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A Correlative Study of Estrogen Receptor Signaling: Molecular and Histological Perspectives in ER-Positive Breast Tumors

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Abstract

Breast tumor remains the most widespread and lethal malignancy affecting women worldwide. Approximately two-thirds of cases are classified as hormone receptor-positive, characterized by the expression of estrogen and progesterone receptors, and are closely regulated by estrogen signaling pathways. The primary therapeutic approach for these tumors involves antiestrogen agents; however, resistance to such treatments inevitably develops due to various molecular mechanisms. These include aberrant activation of the PI3K signaling cascade, mutations in the ESR1 gene, functional alterations of estrogen receptors, and disruptions in cell cycle regulation. In response to these challenges, novel therapeutic strategies have emerged, such as selective estrogen receptor degraders (SERDs) and combination regimens incorporating cyclin-dependent kinase (CDK) 4/6 inhibitors or PI3K pathway inhibitors. A comprehensive understanding of estrogen receptor biology is therefore essential for optimizing treatment outcomes and guiding the development of next-generation therapies. This study highlights current advances in the molecular mechanisms, signaling dynamics, and clinical implications of estrogen receptor activity in hormone-dependent breast cancer.

Keywords: estrogen; endocrine resistance; breast tumor

Introduction

In 2020, breast cancer was the most frequently diagnosed cancer globally, accounting for 11.7% of the 19.3 million new cases, slightly surpassing lung cancer at 11.4% . While lung cancer remains the leading cause of cancer-related deaths across all genders (18% of 10 million deaths), breast cancer is the most fatal malignancy among women, responsible for 15.5% of female cancer deaths and 6.9% of total cancer

mortality . Although breast cancer predominantly affects women, approximately 1 in every 100 cases in the United States occurs in men, who share similar pathological features. (Sung *et al*., 2021)

Healthy mammary epithelium—whether ductal or lobular—consists of two main cell types: basal cells, which contribute to milk ejection through contractile activity, and luminal cells, which are responsible for milk production (Pandya & Moore, 2011) . Luminal cells express cytokeratins 8 and 18, the epithelial adhesion molecule EpCam, and hormone receptors such as estrogen (ER), progesterone (PR), and prolactin receptors (Pellacani *et al*., 2019). Basal cells, on the other hand, are characterized by the expression of cytokeratins 5, 14, and 17, as well as P-cadherin and desmosomal cadherins, along with markers associated with smooth muscle differentiation (Rodriguez-Boulan & Macara, 2014).

The development and differentiation of mammary epithelial cells are primarily regulated by estrogen, progesterone, and prolactin. Additionally, growth factors such as insulin-like growth factor (IGF), fibroblast growth factor (FGF), amphiregulin (AREG), and members of the epidermal growth factor (EGF) family play essential roles in mediating estrogen's effects during pubertal mammary gland development (Ciarloni *et al*., 2007), (Troyer & Lee, 2001).

Breast cancer arises from the malignant transformation of ductal or lobular epithelial cells, resulting in a highly heterogeneous disease. This intratumoral heterogeneity enables cancer cells to dynamically reprogram their gene expression and behavior in response to microenvironmental cues, promoting tumor progression and resistance to therapy. Once locally advanced, the disease may metastasize to distant organs such as the brain, liver, lungs, or bones (Liang et al., 2020).

Due to variations in anatomical origin, histological subtype, genetic profile, and hormonal dependency, breast tumors exhibit diverse levels of aggressiveness and clinical outcomes. These differences necessitate individualized therapeutic approaches (Harbeck *et al*., 2019).

The estrogen receptor (ER) acts as a transcription factor that regulates genes involved in apoptosis, cell proliferation, and cell cycle progression. Upon activation, ER promotes the expression of oncogenic mediators such as MYC, Cyclin D1, FOXM1, GREB1, BCL2, amphiregulin, IGF-1, and CXCL12, which contribute to DNA damage and uncontrolled cell growth in response to estrogen signaling (Harbeck et al., 2019).

When estrogen (E2) binds to ER, the receptor undergoes dimerization, translocates to the nucleus, adopts an active conformation, and recruits transcriptional coactivators. In contrast, antagonists like tamoxifen induce an inactive ER conformation that attracts corepressors, thereby inhibiting gene transcription (Shiau *et al*., 1998).

Activated ER binds to estrogen-responsive elements (EREs) in the promoters of target genes. Additionally, ER can regulate genes lacking EREs by interacting with transcription factors such as AP1 and SP1 via serum-responsive elements (SREs) (Mal et al., 2020), (Girault et al., 2003). This genomic activity governs the transcription of hundreds of genes linked to cellular growth and differentiation. Most ER-positive (ER+) or luminal breast cancers arise from dysregulated ER expression, altered receptor activity, or disrupted function of ER-associated cofactors and target genes. (Le Romancer et al., 2011).

Estrogens also activate other receptors, including ERβ and GPER. ERβ, encoded by the ESR2 gene, shares structural similarities with ERα and is expressed in both reproductive tissues (e.g., mammary glands, ovaries, uterus, testes) and non-reproductive organs (e.g., brain, lungs, adrenal glands, adipose tissue) (Acconcia et al., 2005). ERβ interacts with various transcriptional cofactors and shares ligands with ERα, including estrogens and selective estrogen receptor modulators (SERMs). Unlike ERα, ERβ activation

often leads to reduced proliferation and increased apoptosis, although these effects depend on tissue context, cellular environment, and coexpression patterns (Barton et al., 2018).

While ERβ expression is generally associated with favorable prognosis in breast cancer, some studies suggest a more complex role. Coactivators such as AIB1, NF-κB, and TIF-2 have been shown to enhance ERα-driven tumor growth and metastasis (De Francesco et al., 2014).(Dustin et al., 2019).

High expression of these cofactors in aggressive tumor subtypes correlates with poor clinical outcomes, indicating that they may amplify ERα signaling in malignancy (Hanker et al., 2020). Further investigation is needed to clarify ERβ's physiological role and its impact on breast cancer progression (Kharb et al., 2020) (Wittmann et al., 2007).

This study aims to provide an overview of estrogen receptor signaling in breast cancer.

Materials and methods

This study included 50 breast tissue specimens preserved in formalin and embedded in paraffin, all diagnosed histologically as invasive ductal carcinoma. The cohort comprised 22 male and 28 female patients. Samples were retrieved from the pathology archive of the Oncology Center in Wasit, following approval from the institutional ethics committee.

Tissue sections were prepared at a thickness of 4 µm and stained with hematoxylin and eosin (H&E) to assess general histological architecture. For the evaluation of estrogen receptor alpha (ERα) expression, immunohistochemical (IHC) staining was performed using monoclonal anti-ER antibodies. The extent and intensity of nuclear staining were assessed using the Allred scoring system, which combines proportion and intensity scores to provide a semi-quantitative measure of receptor expression.

Results

Microscopic examination revealed typical features of invasive ductal carcinoma, including irregular glandular structures, nuclear pleomorphism, and increased mitotic activity. ERα expression was predominantly nuclear and varied in intensity across samples.

Male samples (n = 22),44% showed moderate to strong ERα positivity. Female samples (n =28) 56% demonstrated high ERα expression, with luminal A and B subtypes predominating (figures 1 & 2) . The histological grade correlated with ERα expression, where lower-grade tumors exhibited stronger receptor positivity. Additionally, ERα-positive tumors showed reduced necrosis and better glandular differentiation.

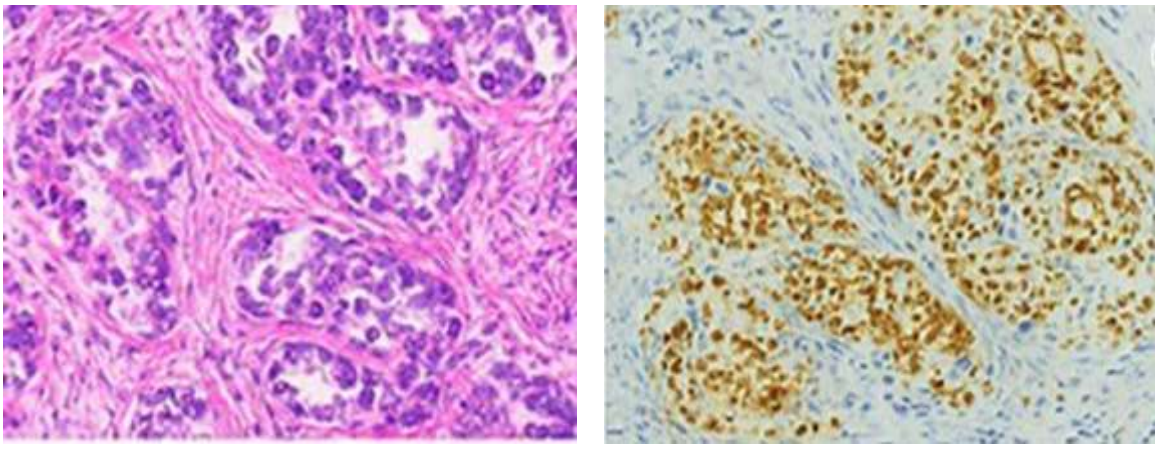

Figure 1. Histological microphotographs of breast tissue from a 55-year-old female patient diagnosed with invasive ductal carcinoma, classified as estrogen receptor-positive luminal A subtype. (a) H&E staining reveals irregular glandular architecture, marked nuclear pleomorphism, and dense fibrous stroma. (b) IHC staining for ERα shows strong nuclear positivity (brown staining) in tumor cells, confirming ER-positive status consistent with luminal A classification.

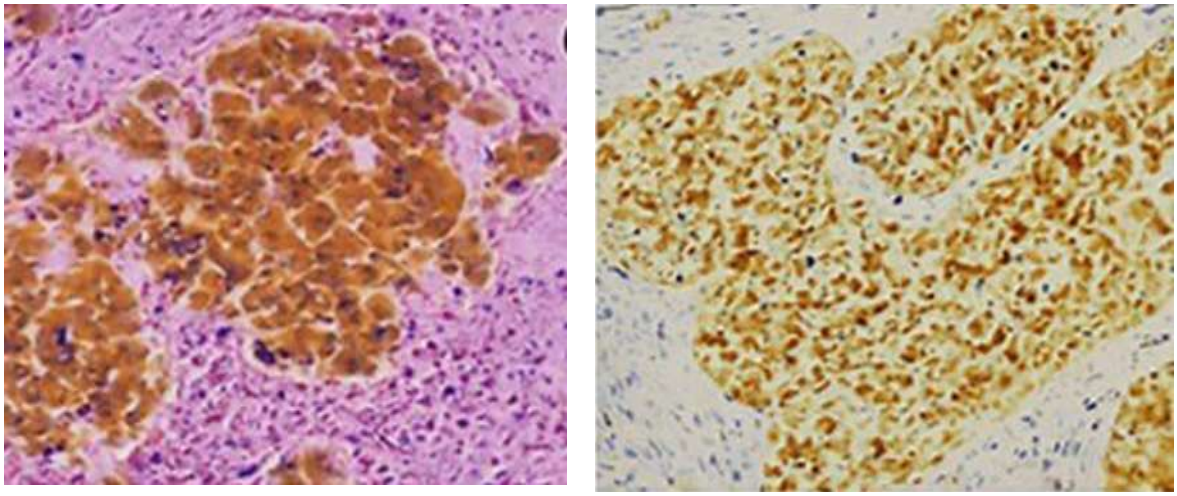

Figure 2. Histological assessment of ERα expression in ER-positive breast cancer biopsies from male and female patients. (a) IHC staining of male breast cancer tissue (n = 22) shows moderate to strong nuclear ERα expression. (b) IHC staining of female breast cancer tissue (n = 28) reveals intense and uniform ERα nuclear positivity, consistent with luminal A and B subtypes.

Discussion

The histopathological evaluation confirmed hallmark features of invasive ductal carcinoma, including architectural distortion, nuclear pleomorphism, and elevated mitotic activity. These findings are consistent with the aggressive nature of this subtype and reinforce its predominance in breast cancer diagnoses (Garrido-Castro *et al*., 2019).

Immunohistochemical analysis revealed that estrogen receptor alpha (ERα) expression was primarily nuclear and varied between male and female patients. Notably, 56% of female samples exhibited high ERα positivity, predominantly within luminal A and B subtypes, while 44% of male samples showed moderate to strong expression. This sex-based variation in ERα intensity may reflect underlying biological differences in tumor behavior and hormone responsiveness (Slepicka *et al*., 2019).

The observed correlation between histological grade and ERα expression—where lower-grade tumors demonstrated stronger receptor positivity—supports the established notion that ERα-positive tumors tend to be more differentiated and less aggressive (Łukasiewicz et al., 2021). Additionally, the reduced necrosis and improved glandular organization in ERα-positive cases further suggest a more favorable prognosis. (Prat *et al*., 2013)

Figures 1 and 2 visually reinforce these findings, highlighting the contrast in ERα staining patterns and architectural features between male and female tissues. The intense and uniform nuclear staining in female luminal tumors aligns with their classification and potential responsiveness to hormone therapy. (Garrido-Castro et al., 2019)

Importantly, these results underscore the clinical relevance of ERα as both a diagnostic marker and a therapeutic target. The differential expression across sexes and tumor grades may influence treatment planning, particularly in selecting candidates for endocrine therapy (Prat et al., 2015). Moreover, the presence of ERα in male breast cancer—though less frequent—warrants further investigation into tailored hormonal strategies for this subgroup (Winters et al., 2017). Overall, the data support the utility of ERα immunohistochemistry in stratifying breast cancer cases and guiding personalized treatment approaches (Godet & Gilkes, 2017).

Conclusions

This study highlights the central role of estrogen receptor (ER) signaling—both genomic and non-genomic—in the development, progression, and therapeutic targeting of breast cancer. The identification of ER isoforms and mutations, along with their contribution to endocrine resistance, underscores the complexity of hormone-dependent tumors. Advances in molecular profiling and targeted therapies, including SERMs, SERDs, CDK4/6 inhibitors, and epigenetic modulators, offer promising strategies to overcome resistance and improve patient outcomes. Continued research into ER biology and its variants remains essential for optimizing personalized treatment approaches.

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Conflicts of interest

The authors declare no conflict of interest.

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