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IN SILICO ASSESSMENT OF ESR1 GENE EXPRESSION IN MALIGNANCIES

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The Estrogen Receptor 1 (ESR1) gene plays key roles in regulating ER-responsive genes and affects many physiological processes. This gene encodes the estrogen receptor (ERα), which is essential for cellular proliferation and differentiation and is implicated in various malignancies, including osteoporosis, colon, ovarian, endometrial, and breast cancer. Due to the association of the mutagenic form of ESR1 with many types of cancers, it is also being investigated as a potential biomarker for cancers. The bulk tissue expression of the ESR1 gene is found mainly in the tissues associated with female reproductive organs (breast, cervix tissue, fallopian tubes, uterus, and vagina). This study analyzed ESR1 expression in malignancies using *in silico* tools. TNMplot, TIMER2.0, GTEx, GEPIA, TCGA, etc., were used to investigate differential expression of ESR1 genes across various cancers, explore gene correlations, and assess prognostic impact and survival outcomes in patients. This study revealed that tumor tissue showed higher ESR1 expression than normal or metastatic tissues. ESR1 expression was high in all pathological stages throughout the course of the malignancy. Differential overall survival was observed among breast, cervical, uterine, and ovarian malignancies. Insights from this research could lead to the development of more effective targeted therapies, improving patient outcomes, and advancing cancer treatment strategies. This aspect of gene co-expression and linked transcription may be the subject of future molecular research.

Key words: endocrine receptor; ESR1; gene expression; endocrine therapy; overall survival; cancer cells; metastasis

INTRODUCTION

ESR1, a nuclear hormone receptor, influences cellular differentiation and proliferation in target tissues and contributes to the regulation of eukaryotic gene expression. In humans ESR gene is more than 140 kb long, 595 amino acids in length, and has a molecular mass of 66216 Da. According to Geneloc, the location of the ESR1 gene in the genome is chromosome six, having a size of four lakh seventy two thousand nine hundred forty eight bases and 6q25.1 q25.2 by NCBI [4, 21]. It has eight exons and mostly conserved intron positions [15]. The ESR1 gene encodes a ligand-activated transcription factor and estrogen receptor. An N-terminal ligand-independent & transactivation domain, a hinge domain, a central DNA binding domain, and a C-terminal ligand-dependent transactivation domain are all present in the canonical protein [17]. The protein localizes to the nucleus, where it can form homodimers and a heterodimer with the estrogen receptor [7].

To initiate ERE-independent signalling, ligand-dependent nuclear transactivation either directly binds homodimers to a palindromic (ERE) seq. and associates with other transcription factors that bind DNA, such as Sp1, Sp3, c-Fos, ATF-2, and AP-1/c-Jun [31]. Ligand binding causes a conformational shift through each component's LXXLL motifs, enabling a subsequent or combinatorial interaction with multiprotein coactivator complexes [1]. Alternative mRNA splicing generates additional isoforms (ESR-alpha and ESR-beta), which are found in various tissues and are implicated in tumor development and estrogen response regulation in breast, ovary, cervix, uterus etc [13].

Many researchers highlighted the increased ESR1 expression in tumors, as compared to normal tissues, and underscored its role in tumor development [23]. Approximately sixty percent of tumor tissues show positive expression for estrogen receptor (ER), and many of such individuals have a good expectancy [3]. Endocrine therapy is the main treatment option for ER-positive malignancies since it plays a significant role in the development of malignant tumors [2, 5]. In some cases, lower ESR1 mRNA levels are linked to poorer prognosis, highlighting its potential as a prognostic marker. However, its therapeutic role is

under great consideration as some ESR1-negative patients also showed positive responses toward endocrine therapy as well [9, 26]. The development of mutant & variant versions of the estrogen receptor, or their altered expression, has been proposed as one mechanism involved in the development of carcinoma in the breast of humans from hormone-dependent to independent [8].

It is crucial to understand how ESR1 affects endocrine resistance, tumor growth, and other related variables to develop tailored treatments and enhance patient outcomes [27]. The period and the context of the patient's previous endocrine therapy determine the incidence of ESR1 mutations. Mutations in ESR1 are a key mechanism behind resistance to endocrine therapies, impacting treatments like tamoxifen and fulvestrant. Many genomic regions have been shown to have linked transcription, and studies have shown that these are expressed differentially based on the tissue and parental allele, suggesting a potential relationship with spatial expression [22, 32].

Researchers are considering the significance of ESR1 in therapies, and various findings are being made to determine the involvement of ESR1 in tumor growth. It is imperative to focus on ESR1 signal transduction, co-expression, and related gene transcription in order to solve the problems with therapeutic management. This study examined the impact of the ESR1 gene as a prognostic and therapeutic factor by examining the differential expression levels of the gene in different cancers using online databases. The databases are useful for research studies as they provide researchers rapid and effective access to high-quality, peer-reviewed data.

Aim – to analyze ESR1 expression in malignancies using *in silico* tools.

MATERIALS AND METHODS

The differential expression levels of the ESR1 gene were studied using the TNM plot database (http://www.tnmplot.com). The information about up-regulation and down-regulation of the ESR1 gene was analysed using the Tumor Immune Estimation Resource (TIMER 2.0) database (http://timer.comp-genomics.org/timer). TIMER 2.0 database was also used to confirm ESR1 expression in different cancers. Additionally, RNA sequencing data from the TNM plot database was utilized to study ESR1 gene expression in breast cancer metastatic tumors, normal tissues, and tumor tissues.

Bulk expression of ESR was studied from the GTEx portal (https://gtexportal.org/home/gene/ESR1). The gene expression profiling and interactive analyses (GEPIA) (http://gepia.cancer-pku.cn/detail.php) were used to download information about differential ESR1 gene expression in breast tissue malignancies.

The Kaplan – Meier Plotter database was utilized to assess the prognostic value of ESR1 and survival information of cancer patients (https://kmplot.com/analysis). This tool aids in the discovery & validation of survival biomarkers through meta-analysis.

RESULTS

The Tumor Nodes Metastasis Plotter Database revealed variations in ESR1 expression levels across a range of normal and malignant tissues. The expression of ESR1 messenger RNA was significantly higher in tumor tissue as compared to normal tissue, as shown in Figure 1.

Using the Tumor Immune Estimation Resource (TIMER2.0), a variance was observed in gene expression between the tumor and the surrounding normal tissues for all TCGA cancers. The distribution of gene expression levels was depicted using box plots. According to the outcomes of the Wilcoxon test, the no. of stars – (*: $p<0.05$; **$p<0.01$; ***$p<0.001$) denotes statistical significance. The genes that were either up-regulated or down-regulated in the cancers in comparison to healthy tissues for each type of cancer are displayed in gray columns, despite the availability of normal data as given in Figure 2.

Using the RNA-sequence information from multiple cancers in the Cancer Genome Atlas, the expression of ESR1 in pan-cancer analysis was verified. These results showed that ESR1 was expressed more in breast-invasive carcinoma (BRCA) and colon adenocarcinoma (COAD) than in cholangiocarcinoma (CHOL), kidney chromophobe (KICH), kidney renal papillary cell carcinoma (KIRP), and kidney renal clear cell carcinoma (KIRC), & uterus corpus endometrial carcinoma (UCEC) than in the normal tissue depicted in figure 2. Interestingly, ESR1 expression was markedly elevated in all breast cancer subtypes.

The bulk tissue expression of the ESR1 gene is shown in Figure 3. The figure made it evident that the ESR1 gene was mainly expressed in the tissues associated with female reproductive organs (breast, cervix tissue, fallopian tubes, uterus, and vagina). ESR1 gene expression has been studied in Breast, Cervical, Ovarian, and Uterine tumors and normal tissues, as per GEPIA database analysis.

Variations in the expression of the ESR1 gene between healthy and malignant female reproductive tissues (Matched TCGA normal and GTEx data) are shown in Figure 4. A much higher expression of ESR1 is observed in breast and ovarian tumor tissue than in normal tissue. The expression of ESR1 was distributed rather evenly among uterine tissues. However, there was less ESR1 gene expression in cervical malignant tissue.

This study revealed that tumor tissue showed a higher expression level of ESR1 than normal and metastatic samples based on the RNA-sequence information of ESR1 expression in tumor tissues with normal, tumor, and metastases, which was obtained using the TNM plot database (Figure 5). Remarkably,

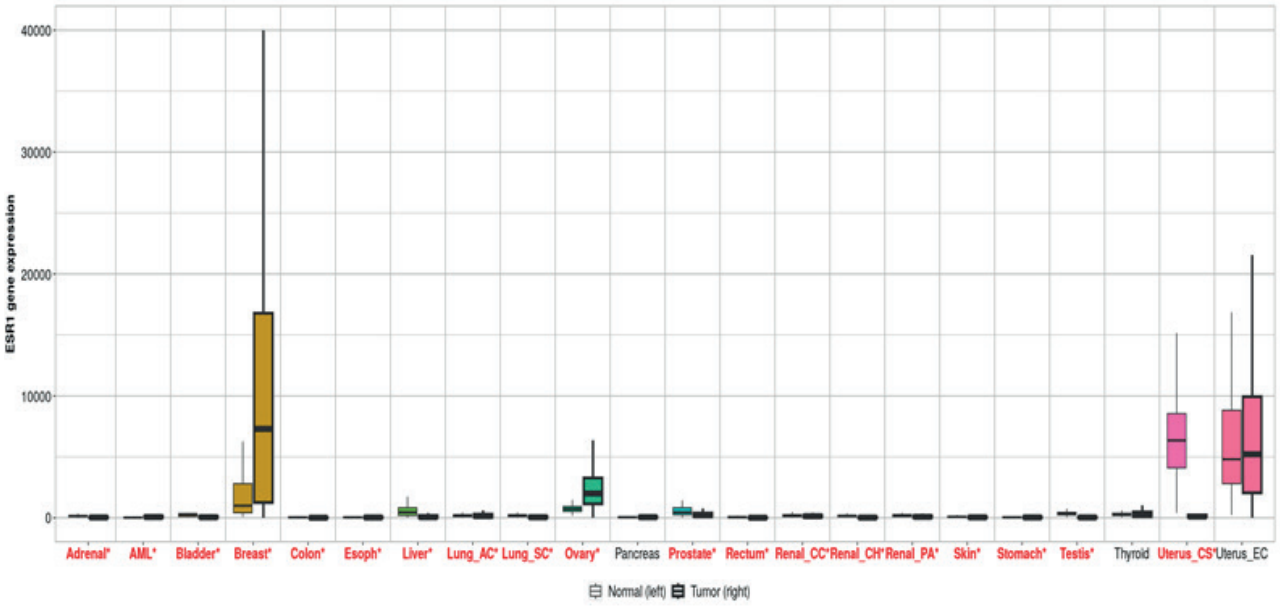


Figure 1 – The comparison of ESR1 gene expression levels in various malignancies

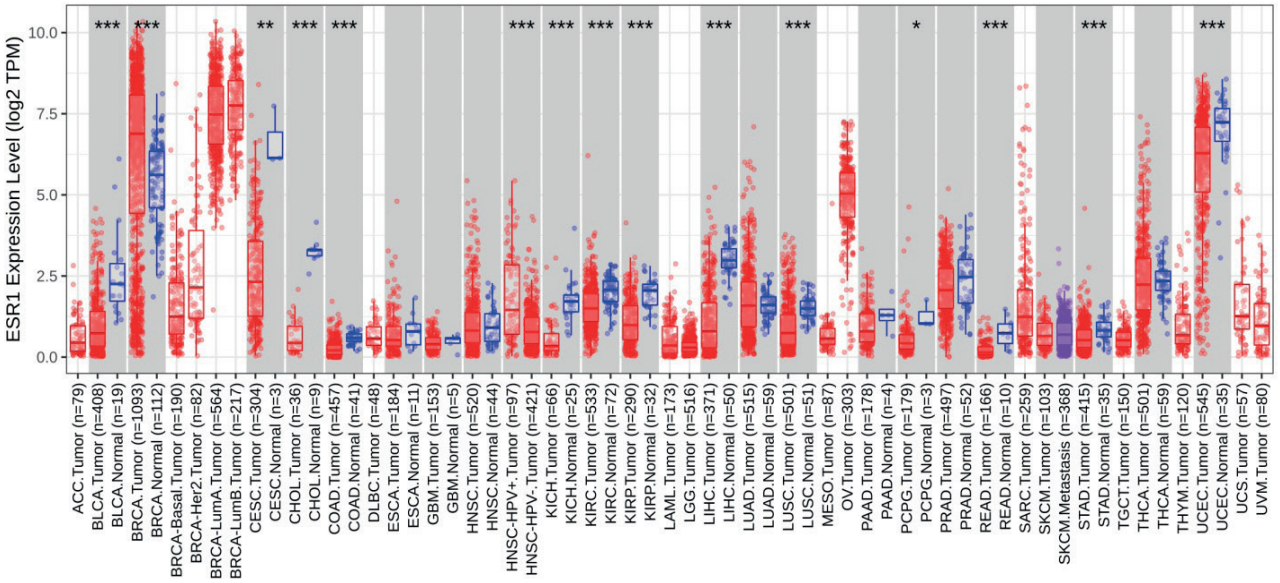


Figure 2 – The human ESR1 expression levels in various tumor types (TCGA database)

ESR1 expression is lower in metastatic samples than in normal samples.

The overall survival of ESR1 gene expression of various tissues, showing maximum ESR1 expression in terms of clinical relevance and other aspects such as age, gender, race, and stage, was analyzed using the TIMER2.0 database in order to find out the Prognostic potential. Data pertaining to ovarian, breast, cervical, and uterine cancers was examined. The findings showed that breast cancer patient groups with lower ESR1 expression in the graph showed lower survival rates, and higher expression of the gene showed a better survival in breast and uterus cancer patient groups (Figure 6) (Hazard ratio=0.839, p=0.01; Hazard ratio=0.748, p=0.06, respectively).

In case of cervical cancer patients with low ESR1 expression, a better survival was observed (Hazard ratio=1.03, p=0.785). Ovarian cancer patients with a low ESR1 expression showed a higher survival at a certain point, and after that, it declined immediately (Hazard ratio=1.05, p=0.475). The correlation between ESR1 expression and hormone therapy response is not perfect; 30% of ER-positive

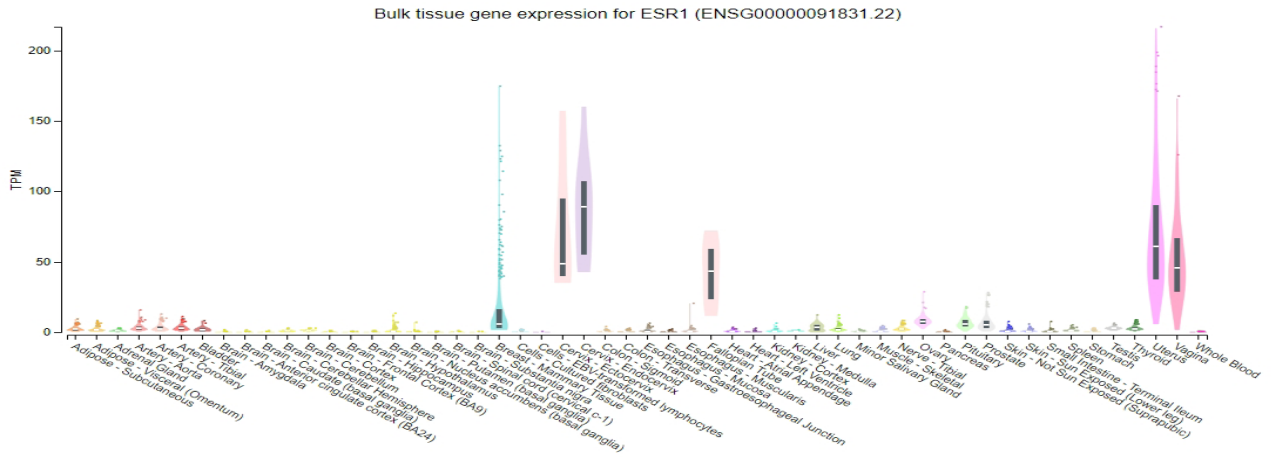


Figure 3 – Bulk tissue expression for ESR1 (Data Source: GTEx Analysis Release V8)

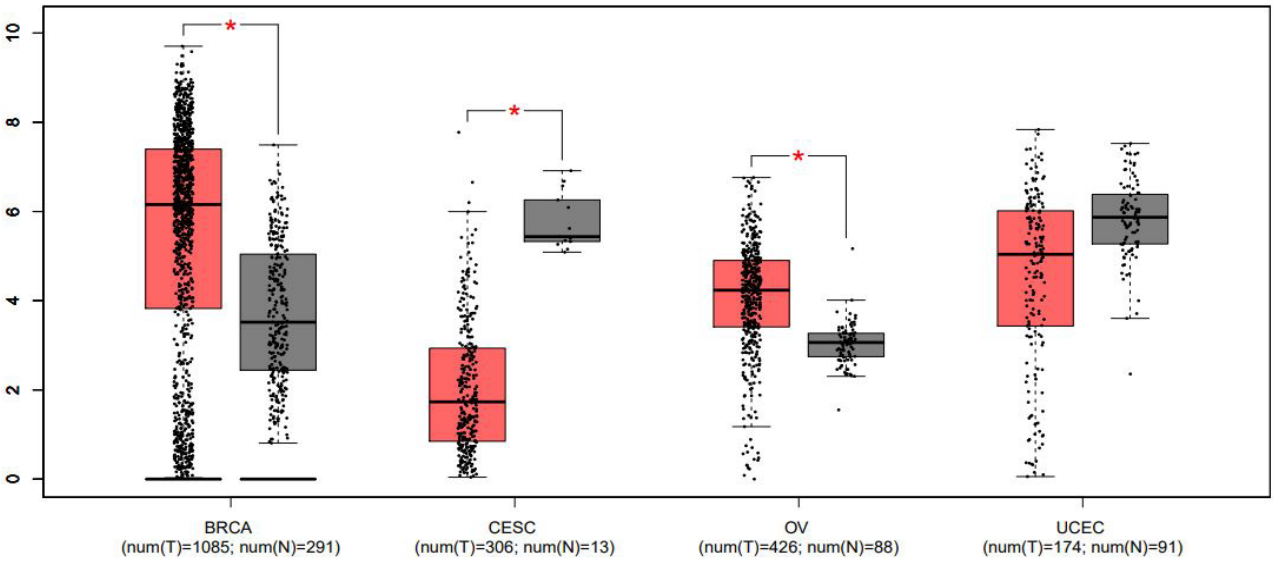


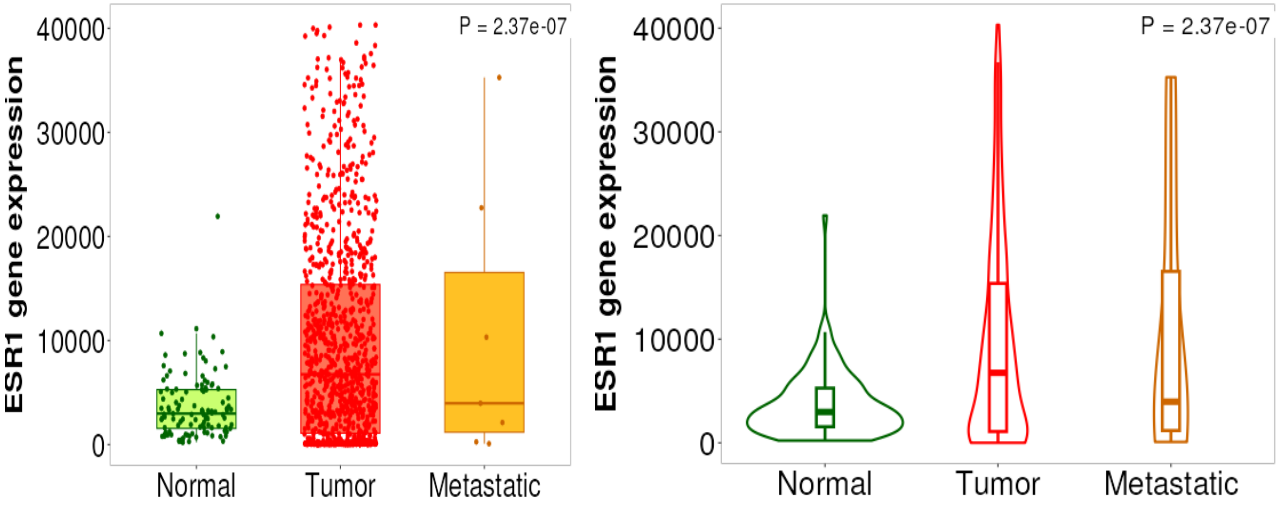
Figure 4 – Differential expression of ESR1 gene in Breast, Cervix, Ovary, Uterine tumor, and normal tissue (Matched TCGA normal and GTEx data)

tumors do not respond to treatment, while 5-15% of ER-negative malignancies give a positive response. It is yet unknown what molecular processes underlie the correlation between ESR1 expression, hormone responsiveness, and cancer prognosis. Certain gene sets that co-express ESR1 have been proposed to be an essential component in determining the hormone-responsive phenotype of breast carcinoma.

DISCUSSION

ESR1 plays an important role in the control of eukaryotic gene expression, according to the molecular function of the gene as described by GENATLAS. Multiple research studies established baseline evidence that ESR1 is triggered by estrogen, which is implicated in the emergence of certain cancers, such as breast, cervical, endometrial, and ovarian cancers, which is also consistent with the current findings [20, 24]. Using data from the TIMER2.0 database, the current study found differential ESR1 expression in human malignancies, demonstrating overexpression in cancers such as breast, cervix, colon, kidney, ovarian, and uterine, etc., which is consistent with previous findings [12, 30].

The RNA-sequence data of ESR1 expression in tumor tissues, normal tissues, and metastases were collected using the TNMplot database. This study showed that tumor tissue expressed more ESR1 than both normal and metastatic samples. ESR1 expression levels were higher in breast, ovarian and uterine tumor tissue than in normal tissues, as per the analysis of ESR1 expression using the GEPIA database. This finding is consistent with prior investigations [14, 28].



TNM plot							
Tissue	Min	Q1	Med	Q3	Max	Upper whisker	n
Normal	218	1550	2975	5278	21932	10685	113
Tumor	4	1245	7196	17086	164851	40314	1097
Metastatic	85	1185	3964	16535	35272	35272	7

Figure 5 – The ESR1 gene expression in normal, tumor, & metastatic tissues (TNM plot database RNA-Seq-based data)

Several clinical studies have demonstrated that ESR1 responds to hormonal treatments like aromatase inhibitors and tamoxifen, which prevent androgen from being converted to estrogen and lower the amount of estrogen in the blood [20, 24]. Mechanisms of acquired or innate resistance lead to the failure of endocrine therapy. One possible cause of resistance to endocrine therapy is mutations in ESR1 [29]. Such mutations are responsible for around 50% of endocrine resistance cases, while other recent discoveries indicate roles for the RAS-MAPK, & CDK4/6-RB-E2F pathways, as ESR1 deletion, amplification, & translocation [13, 19]. The ESR1 pathway is involved in tumor growth and maturation and influences cells through genomic as well as non-genomic mechanisms. Differential ESR1 mRNA expression has been identified in human malignancies by analysis of mutiomics information, showing upregulation in cancers such as breast, ovary, and uterus [12, 21].

Using the TIMER database, an examination of the clinical significance of ESR1 gene expression across various cancer types revealed differing survival outcomes. These findings highlight the diverse impact of ESR1 expression on cancer prognosis across different cancer types. The findings outlined in this study underscore the complexity of estrogen receptor (ER) signalling in various cancer types and its implications for treatment outcomes [6, 10]. Similar to prior studies, groups of patients with breast and uterine cancer who had increased ESR1 expression showed higher survival rates [16].

Patients with cervical cancer who expressed less ESR1 had a higher chance of survival, similar to other studies [11, 32]. Patients with ovarian cancer who had reduced ESR1 expression initially had a greater survival rate, but it quickly dropped after that. No clear predictive impact was identified by other researchers who also examined the role of ESR1 expression in ovarian cancer [14, 18]. Further studies in this field focusing on molecular aspects could provide significant insights to improve cancer prognosis and therapy approaches.

The correlation between ESR1 expression and hormonal therapy response emphasized the significance of understanding the mutant ESR1 and the molecular mechanisms that underlie this aspect correlation, including the possible influence of co-expressed gene sets. Additional studies in this field focusing on molecular aspects could provide significant insights to improve cancer prognosis and therapy approaches.

CONCLUSION

The diverse roles of ERs and their expression levels in various tissues have been highlighted in this study. While substantial progress has been made in understanding the genetic and other factors involved in cancer, there is a need for more focused research on ESR1-positive cancers. The ESR pathway plays a

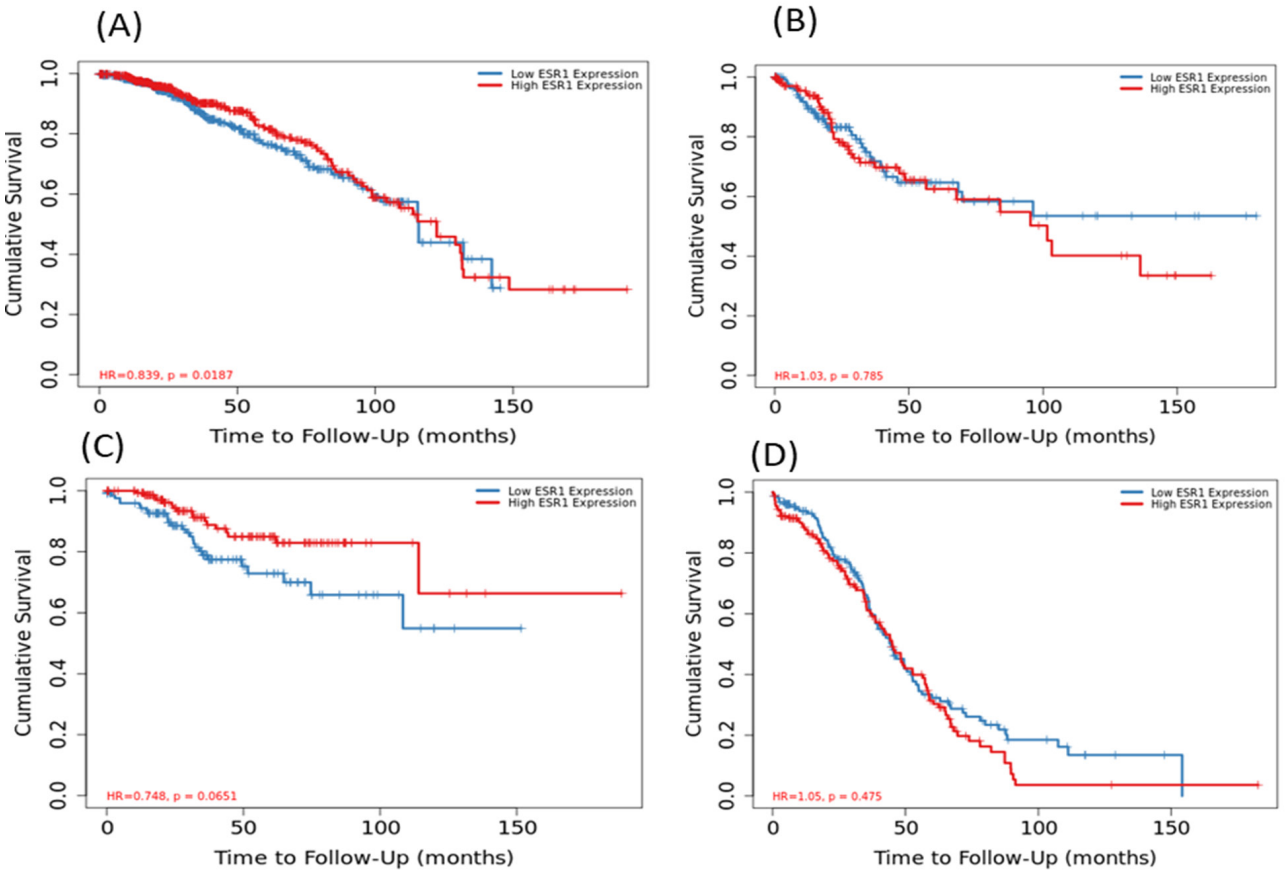


Figure 6 – Kaplan – Meier analysis of the relationship between cumulative survival difference of ESR1gene expression for (A) BRCA (n=1 100), (B) CESC (n=306) (C) UCEC (n=545), (D) OV (n=303) HR, hazard ratio

crucial role in tumor growth and maturation through estrogen regulation; it is essential to comprehend the formation and progression of many cancers. Studying the genomic and non-genomic mechanisms by which estrogen affects cell proliferation will help us better understand how changes in the ESR1 pathway lead to the development of tumors. Comparative analysis of ESR1 expression in tumors and normal tissues using many databases can provide deeper insights, ultimately aiding in the development of targeted therapies and improving patient outcomes. The analysis indicates that ESR1 expression is significantly elevated in tumor samples relative to normal and metastatic tissues. These findings underscore the potential role of ESR1 in tumor development and highlight the importance of further research to understand its contribution to cancer progression and metastasis.

Author contributions:

Sole authorship.

***Conflict of interest*:**

The author declares that there are no potential conflict of interest.

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ОЦЕНКА ЭКСПРЕССИИ ГЕНА ESR1 IN SILICO ПРИ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЯХ

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Ген рецептора эстрогена 1 (ESR1) играет ключевую роль в регуляции генов, чувствительных к ER, и влияет на многие физиологические процессы. Этот ген кодирует рецептор эстрогена (ERa), который необходим для пролиферации и дифференцировки клеток, и участвует в развитии различных заболеваний, включая остеопороз, а также злокачественных новообразований, таких как рак толстой кишки, яичников, эндометрия и молочной железы. В связи с ассоциацией мутагенной формы ESR1 со многими видами рака, она также исследуется в качестве потенциального биомаркера рака. Наибольшая экспрессия гена ESR1 в тканях обнаружена в основном в тканях, связанных с женскими репродуктивными органами (молочные железы, ткани шейки матки, фаллопиевы трубы, матка и влагалище). В представленном исследовании анализировалась экспрессия ESR1 при злокачественных новообразованиях с использованием инструментов *in silico*. TNMplot, TIMER2.0, GTEx, GEPIA, TCGA и др. были использованы для изучения дифференциальной экспрессии генов ESR1 при различных видах рака, изучения корреляции генов и оценки прогностического воздействия и выживаемости пациентов. Исследование показало, что опухолевая ткань демонстрирует более высокую экспрессию ESR1, чем нормальные или метастатические ткани. Экспрессия ESR1 была высокой на всех стадиях развития злокачественного новообразования. Наблюдались различия в общей выживаемости при злокачественных новообразованиях молочной железы, шейки матки, матки и яичников. Результаты исследования могут быть полезны при разработке более эффективных таргетных методов лечения, послужить улучшению результатов лечения пациентов и совершенствованию стратегий лечения рака, а аспект совместной экспрессии генов и связанной транскрипции может стать предметом будущих молекулярных исследований.

Ключевые слова: эндокринный рецептор; ESR1; экспрессия гена; эндокринная терапия; общая выживаемость; раковые клетки; метастазирование

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ҚАТЕРЛІ ІСІКТЕРДЕГІ ESR1 IN SILICO ГЕНІНІҢ ЭКСПРЕССИЯСЫН БАҒАЛАУ

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Эстроген рецепторы 1 гені (ESR1) ER сезімтал гендерді реттеуде шешуші рөл атқарады және көптеген физиологиялық процестерге әсер етеді. Бұл ген жасушалардың көбеюі мен дифференциациясы үшін қажет эстроген рецепторын (ERa) кодтайды және әртүрлі аурулардың, соның ішінде остеопороздың, сондай-ақ тоқ ішек, аналық без, эндометрия және сүт безі қатерлі ісігі сияқты қатерлі ісіктердің дамуына қатысады. ESR1 мутагендік түрінің көптеген қатерлі ісіктермен байланысына байланысты ол қатерлі ісіктің ықтимал биомаркері ретінде де зерттелуде. Тіндердегі ESR1 генінің ең үлкен экспрессиясы негізінен әйелдердің ұрпақты болу мүшелерімен (сүт бездері, жатыр мойны тіндері, жатыр түтіктері, жатыр және қынап) байланысты тіндерде кездеседі. Ұсынылған зерттеу in silico құралдарын пайдалана отырып, қатерлі ісіктердегі ESR1 экспрессиясын талдады. TNMplot, TIMER2.0, GTEx, GEPIA, TCGA және т. б. әртүрлі қатерлі ісіктердегі ESR1 гендерінің дифференциалды экспрессиясын зерттеу, гендердің корреляциясын зерттеу және пациенттердің болжамды әсері мен өмір сүруін бағалау үшін пайдаланылды. Зерттеу ісік тінінің қалыпты немесе метастатикалық тіндерге қарағанда ESR1 жоғары экспрессиясын көрсететінін көрсетті. ESR1 экспрессиясы қатерлі ісік дамуының барлық кезеңдерінде жоғары болды. Сүт безінің, жатыр мойнының, жатырдың және аналық бездің қатерлі ісіктерінің жалпы өмір сүруінде айырмашылықтар байқалды. Зерттеу нәтижелері тиімдірек мақсатты емдеу әдістерін әзірлеуде пайдалы болуы мүмкін, пациенттердің нәтижелерін жақсартуға және қатерлі ісік стратегияларын жақсартуға қызмет етеді және бірлескен ген экспрессиясы мен байланысты транскрипция аспектісі болашақ молекулалық зерттеулердің тақырыбы болуы мүмкін.

Кілт сөздер: эндокриндік рецептор; ESR1; ген экспрессиясы; эндокриндік терапия; жалпы өмір сүру; рак клеткалары; метастаз