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A REVIEW OF BREAST CANCER AND HORMONAL THERAPY

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ABSTRACT: Breast cancer is a malignant tumor that develops from ductal and lobular cells of the breast. It is the most commonly occurring female cancer in the world. After cervical cancer, breast cancer is the second most common cancer in India. Several factors are known to affect the risk of breast cancer. There is mainly two types of breast cancer: ductal and lobular carcinoma. Estrogen, directly and indirectly, stimulates the growth of tumor cells. Several procedures can be used to diagnose breast cancer mainly radiological investigations, estrogen, and progesterone receptor test, and genomic assay. Breast cancer stages describe by the TNM staging system. Breast cancer treatment includes surgery, radiotherapy, chemotherapy, and hormone therapy. The estrogen receptor (ER) is an important target to develop drugs for the treatment and prevention of breast cancer. The interaction of estrogen with the ER can result in increased proliferation of target cells, so the rationale for endocrine therapy is to block the interaction of estrogen with the ER. This goal can be accomplished by using SERMs or by using aromatase inhibitors.

INTRODUCTION: Breast Cancer: Breast cancer is a malignant tumor that develops from ductal and lobular cells of the breast. A malignant tumor is a group of cancer cells that tend to invade surrounding tissues or spread (metastasize) to distant areas of the body.

Breast Cancer Prevalence: Breast cancer is the most commonly occurring female cancer in the world with an age-standardized incidence rate (ASR) of 39%. Breast cancer accounts for 23% of all newly occurring cancers in women worldwide and represents 13.7% of all cancer deaths in India, breast cancer is the second most common cancer (after cervical cancer) with an estimated 1,15,251 new diagnoses and the second most common cause of cancer-related deaths with 53,592 breast cancer deaths in 2008. [1]

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The age-standardized incidence rate for breast cancer in India is 22.9%, one-third that of Western countries, and the mortality rates are disproportionately higher breast cancer accounts for 22.2% of all new cancer diagnoses and 17.2% of all cancer deaths among women in India.

Breast cancer in urban areas of India is three times higher than in rural parts of the country. In metropolitan cities, breast cancer is the leading cancer diagnosis in women, with rates nearly twice as common as cervical cancer [2].

Epidemiology of Breast Cancer in India: Age incidence rates in India suggest that the disease peaks at a younger age (*e.g.*, 40-50 years) than in Western countries and as a result, the majority of new diagnoses occur in pre-menopausal women. The majority of new cases are an advanced stage - locally advanced or higher stage- at the time of diagnosis. The increasing burden of disease may be associated with lifestyle factors such as later age at marriage, age at first birth, reduced breastfeeding and westernization of diet and physical activity patterns. Breast cancer rates tend to be higher in women of higher education and in specific

communities that have adopted a more westernized lifestyle [3].

Etiology: Throughout a lifetime, 1 in 8 women will be diagnosed with breast cancer. Several factors are known to affect the risk of breast cancer in the population. The strongest risk factors for breast cancer include age, familial and reproductive factors. Lifestyle and hormonal factors have also been linked to breast cancer risk [4].

Risk Factors of Breast Cancer:

Age and Gender: There is a risk of developing breast cancer increases as a person gets older. Most advanced breast cancer cases are found in women over age 60 although there is evidence that Indian women are more likely to develop breast cancer at earlier ages than their Western countries and that breast cancer peaks from ages 45-50 years in India. Women are 100 times more likely to get breast cancer than men [4].

Family History of Breast Cancer: A family history of breast cancer in the mother, father, sister or daughter increases the risk of breast cancer, and the risk is even stronger if the family member was diagnosed before the age of 50 years old and with pre-menopausal breast cancer. Specifically, if a woman has a first-degree relative >50 years diagnosed with post-menopausal breast cancer, her risk increases by 80% whereas a first-degree relative with pre-menopausal breast cancer increases a woman's risk by 330%.

The risks increase for a higher number of first- and second-degree relatives diagnosed with breast cancer. A history of ovarian cancer in other relatives (in the mother's or father's families) also increases the risk of breast cancer [4].

Genetic Alteration: The most common gene defects are found in the BRCA1 and BRCA2 genes. These genes normally produce proteins that protect the body from cancer. Having mutations in BRCA1, a gene on chromosome 17 that controls cell growth or BRCA2, a gene on chromosome 13 that suppresses cell growth, is associated with a 40-80% increased risk of breast cancer. If a parent passes you a defective gene, a person has an increased risk for breast cancer. Women with one of these defects have up to an 80% chance of getting breast cancer sometime during their life [5].

Menstrual History: Ages at Menarche and Menopause: Women who have an early age at menarche (<12 years) have a 30% increased risk of breast cancer while those who have a late age at menopause (>60 years) will have a 20-50% increased risk of disease [6].

Alcohol Use: Drinking more than 1-2 glasses of alcohol a day may increase your risk for breast cancer.

Childbirth: Women who have never had children or those who are more than 30 years at the time of their first child's birth are twice as likely to develop breast cancer as women who had their first child before the age of 20 years. Moreover, women who have five or more children have half the risk of breast cancer as women who have never had a child[4].

DES: Women who took diethylstilbestrol (DES) to prevent miscarriage may have an increased risk of breast cancer after age 40. This drug was given to the women in the 1940s-1960s.

Hormone Replacement Therapy (HRT): Women who have taken menopausal hormone therapy (estrogen + progestin for at least 5 years) have a 20% greater risk of developing breast cancer.

Obesity: Obesity has been linked to breast cancer although this link is controversial. The theory is that obese women produce more estrogen, which can fuel the development of breast cancer [7].

Radiation: If women received radiation therapy as a child or young adult to treat cancer in the chest area, women have a much higher risk of developing breast cancer. The younger women started such radiation and the higher the dose; the higher women risk especially if the radiation was given during breast development [8].

Breast Density on Mammogram: Women with higher breast density have a higher risk of being diagnosed with breast cancer [8].

Breastfeeding: Women who do not breastfeed or breastfeed for shorter durations are at a higher risk of developing breast cancer [8].

Symptoms of Breast Cancer: Early breast cancer usually does not cause symptoms. Therefore,

regular breast exams are important. As cancer grows symptoms may include:

- Breast lump or lump in the armpit that is hard has uneven edges and usually does not hurt.
- Change in the size, shape or feel of the breast or nipple, for example, redness, dimpling or puckering of the skin.
- Fluid coming from the nipple-may be bloody, clear to yellow, green and look like pus.
- Symptoms include breast lump and breast pain and tenderness.

Symptoms of advanced breast cancer may include:

- Bone pain.
- Breast pain or discomfort.
- Skin ulcers.
- Swelling of one arm (next to the breast with cancer).
- Weight loss [9].

Breast Cancer Types: Breast cancer is cancer that starts in the tissues of the breast. There are two main types of breast cancer. Breast cancer may be invasive or non-invasive. Invasive means it has spread from the milk duct or lobule to other tissues in the breast. Non-invasive means it has not yet invaded other breast tissue. Non-invasive breast cancer is called "*in-situ*."

Ductal Carcinoma: Ductal carcinoma starts in the tubes (ducts) that move milk from the breast to the nipple. Most breast cancers are of this type. Ductal carcinoma *in-situ* (DCIS) or intraductal carcinoma is breast cancer in the lining of the milk ducts that has not yet invaded nearby tissues. It may progress to invasive cancer if untreated [10].

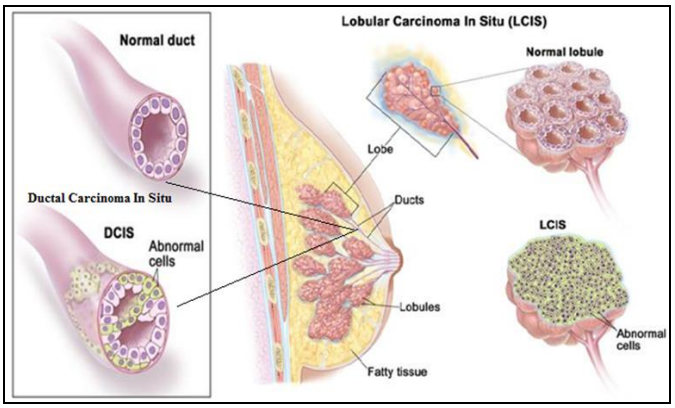

FIG. 1: TYPES OF BREAST CANCER

Types of Breast Cancer:

Lobular Carcinoma: Lobular carcinoma starts in the parts of the breast, called lobules that produce milk. In rare cases, breast cancer can start in other areas of the breast. Lobular carcinoma *in-situ* (LCIS) is a marker for an increased risk of invasive cancer in the same or both breasts.

Many breast cancers are sensitive to the hormone estrogen. This means that estrogen causes the breast cancer tumors to grow. Such cancers have estrogen receptors on the surface of their cells. They are called estrogen receptor-positive cancer or ER-positive cancer [10].

Pathophysiology of Breast Cancer: The development of breast cancer occurs when breast cells lose their normal differentiation and proliferation controls. Various hormones, oncogenes, and growth factors influence the proliferation of these abnormal or tumor cells. There is strong evidence to suggest that estrogen, directly and indirectly, stimulates the growth of tumor cells. Furthermore, numerous growth factors that also play a role in tumor development are secreted by breast cancer cells themselves.

These factors can be classified as either autocrine (if they stimulate their growth) or paracrine (if they affect other cells). Examples of the autocrine growth factors including transforming growth factor alpha (TGF-α) and insulin-like growth factors I and II (IGF-I and IGF-II). Transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and procathepsin D (52K protein) are all paracrine growth factors [11].

Breast Cancer Diagnosis: Several procedures can be used to diagnose breast cancer. The evaluation is based upon the patient's examination and physician recommendations [12].

A. Radiological Investigations:

1. Mammogram: Diagnostic mammograms are X-ray pictures of the breast. It can often show a breast lump before it can be felt. They also can show a cluster of specks of calcium called micro-calcifications. Mammograms should be conducted every year beginning at age 40 and possibly earlier if a woman has certain risk factors such as inherited genetic mutations.

2. Magnetic Resonance Imaging (MRI): Images of the breast are created with powerful magnets that interact with a computer.

3. Ultrasound: A special instrument placed against the skin transmits sound waves, which bounce off breast tissue and are used create an image on a monitor.

B. Estrogen and Progesterone Receptor Test: A test which is used to measure the amount of estrogen and progesterone (hormones) receptors in cancer tissue. If there are more estrogen and progesterone receptors than normal, cancer may grow more quickly. The test results show whether treatment to block estrogen and progesterone may stop cancer from growing.

C. Genomic Assay: A genomic assay is a type of test that uses a sample of breast cancer tissue to analyze the activity of a group of genes, rather than just a single gene. Three genomic assays are currently in use for breast cancer: Oncotype DX, MammaPrint, and Mammostrat. After breast cancer has been diagnosed, tests are done to find out if cancer cells have spread within the breast or to other parts of the body like CT scan, chest X-ray, PET scan and Bone scan [13, 14].

Breast Cancer Stages: The system most often used to describe the extent of breast cancer is the TNM staging system. In this system, each of the letters-T, N and M- describes the growth of cancer. The T category describes the size of the tumor measured in centimeters and growth into nearby tissues. The N category specifies the extent of cancer in the lymph nodes. The M category tells if cancer has spread to distant organs.

The extent of cancer growth for the T category is as follows:

T0- no evidence of primary tumor.

Ti- carcinoma in situ in ductal or lobular.

Tis- Paget's disease of the nipple with no tumors.

T1- Tumor ≤ 2 cm in greatest dimension.

T2- tumor > 2 cm but not < 5 cm in greatest dimension.

T3- Tumor >5 cm in greatest dimension.

T4- extension to chest wall or skin.

The N category has two sets of descriptions. The first set is marked with the letter “c” for clinical stages.

cN0- no growth to lymph nodes.

cN1- tumor growth to ipsilateral, unattached axillary lymph nodes.

cN2- tumor growth to ipsilateral, attached axillary lymph nodes or internal mammary lymph nodes.

cN3- tumor growth to ipsilateral supraclavicular lymph nodes or both the ipsilateral axillary and internal mammary lymph nodes.

The second set is marked with the letter “p” for the pathologic stage:

pN0- no growth to lymph nodes.

pN1- tumor growth to 1-3 axillary lymph nodes.

pN1mi- lymph node tumor is 2.0 mm or smaller in size.

pN2- tumor growth to 4 to 9 axillary lymph nodes.

pN3- tumor growth to 10 or more axillary lymph nodes or growth to lymph nodes in other areas around the breast.

The M category includes:

M0- no distant cancer spread.

M1- cancer has spread to distant organs [15].

5 Stages of Breast Cancer: The information from each TNM category is combined to assign cancer a stage. Each stage is represented from 0 to IV [16].

0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	ANY T	N3	M0
IV	ANY T	ANY N	M1

FIG. 2: TNM STAGING SYSTEM

Breast Cancer Treatment:

1. Surgery: Most patients with breast cancer will have surgery. There are two common types of surgery for removing tumors in the breast tissue:

lumpectomy and mastectomy. Also, women usually have at least one lymph node surgically removed. This surgery is called a lymphadenectomy [17].

Lumpectomy: The entire breast lump with some normal breast tissue is removed in a lumpectomy. This is a breast-conserving surgery.

Partial Mastectomy: Surgery to remove the part of the breast that has cancer and some normal tissue around it. The lining over the chest muscles below cancer may also be removed. This procedure is also called a segmental mastectomy.

Total Mastectomy: Surgery to remove the whole breast that has cancer. This procedure is also called a simple mastectomy. Some of the lymph nodes under the arm may be removed for biopsy at the same time as the breast surgery or after. This is done through a separate incision.

Modified Radical Mastectomy: Surgery to remove the whole breast that has cancer, many of the lymph nodes under the arm, the lining over the chest muscles, and sometimes, part of the chest wall muscles.

2. Radiotherapy: Radiation therapy is a cancer treatment that uses high-energy X-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy:

External Beam Radiation Therapy (EBRT): It delivers radiation from a machine outside the body. This type of radiotherapy is most often given after a lumpectomy. Radiation is given to the entire breast with a booster dose to the site of the tumor. It is usually given 5 days a week for 6 to 7 weeks.

Brachytherapy: It is also called interstitial radiation. It involves placing radioactive objects in or near to where the tumor was removed. Brachytherapy may also be given to boost EBRT in women who received a lumpectomy [18].

3. Chemotherapy: Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated [19].

Hormone Therapy:

Hormones of Female Reproductive Organs: The female hormonal system, like that of the male, consists of three hierarchies of hormones, as follows:

- A hypothalamic releasing hormone, gonadotropin-releasing hormone (GnRH).
- The anterior pituitary sex hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), both of which are secreted in response to the release of GnRH from the hypothalamus
- The ovarian hormones, estrogen, and progesterone, which are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland [20].

Function of the Gonadotropin Hormone: A releasing factor, the gonadotrophin-releasing hormone (GnRH), is secreted from peptidergic neurons in the hypothalamus in a pulsatile fashion, the frequency is about one burst of discharges per hour. GnRH stimulates the anterior pituitary to release gonadotrophic hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

These act on the ovaries to promote the development of small groups of follicles, each of which contains an ovum. One follicle develops faster than the others and forms the Graafian follicle, and the rest degenerate [21]. The ripening Graafian follicle consists of thecal and granulosa cells surrounding a fluid-filled center, within which lies an ovum. Estrogens are produced by the granulosa cells stimulated by FSH, from androgen precursor molecules derived from thecal cells stimulated by LH. Estrogens are responsible for the proliferative phase of endometrial regeneration, which occurs from day 5 or 6 until mid-cycle of menstruation.

During this phase, the endometrium increases in thickness and vascularity, and at the peak of estrogen secretion, there is a prolific cervical secretion of mucus of pH 8-9, rich in protein and carbohydrate, which facilitates entry of spermatozoa.

Estrogen has a negative feedback effect on the anterior pituitary, decreasing gonadotrophin release during chronic administration of estrogen as oral contraception. In contrast, the high endogenous estrogen secretion just before mid-cycle sensitizes LH-releasing cells of the pituitary to the action of the GnRH and causes the mid-cycle surge of LH secretion. This, in turn, causes rapid swelling and rupture of the Graafian follicle, resulting in ovulation. If fertilization occurs, the fertilized ovum passes down the fallopian tubes to the uterus, starting to divide as it goes [22].

Stimulated by LH, cells of the ruptured follicle proliferate and develop into the corpus luteum, which secretes progesterone. Progesterone acts, in turn, on estrogen-primed endometrium, stimulating the secretory phase of the cycle, which renders the endometrium suitable for the implantation of a fertilized ovum. During this phase, cervical mucus becomes more viscous, less alkaline, less copious and in general less welcoming for sperm. Progesterone exerts negative feedback on hypothalamus and pituitary, decreasing the release of LH. It also has a thermogenic effect, causing a rise in body temperature of about 0.5 °C at ovulation, which is maintained until the end of cycle [22].

Effect of Estrogens on the Breasts: Estrogens cause;

- Development of the stromal tissues of the breasts,
- The growth of an extensive ductile system, and
- Deposition of fat in the breasts.

The lobules and alveoli of the breast develop to a slight extent under the influence of estrogens alone, but it is progesterone and prolactin that cause the ultimate determinative growth and function of these structures. In summary, the estrogens initiate growth of the breasts and the milk-producing apparatus. They are also responsible for the character growth and external appearance of the mature female breast. However, they do not convert the breasts into milk-producing organs[23].

Effect of Progesterone on the Breasts: Progesterone promotes the development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory. However, progesterone does not cause the alveoli to secrete milk; milk is secreted only after the prepared breast is further stimulated by prolactin from the anterior pituitary gland [24].

Estrogen Receptors: The therapeutic targets estrogen receptors *α* (ERα) and *β* (ERβ) are members of the nuclear receptor superfamily of transcription factors. ERα regulates the transcription of various genes as a transcription factor, which binds to estrogen response elements (ERE) upstream of the target genes. ER*α* and ER*β* are known to be localized in the breast, brain, cardiovascular system, urogenital tract, and bone.

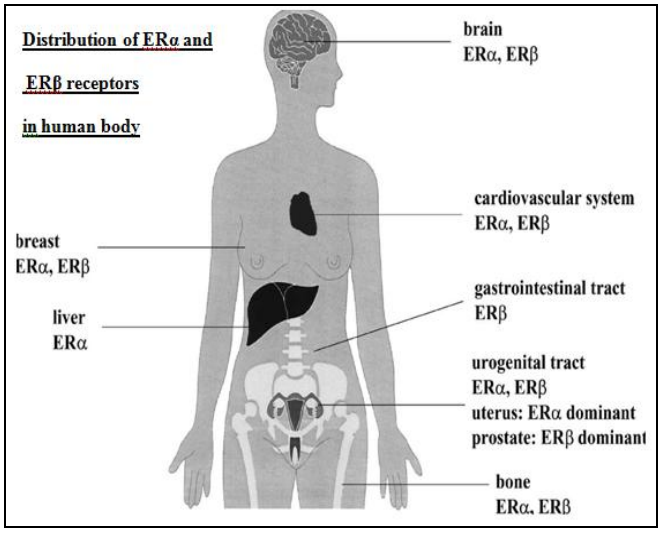

FIG. 3: LOCATION OF ESTROGEN RECEPTORS

ER*α* is the main ER subtype in the liver, whereas ER*β* is the main ER in the colon. ER*α* and ER*β* may also localize to distinct cellular subtypes within each tissue. For example, within the ovary, ERα is largely present in the thecal and interstitial cells, whereas ER*β* is predominantly in the granulosa cells. In the prostate, ER*α* localizes to the epithelium, whereas ER*β* localizes to the stroma [25].

Molecular Mechanism of Estrogen Signaling: Estrogen diffuses freely across the cell membrane and binds to the receptor which then dissociates from cytoplasmic chaperones that keep it in an inactive state. Subsequently, the liganded receptor

translocates to the nucleus and binds as a homodimer to a specific response element within the promoter region of the target gene and hence activates transcription [26].

Estrogen Receptors in Breast Cancer: Estrogen and its receptor (ER) play important roles in the genesis and malignant progression of breast cancer. Two current hypotheses exist to explain this relationship. In the first, binding of estrogens to the ER stimulates proliferation of mammary cells, increasing the target cell number within the tissue. The increase in cell division and DNA synthesis elevates the risk for replication errors, which may result in the acquisition of detrimental mutations that disrupt normal cellular processes such as apoptosis, cellular proliferation, or DNA repair. In the second hypothesis, estrogen metabolism leads to the production of genotoxic by-products that could directly damage DNA, again resulting in point mutations [27].

Hormonal Therapy / Endocrine Therapy: The ER is an important target to develop drugs for the treatment and prevention of breast cancer. The interaction of estrogen with the ER can result in increased proliferation of target cells, so the rationale for endocrine therapy is to block the interaction of estrogen with the ER. This goal can be accomplished by blocking the production of estrogen by ovariectomy or inhibiting the conversion of steroidal precursors to estrogen using aromatase inhibitors. The ER can also be targeted directly using SERMs such as tamoxifen and raloxifene as competitive inhibitors of estrogen action, or by the removal and degradation of the ER by pure antiestrogens such as fulvestrant. Endocrine manipulations are among the least toxic and most effective therapies for the treatment of hormone-responsive breast cancers. In the clinic, factors such as ER-PR status have historically predicted response to endocrine therapy [28].

Selective Estrogen Receptor Modulators: SERMs bind to the estrogen receptor and exert either estrogenic or antiestrogenic effects depending on the specific organ. Tamoxifen, a selective estrogen receptor modulator has been considered the endocrine therapy of choice for the treatment of women with hormone-sensitive breast cancer.

Tamoxifen: Tamoxifen is prescribed for the prevention of breast cancer in high-risk patients, for the adjuvant therapy of early-stage breast cancer, and the therapy of advanced breast cancer. It competes with estrogen for binding to the estrogen receptor in breast tissue.

Metabolism of Tamoxifen: It is extensively metabolized by demethylation and to a small degree by subsequent deamination and by hydroxylation. It is metabolized to N-desmethyl-tamoxifen and 4-hydroxytamoxifen. Major metabolite N-desmethyl tamoxifen is a weak antiestrogen with an affinity for ER that is similar to that of tamoxifen whereas 4-hydroxytamoxifen is believed to provide the major antiestrogenic activity. Tamoxifen may act as a weak estrogen agonist in tumors that overexpress epidermal growth factor receptors or HER-2. [29]

Side Effects of Tamoxifen: It is structurally related to the synthetic estrogen diethylstilbestrol and has weak estrogenic activity. The most frequent adverse effects of tamoxifen treatment are hot flashes and nausea. Menstrual irregularities and vaginal bleeding can also occur. Although the partial estrogen agonist activity of tamoxifen might be beneficial with a mild protective effect, it can result in potentially life-threatening side effects, including endometrial cancer and thromboembolic events [30].

Aromatase Inhibitors: The aromatase enzyme is responsible for the extra-adrenal synthesis of estrogen from androstenedione, which takes place in the liver, fat, muscle, skin, and breast tissue, including breast malignancies.

For postmenopausal women, the major source of estrogen is from the peripheral aromatization of androgens, the rate-limiting step catalyzed by the aromatase enzyme. Aromatase inhibitors decrease the production of estrogen in these women by inhibiting the aromatase enzyme [31]. Aromatase inhibitors are broadly categorized as nonselective and selective aromatase inhibitors. Nonselective aromatase inhibitors block not only aromatase but also other enzymes in the cytochrome P-450. Selective aromatase inhibitors inhibit only aromatase alter only the estrogen level by inhibiting aromatase enzyme selectively.

Another classification of aromatase inhibitors is general type; first, that is suicidal also known as type-1 or steroidal aromatase inhibitors and a second class that is competitive also known as type-2 or nonsteroidal aromatase inhibitors.

Steroidal AI: it binds with the active enzyme site. The enzyme initiates its typical sequence of hydroxylations, but hydroxylation produces an unbreakable covalent bond between the inhibitor and the enzyme. So, the enzyme activity is permanently blocked even if all the unattached inhibitor is removed. Activity can be restored only by synthesis of new enzyme. *e.g.,* formestane and exemestane.

Nonsteroidal AI: It binds with the active enzyme site. It can dissociate from the binding site, allowing renewed competition between the inhibitor and the normal substance for binding to the active enzyme site. The effectiveness of competitive inhibitors depends on the relative concentration and affinities. Continued activity requires the constant presence of the inhibitors. *e.g.*, anastrozole, letrozole [32].

Unlike tamoxifen, aromatase inhibitors have no partial estrogen agonist activity. The most frequent adverse effects of 3rd generation aromatase inhibitor are hot flashes, nausea, vomiting, headache, fatigue and rare incidence of fractures, musculoskeletal disorders.

CONCLUSION: There is a greater improvement in breast cancer care with increased specialization and targeted treatment with hormonal therapy. The effectiveness and benefits of a hormonal approach to the treatment of breast cancer have been empirically established.

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CONFLICT OF INTEREST: Nil

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