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# Deciphering the Roles of Estrogen Receptors and 27-Hydroxycholesterol in BC Progression

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***Abstract***

*Breast cancer (BC) ranks among the top causes of cancer-related deaths in women worldwide. Many risk factors of BC are linked to estrogen. Experiments of Beatson in 1896 show the role of steroid hormones as major determinant in BC. Action of steroid hormones is mediated by their receptors including Estrogen receptors (ERs). ERs are part of a subfamily of ligand-regulated transcription factors. Their primary role is to translate hormone signals into a wide range of physiological responses across different organs. One of the widely studied ER is ER-alpha. One of the major strategies for the treatment of BC is the prevention of the expression of ER-alpha by using antiestrogens, such as tamoxifen and ICI 182,780. The complete understanding of ER-alpha function and inhibition has been gone far by new discoveries of ER-alpha mutations, coregulatory proteins modulating ER activity, alternative downstream signaling pathways, and crosstalk with other intracellular signal transduction pathways. Since hormone therapy based on ER-alpha involves the utilization of antiestrogens and aromatase inhibitors, on other hand 27-hydroxycholesterol (27HC) can bind and activate ERs, which make them supportive to BC. 27HC is synthesized from cholesterol by the enzyme sterol 27-hydroxylase, also known as cytochrome P450 27A1 (CYP27A1). Since the presence 27HC is directly proportional to the presence of cholesterol, their role in obesity associated BC is evident. 27-HC also involved auxiliary targets that facilitate the metastatic phenotype. 27-HC is not engaging in metastasis through ER receptors, instead the act by the activation of the liver X receptors. Amy E. Baek et al. came forward to address this possibility through an experiment with mice. The results of these experiments showed that mice pretreated with 27HC developed significantly more metastatic nodules compared to those pretreated with a placebo.*

**Keywords:** 27-hydroxycholesterol, breast cancer, estrogen receptors, SERM, X receptors

## INTRODUCTION

Breast cancer (BC) is a major cause of cancer-related deaths among women worldwide, with global rates varying by up to five times. It is disturbing to know that they are escalating in regions where the rate of disease was low until recent times. About 1.38 million novels BC cases were reported in 2008. Among these 1.38 million cases, almost 50% of patients and 60% of fatalities are culminating in developing countries. The global disparity in BC survival rates is significant, with the estimated 5-year survival rate exceeding 80% in developed nations but falling below 40% in developing regions. Based on the data of 2013, in developed countries like the United States, around 232,340 women will be diagnosed with BC and 39,620 women will be dead due to BC. The lifetime threat of evolving BC in an American woman is 12.38%.

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Some of the threat vectors of BC are early menarche, late menopause, and obesity in postmenopausal women. Many of the threat factors are estrogen related. Notable longitudinal studies have demonstrated that elevated levels of endogenous estradiol (E2) are correlated with an augment in risk. Various investigations demonstrate that childbearing minimizes risk and early births and a larger number of births minimizes the risk. Some other pieces of research suggest that breastfeeding is likely to have a preventive effect. Oral contraceptives and hormonal therapy for menopause triggers a slight uptick in breast-cancer risk, which observed to decline when stop to use. Alcoholism elevates the risk, whereas exercise reduces the risk. Mutations of specific genes significantly elevate BC risk, but it is happening for a small number of cases. Genetic research on tumor cells revealed the involvement of frequently mutated genes. More than 50% of the tumors analyzed showed mutations in the p53 tumor suppressor gene. BCs frequently exhibit mutations that disrupt the retinoblastoma protein (pRB) pathway, such as the loss of expression of pRB or p16INK4a [1–4].

Different modern treatments are available for BC. Antiestrogens like raloxifene and tamoxifen may help prevent BC in individuals at elevated risk [5]. Additionally, surgical intervention on both breasts serves as a preventive option for those at high risk. BC patients receive a variety of treatments, including targeted therapy, hormonal therapy, radiation, surgery, and chemotherapy [6]. One troubling side effect of BC treatment is that some individuals may turn to alternative methods. For instance, some patients may use herbal remedies, viewing them as natural options, since certain plants are believed to have properties that could help treat BC. However, relying on unverified treatments can be very risky, as they often lack scientific validation [7]. Breasts consist of adipose tissue and are found in both males and females [8, 9]. Female breasts have a higher proportion of glandular tissue compared to male breasts. Each female breast contains 12–20 lobes, which are subdivided into smaller lobules [10], and these lobes and lobules are interconnected by milk ducts. The adipose tissue is supported by a network of nerves, blood vessels, lymphatic vessels, and lymph nodes, along with fibrous connective tissue and ligaments [11]. Cancer develops from the uncontrolled growth of cells that undergo mutations in the genes responsible for regulating cell proliferation and survival. Most BCs originate from epithelial cells. Genetic analyses of tumor cells from patients have identified several frequently mutated genes, with mutations in the p53 tumor suppressor gene found in more than half of the tumors studied. BCs frequently harbor mutations that impair the pRB pathway, which can involve the loss of expression of either pRB or p16INK4aThis disruption can lead to the amplification or overexpression of cyclin D1 [12]. Breast carcinoma cells often exhibit changes in the Ras signaling pathway [13], these changes can occur through different mechanisms, with the most notable being the amplification or overexpression of the HER-2/neu gene [14]. However, genetic analyses of different BCs show that no single mutation is consistently found in all cases. Furthermore, it remains unclear how many mutated genes are necessary to transform a normal human mammary epithelial cell (HMEC) into a tumor cell. One approach to investigating this question involves introducing mutant cancer-associated genes into immortalized HMEC cell lines. Although this approach has facilitated the creation of tumorigenic derivative lines, the genetic characteristics of these lines are often indeterminate due to the methods used for their immortalization. Such methods may include treating HMECs with chemicals like benzo(a)pyrene or selecting immortalized cell clones after prolonged culture, complicating the understanding of how these genes contribute to tumor formation [15, 16]. Prolonged estrogen exposure is associated with a higher risk of BC development. While the exact mechanisms underlying estrogen-mediated carcinogenesis are not fully understood, the prevailing theory suggests that E2 acts through an estrogen receptor (ER) known as estrogen receptor alpha (ER-alpha). ER-alpha promotes cell proliferation and can trigger mutations arising from replication errors during pre-mitotic DNA synthesis. The subsequent effects of E2 support the growth of mutated cells, allowing for the accumulation of mutations that can eventually lead to neoplastic transformation. Additionally, laboratory and epidemiological studies suggest that non-receptor mediated mechanisms, resulting from the genotoxic effects of estrogen metabolites, may also play a role in the development of BC.

 

## ESTROGEN RECEPTORS (ERS) AND BC

In 1896 Beatson used ovariectomy to prevent tumor recurrence and literally, he induces regression of the primary tumor, which gave a clue about the role of steroid hormones being a major determinant of BC [17]. Steroid hormones influence cellular activity by binding to their receptors, which function as transcription factors. ERs are part of a subfamily of ligand-regulated transcription factors that transmit hormonal signals, leading to a wide range of physiological responses across different organs [18]. The two structurally related ERs, such as ER-alpha and the ER-regulated progesterone receptor (PR) are widely studied, because of their elevated protein levels in premalignant and malignant breast lesions as opposed to normal tissue [19]. Both receptors proved their importance in predictive and prognostic factors in the clinical management of the disease [20]. Inhibition of the ER-alpha has become one of the major strategies for the prevention and treatment of BC. Steroid hormones achieve their effects by interacting with their receptors, which serve as transcription factors. The problem of antiestrogen resistance arises and the mechanisms are not fully understood. The complete understanding of ER-alpha function and inhibition has been gone far by new discoveries of ER-alpha mutations, co-regulatory proteins modulating ER activity, alternative downstream signaling pathways, and crosstalk with other intracellular signal transduction pathways. A second ER, called ER-beta, has also been discovered recently. The structure and activity of ER-beta are similar but not identical to ER-alpha. ERs are part of a subfamily of ligand-regulated transcription factors that translate hormonal signals into diverse physiological responses across various organs. There are two closely related ERs, ER-alpha and ER-beta, which are encoded by distinct genes and exhibit differential expressions in tissues. ER-alpha is essential for mediating estrogen-driven mitogenic signaling in epithelial cells found in breast, uterine, and ovarian tissues [21]. In normal breast tissue, both ER isoforms are present at low levels; however, BC cells primarily express ER-alpha rather than ER-beta. Indeed, ER-alpha is the sole receptor detected via immunohistochemistry in BC biopsies. Tumors that do not exhibit nuclear ER are categorized as “ER-negative,” while those with nuclear ER are labeled “ER-positive.” At least 70% of BCs are categorized as ER-positive (ER+), commonly characterized by the expression of ER-alpha, PR, or erythroblastosis oncogene B2 (ErbB-2, HER2/NEU), often in varying combinations. ErbB-2 belongs to the HER family of transmembrane receptor tyrosine kinases (RTKs), which also includes the epidermal growth factor receptor (EGFR/HER1) [22]. A small fraction of ERs is found in the cytoplasm and at the cell membrane, where they closely interact with adaptor proteins to form multiprotein complexes that activate the MAPK and AKT signaling pathways (Figure 1) [23].

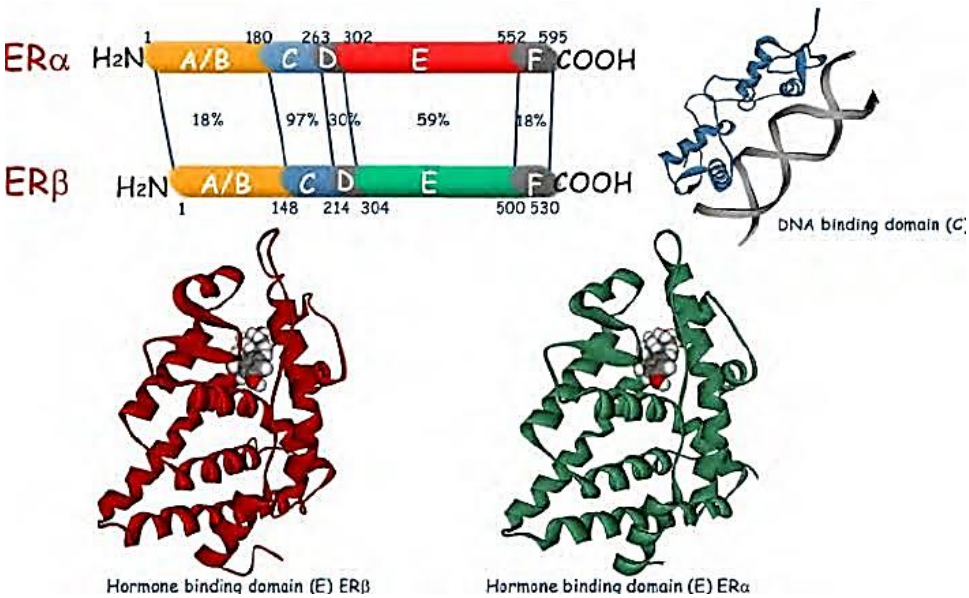


**Figure 1.** A comparison of the structural domains of estrogen receptor alpha (ERα) and beta (ERβ) highlights.

 

"The top panel shows the domain organization of both receptors, with the percentage identity between ERα and ERβ indicated for each domain. The bottom panel presents the 3D structures of the hormone-binding domains (E) for both ERα (green) and ERβ (red), with the DNA-binding domain (C) shown in blue for ERα."

It is thought that ER proteins usually move back and forth between the cytoplasm and the nucleus. In vitro studies indicate that ligand-free ER-alpha, like other steroid nuclear receptors, exists in a non-DNA binding form within a multi-chaperone complex organized around Hsp90 [23]. Although information on ER-beta is more limited, both receptors are thought to activate gene transcription similarly upon estrogen binding. ER-mediated transcription is a intricate process that requires the involvement of various coregulatory factors and the interaction ("cross-talk") between multiple signaling pathways. The mechanisms include:

## THE CANONICAL GENOMIC ER-MEDIATED TRANSCRIPTION MECHANISM

The canonical genomic mechanism of ER-mediated transcription begins with the binding of E2, which causes conformational changes in ER-alpha. These changes regulate its interactions with heat shock proteins and coregulators, although the relationship between ER-beta and Hsp90 is not as well understood. This interaction allows the ER to bind to the 13-bp estrogen response element (ERE) located in the promoter region. ER dimers greatly enhance transcriptional activity by engaging in chromatin remodeling through various regulatory proteins in a dynamic and sequential fashion [24]. Key nuclear receptor coactivators linked to ER include the general transcription factor p300/CBP, which acts as a coadaptor between nuclear receptors and DNA. P300/CBP is vital for regulating the cell cycle, cell differentiation, and apoptosis, and it has histone acetyltransferase (HAT) activity [25, 26, 27]. HATs are essential for the complete transcriptional activation mediated by ER, and P300/CBP interacts with other HATs, such as PCAF [28], to promote the acetylation of components within the basal transcription machinery. Moreover, methyltransferases like CARM1 and PRMT1 associate with ER-alpha, while members of the p160 protein family – such as steroid receptor coactivator 1 (SRC-1), SRC-2, and SRC-3 (also known as ACTR, RAC-3, pCIP, TRAM-1, and AIB1) – are essential for recruiting the pre-initiation complex DRIP/TRAP.

## THE NON-GENOMIC PATHWAYS

There various non-genomic pathways are

- *Membrane ER:* E2 triggers rapid effects from the membrane, activating various signaling cascades in the extranuclear compartment (non-genomic mechanism). This process involves direct interactions between a small pool of ERs (mainly ER-alpha) localized at the membrane (mbER) and other proteins. ER-alpha forms multiprotein complexes with growth factor-dependent kinases and adaptor proteins, facilitating their interactions and signaling pathways [29]. When E2 binds to membrane-bound ER (mbER) complexes, ER-alpha undergoes de-palmitoylation and detaches from caveolin-1. This event triggers the activation of several downstream signaling pathways, including tyrosine kinase Src, the p85 subunit of PI3K, MAPK, AKT, p21ras, and protein kinase C. This mechanism facilitates the relocation of ER-alpha to other membrane microdomains [30]. The non-genomic effects of E2 binding to mbERs play a significant role in regulating cell proliferation, survival (via ER-alpha), and apoptosis (via ER-beta) [31].
- *GPER:* Estrogen can signal through a seven-transmembrane G protein-coupled receptor called GPCR-30. When E2 binds to GPCR-30, it activates Erk-1 and Erk-2. Alternatively, some researchers propose that non-nuclear effects might result from E2 binding to ERα36 instead of GPCR-30 [32]. Nonetheless, a significant body of evidence supports GPCR-30's role as a membrane ER with specific binding properties [33]. This receptor is now known as GPER-1 (G-protein-coupled ER-1), which stimulates adenyl cyclase, resulting in cAMP-mediated regulation of the EGF-MAPK signaling pathway [34].

 

- *Hormone Therapy***:** Hormone therapy targeting ER includes the use of anti-estrogens and aromatase inhibitors (AIs). Two primary classes of synthetic antiestrogens have been developed for treating ER+/PR+/ErbB2- tumors. One class, selective ER modulators (SERMs), includes well-known agents like tamoxifen (Tam, Nolvadex) and raloxifene. These SERMs can function as either antagonists or agonists depending on the tissue and cellular context. Tamoxifen has been clinically used for over 30 years and is metabolized in the liver to 4-hydroxy-tamoxifen (4-OHTam), which has a 100-fold higher affinity for ER-alpha than tamoxifen itself [35]. The second class, selective ER down regulators (SERDs), includes steroidal anti-estrogens that do not exhibit any agonistic activity in tissues. The only SERD approved for clinical use is Faslodex (fulvestrant, ICI 182780), which is primarily used in cases of tamoxifen resistance [36].

In the context of AIs, aromatase plays a crucial role in converting androstenedione into estrone and E2. This enzyme is found in multiple endocrine tissues as well as in BC cells. Consequently, selective AIs have been developed to lower circulating estrogen levels [37]. Research indicates that approximately 50% of patients with advanced BC do not respond to first-line treatment with tamoxifen, and nearly all patients with metastases experience relapse and ultimately succumb to the disease [38]. A second strategy in endocrine therapy involves utilizing AIs to decrease estrogen production both in peripheral tissues and within the tumor itself. From above information it is evident that the ERs have a major role in BC and their importance is extended through 27 HC.

## HYDROXYCHOLESTEROL (27HC)

SERMs which are a class of ER ligands exhibiting tissue-specific agonistic or antagonistic activities. They are used in the hormonal therapy for estrogen-dependent BCs [39], but they are often ineffective and illicit drug resistance in postmenopausal women. Subsequently, the comorbidity of hypercholesterolemia with obesity has been identified as an independent risk factor for BC in postmenopausal women. Later, along these lines: the discovery of oxysterol 27-Hydroxycholesterol (27HC) as endogenous SERM provides new insight into obesity associated postmenopausal BCs and their response to various therapies. Recent studies show how the 27HC impacts the growth and metastasis of tumors in established animal models of BC [40]. Recognition of 27HC as an endogenous SERM reveals that there is an unidentified ER-mediated mechanism in BC patients where synthetic SERM or AI or hormone replacement failed to act [41]. Limer and Speirs [42] reported that high intake of phytoestrogens, which are weak mimics of natural estrogens, is linked to a reduced incidence of BC. The above report shows insight into the role of SERMs in BC. It is well-established that obesity and hypercholesterolemia are linked to an increased risk of developing estrogen receptor-alpha (ERα)-positive BCs, especially in postmenopausal women [43–45]. However, the molecular factors that link these conditions to the onset and progression of BC remain unclear (Figures 2(a) and (b)).

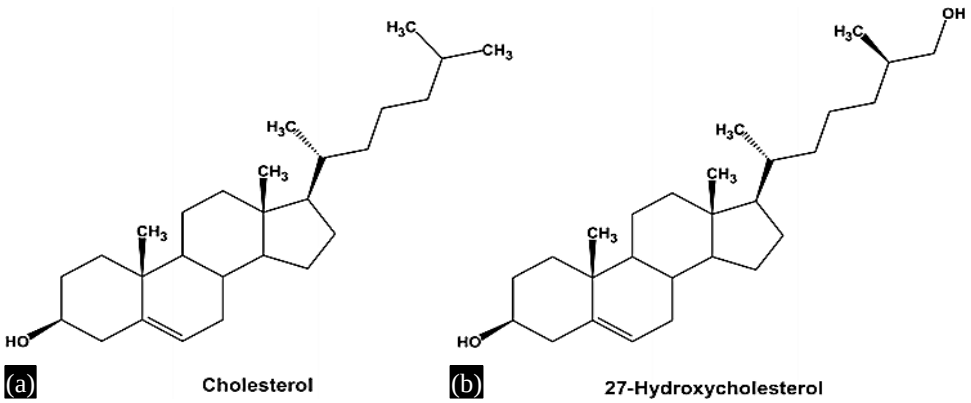


**Figure 2(a, b).** 27-Hydroxycholesterol suppresses lipid accumulation in 3T3-L1 cells by downregulating the expression of lipogenic and adipogenic genes.

 

Some studies have demonstrated that 27HC, which is produced from cholesterol by the sterol 27-hydroxylase cytochrome P450 27A1 (CYP27A1), functions as a true SERM, displaying partial agonist activity in ERα-positive BC cells [46]. Circulating levels of 27HC have been shown to be significantly positively correlated with cholesterol levels. Furthermore, plasma 27HC levels tend to rise with hypercholesterolemia and advancing age [47–49]. Additionally, the concentration of 27HC has been found to be higher in ERα-positive breast tumors compared to normal breast tissue. This increase in 27HC has been attributed to a corresponding reduction in the expression of the oxysterol 7α-hydroxylase, the enzyme responsible for metabolizing 27HC in breast tumors. 27HC acts as a SERM, displaying agonist activity in BC cells and facilitating the growth of ER-positive tumors. Beyond enhancing primary tumor growth, elevated 27HC levels also increase metastatic burden. Interestingly, the pro-metastatic effects of 27HC do not appear to involve ERs; instead, they engage liver X receptors (LXRs). Synthetic LXR agonists can induce BC cell metastasis, albeit less effectively than 27HC, suggesting that 27HC may activate additional targets contributing to its metastatic properties. The effect of 27HC on primary tumor growth is reliant on ERα, and its growth-promoting properties can be blocked by specific antiestrogens, suggesting that this activity is inherent to the tumor cells themselves. However, the significant impact of 27HC on metastasis in both ERα-positive and ERα-negative tumors raises questions about the involvement of alternative targets, whether intrinsic to the tumor cells or influenced by host factors. Supporting the hypothesis of extrinsic activity, a study demonstrated that a high-cholesterol diet enhanced lung colonization by ER-negative cancer cells when injected intravenously, thereby minimizing any potential intrinsic effects of cholesterol. To investigate this further, Amy E. Baek et al. conducted experiments where naive wild-type mice were pretreated with either placebo or 27HC before being injected with Met1 mammary cancer cells, after which 27HC treatment was halted. The results indicated that the mice pretreated with 27HC exhibited a significantly higher number of metastatic nodules compared to those pretreated with placebo ($p = 0.016$, Mann–Whitney test) [50].

## CONCLUSIONS

It is evident from the past research that 27HC has a positive impact on the BC, especially in metastasis activity. From the above data we can reach in a conclusion that when the cholesterol uptake increases which results in the elevation of 27HC circulating blood. Antagonizing ability of 27HC results in the expression of ERs, whose role in the BC is proved. 27HC shows a positive effect on BC along with estrogen through ERs.

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