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Estrogen and Estrogen Receptor a Risk Factor in Breast Cancer - A Review

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Abstract

There are many evidences which show that estrogens play a crucial role in the development of breast cancer. Most established risk factors for breast cancer in humans probably act through hormone-related pathways, and increased concentrations of circulating estrogens have been found to be strongly associated with increased risk for breast cancer in postmenopausal woman. In this review we describe in detail estrogen metabolism and associated genetic variations, and provide a critical review of the current literature regarding the role of estrogens and their metabolites in breast cancer risk. Estrogens display intriguing tissue selective action that is of great biomedical importance in the development of optimal therapeutics for the prevention and treatment of breast cancer. Tamoxifen has been the only drug of choice for more than 30 years to treat patients with estrogen related (ER) positive breast tumor.

Keywords: Estrogen, Estrogen receptors, Sulfatase pathway, Aromatase pathway, Tamoxifen.

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1. Introduction

Breast cancer is the most common cancer in women worldwide and one of the leading causes of cancer-related deaths in women. Age is the strongest risk factor for breast cancer. There are three types of estrogens i.e. E1 (estrone), E2 (estradiol), and E3 (estriol).

E1 is made after menopause and synthesized in adipose tissues from adrenal dehydroepiandrosterone [1] E2 is the most common type of estrogen and present in all ages of women. Many additional risk factors for breast cancer have been identified. Some risk factors are non-selectable, such as age, BRCA1 and BRCA2 gene mutations, family history, reproductive history, and high-dose radiation to the chest. Others are modifiable like high endogenous estrogens, obesity and alcohol consumption. [2]

Since a number of these known risk factors are related to endogenous estrogen levels. Studies have shown that tamoxifen reduce the risk of breast cancer. Increased concentrations of endogenous estrogens are strongly increased risk factor in postmenopausal women. Most established risk factors in humans are thought to influence risk from hormone related pathways [3].

1.1 Estrogen

Estrogen is a female hormone made mainly in ovaries. It has an essential role, together with other hormones, in the development of the female sex organs and secondary sex characteristics, the regulation of the menstrual cycle and reproduction. Higher exposure to estrogen may increase the risk of breast cancer like starting of menstrual cycle at a young age or go through menopause at a later age.

1.1. a Endogenous estrogen

The endogenous production of and exposure to endogenous estrogen varies greatly during a woman's life. In premenopausal women, the predominant form of

circulating estrogen is estradiol secreted by the ovaries [4]. After the menopause, however, the production of estrogens in the ovaries ceases and the major source of estradiol are by conversion from estrone. Significant increase with increasing concentrations of estradiol, free estradiol and estrone in the blood. Non- significant increase means estradiol concentrations in comparison with controls.[5]

1.1.b Exogenous estrogen

Exposure to exogenous estrogens from a variety of sources has become increasingly common, particularly from hormonal preparations for use as contraceptives. Hormonal contraception, using estrogens and progestins in various forms and doses, is now one of the most widely used forms of contraception. The prescription of hormone replacement therapy (HRT) for aged women, containing oestrogens with or without progestins or long term use of progestins is more noxious that use of estrogens.[6] Trials confirmed that exposure to estrogens plus progestins for 5 years linked with 26- 30% increase in breast cancer risk.[7]

2. Pathway for estrogen synthesis

2a. Sulphatase pathway:

Steroid sulphatase is enzyme which is also known as aryl sulphatase-C and it is located in endoplasmic reticulum of various tissues. It hydrolyses the steroid sulfate to the unconjugated biologically active form. Estrone synthesizes is rapidly sulfated to estrone sulfate (E1S) by sulfotransferases. E1S concentration in plasma is 10-20 times higher and also the half life of E1S is (10-12 hr) considerably longer than that of unconjugated estrogen, estrone and estradiol. Hence, E1S converts into active estrogen by the action of STS, First converts into estrone and then reduced to biologically active estrogens, estradiol by 17HSD which is then over expressed in breast tumors. STS is more active i.e. 50 times greater in both pre- and post- menopausal tumors than normal breast tissue and detected in 90% of breast tumors.

2b. Aromatase pathway:

Aromatase, a number of CYP450 enzyme family, is expressed in brain, gonads, blood vessels, liver, bone, skin, adipose tissue and endometrium. Aromatase expressed in specific tissues and depends on three major factors i.e. alternative splicing mechanism tissue specific promoters and transcription factors[12].

The human aromatase gene CYP19 comprise a 93kb 5' regulatory region and 30kb 3' coding region. In the ovaries aromatase gene expression is regulated by FSH (Follicle stimulating hormone). There is increase in aromatase expression in breast adipose tissue in breast cancer patient. Aromatase activity can be changed by post translation modification such as phosphorylation.

The“aromatasepathway,”5alpha-androstenediol-sulfat(Diol-S) and dehydroepiandrosterone(DHEA), are mainly derived from the circulation. Diol-Sis converted 5alpha-androstenediol (5-Diol) by STS[13] .It is converted into testosterone by 3beta-HSD. DHEA-Sishydrolyzed to form DHEA, which is further converted by 3beta-hydroxysteroiddehydrogenase to form androstenedione (4dione).Testosterone is formed by 17-beta-HSD from 4-dione.Testosterone is converted to E2 by the aromatase (CYP19). 5-Diol bind sand activates estrogen receptors, but with lower affinity than E2[16].

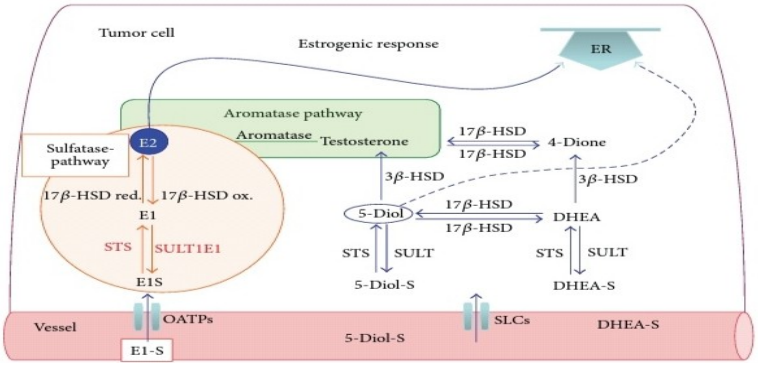

Figure 1: Sulfatase pathway and Aromatase pathway

Courtesy: The sulfatase pathway for Estrogen formation: Targets for the Treatment and Diagnosis of Hormone-Associated Tumors. (Review article)

3. Estrogen Metabolism

All steroid hormones originate from C27 cholesterol. The main source of cholesterol required for the synthesis of steroid hormones (steroidogenesis) is LDL-cholesterol. [8] Cholesterol is metabolized down a number of enzymatic pathways and is converted to the 21-, 19-, and 18-carbon steroid hormones, respectively.

The first step in ovarian steroidogenesis is the movement of cholesterol into the mitochondrion. This step is regulated by the steroidogenic acute regulatory protein (*StAR*) encoded by the *STAR* gene.[9] The next step involves the conversion of cholesterol to pregnenolone, catalyzed by the mitochondrial side-chain cleavage enzyme complex. All C18 steroids and consist of one benzene ring,

a phenolic hydroxyl group at C3, and a hydroxyl group (17β-estradiol) or a ketone group (estrone) at C1.

The main estrogens circulating in the human body are estradiol and estrone, as well as 16-hydroxyestradiol (estriol). Estrone is reversibly converted to estradiol through the action of 17β-hydroxysteroid dehydrogenase enzyme[10]. Androstenedione, the most important product of the cells during the follicular phase of the menstrual cycle, is not biologically active; nevertheless it acts as a precursor for both estrone and testosterone in the ovaries and peripheral tissues. Aromatase (CYP19, encoded by CYP19A1 gene, rate limiting enzyme is catalyzing conversions of androgens to estrogens [11].

3.1 Hydroxylation pathways

3.1.a 2- Hydroxylation pathway:

The 2-hydroxylation pathway is the major metabolic pathway. The cytochrome P-450 enzymes, including CYP1A1 and CYP1B1, are major phase- I enzymes mainly expressed in breast and liver tissues[12]. These enzymes, along with CYP1A2, catalyze the C2 hydroxylation of parent estrogens to their respective catechol estrogens. Two-hydroxylated estrogens possess low binding affinity for the estrogen receptor (ER). These metabolites demonstrate reduced hormonal potency when compared with estradiol, and both non-estrogenic and anti-estrogenic activities have been assigned to them. There is some evidence from cell culture studies in ER+ human MCF-7 breast cancer cells suggesting that 2-hydroxyestrone and 2-hydroxyestradiol inhibit cell growth and proliferation. metabolites has been attributed to a few mechanisms including a high rate[13]. At the same time, it has been shown that 2-hydroxyestrogens can damage DNA and generate free radicals as they go through redox cycling or when COMT is inhibited. Methoxyestrogens including 2-methoxyestradiol, have been confirmed to inhibit carcinogenesis by suppressing cell proliferation due to effects on microtubule stabilization [14].

3.1.b 4- Hydroxylation pathway:

CYP3A4/3A5 has been shown to be the primary enzyme in the 4 hydroxylation of estradiol in human liver microsomes[15]. 4-hydroxylated catechol estrogens possess carcinogenic potential due to their ability to cause DNA damage by forming depurinating adducts, which in turn, generate mutations with subsequent oxidative damage and initiation of breast cancer[16].. Iit has been shown that the 4-methoxyestrogens prevent oxidative metabolism of estradiol and oxidative DNA damage[17].

3.1.c 16- Hydroxylation pathway:

16α-hydroxyestrone is the most important metabolite of the 16-hydroxylation pathway. 16α-hydroxyestrone is a probable tumor initiator, which promotes unscheduled DNA synthesis[18]. Studies have shown that urinary concentrations of 16α-hydroxyestrone are associated with increased proliferation of mammary cells. 16α- hydroxysterone production may play an important role in breast cancer induction[19].

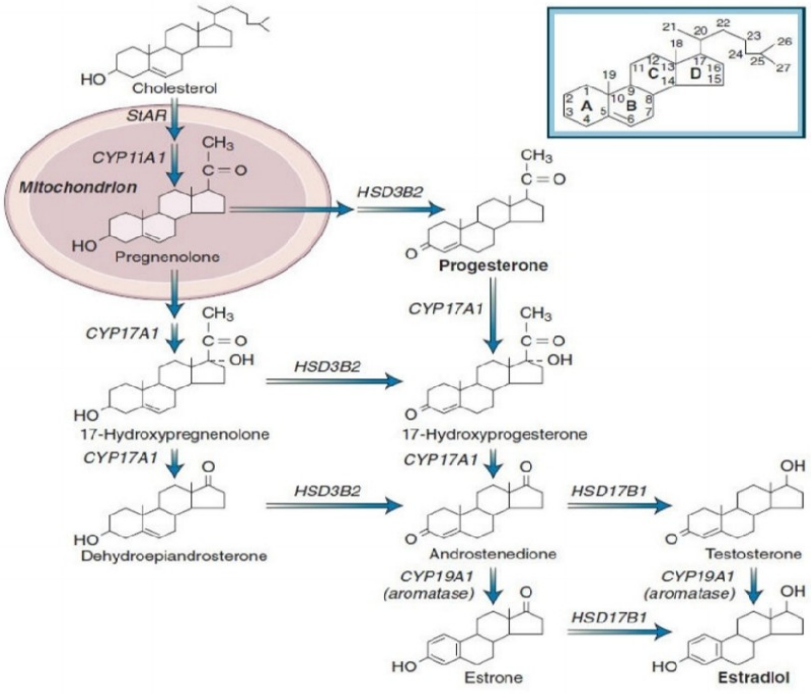

Figure 2: Pathways of steroid hormome synthesis in humans

Abbreviations: StAR, Steroidogemic acute regulatory proteins; CYP11A1, side- chain cleavage of P450; CYP17A1, 17-hydroxylase/17,20-lyase; HSD3B2, 3beta-hydroxysteroid dehydrogenase- 5,4 isomerase type2; CYP19A1, aromatase; HSD17B1, 17beta- hydroxysteroid dehydrogenase type 1. **Courtesy**: Estrogen Metabolism amd Breast cancer.

3.2 Role of Genetic Variation in Estrogen Metabolism:

Genetic polymorphisms in genes encoding enzymes involved in estrogen metabolism pathways and the genes encoding the ERs are associated with breast cancer risk. Polymorphic variations in genes encoding COMT, CYP1A1, CYP1B1, estrogen receptor alpha (ERα), estrogen receptor -beta (ERβ), CYP17A1, and CYP19A1 have received deep atrention[20].

COMT is a phase-II enzyme that inactivates catechol estrogens by conjugating them into non-genotoxicmethoxyestrogens. COMT also prevents biotransformation of catechol estrogens to quinone-DNA adducts and development of reactive oxygen species (ROS) capable of damaging cellular macromolecules such as DNA, lipids, and proteins [21]. COMT, located on chromosome 22q11, is polymorphic; a single G to A transition at codon 158 of *COMT* (single nucleotide polymorphism (SNP) rs4680) results in a 3- to 4-fold decrease in enzymatic activity (GG vs. AA genotype). Individuals with heterozygous genotype (A/G) show intermediate levels of COMT activity.

It has been hypothesized that polymorphic variations in CYP1A1 and CYP1B1 genes are linked with increased risk. Individuals with heterozygous genotype (A/G) show intermediate levels of COMT [22]. Greater risk due to higher concentration of catechol estrogen intermediates. SNPs in CYP1B1 genes have been investigated in relation to cancer risk [23].

3.3 Postmenoposal women

In postmenopausal women, increased circulating concentrations of estradiol, estrone, estrone-sulfate, and androstendione have been associated with higher breast cancer risk, whereas higher levels of sex hormone binding globulin (SHBG) have been associated with lower risk [24-25]. Estradiol was directly linked with ER-ve breast cancer cases was very small, no form conclusion could be established [26]. Key *et al.*, in a pooled analysis of 9 prospective studies of 663 women who developed breast cancer and were not on any exogenous sex hormones, showed that risk of breast cancer significantly increases with higher levels of total estradiol, free estradiol, estrone, estrone-sulfate, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and testosterone. Magnitude of associations of esteogens with the number of breast cancer risk factors including obesity, reproductive and life style factors has been investigated by endogenous hormones. Mammographic density, a major known factor for breast cancer development, is a measure of amount of fibroglandular tissue that appears on mammogram [27]. Studies showed that estrogens and androgems levels were positively associated with obesity, smoking (15+ cigrettes daily) and alcohol consumption (20+ g alcohol daily) and inversely linked with age[28].

By contrast SHBG concentrations were greater in older women and lower younger women and those consuming alcohols. The leading methodology for measurement of estrogens metabolites was ELISA, which has limiting specificity and sensitivity. Epidermiological studies have continuously shown 2-4 fold increases in breast cancer risk in women with elevated blood estradiol levels.

3.4 Premenoposal Women:

Estrogens are produced primarily in ovaries corpus luteum, in placenta, small and significant amount of estrogen can be also be produced by non- gonard organs such as liver, heart, skin, and brain. This is likely due to the much smaller number of breast cancer cases in premenopausal women [29]. Another potential reason may be the large inter- and intra-individual variations in sex hormone concentration during the menstrual cycle. To the best of our knowledge, only nine prospective studies have evaluated the associations between serum estrogens and breast cancer risk in premenopausal women.

Four prospective studies have investigated the relationships between breast cancer incidence and concentrations of individual estrogen metabolites, their ratios or metabolic pathways in premenopausal women [30]. The ratio of 2/16-hydroxyestrone has been studied in either urine or blood samples with inconsistent results. Muti *et al*. [137] reported that relative to the lowest quintile, cases in the highest quintile of luteal phase urinary 2/16-hydroxyestrone had a 45% reduction in breast cancer risk (*n* =67 cases; adjusted RR= 0.55; 95% CI, 0.23–1.32). Additionally, both 2-hydroxyestrone and 16α-hydroxyestrone were positively but non-significantly linked with risk. Consistent with these results was a study conducted by Meilahn *et al* in which 60 breast cancer cases were matched to 184 controls on age, baseline visit date, and menstrual cycle phase. Results showed that women in the top tertile of the 2/16-hydroxyestrone ratio had a lower breast cancer risk compared to those in the bottom tertile (OR= 0.75; 95% CI, 0.35–1.62; *P* value= 0.46).

Recently, two systematic reviews and combined analyses have examined the relationships between circulating or urinary 2-hydroxyestrone, 16α-hydroxyestrone, and their ratio with breast cancer risk[31]. Obi *et al*., in a study of 682 premenopausal cases and 1027 matched controls, concluded that the urinary 2/16-hydroxyestrone ratio, but not circulating levels, is non-significantly associated with lower risk of breast cancer (range of ORs=0.5–0.75; 95% CI, 0.25–1.01 and 0.35–1.62; respectively). Similarly, Dallal *et al*., in a combined analysis of 726 women (*n*=183 cases) demonstrated that

elevated urinary 2/16-hydroxyestrone is suggestive of lower breast cancer risk (ORtoptertile vs. low tertile= 0.74; 95% CI, 0.45–1.23). Additionally, data from the same analysis showed that higher urinary 2/16-hydroxyestrone is indicative of decreased risk of breast cancer for ER− cases (ORtoptertile vs. low tertile= 0.33; 95% CI, 0.13–0.84). This latter finding is based on small number of 31 cases; therefore, it may be due to chance and needs more research to be confirmed.

4. Estrogen Receptor (ER) in Breast Cancer

4.1 Structure

Two different forms of estrogen receptor are: α and β, coded by ESR1 and ESR2 genes respectively.ERα gene is located on chromosome 6 while the ERβ gene is onchromosome14, ERα protein has 595 aminoacids andmolecular size of 66 kDa while ERβ protein has 530 amino acids and molecular size of54 kDa [32,33].

These genes are responsible for cell proliferation.ERα isq in Uterus,Vagina and ovaries and Mammary gland & also in vascular smooth muscle while ERβ is present in Prostrate,Ovaries,Lung ,Bone and Brain[34].

Six structural domains are there in ER receptor i.e. A, B, C, D, E, F. Each domain homology is differ between. The N-terminal of the A/B domains subsist activation function1 (AF-1) which is least conserved (30% identitcal),contains aminoacids for post transcriptional modification such as splicing to stimulate AF-1 activity[35,36]. C domain,the DNA-binding domain (DBD),the most conserved region(95%) regulating the target gene expression [37].D domain, Hinge region (36% homologous)stimulate nuclear localization signaling. Finally, the E/F domain are 53% homologous & located in the C-terminal region .E domain, a ligand-binding domain (LBD), contains a dimerization surface and a ligand-dependent activation function 2(AF-2) that control the transcriptional activity of ERs & F domain control the transcriptional activity of target specific genes[38,39].

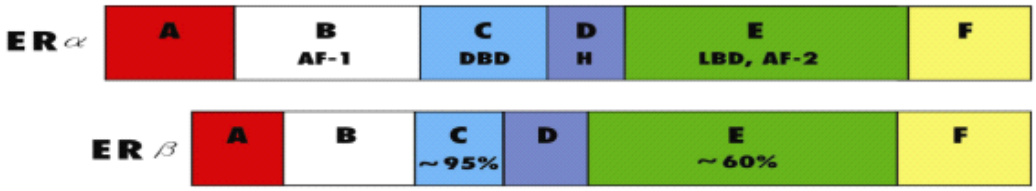

Figure 3: Domain organization of human ERα and ERβ

Courtesy: Estrogen Receptor Agonists/ Antagonists in Breast Cancer Therapy: A Critical Review.

4.2. ER status

Younger patients are more likely to be ER-negative (ER-) compared with older patients. The Surveillance, Epidemiology and End Results(SEER) cancer registries in the USA showed that the ER-positive (ER+) is age-specific breast cancer & rates increased with age, but at a slower pace after ages 50–54 years, while the ER- breast cancer rates did not increase after ages 50–54 years[40]. In Chinese women ER+ cancers were seen in 53 and 61.6% of pre- and post-menopausal women with breast cancer[41].ER+ rate can vary between different ethnic groups even in the same country, as seen in a multiethnic Asian country[42,43].

Breast cancer is a heterogeneous disease and hormone receptor status can separate breast cancer into distinct subgroups, ER+PR+, ER+PR-, ER-PR+ and ER-PR- [41]. Risk factors for each subtype are also differ, being crucial for age, menopausal status, BMI after menopause, parity and past use of postmenopausal hormone-replacement therapy (HRT)[44]. The increase in incidence of ER+breast cancers is the main reason in increase of breast cancer cases while ER- cases remains constant[45].

Hormonal factors are believed to be the cause of this trend, as there are many chemicals in the environment that possess estrogen-mimicking properties, such as the organochlorine pesticides and polychlorinated biphenyls, which can enter the human breast and that have estrogenic activity[45]. There are differences in ER+ breast cancers between urban and rural areas, the urban ER+ incidence rate was two-times higher than the rural incidence rate[46].

4.3 ER and epithelial cell transformation

ER mainly expresses in less than 25% of luminal epithelial cells and has no expression in basal or stromal cells[47]. Not all the ER+ cells actively proliferate as there is no correlation between the proliferating cell marker Ki67 and ER positive cells. Luminal epithelial cells proliferate more than 90% of mammary gland epithelial cell[48]. ER+ cells actually promote neighbor cells proliferation by secreting paracrine growth factors [49,50]. Consistently, the exposure of ER- mammary epithelial cells to ER positive cells, they regain the proliferative capacity and contribute to mammary gland development[51].

In BRCA1 related breast cancer, 70~80% cases are ER negative and less than 20% are ER positive, while ER positive cases are more prevalent in sporadic breast cancer[52]. The ER+ BRCA1 related breast cancers are age dependent. In BRCA1 mutant mice, exogenous estrogen stimulate the proliferation of the mammary epithelial cells and tumor growth. It was observed that ER positive cells gradually disappear along with the growth of tumor[53].

E-ER signaling is critical to promote the tumor growth, to decrease the risk in BRCA1 mutation carriers estrogen effect should be decreased by either prophylactic oophorectomy or Tamoxifen[54,55].

ER positive cells contribute to the oncogenic transformation of ER negative cells by providing mitogenic signaling stimulation and thus the mammary epithelial cells that have oncogenic transformation are from ER negative cells.ER positive cells also experience the oncogenic transformation and de-differentiation that results in loss of ER expression[56].

4.4 Testing for ER in the clinical laboratory

Radio labeled ligand-binding assays (LBAs) is the original assays to measure hormone receptor levels in breast cancer tissues. A frozen tissue from the tumor was taken then homogenized and mixed with known quantities of radiolabeled estradiol. Dextran-coated charcoal is used to separate the receptor-bound radiolabeled estradiol from the unbound ligand, and by the use of Scatchard analysis, the amount of bound ligand is estimated. It is a quantitative analysis[57].

With LBA studies showing that patients with higher levels of receptor in their tumors responded better to hormonal therapy than those with only small amounts of ER[57,58,60]. The amount of receptor present can also be estimated with the immune-histochemical assay. Main disadvantage of the immune-histochemical approach is that it does not readily allow for quantitation and is extremely expensive and not widely used[61].

5. Therapy Of Breast Cancer

5.1 Role of ER in Treatment

ER is essential in the statistics for treatment decision-making. ER+ patients may go for hormonal therapy[62], women with ER+ breast cancer, 5 years of a selective estrogen receptor modulator such as tamoxifen reduces the annual breast cancer death rate by 31%, nonetheless of use of chemotherapy[63] .Another important aspect is, instability in hormone receptors throughout tumor progression, hence it is important to biopsy the metastatic site to procure hormone receptor status before treatment because ER alteration occurs in 1 of 3 patients[64]. In patients with ERα positive breast cancer, treatment has long relied on endocrine therapies such as tamoxifen & its active metabolite [65] and anastrozole[66], both prevent ligand-dependent activation of ER transcriptional activity[67].

5.2 Selective ER Modulators

Selective estrogen receptor modulators (SERMs) are a new category of therapeutic agents, for the prevention and treatment of diseases such as osteoporosis besides uterus and breast cancers, these modulators are used . They have high affinity for ERs, but no specific affinity for any other steroid hormone receptors, also they can stimulate estrogenic actions (ER agonist) in tissues, such as the bone, liver, and cardiovascular system, but block estrogen action on other sites (ER antagonist) such as the breast and uterus where stimulation is not required. This agonistic or antagonistic activity causes different conformational changes of the receptors, particularly at the helix 12, resulting in activation (transactivation) or repression (transrepression) of the estrogen target genes[68] .

Tamoxifen, a non steroidaltriphenyl ethylene derivative **,**was first reported in the 1960s by ICI now known as Astra Zeneca, brand name Nolvadex, used as the first-line therapy for breast cancer since 1970s and used even today. It was approved for breast cancer treatment and prevention by the FDA in 1977 & marketed in 1973. It act as antiestrogen as it was observed that tamoxifen function as an antagonist in the reproductive systems of mice as a partial agonist in rats and as a pure antagonist in chickens[69].The need for developing SERMs is arises due to the failure of Tamoxifen. The structure of tamoxifen is given below :

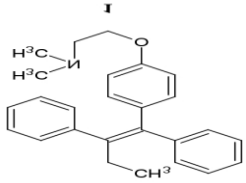

Figure 4: Tamoxifen

Courtesy: Estrogen Receptor Agonists/ Antagonists In Breast Cancer Therapy: A Critical Review.

5.3 Selective ER Degraders (SERD)

De novo and acquired resistance of these drugs like tamoxifen and SERM, ultimately leads to disease progression & hence SERDs development occur [71]. Aromatase inhibitors (AI) inhibits the enzyme aromatase responsible for the production of estrogen [72]but unfortunately these inhibitors are also subject to therapeutic resistance and can eventually lead to disease relapse[73]. So, SERDs selective estrogen receptor degrades, they induce the receptor degradation which overcome the mechanism of resistance to AIs and SERMs. The SERD fulveltrant is the currently approved degrader for the treatment of ER positive breast cancer[74,75]. It binds and

accelerate the degradation of the ER by inducing a denaturing structural change within the receptor[76]. Efficacy may be limited due to its poor physicochemical properties. So it is administered intramuscularly in two 5 ml injections once monthly[77].

5.4 ER as Antagonist

For the treatment of postmenopausal women with hormone-dependent breast tumors, development of ER antagonists a new approach have been carried out[78]. The high levels of estrogen, as a result of it *in situ* synthesis, are associated with the growth of tumors in endocrine dependent tissues. Estrogens are formed exclusively in peripheral tissues, and there are two pathways associated with their synthesis in such tissues, the aromatase (AR) and sulfatase (STS) pathways[79]. Hence potent STS and Aromatase inhibitors have now been developed, paving the way to use this new type of therapy for breast cancer[80,81].

Sulfatase inhibitor inhibits the activity of sulfatase enzyme (estrone - O-sulphamat)[82]. Aromatase inhibitors inhibits the activity of aromatase enzyme (4-Benzyl-3-(4'-chlorophenyl)-7-methoxycoumarin)[83].

6. Conclusion

Estrogens have a key role in the aetiology of breast cancer. There is currently convincing evidence that endogenous estrogens are associated with breast cancer in post menopausal women. Nevertheless this relationship has not been confirmed in premenopausal women. The role of estrogen metabolites in etiology of breast cancer has been studied, but no completion can be drawn in either pre or post menopausal women. The subsequent discovery of tamoxifen has made a significant impact on survival of women with hormone receptor- positive breast cancer. There is no significant data to confirm the role of estrogen metabolities as predictors of breast cancer. SERDs have recently appeared as significant biologicals for breast cancer. Evidences showed that endogenous estrogens are associated with breast cancer in post menopausal women.

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