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Receptor tyrosine kinases and steroid hormone receptors in breast cancer: *Review of recent evidences*

Awgichew Behaile Teklemariam [a,*], Zelalem Tilahun Muche [c], Melaku Mekonnen Agidew [a], Anemut Tilahun Mulu [a], Edgeit Abebe Zewde [c], Nega Dagnew Baye [b], Dagnew Getnet Adugna [b], Lemlemu Maru [e], Teklie Mengie Ayele [d]

[a] *Department of Medical Biochemistry, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia*
[b] *Department of Human Anatomy, School of Medicine, College of Health Sciences, University of Gondar, Gondar, Ethiopia*
[c] *Department of Medical Physiology, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia*
[d] *Department of Pharmacy, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia*
[e] *Department of Medical Physiology, School of Medicine, College of Health Sciences, University of Gondar, Gondar, Ethiopia*

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ABSTRACT

Breast cancer development and progression are driven by intricate networks involving receptor tyrosine kinases (RTKs) and steroid hormone receptors specifically estrogen receptor (ER) and progesterone receptor (PR). This review examined roles of each receptor under normal physiology and in breast cancer, and explored their multifaceted interactions via signaling pathways, focusing on their contributions to breast cancer progression. Since defining the mechanism by which these two-receptor mediated signaling pathways cooperate is essential for understanding breast cancer progression, we discussed the mechanisms of cross-talk between RTKs and ER and PR and their potential therapeutic implications as well. The crosstalk between RTKs and steroid hormone receptors (ER and PR) in breast cancer can influence the disease's progression and treatment outcomes. Therefore, understanding the functions of the aforementioned receptors and their interactions is crucial for developing effective therapies.

1. Introduction

Breast cancer (BC) is the most prevalent and life-threatening malignancy in women worldwide and is the leading cause of cancer related deaths among them. It is a complex disease in which various factors contribute to its occurrence. Despite the fact that the disease is widespread, there are significant regional differences in its incidence, mortality, and survival rates. These variations could be caused by a variety of factors including environment, genetics, lifestyle, and population structure [1–4].

The incidence of breast cancer is increasing steadily across the globe with the highest incidence being in developed countries. The lifetime risk of dying from the disease is 3.4 % and one in eight women will be diagnosed with breast cancer. In 2018, breast cancer was reported as the second highest malignant tumor following lung cancer with an estimated number of 2.09 million new registered cases [1,5,6]. In industrialized nations, about half of breast cancer cases are there worldwide. In contrast to morbidity, developing nations have the greatest breast cancer death rate. These days, there is a significant improvement in breast cancer survival rates due to early identification and advancements in treatment [1,3,7].

Breast cancer can be classified into four molecular subtypes: Luminal A, luminal B, human epidermal growth factor receptor 2(HER2)-enriched and basal-like, each of which have distinct characteristics and implications for treatment and prognosis [8]. About 60–70 % of BCs are luminal, both of which are characterized by expression of estrogen receptor. However, luminal A tumors typically express PR and have low or no HER-2 expression at all. In contrast, luminal B tumors may have variable PR expression and can show higher HER-2 levels. Among all BC subtypes, luminal A tumors have the best prognosis, whereas luminal B tumors have worst survival rates and need more aggressive therapy. Although both luminal cancers appear as irregular lumps on mammography without any accompanying calcification, the majority of luminal B tumors have axillary involvement at diagnosis. Low

* Corresponding author. P. O. Box: 272; 6300, Debre Tabor, Ethiopia
E-mail address: awgich85behaile@gmail.com (A.B. Teklemariam).

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expression of the ER and overexpression of the HER2 oncogene are characteristics of HER2-enriched cancers. Although the development of anti-HER2 drugs has considerably improved the outcomes of patients with HER2-enriched tumors, historically they had poor prognosis. Basal-like BCs, subtype of triple negative breast cancer (TNBC), characterized by absence of three of the receptors namely; HER-2, ER and PR. are high grade, often large at diagnosis, and have significant recurrence rates. High grade cancers have cells that look very different from normal cells under the microscope and are usually more aggressive which tend to grow and spread more quickly than low-grade cancers, often requiring more intensive treatment. More than 15 %–20 % of all BC cases are triple negative, which is of great study interest since it poses therapeutic challenge by virtue of its high invasiveness and poor response to treatment [1,8].

Breast cancer emerges as a consequence of dysregulation of different signaling pathways in mammary epithelial cells. The major receptors involved in the complex signaling pathways of BC progression include receptor tyrosine kinases (RTKs) and steroid hormone receptors, most notably, estrogen receptor (ER) and progesterone receptor (PR). Dysregulation of these receptors and their interplay profoundly affect breast cancer initiation, progression, and metastasis [2]. In this review, we discussed the physiological roles of RTKs and steroid hormone receptors (ER and PR) for breast tissue development under normal condition and their role in breast cancer tumorigenesis and progression, mechanism/s of cross-talk between RTKs and ER and PR, and their potential therapeutic implications. The cross-talk between RTKs and steroid hormone receptors (ER and PR) in breast cancer can influence disease progression and treatment outcomes. Hence, understanding the functions of RTKs and ER and PR and their interactions is supposed to shed light for developing effective therapies targeting both receptor types which in turn enhances survival rate of BC patients.

2. Receptor tyrosine kinases in breast cancer

Receptor tyrosine kinases are single-pass trans-membrane proteins having a C-terminal cytoplasmic catalytic domain and an N-terminal extracellular domain that functions as a ligand binding site. They are members of cell surface receptors with unique biological and structural characteristics that are crucial for initiating various intracellular signaling cascades in response to extracellular stimuli [9,10].They regulate vital biological functions such as cell division, proliferation, survival, and metabolism by triggering a variety of downstream signaling pathways [7,10,11]. They constitute a class of receptors that are highly significant in the advancement of cancer and are expressed on a variety of cell types, including those in the tumor microenvironment. RTK overexpression or mutations are frequently linked to the development of breast cancer and treatment resistance [7,12,13].

3. Structure & classification of RTKs

In humans, fifty-eight different RTKs have been characterized which are further classified into 20 different subfamilies on the bases of their structural features. Each RTK subfamily possesses a prototype structural organization and class-specific characteristics. An extracellular ligand-binding domain, a transmembrane domain, and an intracellular/cytoplasmic tyrosine kinase domain are the basic components present in a prototype RTK [7,14–16]. The 20 subfamilies of RTKs, their subclasses and physiological roles are summarized in the table below (Table 1).

4. RTKs commonly implicated in breast cancer

Many RTKs play a role in the pathogenesis and prognosis of breast cancer, acting as prognostic and predictive markers. RTKs that are often expressed in breast cancer include HER2/neu (ErbB2), epidermal growth factor receptor (EGFR), and SRC (Src Family Kinases). HER2 overexpression/amplification occurs in 20–30 % of breast cancer

Table 1
Brief description of subfamilies of RTKs, subclasses and their physiological roles.

RTK subfamily name	Subclasses	Physiological role/s	Reference
Epidermal Growth Factor Receptor (EGFR)	EGFR (ErbB1), HER2 (ErbB2/neu), HER3 (ErbB3), and HER4 (ErbB4)	Regulate cell proliferation, migration, differentiation and survival	[7,17]
Platelet-Derived Growth Factor Receptor (PDGFR)	PDGFR-α and PDGFR-β		
Fibroblast Growth Factor Receptor (FGFR)	FGFR1, FGFR2, FGFR3 and FGFR4	Promotes cell proliferation, angiogenesis and tissue repair	[18]
Vascular Endothelial Growth Factor Receptor (VEGFR)	VEGFR1- 4	Enhances angiogenesis, vascular permeability and endothelial cell survival	[19]
.Insulin Receptor	InsR, IGF1R, IRR	Controls metabolic functions, growth, and development	[20]
Hepatocyte growth factor receptor (HGFR) aka Met	Not specified	Regulates cell growth and development, angiogenesis, oncogenesis and tissue regeneration	[21]
Discoidin domain receptors (DDR)	DDR1 and DDR2	Play a role in cell adhesion, migration, and remodeling	[17]
Neurotrophin receptor	Nerve growth factor, brain derived neurotrophic factor, neurotrophin-3, 4 and 5	Facilitate growth, differentiation, and survival of neurons	[22]
TAM receptor	Tyro 3, Axl, MerTK	Regulation of immune response, cell survival and development, nervous system development	[17,23]
Protein tyrosine kinase (PTK7)/ Colon carcinoma kinase (CCK4)	Not-specified	Embryonic development	[17]
REarranged during Transfection (RET) family	RET9 and RET51	Crucial for kidney and neural development	[17]
RTK like Orphan Receptor (ROR)	ROR1, ROR2	Contribute to skeletal development and cell polarity	[24]
ROS Receptor	ROS1	Implicated in cell growth and differentiation	[17]
Leucocyte Tyrosine Kinase (LTK)	Not specified	Involved in neural development and function, regulation of apoptosis	[25]
LMR (Lemur Receptor)	LMR1, LMR2 and LMR3	Function in the development of the lymphatic system	[17]
Tropomyosin-related kinase (Trk)	Trk A, Trk B and Trk C	essential functions during the development of both the central and peripheral nervous system	[17]
MuSK Receptor	MuSK	Essential for neuromuscular junction development	[17]
Eph Receptor	Eph A and Eph B	Key in cell-cell interactions, especially in the nervous system	[26]
TIE Receptor	TIE1 and TIE2	Involved in angiogenesis and	[17]

(*continued on next page*)

Table 1 (*continued*)

RTK subfamily name	Subclasses	Physiological role/s	Reference
		maintenance of blood vessel integrity	
Related to tyrosine kinase (RYK) Receptor	Not specified	Involved in Wnt signaling and neural development	[27]

InsR: Insulin receptor; IGF1R: Type 1 insulin like growth factor receptor: IRR: Insulin receptor related receptor; LTK: Leucocyte Tyrosine Kinase; MuSK: Muscle Specific Kinase.

patients and is related with poor clinical outcomes and disease progression. Overexpression of HER2 is predominantly caused by HER2 gene amplification, which results in constitutive activation of the HER2 signaling pathway. Nuclear HER2 also acts as a STAT3 transcriptional co-activator and stimulates breast cancer cell proliferation [7,9,28].

Another RTK that is typically overexpressed in breast cancer is EGFR, which is associated with increased aggressiveness and poor clinical outcomes. EGFR is regarded as a critical regulator of cancer stem cell phenotype and metastasis in inflammatory breast cancer [9]. Like HER2, abnormal EGFR activity has been shown to enhance STAT3 activation, which leads to tumor start, growth, and metastasis. Overexpression of EGFR occurs in 15–30 % of breast carcinomas and is related with high tumor size and poor clinical outcomes. More specifically, it is typically overexpressed and associated with a poor prognosis in TNBC, a breast cancer subtype for which numerous EGFR-targeting therapies have been investigated [7,16].

Overexpression of EGFR is caused in part by EGFR gene amplification and has been reported in a variety of cancer types, including breast, lung, colorectal, and esophageal cancers, as well as glioblastoma. Other proposed mechanisms for EGFR expression upregulation include the downregulation of BRCA1, a tumor suppressor gene necessary for DNA damage repair that increases both EGFR messenger RNA (mRNA) and protein levels. Furthermore, tissue transglutaminase (tTG), a guanosine triphosphate (GTP) binding protein/acyltransferase associated with drug resistance and metastasis whose expression is upregulated in glioblastoma, has been shown to increase EGFR levels by inhibiting ubiquitination-mediated EGFR degradation in glioblastoma. tTG protein is also elevated in various cancer types, including breast cancer, however whether the tTG-EGFR pathway exists in breast cancer or not remains obscure [29].

In addition to EGFR family members, several other RTKs are implicated in breast cancer. Hepatocyte growth factor receptor (HGFR), also known as c-MET, and type I insulin-like growth factor receptor (IGFIR) are among several RTKs implicated in breast cancer. The proto-oncogene MET encodes c-Met, which is overexpressed in 20–30 % of breast tumors and has been demonstrated to be an independent predictor of poor prognosis for breast cancer patients. Aberrant c-Met signaling mechanisms include gene amplification, gene mutation activation, protein overexpression, ligand-dependent paracrine or autocrine loops, and interaction with other cell surface receptors. A large body of evidence indicates that IGFIR plays a role in several cancer types, especially breast and colorectal cancers, where it is highly expressed. Studies have shown that IGF1R mRNA expression is higher in luminal A and B subtypes than in basal-like and HER2-positive subtypes of BC [29,30].

The SRC family kinases (SFKs), which are frequently linked to breast cancer, are members of the non-receptor tyrosine kinase (nRTK) family. SRC, the first proto-oncogene discovered in mammalian cells, is important for breast cancer growth. It is implicated in tumorigenesis, growth, metastasis, treatment resistance, and stem cell control. Despite lack of promising agents, researchers are actively investigating SRC-based targeted therapies for breast cancer [31].

5. Mechanisms of RTK signaling in tumor progression

RTKs are essential for cellular communication and regulate a wide range of biological activities. In normal physiology, certain ligands activate RTKs, resulting in receptor dimerization, kinase activation, and subsequent signaling cascades. They can regulate cell growth, motility, differentiation, and metabolism [32]. RTK-regulated pathways play key roles in various facets of cancer progression. Aberrant activation of RTKs, through overexpression or mutation, is associated with breast cancer progression. They regulate cancer stemness, angiogenesis, and metastasis, and are targets for therapeutic intervention. RTKs also regulate vasculogenic mimicry, a process wherein cancer cells themselves form vascular-like structures to increase access to the blood supply to assist in tumor growth [13].

RTKs initiate signaling pathways upon binding with their respective ligands. This binding causes conformational changes leading to dimerization of RTKs which is followed by autophosphorylation by intracellular tyrosine kinase domain of the receptors thereafter recruitment and activation of downstream signaling pathways such as mitogen-activated protein kinase (MAPK), Janus kinase (JAK)/signal transducer and activator of transcription (STAT3) and phosphatidyl inositol-3-kinase (PI3K)/Akt, all of which are involved in promoting a myriad of biological outcomes and contribute to tumor initiation, growth and progression will ensue [10,13,16]. Due to their inherent roles in proliferation and survival, dysregulated RTK signaling is implicated in many cancers including breast cancers. RTKs can become aberrantly activated via mechanisms driven by overexpression, mutation/translocation and atypical ligand induction. Four principal mechanisms lead to constitutive RTK activation in human cancers: gain-of-function mutations, genomic amplification, chromosomal rearrangements, and/or autocrine activation [16].

The PI3K/AKT/mTOR signaling pathway, one of the most common overactivated pathways via RTK mediated signaling in human cancers, is abnormally altered in nearly 70 % of BC. It links RTK signaling to cell growth and survival regulation, and its excessive activation can promote increased cell proliferation, suppression of apoptosis, and contribute to abnormal cell differentiation and autophagy forming tumors and promoting metastasis [4].

Receptor tyrosine kinases can also be activated by ligand independent mechanisms through gene rearrangements and mutations. Gene rearrangements can result in an abnormal coiled coil and leucine zipper conformations of the extracellular domain which in turn induce ligand independent association of RTKs. Likewise, mutations resulting in cysteine residues in the extracellular domain can induce permanent association of two RTK monomers. Mutations pertaining to transmembrane domain can also lead to constitutive dimerization of RTKs resulting in certain pathophysiologies [5,15].

6. Estrogen and progesterone receptors in breast cancer

6.1. *Structure and function of ER and PR*

Estrogen receptor and progesterone receptor are members of the steroid hormone superfamily of nuclear receptors. Even though members of steroid hormone receptor family are mostly localized in nucleus, a distinct pool of them including ER and PR and androgen receptor, which accounts for about 5 %, are localized at the plasma membrane. ER and PR are ligand-activated transcription factors which modulate gene expression. They are activated by estrogen and progesterone respectively and, promote cell proliferation and differentiation in normal breast tissue [33]. Nevertheless, dysregulation of these receptors in breast cancer contributes to tumorigenesis and endocrine therapy resistance [34,35].

Structurally, ER does contain five main domains, namely; N-terminal A/B domain, C domain which contains the DNA-binding domain (DBD) and occupies the central position, D domain which is a hinge region

containing a nuclear localization signal, E domain which harbors the ligand-binding domain (LBD), and ligand-dependent transactivation function domain (AF-2) and C-terminal F domain, a variable domain whose function still remains an area requiring further elucidation [35] (Fig. 1). The DBD is composed of two zinc finger motifs each having four cysteine residues, and is the centrally located and most conserved domain, whilst the N-terminal A/B domain, the most variable domain in length and sequence which bears the constitutively active ligand-independent activation function (AF-1), is not conserved and is the target for varied post-translational modifications with variable effects in driving or repressing transcription. Hinge region, a small, versatile domain with the least conserved amino acid sequence, is found connecting the DBD and LBD. Although the precise function of this domain is unclear, it acts as a site for post translational modifications associated with increased transcriptional activation [33,35–38].

Estrogen receptors are of three types; ERα and ERβ, which are members of nuclear ERs and GPR-30, a plasma membrane ER or G-protein coupled estrogen receptor (GPER) [28,33]. All three ERs are encoded by different genes located on different chromosomes. ERα is encoded by ESR1 gene located on chromosome 6; ERβ is encoded by ESR2 gene on chromosome 14, and GPR-30 is encoded by the GPER gene on chromosome 7 [2,28,39]. ERβ does contain 530 amino acids and has a molecular weight of 59 kDa, whereas ERα has 595 amino acids with 66 kDa molecular weight. On the basis of their molecular weight, five different isoforms of ERα exist in breast cancer (ERα 62, ERα53, ERα46, ERα 45, and ERα 36). Likewise, five variants of ERβ (ERβ1– ERβ5) are detected in breast cancer [40].

ERα and ERβ are expressed in many different human tissues, such as the endometrium, ovary, testes, cerebral cortex, heart, and thyroid, despite the fact that they both bind to estrogen with similar affinities and are expressed in breast tissue. The only estrogen receptor expressed in the hippocampus is ERα, while the only estrogen receptor present in prostate tissue is ERβ [33]. While the significance of ERβ is still unknown, the isoform ERα is clinically relevant since its presence or absence determines whether a breast cancer is classified as estrogen receptor positive or negative [2]. About 75 % of breast cancer diagnoses in women are ERα-positive cases, making them the most common type of the disease. Furthermore, activation of ERα promotes carcinogenesis in different forms of cancer, including breast cancer. Additionally, ERα regulates PR expression, which is a sign that the estrogen–ERα signaling pathway is active. Activated PR, however, is deleterious for advanced breast malignancies and offers some rationale for combined targeting of PR and ER in advanced tumor treatment [40–42].

However, other researchers suggest that ERβ has a role in counteracting ERα activity and that its low levels are linked with tamoxifen therapy resistance. With its distinct roles, ERβ presents itself as a promising new target for pharmaceutical intervention. Breast cancer cells' extracellular matrix (ECM) composition and cell activities are also significantly influenced by ERβ. It may also have an impact on key chemokine receptors that are engaged in the beclin1-dependent autophagic cascade [39,40]. Unlike ERα, which is essential for the normal development of the mammary gland, the function of ERβ in normal breast tissue is unknown. Therefore, more molecular level studies are required to determine its precise physiological role(s).

G protein-coupled receptor 30 (GPR30), a seven transmembrane domain receptor which mediates non-genomic estrogen signaling, is expressed in both ER^+ and ER^- breast cancer cells and tumors. By activating the phospholipid transacylase tafazzin (TAZ), it controls the

Fig. 1. ER structure depicting the five domains. *AF-1: Activation function-1: DBD: DNA binding domain, LBD: ligand binding domain.*

Hippo signaling pathway [28,41,43].

Progesterone receptor is a heterodimeric protein composed of A and B subunits that vary in their inherent molecular-weight values and are encoded by the same PGR gene. The three components of PR are the amino-terminal domain, which is composed of intrinsically disordered proteins, the C-terminal ligand-binding domain (LBD), and DNA binding domain (DBD), the central region. PR contains two transcriptional activation function domains (AFs): AF1, found in the N-terminal domain (NTD), and AF2 which is located in the LBD. Both AFs serve as contact surfaces for coregulatory proteins [44,45].

PR-A and PR-B are the two naturally occurring and well-known isoforms of PR with PR-A being an isoform more frequently overexpressed in breast cancer [33,44]. Both isoforms are transcribed from the same gene through different translational start sites. Accordingly, PR-A is the shortened form of PR-B (it lacks the first 164 amino acids present in the NH2-terminal side of PR-B), while PR-B is the full-length receptor. Furthermore, PR-B's upstream segment has a distinct activation function domain (AF3) that PR-A lacks. In PR + cells, both isoforms are typically co-expressed. A greater PRA:PRB ratio, however, indicates a less favorable prognosis for breast cancer [41,44,46–48].

In vitro experiments using a recreated progesterone-responsive transcription system in mammalian cells have shown that PR-A and PR-B do not have the same function despite having similar structures and identical DNA and ligand binding affinity. In contrast to PR-A, which functions as a dominant regulator of PR-B transcription as well as a few other nuclear receptors, PR-B primarily operates as a strong activator of target gene transcription. The greater transcriptional activity of PR-B is thought to be partially attributed to the AF-3 domain in PR-B. Additionally, it has been determined that the N-terminus of both PR isoforms has an inhibitory function domain. The inhibitory function domain is capable of suppressing AF-1 and AF-2 activity, but not AF-3, which explains why PR-B is a strong transcription activator. Because the inhibitory function domain is transferable and functionally independent, it can also reduce ER activity when positioned upstream of the ER [48].

6.2. ER and PR status as predictive and prognostic markers in breast cancer

Estrogen receptor alpha and PR are crucial prognostic and predictive markers that are usually co-expressed in breast cancer [28,41,49]. In breast cancer patients on endocrine therapy with ER^+ and lymph node-negative, PR expression is a powerful and independent predictive marker [50,51]. Breast cancers with a better baseline prognosis (luminal A) are more likely to have high expression of PR than cancers with a worse baseline prognosis (luminal B) [44].

Breast cancer is a diverse disease that can be divided into four categories based on the presence or absence of hormone receptors status, namely; ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-. Less than 5 % of initial breast cancers are negative for ER but still positive for PR, whereas over half of them are positive for both ER and PR [5,47]. As compared to ER+/PR+ (estrogen receptor positive and progesterone receptor positive) tumors, PR-negative/ER-positive breast cancer has worse prognosis, and is linked to endocrine resistance as well as poor outcome [52]. On the other hand, neoadjuvant chemotherapy may be more effective in treating ER^+/PR^- BCs than double-positive tumors. Reduced transcription of the PGR gene, post-translational modifications, and pre-transcriptional changes can all lead to loss of PR expression. PR expression is supposed to improve the prognostic accuracy of ER measurement in primary BC by providing independent prognostic information [5,44,46,47,49]. Since there is an ongoing debate over the effectiveness of hormone blocking therapy for patients with ER+/PR− malignancies, further research involving clinical trials shall be undertaken in the future as per our suggestion. From the standpoint of practical application, we can attest that identification of molecular marker status in patients with breast carcinoma is helpful for oncologists to

decide on the treatment choice and predict the disease's outcome/prognosis. In general, the three prognostic and predictive markers for invasive breast cancer that are required to be employed in routine clinical practice these days are ERα, PR, and HER2 (also known as HER2/neu or erbB2) [28].

6.3. Role of ER and PR in breast cancer development and progression

The two ERs, ERα and ERβ, are kept at low levels under normal conditions. However, in pathological conditions, particularly in breast cancer, the ratio of ERα to ERβ increases vertically owing to low ERβ expression. According to some studies, ERα and ERβ have antagonistic effect which regulate cell behavior differently throughout the onset and progression of BC. Because its level is raised in premalignant and malignant breast tumors but not in normal tissue, ERα is of particular interest and plays a significant role in the development, progression, and therapy of breast cancer [28]. Studies conducted using mouse models have shown that PR activity plays a critical role in the initiation of carcinogenesis. The primary factor involved in the carcinogenesis process is paracrine signaling, which is mediated by PR-induced TNFSF11 and possibly by WNT1 and WNT4. Nevertheless, as the tumor progresses into later stages of growth, its contribution to the process gradually diminishes. Additionally, PR increases the invasiveness of breast cancer by suppressing the transcription factor GATA3 [40].

7. Discussion

7.1. Mechanism of crosstalk between RTK with ER and PR in breast cancer

RTKs, such as the human epidermal growth factor receptor 2 (HER2) and the epidermal growth factor receptor (EGFR), interact with the PR and ER via intricate signaling pathways. RTK-mediated signaling cascades can activate PR and ER, which in turn can regulate target genes involved in cell survival and proliferation through transcription. When RTKs are activated, downstream effectors in the signaling cascade like PI3K/AKT and MAPK are phosphorylated leading to further phosphorylation and activation PR and ER. Advanced researches on ER biology has provided new perspectives on how ER functions in breast cancer and has brought attention to the critical role of close communication between the EGFR/HER2 and ER signaling pathways in the emergence of resistance to endocrine therapy in breast cancer. It is believed that the phosphorylation process of certain serine residues on ER is responsible for the regulation of cellular responses without the need for hormones as ligands. However, there is paucity of data regarding which specific serine residues on ER are phosphorylated through growth factor signaling cascades in humans [39,40]. ER and EGFR/HER2 signaling pathways have a constant and bidirectional molecular crosstalk, though the former receptor upregulates growth factor signaling through its nuclear and membrane activities [39]. The physiological function/s of ER as well as endocrine therapy resistance and growth factor receptor signaling are both significantly influenced by the interaction of ER with EGFR/HER2 pathway and maybe with other growth factor receptor pathways in breast cancer [53,54].

On the other hand, PR activates mitogenic Wnt signaling in human breast cancer cell lines through Wnt1 leading to epidermal growth factor receptor (EGFR)-mediated downstream activation of Erk 1/2 mitogen activated protein kinase (MAPK) activity. EGFR is upregulated and activated by progesterone (cognate ligand for PR) in breast cancer. Besides, though the HER2 gene has not been reported as directly regulated by progestins and progesterone, activated PRs increase HER2 signaling during tumor progression. These data implicate that several progesterone-activated signaling pathways through PR contribute to breast cancer stem cell expansion [41]. The aforementioned study has not yet indicated the precise mechanism/s behind PR mediated activation of EGFR and HER2 downstream signaling cascades in breast cancer and hence, further investigations are required which might be valuable for drug discovery targeting these receptors in breast cancer.

Progesterone receptor has the ability to directly activate SRC kinase, a non-genomic function of PR, by binding the proline-rich motif found inside the N-terminal domain of PR through the SH3 (SRC Homology 3) domain of SRC. The other instance of crosstalk involves PR and MAPK signaling, which can happen in both ways. PR activity is significantly increased following the phosphorylation of its Ser 294 residue by MAPKs, which promotes the growth of breast cancer by lessening its reliance on progestins and subsequently leads to the emergence of resistance to hormone therapy [40]. The crosstalk between RTKs and ER/PR has significant clinical implications for breast cancer treatment. Endocrine therapies targeting ER and PR are less effective in tumors with high RTK activity. On the contrary, combining RTK inhibitors with endocrine therapies may be more effective.

8. Methods

A comprehensive literature search was conducted from search engines; PubMed, google Scholar, Cochrane library, EMBASE and Web of Science to identify recent studies focusing on RTKs and steroid hormone receptors (ER and PR) in breast cancer. Search terms used for all databases and registers included keywords such as 'Breast cancer,' 'Receptor tyrosine kinase', 'Estrogen receptor', 'progesterone receptor', 'insulin-like growth factor', 'signaling pathway', and 'mechanism of interaction' and 'crosstalk'. Research articles investigating the roles and interactions of RTKs and steroid hormone receptors (ER and PR) in breast cancer as of 2000–2024 were manually retrieved and included in this review. Methods and results/discussion sections of all eligible articles were subject to thorough reading before being included in our review (Fig. 2).

9. Conclusion and future perspectives

Receptor tyrosine kinases and steroid hormone receptors (ER and PR) have invaluable roles in the initiation, development and progression of breast cancer. In addition, they showed promising use as prognostic and predictive biomarkers for breast cancer. The interplay between RTKs and steroid hormone receptors (ER and PR) via signaling pathways plays a critical role in breast cancer progression, hence, deeper understanding of the mechanism/s of their interaction will pave the way for developing more effective targeted therapies and improving patient outcomes.

From the standpoint of this review, further research is needed to explore novel therapeutic strategies targeting both RTKs and ER/PR in breast cancer since endocrine therapy alone has shown to be less effective in many clinical trials. For clinical practice, targeting the crosstalk between RTKs and ER/PR presents challenges due to the redundancy and complexity of signaling pathways. Therefore, we recommend future researches aimed at identifying biomarkers for predicting response to combined RTK and ER/PR targeted therapies and understanding resistance.

CRediT authorship contribution statement

Awgichew Behaile Teklemariam: Software, Methodology, Formal analysis. **Zelalem Tilahun Muche:** Writing – review & editing, Validation, Software. **Melaku Mekonnen Agidew:** Writing – original draft, Validation, Investigation. **Anemut Tilahun Mulu:** Writing – review & editing, Supervision, Resources, Investigation. **Edgeit Abebe Zewde:** Writing – review & editing, Supervision, Resources, Methodology. **Nega Dagnew Baye:** Methodology, Investigation, Formal analysis, Conceptualization. **Dagnew Getnet Adugna:** Supervision, Software, Investigation. **Lemlemu Maru:** Writing – original draft, Supervision, Formal analysis. **Teklie Mengie Ayele:** Writing – review & editing, Validation, Resources, Formal analysis.

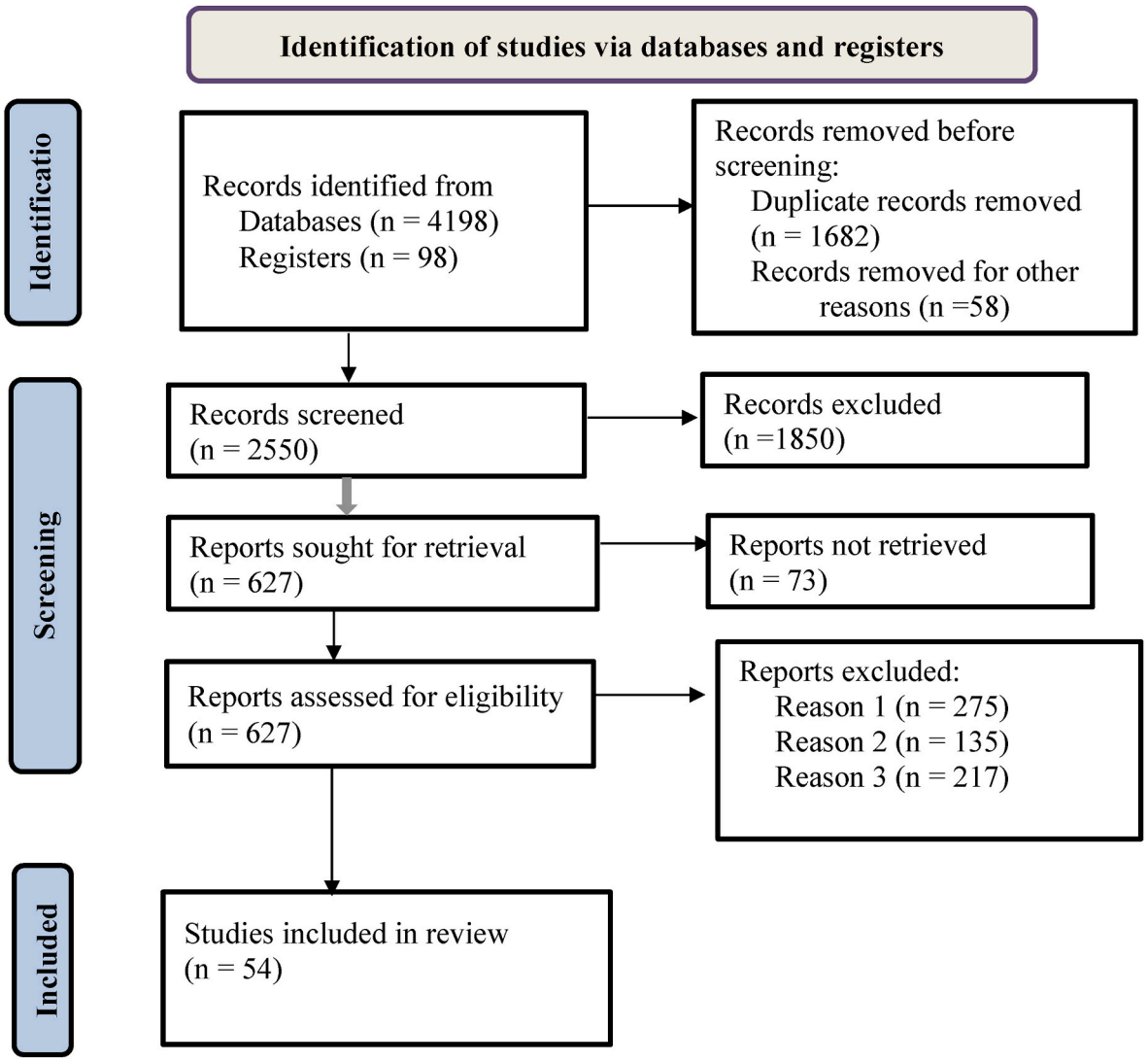

Fig. 2. PRISMA flow diagram showing flow of literature search
Reason 1: year of publication; Reason 2: title not matched; Reason 3: full text review not matched.

Disclosure of interest

The authors declare that they have no competing interests.

Abbreviations

EGFR	Epidermal Growth factor receptor
PR	Progesterone receptor
ER	Estrogen receptor
HER2	Human epidermal growth factor 2 receptor
MAPK	Mitogen Activated protein kinase
InsR	Insulin receptor
STAT3	Signal transducer and activator of transcription 3
TNBC	Triple negative breast cancer
LBD	ligand binding domain
DBD	DNA binding domain
TNFSF11	Tumor Necrosis Factor Superfamily Member 11
WNT1/4	Wingless-Related Integration Site 1/4
GATA3/4	(GATA Binding Protein 3/4)

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