESR1* plays a role in BRCA progression.

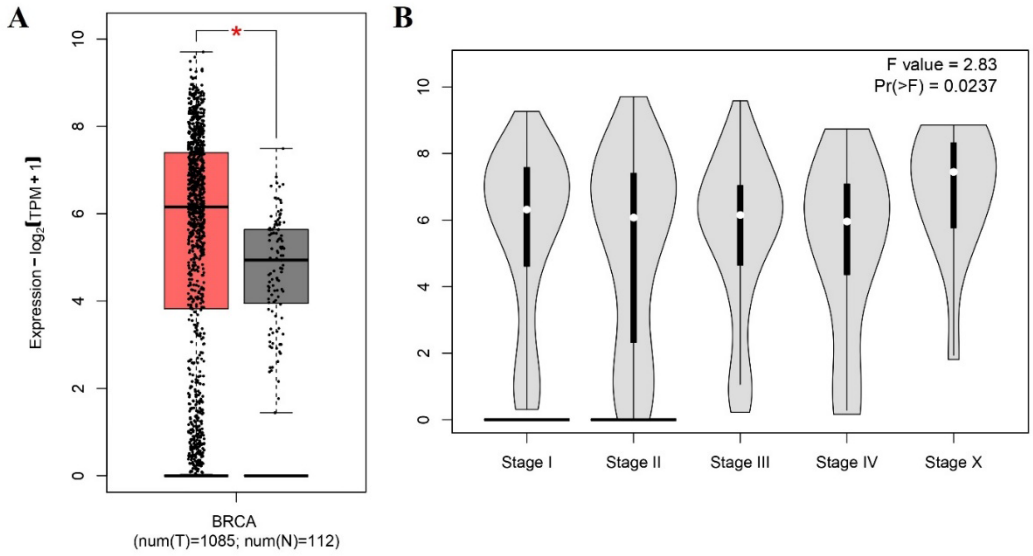

Figure 6. (A) Expression analysis of *ESR1* in BRCA and normal control samples using GEPIA2; **(B)** Expression analysis of ESR1 in BRCA based on pathological stages using GEPIA2

The survival analysis module of GEPIA2 was then employed to evaluate the role of *ESR1* expression in the OS of BRCA patients. The analysis revealed that lower *ESR1* expression was associated with better OS, while elevated *ESR1* expression correlated with worse OS (**Figure 7**). The observed *P*-value of 0.52 indicates a marginal difference between the groups. These results align with previous findings and suggest that ESR1 contributes to the development and progression of BRCA.

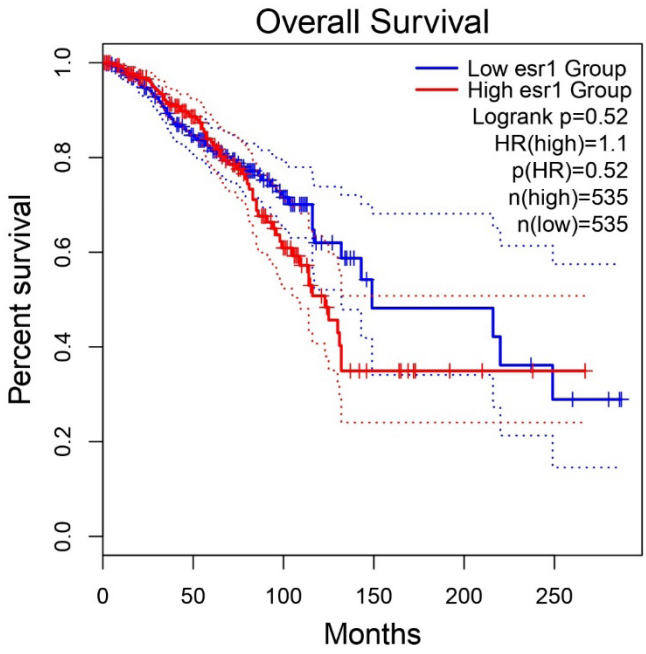

Figure 7. Survival analysis of *ESR1* in BRCA using GEPIA2

3.7. Genetic mutations of ESR1 in BRCA

To evaluate the genetic alterations of *ESR1* in BRCA and their impact on BRCA progression, cBioPortal was utilized. A low frequency of *ESR1* mutations was observed, with only 2.5% of BRCA cases showing alterations, including amplification and deep deletion (**Figure 8**). These findings suggest that *ESR1* mutations play a minor role in BRCA proliferation, yet provide valuable insights into the genetic landscape of *ESR1* in BRCA.

Figure 8. Genetic mutations of *ESR1* in BRCA using cBioPortal

3.8. Gene enrichment analysis

STRING and DAVID tools were used to conduct a comprehensive examination, including PPI network construction, Gene Ontology (GO) analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses, to explore the biological functions of *ESR1* (**Table 1**). A PPI network of *ESR1* was constructed using the STRING tool, revealing interactions with 10 genes (**Figure 9**), which shed light on the functional role of *ESR1*.

Table 1. Gene enrichment analysis

Gene term	Gene count	Genes	*P*-value
BP			
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	8	*NCOA1*, *NCOA2*, *JUN*, *SP1*, *NCOA3*, *NRIP1*, *FOS*, *ESR1*	4.316633463367988E-7
GO:0032570~response to progesterone	3	*NCOA1*, *NCOA2*, *FOS*	1.3497253797827575E-4
GO:0071392~cellular response to estradiol stimulus	3	*NCOA3*, *NRIP1*, *ESR1*	1.689493584985378E-4
GO:0032870~cellular response to hormone stimulus	3	*NCOA1*, *NCOA2*, *NCOA3*	1.8735062934716631E-4
GO:0045893~positive regulation of transcription, DNA-templated	5	*NCOA1*, *JUN*, *SP1*, *FOS*, *ESR1*	3.362932589262899E-4
CC			
GO:0000785~chromatin	9	*NCOA1*, *NCOA2*, *JUN*, *NCOR1*, *SP1*, *NCOA3*, *NRIP1*, *FOS*, *ESR1*	2.6594084651584337E-9
GO:0005654~nucleoplasm	11	*NCOA1*, *NCOA2*, *HSP90AA1*, *JUN*, *NCOR1*, *SRC*, *SP1*, *NCOA3*, *NRIP1*, *FOS*, *ESR1*	7.313672569344439E-8
GO:0090575~RNA polymerase II transcription factor complex	4	*NCOA1*, *NCOA2*, *JUN*, *FOS*	2.5663102058774573E-5
GO:0005634~nucleus	10	*NCOA1*, *NCOA2*, *HSP90AA1*, *JUN*, *NCOR1*, *SP1*, *NCOA3*, *NRIP1*, *FOS*, *ESR1*	1.1814041714380625E-4
GO:0005667~transcription factor complex 4	4	*NCOA1*, *NCOA2*, *JUN*, *ESR1*	1.45523934603438E-4
MF			
GO:0016922~ligand-dependent nuclear receptor binding	5	*NCOA1*, *NCOA2*, *NCOR1*, *NCOA3*, *NRIP1*	4.845351136764623E-9
GO:0030331~estrogen receptor binding	4	*NCOA1*, *SRC*, *NRIP1*, *ESR1*	1.1281165912027505E-6
GO:0042826~histone deacetylase binding	4	*HSP90AA1*, *NCOR1*, *SP1*, *NRIP1*	3.609105102658606E-5
GO:0061629~RNA polymerase II sequence-specific DNA binding transcription factor binding	4	*JUN*, *NCOR1*, *SP1*, *FOS*	1.0554759656852471E-4
GO:0000978~RNA polymerase II core promoter proximal region sequence-specific DNA binding	6	*NCOA2*, *JUN*, *SP1*, *NRIP1*, *FOS*, *ESR1*	1.7546914941193677E-4
KEGG			
hsa04915:Estrogen signaling pathway	9	*NCOA1*, *NCOA2*, *HSP90AA1*, *JUN*, *SRC*, *SP1*, *NCOA3*, *FOS*, *ESR1*	2.8282454696593787E-14
hsa01522:Endocrine resistance	7	*JUN*, *NCOR1*, *SRC*, *SP1*, *NCOA3*, *FOS*, *ESR1*	1.4689368682759732E-10
hsa04919:Thyroid hormone signaling pathway	6	*NCOA1*, *NCOA2*, *NCOR1*, *SRC*, *NCOA3*, *ESR1*	5.900138396894648E-8
hsa05224:Breast cancer	6	*NCOA1*, *JUN*, *SP1*, *NCOA3*, *FOS*, *ESR1*	1.5689863645171283E-7
hsa05200:Pathways in cancer	7	*NCOA1*, *HSP90AA1*, *JUN*, *SP1*, *NCOA3*, *FOS*, *ESR1*	3.6991021891065767E-6

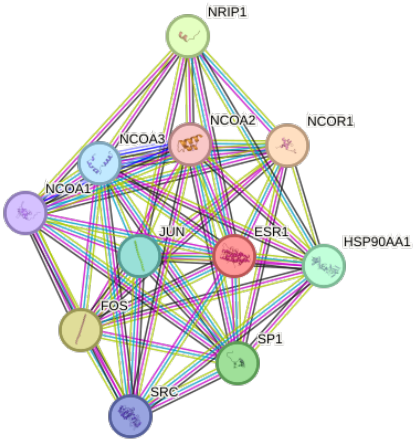

Figure 9. PPI network of *ESR1* using STRING tool

Further, the top five terms from the GO and KEGG analyses were observed using the DAVID tool (**Figure 10**). KEGG pathway analysis identified terms such as the Estrogen signaling pathway, Endocrine resistance, Thyroid hormone signaling pathway, Breast cancer, and Pathways in cancer (**Figure 10A**). GO analysis of biological processes (BP) revealed links to positive regulation of transcription from RNA polymerase II promoter, response to progesterone, cellular response to estradiol stimulus, cellular response to hormone stimulus, and DNA-templated positive regulation of transcription (**Figure 10B**).

Additionally, GO analysis of cellular components (CC) indicated enrichment in chromatin, nucleoplasm, RNA polymerase II transcription factor complex, nucleus, and transcription factor complex (**Figure 10C**). In terms of molecular function (MF), enrichment was observed in ligand-dependent nuclear receptor binding, estrogen receptor binding, histone deacetylase binding, RNA polymerase II sequence-specific DNA-binding transcription factor binding, and RNA polymerase II core promoter proximal region sequence-specific DNA binding (**Figure 10D**). These findings provide valuable insights into the functional role of *ESR1* and its associated genes in various pathways and biological processes.

Figure 10. KEGG and GO analysis of *ESR1* in BRCA using the DAVID tool

4. Discussion

Cancer is a heterogeneous and deadly disease, and comprehensive research has been conducted for many years. Cancer patients continue to experience high mortality rates because early diagnosis remains a challenge [34-36]. Breast cancer, as a diverse disease, is the second most common type of cancer, with millions of cases and deaths. The number of BRCA cases varies by region, with more than 50% occurring in developed countries [37,38]. Major risk factors associated with BRCA include alcohol consumption, aging, hormonal status, family history, nutrition, obesity, and genetic mutations [39]. Treatments for BRCA typically include surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapies. Approximately 75% of BRCA cases are ER^+, making ET a highly recommended and effective treatment. Although most early-stage BRCA cases respond well to ET, the cancer often reappears later. While ET is beneficial for metastatic BRCA, 15%–20% of these cases show resistance to the therapy.

The *ESR1* gene codes for ER, and mutations in the ligand-binding domains, activation of signaling pathways, or stimulation by growth factors can lead to *ESR1* mutations. Studies suggest that these *ESR1* mutations contribute to poor prognosis in BRCA and lead to resistance to ET [40,41]. Therefore, it is essential to assess the potential of *ESR1* as a diagnostic, prognostic, and therapeutic biomarker. The present study conducted a bioinformatics analysis of *ESR1* in BRCA.

Initially, expression analysis of *ESR1* in BRCA was performed using the UALCAN database. The results demonstrated a significant upregulation of *ESR1* in BRCA samples compared to normal samples, suggesting that *ESR1* plays a role in BRCA progression. Following this, expression analysis of *ESR1* was conducted across various parameters, including age, gender, race, and cancer stage, revealing the upregulation of *ESR1* in all categories. These findings suggest that *ESR1* acts as an oncogene and has potential as a diagnostic marker. Additionally, promoter methylation analysis of *ESR1* in BRCA and normal samples, also using UALCAN, indicated hypomethylation of *ESR1* in BRCA samples. Further assessment of promoter methylation based on parameters such as age, race, gender, and cancer stage also revealed hypomethylation of *ESR1*. Given that methylation is inversely correlated with gene expression, hypomethylation of *ESR1* indicates its upregulation and role in BRCA progression.

KM plotter was employed to analyze the survival impact of *ESR1* in BRCA. The results revealed that high *ESR1* expression was associated with poor prognosis, while low expression corresponded with better outcomes. These findings are consistent with the observation that *ESR1* is highly expressed in BRCA, contributing to poor prognosis. Genetic mutation analysis showed a 2.5% mutation rate in *ESR1*, including amplification and deep deletion. Previous studies have noted that *ESR1* amplification is a significant cause of ET resistance, leading to poor prognosis [41]. To verify these results, GEPIA2 was used to conduct a box plot, stage plot, and survival analysis of *ESR1* in BRCA, further confirming that *ESR1* is upregulated and a major factor in poor prognosis. These results emphasize the potential of *ESR1* as a biomarker in BRCA.

Pathway enrichment analysis was also performed to evaluate the biological role of *ESR1*. The construction of a PPI network using the STRING tool revealed 10 genes that interact with *ESR1* (**Figure 9**). Further, KEGG and GO analyses using the DAVID tool indicated pathways linked with *ESR1*. GO analysis of biological processes highlighted positive regulation of transcription from RNA polymerase II promoter, response to progesterone, cellular response to estradiol stimulus, and DNA-templated transcription. Cellular component analysis revealed enrichment in chromatin, nucleoplasm, RNA polymerase II transcription factor complex, and transcription factor complex. Molecular function analysis showed enrichment in ligand-dependent nuclear receptor binding, estrogen receptor binding, histone deacetylase binding, and RNA polymerase II core promoter proximal region sequence-specific DNA binding. These findings provide valuable insights into the functional

role of *ESR1* and its associated genes in various pathways and biological processes. Altogether, these results underscore *ESR1*'s potential as a prognostic, diagnostic, and therapeutic biomarker in BRCA.

5. Conclusion

This study highlighted the diagnostic and prognostic significance of *ESR1* in BRCA by investigating its expression pattern, methylation level, and genetic mutation using various bioinformatics tools. These results support *ESR1* as a potential biomarker in BRCA, and further research in this direction is crucial.

Disclosure statement

The author declares no conflict of interest.

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