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# Relative worth of Estrogen and Progesterone receptors as indicators of prognosis in Breast Cancer

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## Abstract

Breast cancer is one of the most common and most frequently diagnosed cancers in women both in the developed and less developed countries. Estrogens and progesterone play a leading role in regulating the normal growth and differentiation of cells, premalignant and malignant cell types, especially breast epithelial cells. Estrogen is targeted either directly by selective estrogen receptor modulators and pure antagonists or indirectly by aromatized inhibitors that block estrogen production. Estrogen receptor also serves as a prognostic marker for responsiveness to endocrine therapy through its receptors alpha and beta. Mammogram screening is used for the early detection of cancer. An ideal screening test for breast cancer must have a high sensitivity in order to correctly diagnose all women with the disease and a high specificity to avoid false positive results Progesterone is also an ovarian steroid hormone that is essential for normal breast development during puberty and in preparation for lactation and breastfeeding. The actions of progesterone are primarily mediated by its high-affinity receptors, which includes progesterone receptor-A and progesterone receptor-B located in diverse tissues, where progesterone controls development of breast and reproductive organs. There is also an important role of progesterone and progesterone receptors in breast carcinogenesis, including cancer progression to metastasis and of their clinical importance in the prevention, treatment and prognosis of the disease. The role of progesterone is not well known, although it causes the tumor development by regulating proliferative pathways in the cell.

**Key words:** Cancer, Breast Cancer, Progesterone and Estrogen

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## 1. Introduction

Breast cancer is the second leading cause of death in women in worldwide. Estrogen and progesterone are the main cause of unmanageable division of breast tissues and development of tumor. Estrogen leads to proliferation of cells and progesterone leads to increased differentiation by acting through different cascades. Beside these tumorigenesis effects estrogen and progesterone play important role in breast cancer prevention.

### *1.1. Cancer*

Cancer occurs though a progression of molecular actions that basically change the normal characteristics of a cell. The normal control system of a cancer cell that stops overgrowth of cancerous cells and attack of other tissues is disabled. The changed cells multiply and grow in existence of signals that normally slow down the cell growth [1]. So, they do not require any special signal to stimulate the growth of cells and distribution. When the cells grow, they possess new properties like alteration in their structure, decreased cell grip and formation of new enzymes [2].

### *1.2. Breast Cancer*

Breast cancer is the cancer that originates from breast tissue, normally from the thinner lining of milk ducts or the lobules in the breast that supply the ducts with milk. Cancer that originates from the ducts is known as ductal carcinomas and the cancer originates from lobules is known as lobular carcinomas [3].

Breast cancer is a disease in humans and also in other mammals, while majority of cases in humans are found in women, men can also develop breast cancer. Breast cancer is one of the major serious carcinoma along with women in the western world [4, 5].

### *1.3. Breast Cancer Development*

Breast cancer results by the growth abnormality in the normal cells of breast and results in the alteration in stability of the breast tissues. This irregularity develops usually in the inner lining of the milk ducts or lobules in breast [6].

Breast cancer develops in the form of tumor when there is unmanageable production of breast cells. The tumor is known as malignant when these proliferating cells attack the normal neighboring tissues and organs. These mutated cells grow more rapidly than the surrounding normal cells [7].

These early stages of irregular breast cell growth can be tough to detect by the patient and doctors similarly. The growth rate of tumor varies significantly among individual patients and it grows faster among younger women [8].

### *1.4. Risk Factors*

In the risk factors of breast cancer, genetic causes are only 5-10% in breast cancer risk. Most of these environmental factors are mostly linked with reproductive factors which determine the contact of women to circulating estrogens like age of menarche, age of first full time pregnancy, number of children, breast feeding practices age of menopause, use of hormone replacement therapy [9].

Other environmental factors that have been accounted for breast cancer include exogenous estrogens, radiation, alcohol consumption, higher education level and socio-economic status [10].

### *1.5. Screening Mammogram*

The three most common modalities for breast cancer screening are mammogram, clinical breast examination and breast self-examination. The purpose of these screening examinations is to detect occult breast cancer at an early stage-before it is clinically evident-and thereby increase the probability of cure.

Mammogram screening is performed in conjunction with a physical examination of the breast. These two examinations are complementary to one another. Mammographic screening is able to detect some cancers that are not palpable, while some cancers are palpable, but not detectable on mammogram [11].

Women who receive mammographic screening have a decreased relative risk for breast cancer mortality in comparison to women who do not receive mammographic screening [12].

### *1.6. Breast Development and Endogenous Hormones*

Hormones especially estrogen, is a significant part in causing breast cancer. Estrogen and progesterone play important role in the human body and in the development of the breast. During puberty, ductal outgrowth is rapid under the influence of female sex hormones estrogen and progesterone [13].

During the period of normal life, the breast undergoes through multiple cycles of growth and apoptosis as a part of the menstrual cycle [14].

### *1.7. Estrogens*

Estrogens are a group of steroid compounds function as the primary female sex hormones. The three main types of estrogens that occur naturally in women are estradiol, estriol and estrone. Estrogens are produced mainly by ovaries but a smaller quantity of estrogen is produced by the adrenal glands and peripheral tissues such as fat, liver, and kidneys by converting androgens to estrogens [15].

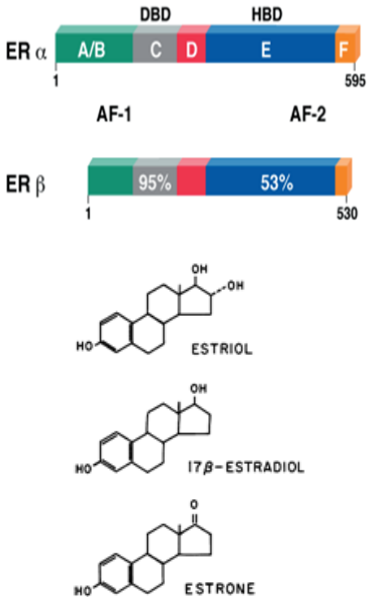


Fig. 1 Structure of estrogen [16]

Estrogen hormones also form in the placenta during pregnancy. Estrogen signaling is essential for mammary gland development and for development and maintenance of other female sex characteristics [17].

### *1.8. Biosynthesis of Estrogen*

Biosynthesis of sex steroids starts from cholesterol, which is a precursor of all steroid hormones. Cholesterol is converted to pregnenolone. In the endoplasmic reticulum, pregnenolone is then converted either to 17-hydroxypregnenolone by 17α-hydroxylase activity or to progesterone [18].

Similarly to pregnenolone, progesterone can be

converted to a corresponding 17α-hydroxyprogesterone. Thereafter, 17- hydroxypregnenolone can be catalyzed to dehydroepiandro sterone [19]. Both the products are then converted into androstenedione which is further catalyzed into estrone, testosterone and estradiol. The final step of aromatization occur which converts estradiol and estrone into estrogens [20].

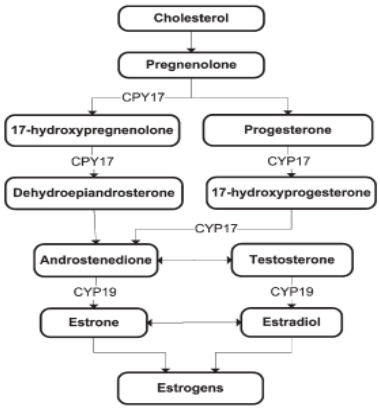


Fig. 2 Biosynthesis of estrogen [21]

## 2. Estrogen Receptors

The effects of estrogens are mediated by estrogen receptors in human body. ERs are present in two isoforms named as ERα and ERβ receptors which are distributed by a specific cell spectrum of tissues in the whole body. All the tissues that were considered as estrogen-insensitive are ERβ positive and estrogen responsive [22, 23]. Both receptors express their effects in cells and tissues, ERβ considered to neutralize the ERα-induced effects [24, 25, 26].

Estrogen molecules diffuse into the cell and bind to ER located in the nucleus, resulting in a conformational change of the ER which allows for interaction with co-regulator complexes that either activates or represses transcription of target genes [27].

### *2.1. Ligands*

Estrogen hormones are the main natural endogenous estrogen receptor ligands. 17β-estradiol is predominant estrogen in the body that is secreted by the ovaries during the female reproductive period [28].

Estradiol metabolites, estrone and estriol are also estrogen receptor ligands. Estrone is the main estrogen before puberty and after menopause and it is synthesized by the ovaries and the adipose tissue [29].

### *2.2. Signaling Pathway*

Estrogen receptor activation can either be ligand-dependent or independent. By non-genomic mechanisms, ligand binds to ERs localized in the cell membrane, which leads to activation of signal transduction pathways in the cytoplasm [30, 31].

Ligand-independent pathways include receptor phosphorylation by growth factor signaling via activation of kinases [32].

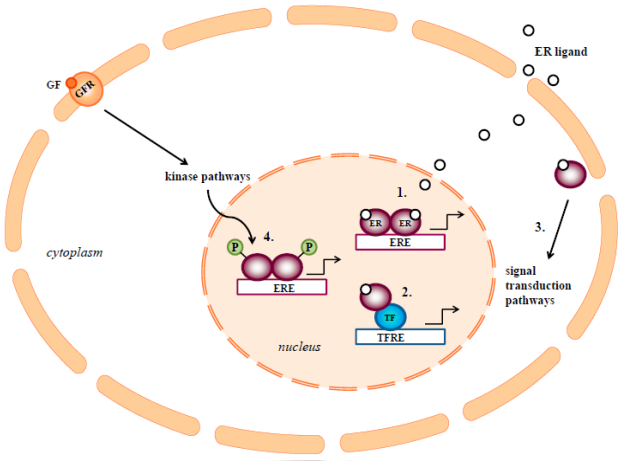


Fig. 3 Signaling pathway [34]

Antagonist-bound receptors interact with co-repressors, such as nuclear receptor co-repressor 1 (NCoR1) and silencing mediator of retinoid and thyroid hormone receptors (SMRT). NCoR1 and SMRT in turn recruit large repressor complexes including histone deacetylases that repress gene activity by maintaining or reinforcing a repressive chromatin state [35].

### *2.3. Estrogen Receptor Signaling and Breast Cancer*

Expressed estrogen receptor-α is found only in 7-10% of the luminal cells of mammary glands but its level increases during menstrual cycle. When the regulation of estrogen alpha receptor increases in breast cancer it is considered as positive regulator of cell proliferation [36].

Patients diagnosed with estrogen receptor breast cancer have generally poor survival rate, increased metastasis and degeneration occurrence [37].

Estrogen receptor-β is found to be expressed in 80-85% of the cells in the normal breast tissue, and that is why it is considered to be a predominant estrogen receptor in breast [38].

### *2.4. Molecular Signaling of Estrogen Receptors*

There are several pathways by which estrogen shows its action in causing breast tumor. Gene regulation is also effected by DNA binding. There is also a mechanism known as non-genomic has rapid effects, is not as well understood as the genomic mechanism but has been observed in many tissues [39].

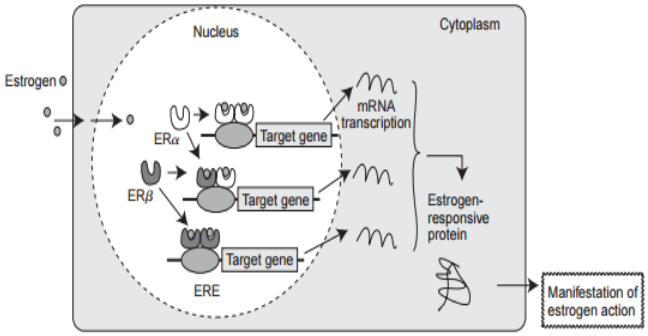


Fig. 4 Molecular signaling of estrogen receptor [40]

In the nucleus, estrogen binds to estrogen receptor via their C-terminal ligand-binding domain. The estrogen-bound estrogen receptors in turn bind to genomic estrogen receptor elements in dimerized forms via a central DNA-binding domain and thus control the transcription of target genes to exert specific physiological actions [40].

### *2.5. Estrogen Receptor-α and Breast Cancer Progression*

Estrogen receptor-alpha regulates a set of genes that overlapped with ER-alpha despite regulating many more genes not involved in estrogen signaling. Majority of genes regulated by estrogen receptor-alpha are involved in energy metabolism, oxidative stress and detoxification. Estrogen receptor alpha also induces vascular endothelial growth factor a highly angiogenic factor [41].

Estrogen receptor alpha-dependent activation of VEGF mRNA expression occurs in several different breast cancer cell lines suggesting that ER alpha promotes tumor cell growth by stimulating VEGF expression. Estrogen receptor alpha functions as a key modulator of intratumoral estrogen production in human breast carcinoma by stimulating the expression of the androgen-estrogen key converting enzyme, aromatase via tumor specific promoter usage. Highly expressed ER alpha is to be considered an overall negative phenotype of breast cancers [42].

### *2.6. Estrogen Receptor-β and Breast Cancer Progression*

Estrogen receptor-beta receptor is detected as a causing agent in breast cancer but its role in breast cancer growth and development has not been delineated. Estrogen receptor-beta has contribution in hormonal sensitivity and resistance. Though, estrogen receptor-beta RNA level was decreased in invasive breast cancer tissues compared with the adjacent normal mammary gland. The mechanism and role of decrease in estrogen receptor-beta in carcinogenesis are unknown [43].

## *3. Bifeceted Role of Estrogen Receptors*

Estrogen receptor-beta has both anti-proliferative, pro-apoptotic behavior, proliferative and survival role for its activity [44]. Therefore, the possibility of a bi-faceted role for ER-beta in breast cancer development and progression has much importance. There are several cases supporting a bi-faceted role of ER-beta [45, 46, 47].

### *3.1. Mechanism of Bifeceted Activity of Estrogen Receptor-β*

Firstly, ligand enters passively into the target cells and binds to the receptor and then initiates a cascade. The receptor is first released from a cytoplasmic chaperone complex containing several proteins including heat-shock proteins 70 and 90. The freed receptor, subjected to following post-translational events including multiple phosphorylations [48], it enters the nucleus, dimerizes and binds to defined genomic enhancer regions, containing specific motifs known as estrogen-responsive elements [49].

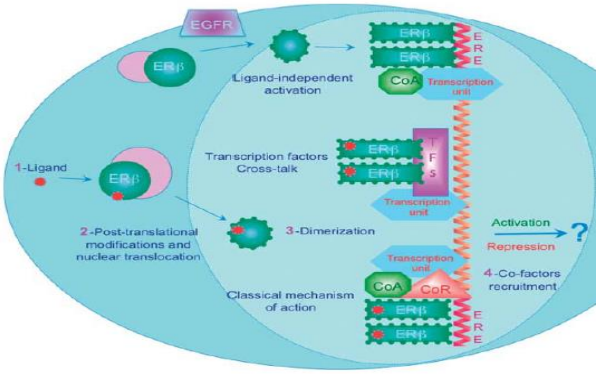


Fig. 5 Mechanism of bifeceted activity of estrogen receptor-β [50, 51]

This binding is followed by the enrollment of co-factors, that can be positive (co-activators) or negative (co-repressors), the balance of these leads to either the activation or the repression of the expression of involved genes.

### *3.2. Classical Mechanism*

Activation of estrogen receptor beta occurs when the ligand penetrates passively in the target cell through the plasma membrane and binds with the receptor. The receptor is then able to form dimers which binds specific enhancer region of target genes. Dimers interact with positive or negative regulators and leads to activation or repression of specific target gene.

### *3.3. Tethering Mechanism*

Activated receptor can bind to transcription factors (such as AP-1) and modulate, positively or negatively, the activity of these factors.

### *3.4. Un-liganded Activation*

The receptor can be activated by post-translational modification phosphorylations resulting from EGFR signaling cascade, for example. Activated receptor can then act through estrogen receptor element or tethering mechanism [48]. Non-classical mechanisms of action are also present for steroid receptors; these include activation by EGF signaling through ligand independent phosphorylations of the receptor [52].

Action of the estrogen receptor-beta depends on many parameters including cyclical interactions between regulatory molecules (ligand, cofactors, ubiquitin, or histone deacetylases), cell context, specific protein degradation (proteasome involvement), and the exact gene considered [53, 49].

### *3.5. Estrogen Receptors as Prognostic Markers of Primary Breast Cancer*

Breast cancer's patients receive an optimal treatment by the use of biomarkers. Established biomarkers like estrogen receptor play important role in the treatment of breast cancer in endocrine therapy and in the selection and management.

### *3.6 Estrogen Receptor-α as a Prognostic Marker*

Estrogen receptor-α is well-established prognostic factor in breast cancer patients. Usually, estrogen receptor-α-positive breast cancers are associated with slow rate of tumor growth, lower histology grade, DNA diploidy and therefore a better generally prognosis [54].

Estrogen receptor-alpha has been used to analyze the response to hormonal therapy. Tumors that express estrogen receptor alpha have the greatest benefit from hormonal therapy. However, estrogen receptor-alpha re-expression in an estrogen receptor-alpha negative cancer cell is not sufficient to return the estrogen receptor alpha-positive phenotype, particularly in terms of therapy response and the pattern of gene expression [55].

Estrogen receptor is used in measuring mRNA levels in primary breast tumors versus normal mammary gland epithelial cells from breast reduction surgery. Estrogen receptor-alpha expression in breast carcinoma is associated with an increased risk of reappearance and an unpleasant clinical product [54].

### *3.7. Estrogen Receptor-β as a Prognostic Marker*

The prognostic value of estrogen receptor-beta has great importance in breast cancer and the majority of cases have provided the evidence of estrogen receptor-beta as a beneficial factor. So, estrogen receptor-beta is a good prognostic indicator for the breast cancer. Expression of estrogen receptor beta is associated with better survival in patients who receive adjuvant tamoxifen [56].

In some cases estrogen receptor-beta is associated with negative axillary node status and low grade tumors [16]. As well, estrogen receptor-beta cases have a better disease free survival rate and levels of estrogen receptor-beta are decrease in proliferative pre invasive tumors [57].

There is a protective role for estrogen receptor-beta in breast cancer. In contrast, estrogen receptor-beta is a poor prognostic indicator. Tumors that expressed both estrogen receptor-alpha and estrogen receptor-beta are node positive and of a higher grade. Estrogen receptor-beta mRNA levels are also important in tumors that exhibit tamoxifen resistance. Beside these, presence of estrogen receptor-beta is a good prognostic marker for breast cancer [58].

### *3.8. Breast Cancer due to Defective Estrogen Receptor Signaling*

Defective signaling of estrogen receptor is the second main cause of breast carcinogenesis. Missing or decreased estrogen receptor reactivity provokes increased estrogen synthesis by the feed-back mechanism that results in hyper-estrogenism [59, 60].

Hyperestrogenism is not a causal factor of breast cancer but it is a protective feedback mechanism that is used to maintain the hormonal and metabolic equilibrium. As physiologic estrogen receptor signaling is crucial for all steps of cellular glucose uptake, even reactive hyper-estrogenism may not always provide sufficient compensation for severe estrogen receptor defect and insulin resistance may develop [61].

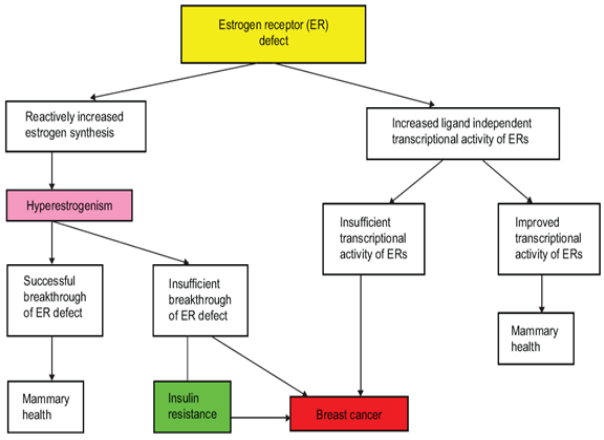


Fig. 6 Breast cancer due to defective estrogen receptor signaling

Breast cancer development is commonly associated with obesity and type 2 diabetes in BARCA mutation carrier women [62]. So, there is a close relationship between defective estrogen signaling and insulin resistance in breast cancer development [63].

An alternative option for the return of defective estradiol-mediated activation of estrogen receptor-α, an increased ligand-independent transcriptional activity of estrogen receptors may develop [64].

In BRCA1-deficient cells, there is a reduction in estradiol-mediated activation of estrogen receptor-α, while there is an increased estrogen-independent expression of estrogen response genes when compared with BRCA1-proficient cells [65].

The improved transcriptional activity of estrogen receptors in a ligand-independent way may help to maintain mammary health. On the other hand, in case of insufficient transcriptional estrogen receptor activity, the risk of breast cancer development is increased [60].

### *3.9. Proliferative Effects of Estrogen*

Breast epithelial mitosis is stimulated by both endogenous and exogenous estrogens. It increases the cell divisions and also for the risk of random genetic errors [66].

The concentration of estrogen is very important for all the stages in the development of breast neoplasm because the stimulus received by the cells to divide from hormone continues all along the progression pathway [67].

The proliferative effects of estrogens start on entering target cells; they bind with the protein receptor there and bind to the hormone response elements on the nuclear DNA and activates or suppresses the specific sequence in the regulatory regions of the genes that responsive to the estrogen and control cell growth and differentiation [68].

### *3.10. Proliferation in Genetic Damage*

In influencing the development of breast cancer, the proliferative mechanism of estrogen is very important in genetic damage. Estrogen has important role in breast cancer because of its effects before the initiation of this disease. High levels of estrogen during fetal life influence the morphology of mammary gland [69].

The increased levels of estrogen are also responsible for the persistence of epithelial tissues structure and also known as sites for malignant transformation [70].

There is a strong relationship between breast cancer risk and estrogen exposure [71]. Birth rate has been found to be positively associated with risk for breast cancer but low birth rate can also be a cause of breast carcinoma [72].

### *3.11. Estrogen as Carcinogen*

Estradiol does not have any mutagenic characteristics because no mutagenic activity has been found in either bacterial or mammalian cell test systems for estradiol. Estrogen and sometimes its metabolites including catechol estrogens and reactive semiquinone/quinone intermediates can act as procarcinogens. They can induce direct and indirect free radical-mediated DNA damage, genetic instability, and mutations in cells in culture [73].

### *3.12. Antiproliferative Role of Estrogen*

With respect to proliferative roles estrogen receptors alpha and beta also have anti-proliferative roles. These are important for the improvement of breast cancer current treatments [74].

Protein assays generally suggest that the estrogen receptor-β protein expression is a favorable prognostic factor, correlating with known biomarkers such as low histological grade, progesterone receptor expression, longer disease-free survival, and response to anti-estrogen therapy [75]. Decreased expression of estrogen receptor-β in pre-invasive carcinoma, and its anti-proliferative and anti-invasive properties suggest that estrogen receptor-β has a role in maintaining the benign phenotype, possibly as a tumor suppressor [58].

Estrogen receptor-β promoter is in some breast cancer tumors leading to loss of estrogen receptor-β expression [76].

### *3.13. Sensitivity of Breast Tissues to Estrogen*

Sensitivity of breast tissues to estrogen depends on the levels of estrogen receptors and on the types of estrogen receptors. It is possible that deviation in the breast cancer risk is partially attributable to the inter-individual variation in receptor levels in the normal tissues of breast [68].

Sensitivity of estrogens can be determined by balance between the two types of estrogen, estrogen receptor-α and estrogen receptor-β. Estrogen receptor-β has lower similarity and affinity with estrogen than estrogen receptor-α, it may decrease the sensitivity of estrogen receptor-α to estrogen [77].

### *3.14. Estrogen in Brest Cancer Prevention*

Clinical evidence also supports a role for estrogen in mammary carcinogenesis. Pharmacologic doses of estrogen also inhibit the growth of breast cancer. Estrogen can also trigger apoptotic pathways, particularly after a period of estrogen deprivation [78].

The role of estrogen in breast cancer has emerged from the experience with the selective estrogen receptor modulator tamoxifen for the treatment and prevention of breast cancer. Individual trials and a meta-analysis of randomized clinical trials show that tamoxifen reduces the

risk of recurrence for women of any age with invasive or in situ breast cancer that expresses estrogen receptor-alpha with the progesterone receptor or both [79].

### *3.15. Tamoxifen*

Tamoxifen reduces the risk of new breast cancer in the contra-lateral breast Tamoxifen reduces the risk of breast cancer by 38 percent in healthy women at high risk for breast cancer. The reduction in risk appears to be limited to estrogen receptor α-positive tumors dependable on a hypothesis that tamoxifen's primary effects are mediated through estrogen receptor pathways [80].

Results from recent clinical trials with aromatase inhibitors, agents that suppress estrogen synthesis through peripheral aromatization, in post-menopausal women with estrogen receptor a- or progesterone-receptor–positive breast cancer support the importance of estrogen in breast-cancer growth [81].

### *3.16. Aromatase Inhibitors*

By comparing aromatase inhibitors with tamoxifen in postmenopausal women with early or advanced steroid-receptor–positive breast cancer, aromatase has high resistance against breast cancer [82]. Women treated with aromatase inhibitors have lower incidence of cancer in the contra-lateral breast than women who receive tamoxifen [83].

Resistance of some steroid-receptor–positive breast cancers to agents like tamoxifen may be abrogated by the use of receptor tyrosine kinase inhibitors and clinical studies are in progress to test the role of combination therapy targeting classic and non-classic signaling [84].

### *3.17. Modulators*

Expression profiling of a breast-cancer cell line that treated with various modulators suggest that tamoxifen and raloxifene have similar effects; whereas the action of fulvestrant (an estrogen-receptor down-regulator) was different.

### *3.18. Progesterone*

Progesterone is an ovarian steroid hormone that is essential for normal breast development during puberty and in preparation for lactation and breastfeeding. The actions of progesterone are primarily mediated by its high-affinity receptors [85].

It includes the classical progesterone receptor progesterone receptor-A and progesterone receptor-B isoforms, located in diverse tissues, including the brain, where progesterone controls reproductive behavior, and the breast and reproductive organs [86].

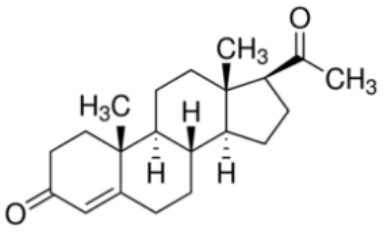


Fig. 7 Structure of progesterone [85]

Progestins are frequently prescribed for contraception or during postmenopausal hormone replacement therapy, in which progestins are combined with estrogen as a means to block estrogen-induced endometrial growth.

### *3.19. Biosynthesis of Progesterone*

In the placenta, as in other steroid synthesizing tissues, cholesterol is converted to pregnenolone within the inner mitochondrial membrane by cytochrome P450scc. This conversion is termed as the cholesterol side-chain cleavage reaction and is the first enzymatic step in the synthesis of steroids [87].

Pregnenolone is subsequently converted to the various steroids produced by the different steroidogenic tissues, by gland specific pathways. In the case of the placenta, pregnenolone is converted to progesterone by type 1 3b hydroxy steroid dehydrogenase [88].

The human placenta cannot convert pregnenolone or progesterone to estrogens because it lacks cytochrome P45017a and so uses androgen substrates from the fetal and maternal adrenal to synthesize estrogens [89].

### *3.20. Progesterone Receptors*

Progesterone receptor + cells usually co-express progesterone receptor-A and progesterone receptor-B isoforms. These receptors have different transcriptional activities within the same promoter context, but can also recognize entirely different gene promoters [90].

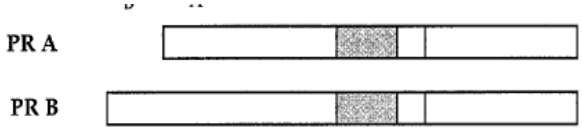


Fig. 8 Structure of progesterone receptors [91]

Progesterone receptor-B is required for normal mammary gland development while progesterone receptor-A is essential for uterine development and reproductive function [92].

### *3.21. Progesterone Action in Breast*

The major developmental role of progesterone in the normal breast has been postulated to be the formation of lobular alveolar structures during pregnancy [93].

The influence of progesterone is likely to be proliferative process mediated by progesterone regulation of cell cycle genes, growth factors, and growth factor receptors. Progesterone also exerts a differentiating effect on the breast through its role in lactation. The role of progesterone in differentiated function at other times has not been extensively explored [94].

There is less known of the mechanisms through which progesterone exerts its effect in the breast, primarily because of the difficulty of obtaining normal breast tissue and the relative paucity of models of progesterone action in the normal breast [95].

### *3.22. Progesterone in Proliferation of Normal Breast Cells*

Progesterone has important effect on proliferating the breast cells and leads to tumor [96]. The increase in DNA synthesis is consistent with the cyclical increase in the number of epithelial mitoses, which peaks toward the end of the luteal phase and is followed by an increase in apoptotic activity [97].

Progesterone levels during pregnancy are responsible for inducing marked lobular-alveolar development of the breast in preparation for lactation. In contrast to this proliferation in breast tissue progesterone has also protective effects [98].

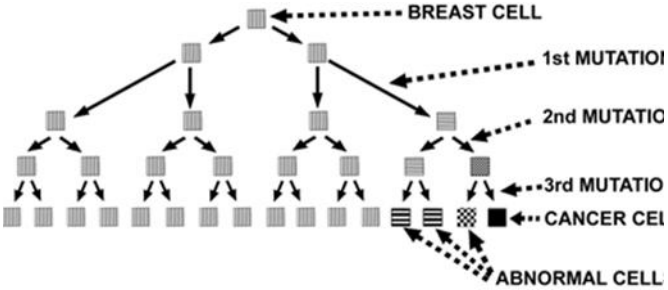


Fig. 9 Breast cells proliferation by progesterone [99]

Role for progesterone in cell proliferation in the breast is difficult to know. Cell proliferation in the breast and the involvement of ovarian hormones in process are required in the role of progesterone in cell proliferation.

## 4. Cellular Mechanism of Progesterone in Mammary Epithelium

### *4.1. Cell Proliferation*

The mammary epithelium is bilayered. The inner layer of luminal cells is surrounded by a meshwork of elongated myoepithelial cells, which are in close contact with the basal membrane [100].

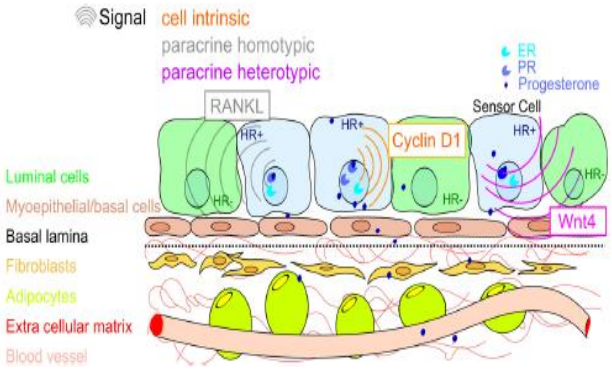


Fig. 10 Cellular proliferation [101]

An inner, luminal layer is surrounded by myoepithelial/basal cells, which are in contact with the basal lamina. Progesterone binds its receptor in a subset of luminal cells, the sensor cells. In certain progesterone receptor cells, it induces cell proliferation by a Cyclin D1-dependent mechanism (cell intrinsic signaling). It induces RANKL, which elicits cell proliferation in neighboring cells (paracrine homotypic) and wnt4, which acts on myoepithelial cells (paracrine heterotypic) an increases stem cell activity [102].

In the adult mammary epithelium, most cell proliferation occurs in the luminal compartment, but few of the proliferating cells expresses progesterone receptor [103].

### *4.2. Tumor Promoting Action of Progesterone*

Progesterone receptor signaling during luteal phase may be tumor promoting. Some of the effects of progesterone are cell-intrinsic, but many biological responses rely on paracrine signaling that can be homotypic, i.e., to neighboring luminal cells, or heterotypic, i.e., to the myoepithelium and possibly to stromal cell types [104].

With each menstrual cycle, breast cancer risk increases through progesterone-induced events during luteal phase. The perinatal exposure to endocrine disruptors increases the sensitivity of the breast to progesterone.

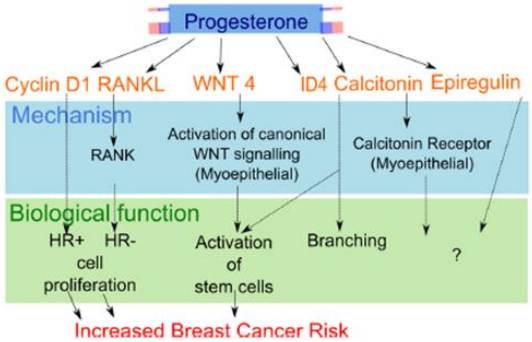


Fig. 11 Tumor promoting action of progesterone [105]

Various factors such as RANKL, WNT4, epiregulin, CyclinD1, ID4 and calcitonin, which act through distinct mechanisms have distinct biologically functions that have been implicated in the biological response to progesterone that may be amplified due to perinatal exposure [105].

### *4.3. Molecular Mechanism of Progesterone in Breast Cancer*

Across species, estrogen receptor-α and progesterone receptor are absent from the myoepithelial cells and basal cells and are expressed by 30–50% of the luminal cells. Most cells co-express estrogen receptor-α and progesterone receptor, which is consistent with progesterone receptor being an estrogen receptor-α target [106].

Progesterone receptor positive may affect neighboring cells in a paracrine fashion by secreting signaling and proliferating factors. Some of the attractive target genes of this hormone include but excluded to WNT, fibroblast growth factors, epidermal growth factor as well as direct intercellular signaling mediated by Notch, ephrins or gap junctions [107].

### *4.4. Paracrine Signaling*

There are two types of proliferation, cell-intrinsic and paracrine proliferation. Cell-intrinsic action of progesterone on hormone receptor+ cell proliferation requires cyclin D1. Whereas the proliferation of hormone receptor– cells does not [108].

Proliferation of hormone receptor–cells on progesterone stimulation requires RANKL, which is a tumour necrosis factor α family member. It was further noted that that RANKL is a crucial mediator of progesterone receptor signaling function [109].

Soluble RANKL controlled intravenously can elicit proliferation in the mammary epithelium and systemic administration of its decoy receptor osteo-protegerin can inhibit proliferation [110].

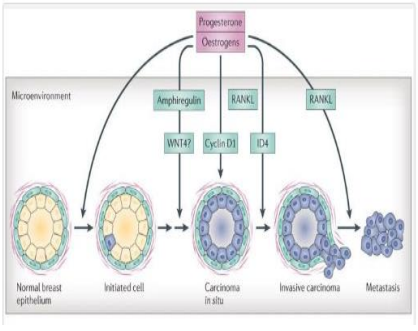


Fig. 12 Paracrine signaling [110]

Progesterone acts on the normal breast epithelium and initiates the proliferation. And estrogen acts immediately at initiated cell through different signaling mechanisms to stimulate the carcinoma. RANKL starts at that point and metastasis occurs [111].

Reproductive hormones impose on breast carcinogenesis at all stages and can determine whether the disease will progress. In particular, progesrterone receptor signaling has an essential role in controlling tumor promotion [112].

### *4.5. Protective Effects of Progesterone*

Unlike the proliferative and carcinogenic effects of estrogen however, progesterone has been considered to be protective against breast cancer because its role in causing differentiation and maturation of the epithelial cells. Progesterone levels increase usually in the third trimester of pregnancy and this is when mammary cells undergo maximum differentiation in preparation for lactation [113].

### *4.6. Progesterone in Breast Cancer Prevention*

Progesterone role in enhances breast cancer was an increased risk among women using hormone replacement therapy with progestin and estrogen as compared to the women using hormone replacement therapy with only estrogen. However, this increased risk may be due to the type of synthetic progestin used rather than progesterone itself [113].

## 5. Future Prospects

Although significant progress has been made in both the understanding and treatment of cancer during the last thirty years, it remains the second leading cause of death. The cancer community has set a goal to eliminate cancer-related suffering and death by 2015. To achieve this goal, not only better therapies are required but also improved methods to assess an individual's risk of developing cancer to detect cancers at early stages when they can be treated more effectively to distinguish between aggressive and nonaggressive cancers and to monitor recurrence and response to therapy.

Recent advances in high-throughput technologies in genomics, proteomics and metabolomics have facilitated biomarker discovery. As more potential biomarkers are discovered, further studies are needed to validate these markers. The ultimate use of these biomarkers is in clinical applications for cancer detection and treatment. Many steroid receptors have been used in breast cancer for predicting outcome and response to therapy for many years. Presently, we lack the targeted therapies for triple negative breast cancer and this continues to direct the focus of ongoing research.

The first judgments of vaccination by direct

injection of tumor antigens or "laden" dendritic cells today suggestion significant hope for patients. In future biomarkers will be used as significant prognosis tool to determine if patient has a disease.

## 6. Conclusion

The estrogen receptor plays a central role in the hormone action. There is much importance of estrogen receptor in the development and progression of breast cancer and this has led to its becoming a major target for breast cancer treatment. The efficacy of anti-estrogen treatment to inhibit the growth of ER-positive breast cancer cells has been extensively documented. Accumulating insights regarding estrogen signaling and mechanisms of action of ligands and ER provide opportunities for the development of novel markers, targets and therapeutic strategies.

Progesterone does not have much cancer-promoting effect on breast tissue. More importantly, many of the progestins have several non-progesterone like actions those potentiate the proliferative effect of estrogens on breast tissue and estrogen sensitive cancer cells. When HRT is indicated, preparations containing progesterone and not a synthetic progestin should be used, according to a sequential or cyclic-combined regimen. In this way, risk of endometrial cancer is minimized without increasing the risk of breast cancer.

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