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Veda A Vasudev
Division of Molecular Biology, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

Mutthuraj D
Division of Molecular Biology, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

GL Aruna
Associate Professor, Postgraduate Department of Microbiology, Maharani's Science College for Women, Mysuru, India

Kanthesh BM
Division of Molecular Biology, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

Corresponding Author:
Kanthesh BM
Division of Molecular Biology, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

A critical review on: Comprehending breast cancer in men with reference to female

Veda A Vasudev, Mutthuraj D, GL Aruna and Kanthesh BM

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Abstract
Although it is more common in women, men can still develop breast cancer. Men are discovered to have breast cancer in about 1 out of every 100 cases that are detected around the world. Breast cancer can affect men as well, even though it is generally associated with women. This is since, while it is far less prevalent, men do have breast tissue that has the potential to develop cancer, albeit in much less amounts than does breast tissue in women. Breast cancer arises from the mutation of breast cells into malignant cells, which proliferate and give rise to tumors. Although it usually affects women over 50, breast cancer can also strike men and younger people. Medical professionals may use chemotherapy to eradicate malignant cells or surgery to remove tumors to treat breast cancer. Male breast cancer [MBC] accounts for only 1% of all cases of breast cancer, which, in comparison to female breast cancer [FBC], is quite low, but it does happen, and it's vital to understand its possibility. Men are equally as likely as women to develop breast cancer if they have a first- or second-degree relative who has the disease. Research has indicated that having a parent or sibling with the condition can raise the risk of breast cancer in both male and female family members. Because of incomplete data, MBC has never received enough attention. Male breast tumors may develop palpable and manifest symptoms earlier than female breast tumors since men's breast sizes are smaller. However, men are more likely to delay seeking medical assistance, have gynecomastia concealing their breast tumors, and be ignorant of breast cancer. A detailed review regarding male breast cancer in respect to that of female breast cancer has been discussed in this article.

Keywords: Male Breast Cancer [MBC], Female Breast Cancer [FBC], BRCA1, BRCA2, HER2

Introduction
Breast cancer is defined as the proliferation of malignant cells in the breast. If neglected, the cancer will spread to other parts of the body. Aside from skin cancer, carcinoma of the breast is the least frequent type of cancer among women in the United States, contributing to one in each three cancer diagnoses [1]. Breast cancer is the most common cancer in women globally and can be cured in around 70-80% of people with early-stage, non-metastatic illness. Advanced breast cancer with distant organ metastases is thought to be incurable using existing treatments. Breast cancer is a diverse disease at the molecular level, with traits such as HER2 activation (encoded by ERBB2), hormone receptor activation (Oestrogen receptor and progesterone receptor), and/or BRCA mutations [2]. Breast cancer is the second most common type of cancer in the world. Statistics show that 1 in every 3 cancers diagnosed annually are breast cancers. Breast cancers are detected both in males and females, even though the chances for the cancer to occur in males are comparatively very low. Breast cancers can be diagnosed by self-examination. Females are recommended to check for any changes in their breasts like a lump formation, change in the color of the skin around the breasts, and blood, or any other discharge from the nipple [3]. It is recommended to do a self-examination every month after the age of 20 years to prevent breast cancer, as all women are at risk of breast cancer in the later stages of their lives [4]. The cancer of the breast can also be diagnosed with the help of mammograms and other techniques of screening like X-rays and MRIs. Many women are diagnosed with this type of cancer due to the lack of knowledge on self-examination or the fear and embarrassment that might occur [5]. The vulnerable causes of breast cancer consist of gender, age, unhealthy habits, menstruation, pregnancy, hormones. Family history is also another cause of the disease [6]. Breast cancer is a type of malignant tumour which can extend to other bodily parts like bone, kidney, and liver through the process of metastasis [7]. Women certainly dominate when it comes to Breast cancer incidence. Breast cancer in Men showed a greater rise in the Estimated Annual Percent Change (EAPC) for BC occurrence (0.91%) compared to women

(0.36%). Male EAPC for Breast cancer incidence is much greater than women's, highlighting the significance of keeping an eye on men's health, particularly in those who consume alcohol and smoke or have other risk factors. For both genders, the EAPC for Breast cancer deaths gradually dropped [8]. In terms of risk factors for Breast cancer fatalities, metabolic hazards accounted for a sizable portion of the total (31.98% in 1990 versus 46.87% in 2019). Other important risk variables included inadequate physical activity, alcohol and tobacco use, and dietary hazards. Globally, metabolic hazards exhibited notable variability, with Southeast Asia and Oceania having the greatest percentages [9]. From 1990 to 2019, the regions with the biggest increases in metabolic risk-related BC fatalities were Southeast Asia, South Asia, Andean Latin America, and Southern Sub-Saharan Africa. Future incidence of breast cancer (BC) is anticipated to be higher in areas with lower socio-demographic index (SDI) values [10]. Estimated hazards account for a sizable share of cancer deaths worldwide and disability-adjusted life years [11]. Three primary risk factors for BC fatalities have been identified: high body mass index, high fasting glucose, and metabolic hazards. An established risk factor, alcohol consumption exhibited a declining burden in middle-high and high SDI nations [12]. Age-Standardized Rates (ASR) of breast cancer incidence in males and females are expected to rise by 2050. Male ASR of breast cancer fatalities is expected to gradually decline by 2050, whereas female ASR is expected to slightly increase [13]. A number of closely interacting factors, like age, genetics, environment, reproductive history, and maybe unidentified ones, interact to cause breast cancer. Women who have gone through menopause are most likely to develop breast cancer, which is more common as people age. Heritable factors and genetics are major contributors to the development of breast cancer [14]. The exposure of the cancer is greatly increased in families with a history of the disease in family members sharing half of the genetic similarities [15]. Breast cancer risk has been linked to a number of potentially modifiable variables, such as physical inactivity, obesity, alcoholism, smoking, and replacement hormone therapy. The reproductive history of women influences risk as well; nulliparity is linked to higher rates than multiparity [16]. Testicular disease-related hormonal changes in men may be a significant contributing factor. Klinefelter's syndrome has been linked to male breast cancer, which could explain about 3% of cases. Individuals with Klinefelter's syndrome exhibit gynecomastia, low testosterone levels, elevated gonadotropins, testicular dysgenesis, and at least one extra X chromosome to the typical XY karyotype (47 XXY). Compared to 46 XY men, these people have a 20–50 times increased risk of breast cancer. Furthermore, boys who have experienced testicular damage, undescended testes, or the mumps are more likely to develop breast cancer as a result of high estrogen or androgen shortage [17]. Male breast cancer may be predisposed by liver cirrhosis, which is characterized by elevated estrogen levels. There have occasionally been reports linking male breast cancer to exogenous estrogens. There have been cases of transsexuals getting breast cancer from exogenous estrogens, and there have also been reports of males getting breast cancer from estrogen therapy for cancer in the prostate [18]. Worldwide, breast cancer is among the most frequent malignant tumors in women. Up to 36% of oncological diagnoses are suffering from breast cancer. In 2018, almost 2.089 million women received diagnoses with breast cancer [19]. Mammography is now accepted as a screening method for breast cancer. The population of women aged 50–69 exhibits the highest mammography value. At the 80–95% threshold, classical mammography exhibits 75–95% specificity as well as sensitivity. A screening procedure called MRI mammography is performed on women who may have hereditary breast cancer. When a worrisome lesion is discovered on mammography, an ultrasound, thick needle biopsy, and histological analysis of the tumor are conducted if needed [20]. Although the precise origin of carcinogenesis is still unknown, there are a number of risk factors that have been linked to the development of breast cancer. One of the most crucial factors is a country's gender, age, and level of economic growth, as well suggested by the epidemiological data discussed above. Hormonal factors, which mostly pertain to the duration of estrogen exposure, and procreative factors, such as the number of children born, the age at which the first kid is born, or breastfeeding, are equally significant.

Table 1: Major risk conditions in occurrence of breast cancer [21].

Cause	Risk factor of breast cancer
Hormonal and reproductive	Early age of the first menstruation. No pregnancies. The first reported pregnancy at a late age (after 30 years of age). Late age of the last menstruation. Use of oral contraception. Use of hormone replacement therapy.
Nutritional	Excessive consumption of fats, especially animal fats. High consumption of red and fried meat. Western type diet. High iron intake. Development of overweight/obesity after menopause. Low consumption of fresh vegetables and fruits. Low intake of phytoestrogens (Isoflavones, lignans).
Pertaining to physiological aspects and state of health	Older age (risk increases starting at age 35). Breast cancer in the family history. In the past, endometrial, breast, and ovarian cancers. harmless breast alterations that lead to the development of atypical hyperplasia. Ionizing radiation, such as that employed in Hodgkin lymphoma treatment. High growth as an adult and rapid growth during adolescence.

	an oncogenic virus infection (e.g., Epstein-Barr)
Additional caused by lifestyle factors	Frequent intake of alcohol, either moderate or high. Absence of consistent exercise. Working at night.

Ninety-nine percent of cases of breast cancer are found in women. Men are affected by this malignant tumor in only 1% of instances; in Poland, the standardized incidence rate is 0.4/105. Annually, no more than 100 instances are documented [22]. Nonetheless, there is a consistent rising trend in the incidence of breast cancer in men as well as women, which is probably related to obesity and longer survival times [23]. Among the most significant risk factors for breast cancer is age. The incidence of breast cancer has increased globally, with women under 50 seeing the highest rate of occurrence across all age categories. However, the significance of variables that increase the risk of breast cancer is increasing. These variables include having a late first child, having few children, using hormone replacement therapy, being obese, not exercising, or following an unhealthy diet [24]. 2018 saw the diagnosis of over 645,000 premenopausal cases and 1.4 million postmenopausal cases worldwide, with over 130,000 and 490,000 fatalities in each menopausal cohort, respectively. In comparison to higher-income nations, premenopausal breast cancer was more common in nations with lower UNDP Human Development Indexes (HDI) in terms of both new cases and fatalities [25]. Premenopausal and postmenopausal breast cancer incidence were highest in very high HDI countries (30.6 and 253.6 cases per 100,000, respectively), while premenopausal and postmenopausal mortality rates were highest in low and medium HDI countries (5 and 53.3 deaths per 100,000, respectively). Through an analysis of breast cancer trends, they discovered that in 20 of 44 populations, the age-standardized incidence rates (ASIRs) for premenopausal breast cancer were considerably rising, and in 24 of the 44 populations, the ASIRs for postmenopausal breast cancer were significantly rising. The burden of postmenopausal breast cancer increased most noticeably in transition countries, whereas growth in premenopausal age alone was concentrated in high-income nations [25].

Role of Hormones, Genetics, Alcohol, Diet, & Obesity in Breast Cancer: There appears to be a significant correlation between a woman's hormonal state and her risk of breast cancer. Numerous research' findings show that the risk of breast cancer rises proportionately to the amount of time spent exposed to estrogen, which delays early menarche, late menopause, the age at which a child is born, and the number of children born [26]. As of right now, this reduction is estimated to be roughly 30%. Conversely, in 2012, the Collaborative Group on Hormonal Factors in Breast Cancer reported in The Lancet Oncology the findings of a meta-analysis, which showed that for every year that an early menarche was initiated, the relative chance of getting breast cancer increased by 5% [27]. Furthermore, it was discovered that early menarche was linked to a higher risk of breast cancer than late menopause; for every year of late menopause, the relative risk rose by 2.9%. It is thought that late menopause, which occurs after the age of 54, doubles the risk of breast cancer in comparison to menopause, which occurs before the age of 45 [27]. In addition, the meta-analysis revealed that, in comparison to postmenopausal women of the same age, women who had not yet reached menopause were at greater risk of breast cancer. The impact of BMI on the chance of contracting the illness was observed in this patient group under analysis; in premenopausal patients, obesity decreased this risk, whereas in postmenopausal individuals, it increased. This meta-analysis also revealed that both late menopause and early menarche were linked to an increased risk of lobular breast cancer. An additional risk factor for steroid-expressed breast cancer is late menopause [27]. Numerous studies have proven that the age at which a child is born, the number of babies born, and breastfeeding are additional reproductive factors that affect the risk of breast cancer. Research suggests that transgender women have a higher risk of breast cancer than cisgender males, but transgender men had a lower risk than cisgender women. For transgender women, the duration of hormone treatment raises the risk of breast cancer, and the disease's features more closely resemble those of a female patient. The study's findings imply that recommendations for cisgender individuals' breast cancer screening are adequate for transgender patients undergoing hormone therapy [28]. According to recent research, long-term usage of estrogen-only and combined estrogen-progestogen therapy is linked to an elevated risk of breast cancer. Estradiol-dydrogesterone is the combination medication linked to the least amount of increased risk. Studies indicate that long-term usage of hormone replacement therapy (HTR) is not connected with a higher risk of breast cancer, and that the risk decreases more noticeably once treatment is stopped [29].

An essential part of the pathophysiology of breast cancer development is played by estrogens. Since breast cancer is thought to be a hormone-dependent tumor, higher estrogen levels and prolonged exposure to the hormone are linked to a higher chance of the disease developing [31, 32]. Epidemiological studies have proven that the risk of getting breast cancer is raised when endogenous and exogenous estrogens are exposed to higher levels. Elevated blood estrogen levels are linked to a higher risk of breast cancer in all postmenopausal women. Unquestionably, the increased risk of breast cancer is influenced by both hormonal and reproductive variables [33]. The length of estrogen exposure and the impact of pregnancy, as determined by factors like the age of the first menstrual period, the age of the first pregnancy (particularly for women exposed after the age of 30), childlessness, or the age at which menopause begins, alter each person's risk of developing breast cancer [34]. Compared to women who began menstruation late (15 years) and stopped it early (40 years), those who begin menstruation early (12 years) and terminate it late (50 years) have twice the risk. Long-term exposure to estrogens is also linked to childlessness and the age of the first pregnancy (over 30 years old) [35]. Those who are nulliparous or who became pregnant beyond the age of thirty are at a two-to five-fold higher risk of illness. While artificial and spontaneous miscarriages (incomplete pregnancies) may not offer the same protective benefits as complete pregnancies, they may raise the risk because progesterone does not have the same protective effect during the second half of pregnancy [36]. The use of hormone replacement treatment

raises the risk of breast cancer significantly. In the 1990s, the first data regarding the harmful effects of hormone replacement therapy (HRT) on the risk of breast cancer emerged. The results of a meta-analysis of 51 studies assessing the association between HRT use and breast cancer were published in The Lancet in 1997 by the Collaborative Group on Hormonal Factors in Breast Cancer. According to this meta-analysis, using HRT for a year raised the risk of breast cancer by 2.7% [37]. The same organization republished a meta-analysis in The Lancet in 2019; this time, it included 58 prospective studies assessing the connection between the kind of HRT used and the chance of breast cancer. According to this meta-analysis, the biggest increase in the risk of breast cancer was shown with HRT that contained both progestogens and estrogens, particularly when progestogens were used daily. A higher risk of breast cancer was also linked to the use of HRT, even for brief periods of time (1-4 years).

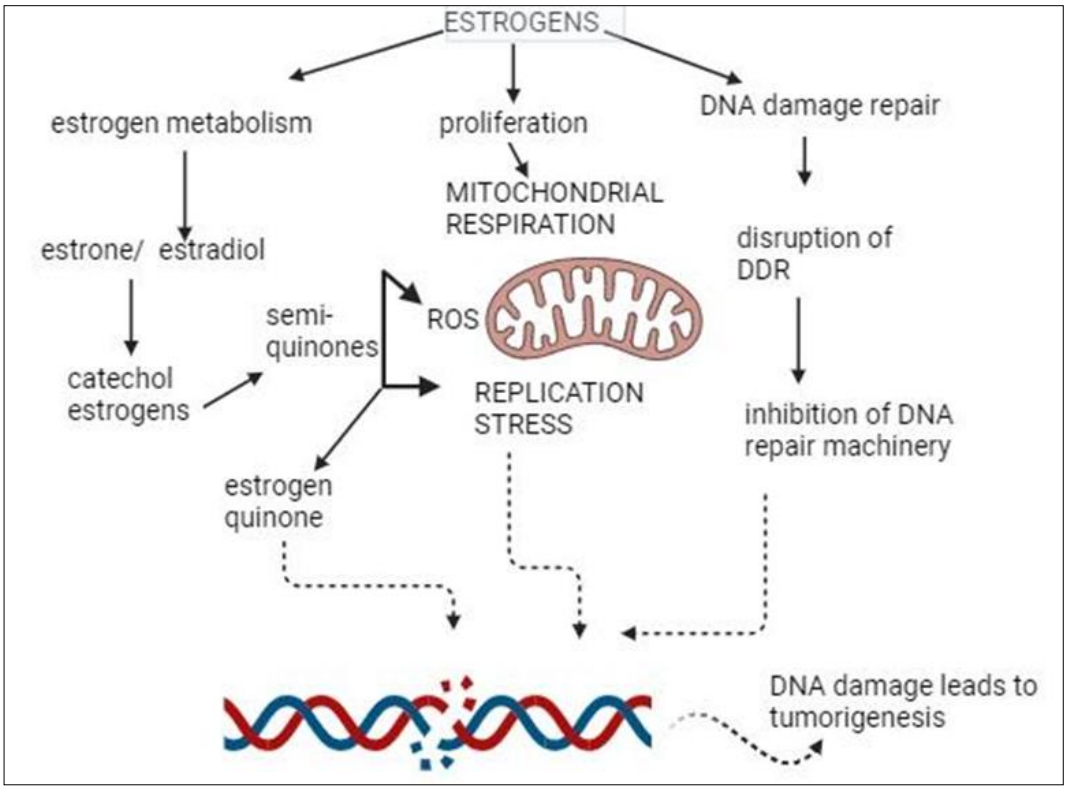

Fig 1: Hormonal effect on breast cancer with respect to breast cancer cell proliferation [103].

Steroid receptor expression in breast cancer was the primary predictor of the disease's development. If HRT was started beyond the age of 60, the chance of getting the condition was somewhat decreased. Obese women had a decreased risk as well, particularly if they used HRT that solely contained estrogens [38]. Only 5–10% of incidences of breast cancer are genetically based. Many genes are involved in the development of cancer in the breast. Tumor onset and advancement are influenced by mutations and overexpression of oncogenes and antioncogenes. The BRCA1 and BRCA2 genes are the most well-known genetic abnormalities linked to this malignancy [39]. Situated on chromosome 17, the BRCA1 gene is a suppressor that produces nuclear protein, which is accountable for preserving genome stability. This protein co-creates a protein complex with the products of other suppressor genes, signal transduction genes, and DNA damage detection that binds to RNA polymerase II and interacts with histone deacetylase, influencing transcription, DNA repair, and recombination processes. In particular, the BRCA1 protein and the BRCA2 gene product—a suppressor gene situated on chromosome 13—are engaged in the homologous recombination process that repairs double DNA strand breaks. The two anti-oncogenes, breast cancer-associated gene 1 and 2, play a key role in the progress of breast cancer [40]. The location of *BRCA1* is on the long arm of chromosome 17 on the 21st band and that of *BRCA2* is on the long arm of chromosome 13 on the 12th band. They are tumor suppressor genes which encode tumor suppressor proteins. The *BRCA1* gene is repressed by p130 and p107, also known as “pocket proteins”. Deficiency of *BRCA1* leads to disruption of the checkpoints of the cell cycle and genetic instability. The mutations in *BRCA1/2* are inherited in an autosomal dominant manner [41, 42]. The suppressor genes TP53 (Li-Fraumeni syndrome) and PTEN (Cowden syndrome) are other genes whose high-penetration mutations contribute to breast cancer. For women with Li-Fraumeni syndrome, the cumulative risk of breast cancer at age 70 is 54%. The lifetime risk of acquiring breast cancer in those with Cowden's syndrome is between 25 and 50 percent. Both genetic disorders are quite uncommon, though. Genes with mutations related to ATM, BRIP1, CHEK2, and PALB2 indicate a moderate susceptibility to breast cancer. Individuals who possess these mutations are 2-3 times more likely to acquire this cancerous growth [43]. Less than 10% of breast cancers are thought to have a hereditary basis. On the other hand, random somatic mutations are the cause of almost 90% of breast cancer cases. Women whose mother or sister, or the nearest relative, has received treatment for the malignant tumor in issue face a twofold increased chance of developing breast cancer; if both of their closest relatives have received

treatment, the risk increases by three to six times. The older the relative was when the cancer was diagnosed, the lower the risk [44]. Benign modifications to the mammary glands are another factor that raises the chance of breast cancer. Certain benign lesions raise the risk four or five times, such as benign neoplasms like atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH), and up to two times for proliferative (proliferative) lesions without atypia like star scar or fibrotic adenoma. Patients with various benign lesion types were evaluated for their risk of breast cancer in the Hartmann *et al*. cohort research. For the total study population, the relative risk of having breast cancer was 1.56 (95% CI, 1.45–1.68) [37]. After the biopsy, this risk remained higher for 25 years. The relative risk of breast cancer in females with benign lesions without proliferation was 1.27 (95% CI: 1.15–1.41). When minor proliferating lesions were present but atypia was absent, the value was 1.88 (95% CI, 1.66–2.12). Women who had benign proliferating lesions with atypia (atypical ductal hyperplasia, atypical lobular hyperplasia, or both) had the highest relative risk of getting breast cancer, up to 4.24 (95% CI, 3.26–5.41).It was also discovered that the likelihood of acquiring a malignant change increased with the sooner benign abnormalities were diagnosed (less than 55 years of age) [45]. An established risk factor for breast cancer is early ionizing radiation exposure. John *et al*. examined the association between exposure to ionizing radiation used in breast cancer detection and treatment and the chance of developing the disease, and their analysis of data from the Breast Cancer Family Registry was published in 2007. According to this investigation, women who had radiation therapy as part of their cancer treatment in the past or who had a control chest X-ray taken while receiving treatment for pneumonia and tuberculosis were at higher risk of developing breast cancer. Patients who had many exposures to ionizing radiation or who were exposed at a very young age had the highest risk of getting breast cancer [46]. Drinking alcohol is linked to a higher risk of breast cancer, according to numerous research. Alcohol intensifies the conversion of androgens to estrogens and inhibits their metabolism in the liver, which both contribute to the rise in estrogen content in the blood. These two mechanisms together account for the dependence. It may also accelerate cellular migration and proliferation and hinder DNA repair mechanisms or the immune system. Ultimately, alcohol's own metabolites are known to cause cancer [47]. The risk of breast cancer is thought to rise by 9% for each 10 g of pure alcohol consumed each day [48, 49, 50, 51]. A number of researches have examined the impact of dietary type on the course of the cancer process. It appears indisputable that a diet high in saturated fats, particularly those derived from animals, and poor in variety increases the risk of developing colon cancer in particular [52]. However, there is a lack of consistency in the studies evaluating the connection between nutrition and breast cancer risk. Dandamudi and colleagues examined comprehensive research works released from 2013 to 2017. Of the seventeen publications reviewed, ten examined the relationship between breast cancer risk and a diet deemed to be "unhealthy." Sweetened soft beverages, processed fruit juices, red and processed meats, solidified fats, saturated fats, salted food (chips, chips, peanuts), refined grains, and sweetened products (sweets, desserts) were the main items of the diet in question. A substantial correlation was discovered in the majority of the examined studies, however not all of them, between the overindulgence in the aforementioned goods and a higher chance of breast cancer development. Saturated fats, sodium, and excessive consumption of red and processed meat were the main factors influencing this association. A diet high in fruits, vegetables, seafood, legumes, oils, and vegetable oils lowers the risk of breast cancer, according to this comprehensive review [53]. Studies indicate that the prognosis of breast cancer is influenced by dietary habits. However, there is currently not enough data to support suggestions based on the findings. To lower global mortality, it should be promoted that people eat a healthy, balanced diet. After a diagnosis of breast cancer, overall survival may be enhanced by a nutritious diet that is high in unrefined grains, fruits, vegetables, nuts, and olive oil, and moderately to low in red meat and saturated fatty acids. Patients with breast cancer who are receiving radiation therapy and/or chemotherapy have a variety of symptoms that make their condition worse. Nutritional counseling and supplementation with specific dietary components, such as eicosatetraenoic (EPA) and docosahexaenoic (DHA) acids, have been shown in studies on nutritional interventions during breast cancer treatment to be beneficial in lowering drug-induced side effects and improving therapeutic efficacy. As a result, dietary management in BC patients can be viewed as a crucial component of a multimodal therapy strategy [53]. Numerous research have proven that obesity is one of the risk factors for breast cancer. A pooled analysis of multiple studies assessing the connection between obesity and the incidence of breast cancer in premenopausal and postmenopausal women was assembled by Jiralerspong and Goodwin. This investigation indicated that in postmenopausal women who did not utilize hormone replacement therapy, being overweight or obese increased the incidence of breast cancer, especially steroid-receptor-expressed breast cancer. For premenopausal women, being overweight or obese lowers the risk of hormone-dependent breast cancer, in contrast to postmenopausal patients. However, the analysis's authors note that research from the literature suggests a link between premenopausal individuals' weight and their chance of developing triple-negative breast cancer. This investigation also revealed that, independent of menopausal status, physical inactivity and obesity raise the risk of breast cancer. Additionally, a poorer prognosis for breast cancer patients both before and after menopause is linked to overweight and obesity, according to the findings of multiple research [54, 55]. The authors speculate that a higher stage of cancer at diagnosis and a more aggressive course of breast cancer in obese patients may be associated with a worse survival rate. Through a number of methods, obesity accelerates the development of cancer. Many cytokines, chemokines, and endocrine hormones, including proangiogenic and promitogenic leptin, are found in overdeveloped adipose tissue and have an impact on the immunological milieu of the tissue in question [56]. There is an immune system cell concentration that is pro-inflammatory and secretes inflammatory cytokines. Overdevelopment of adipose tissue inhibits the synthesis of antiangiogenic and antimitogenic adiponectin and encourages the surrounding hypoxia, which increases leptin and VEGF factor secretion. The development and maintenance of inflammation in excess adipose tissue is caused by the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, which also inhibits

apoptosis through pro-inflammatory cytokines and later encourages the growth of breast cancer cells, cancer invasion, angiogenesis, and metastasis. Insulin resistance, hyperinsulinemia, and elevated production of insulin-like growth factor 1 (IGF-1) are other features of the metabolic syndrome that coexists with obesity. Research has indicated that patients with breast cancer who are insulin resistant or have hyperinsulinemia tend to have lower survival rates [57]. Additionally, the IGF-1 receptor is frequently overexpressed in breast cancer cells, which suggests that this protein may be a mitogen. Compared to women of normal weight, obese women are less likely to have breast reconstructions, and those who have had surgery have higher rates of surgical problems. Hormone therapy and systemic chemotherapy are less effective in obese women. Compared to women of normal weight, obese women are more likely to have a local recurrence. For obese women who survive breast cancer, the effectiveness of cancer treatment is much reduced. In postmenopausal women, adipose tissue serves as the primary source of sex hormones. Estrogens are produced in this tissue through the aromatization of adrenal androgens [58].

Epidermal growth factor receptor and HER 2 in respect to breast cancer

On chromosome 7 p 12 lies a receptor protein called EGFR. It is a member of the family of tyrosine kinases. When it attaches to particular ligands such as amphiregulin, TGF-α (transforming growth factor-alpha), and epidermal growth factor, among others, it becomes active. Within the cell, EGFR activation starts a cascade of signaling processes. Angiogenesis, or the creation of new blood vessels, and cell proliferation, or the development and division of cells, are both influenced by these downstream signals. Some forms of breast cancer have been shown to overexpress EGFR. EGFR overexpression is a common feature of aggressive inflammatory breast cancer. Given that EGFR plays a part in breast cancer, targeting the EGFR pathway in malignant breast tumors may be a viable treatment option. Treatment options for breast tumors with overexpressed EGFR may include investigating the efficacy of medications that block or alter EGFR activity [59].

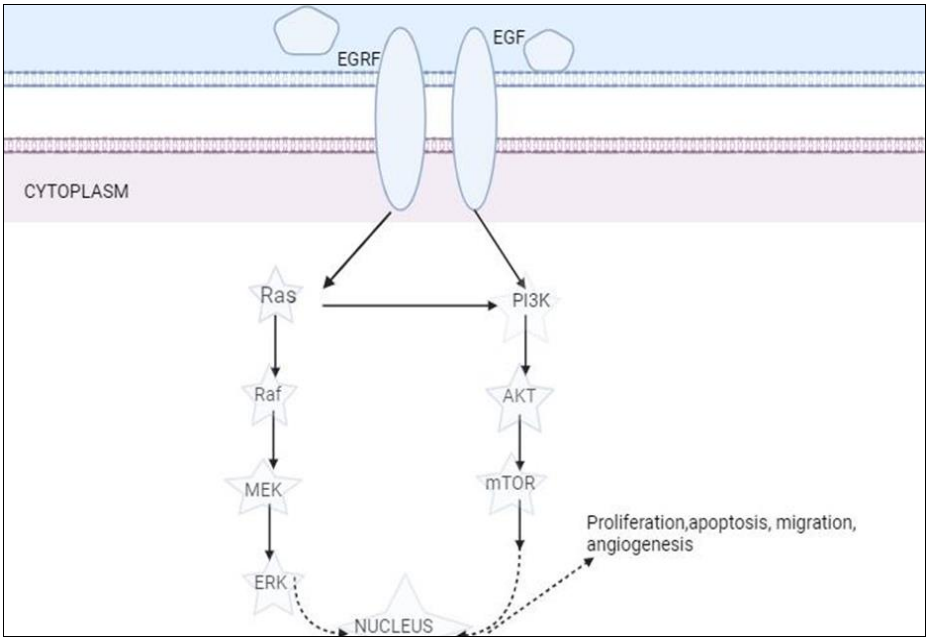

Fig 2: EGF in breast cancer [103].

HER 2 In Comparison with Male Breast Cancer: Since HER2 and HER1, or human epidermal growth factor receptors, have similar structures, they share the same name. Due to its origins in a rodent glioblastoma cell line, a particular kind of neural tumor, Neu got its moniker. ErbB, also known as avian erythroblastosis oncogene B, was determined to code for EGFR and was thus termed because of its resemblance to ErbB-2. Orthologs of HER2, Neu, and ErbB-2 are all encoded by the same genes, according to molecular cloning of the gene. *c-erbB*-2, also known as human epidermal growth factor receptor 2 is an oncogene significant in cancer of the breast, positioned on 17q12. *HER-2* is activated by gene rearrangement and gene amplification. HER-2 protein is an EGF of the TK family which forms heterodimers with Her3 and Her4 and thus stimulates the secondary signaling pathway. Overexpression of HER 2 is seen in most breast cancers. A protein called HER2 promotes the rapid growth of breast cancer cells. HER2-positive breast cancer cells have HER2 levels that are greater than average. Compared to breast cancers that are HER2-negative, these tumors typically grow and spread more quickly, but they also have a higher propensity to react to treatment with medications that target the HER2 protein. The ERBB2 gene encodes the protein known as receptor tyrosine-protein kinase erbB-2, which is typically found in cell membranes. The gene erythroblastic oncogene B, which was first identified from the avian genome, is known by its acronym, ERBB [60]. A member of the HER/EGFR/ERBB family of human epidermal growth factors and their receptors is HER2. However, HER2 does not bind to the ligand like other ERBB family members do. In situations when HER2 concentrations are high, such as in cancer, HER2 activation occurs by homodimerization or heterodimerization via an additional ERBB member [61]. It has been demonstrated that this oncogene's amplification or overexpression is crucial to the onset and spread of several aggressive forms of breast cancer. About 30% of patients with breast cancer now have the protein as a target for

therapy and as a significant biomarker [62]. There are four distinct receptor tyrosine kinases confined to the plasma membrane that make up the ErbB family. The remaining members are erbB-1, erbB-3 (neuregulin-binding; lacking kinase domain), and erbB-4. erbB-2 is one of these members. Every one of the four has an intracellular domain, a transmembrane domain, and an extracellular ligand binding region that can interact with a wide range of signaling molecules and show both ligand-dependent and ligand-independent activity. Interestingly, ligands for HER2 have not yet been found. HER2 is thought to be the preferred dimerization partner of the other ErbB receptors because it can heterodimerize with any of the other three receptors [63, 64].

Signaling pathways activated by HER2 include

- mitogen-activated protein kinase (MAPK).
- phosphoinositide 3-kinase (PI3K/Akt).
- phospholipase C γ.
- protein kinase C (PKC).
- Signal transducer and activator of transcription (STAT) [65].

In between 15% and 30% of cases of breast cancer, the ERBB2 gene is amplified, or overexpressed. Drugs that target HER2 in breast carcinoma have greatly and advantageously altered the otherwise unfavorable outlook of the historically challenging obstacles that accompany HER2-positive breast cancer [66]. HER2-positive breast cancers have been demonstrated to be correlated with increased disease occurrences and a poor prognosis when compared to other identifiably genetically individual breast cancers along with other known, or absence of, genetic markers that are believed to be associated with other breast cancers [67]. It is also known that overexpression happens in lung adenocarcinoma, stomach, ovarian, and aggressive forms of uterine cancer, like uterine serous endometrial carcinoma, e.g. About 7–34% of individuals with stomach cancer and 30% of patients with salivary duct carcinomas had overexpressed HER2 [68]. HER2 is frequently colocalized and co- amplified with GRB7, a proto-oncogene linked to tumors of the breast, testicular germ cells, stomach, and esophagus. It has been demonstrated that HER2 proteins aggregate in cell membranes, which may contribute to carcinogenesis. Moreover, a variety of structural changes that result in ligand-independent firing of this receptor have been found; this firing occurs even in the absence of over-expression of the receptor. Numerous tumors include HER2, and some of these tumors have point mutations in the region that defines HER2's transmembrane domain. In the absence of a ligand, constitutive dimerization of this protein can occur when a valine in the transmembrane domain is substituted for either glutamic acid or glutamine [69]. According to studies, men are more likely than women to present with aggressive-appearing microscopic histopathology of breast tumors that have migrated to neighboring axillary lymph nodes. Nonetheless, a sizable investigation conducted by the National Institutes of Health's Surveillance, Epidemiology, and End Results program graded the severity of breast cancer according to TNM stage. According to the study, there were 63.1% of male cases and 45.4% of female cases with purely local disease (i.e., no metastases); 29.1% of male cases and 43.6% of female cases had spread to local lymph nodes; and 5.7% of male cases and 8.1% of female cases had distant metastases (2.1% of male cases and 2.9% of female cases were not staged).

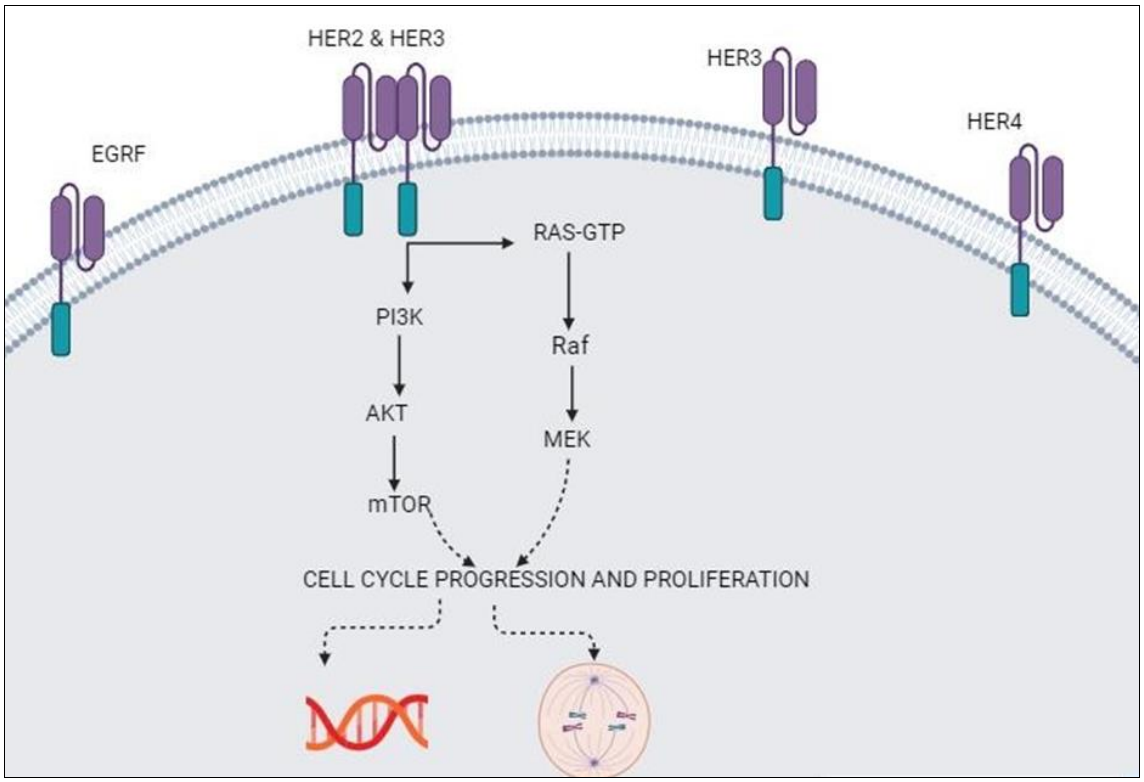

Fig 3: Tyrosine kinase inhibitors and HER2-positive breast cancer [103].

Comparative study of breast cancer in males and females

In Males

Male breast carcinoma is a medical condition in which the surrounding tissues of the breast develop cancerous (malignant) cells. Males can also develop breast cancer [70, 71]. Men can develop breast cancer at any age, but the majority of cases occur in those between the ages of 60 and 70. A little over one percent of incidents involving breast cancer in men are male-specific. Even though breast cancer is more common in females than males, it is seen that males also are at risk of breast cancer [72]. The occurrence of the disease is rare, but it would have a substantial effect on the health of the individual. Invasive ductal carcinoma is the most common type of breast cancer observed in males. The risk factors of the disease include age, more in older men, family history and genetic mutation. Mutations in the BRCA1 and BRCA2 genes increase the risk [73]. The symptoms of the cancer in males are similar to those of females, but due to the failure of diagnosis at the right time, the disease goes unnoticed in men and is diagnosed only in the advanced stages. According to research, male breast cancers tend to be more aggressive than female breast cancers and increased expression of the Ki-67 marker, showing greater cell proliferation [74].

The following types of breast cancer are found in men

A unusual clinical entity, male breast cancer accounts for about 1% of all cases of breast cancer. But over the past few decades, MBC incidence has been gradually rising. Age, color (black), relatives with a history of breast cancer, genetic mutations, liver cirrhosis, and abnormalities of the testicles are risk factors for metastatic breast cancer. About half of patients with MBC had at least one affected lymph node at the time of diagnosis, and the majority of patients present with painless lumps. Just 1% of cases of breast cancer are in men, making it a very uncommon condition [76]. A number of clinical trials that were prematurely closed due to low recruitment have demonstrated that, similar to all other uncommon diseases, conducting prospective clinical research in male breast cancer has proven to be difficult. The fact that men were previously excluded from female-only breast cancer clinical studies has made the problem worse [77, 78]. Since much of the information we currently have for male breast cancer comes from limited retrospective studies and frequently single-center experience, treatment strategies for MBC are extrapolated from recommendations for the care of FBC.

Table 2: Types of breast cancer are found in men [75].

Types of breast cancer in males	Characteristics
Infiltrating ductal carcinoma	cancer that has progressed past the cells lining the breast ducts. For men, this is the most prevalent kind of breast cancer.
Ductal carcinoma in situ	Intraductal carcinoma is another name for abnormal cells present in the duct lining.
Inflammatory breast cancer	a kind of cancer when the breast feels warm, puffy, and looks red.
Paget disease of the nipple	a tumor that has spread from the ducts under the nipple to the nipple's surface.

Age and ethnicity have a significant impact on the incidence of MBC; the non-Hispanic Black population has the highest incidence rate (1.89/100,000), compared to the non-Hispanic White population (1.3/100,000), the Asian population (0.7/100,000), and the Hispanic population (0.8/100,000) [79]. In South and Central Africa, there are higher incidence rates of MaBC, which may be related to hypoestrogenism in the context of more common viral hepatitis. Non-Hispanic Blacks and Whites in the retrospective study by O'Malley *et al*. have similarly low 5-year survival rates (57% and 66%, no confidence interval or p value provided), which are significantly lower than those of other racial/ethnic groups (75%) [80]. When an individual reaches 50 years of age, the incidence rate rises significantly (to 1.7/100,000), reaching a plateau at 80 years of age and beyond (8.3/100,000). Ancestral History Several demographic studies have estimated that 15–20% of male patients diagnosed with breast cancer also have at least one first-degree relative with the disease [81]. Men who have a first-degree male or female relative who has breast cancer are as likely to get breast cancer as women are; their risk is elevated by two to three times. The danger significantly rises as the number of impacted family members rises. The Klinefelter Syndrome Clinically presenting as gynecomastia and testicular dysgenesis, Klinefelter is a rare hereditary condition that arises in men who receive an extra X chromosome [82]. A low androgen and high gonadotropin condition is thought to be the primary cause of the considerable (20–50 times) higher risk of MBC in men with Klinefelter syndrome as compared to the general male population. An imbalance of hormones Interestingly, a meta-analysis combining data from 10 cohort studies and 11 case-control studies found that MBC was associated with higher levels of estrogen rather than lower levels of androgen [83]. Men who suffer from illnesses like obesity and alcoholism that cause a pathological rise in their endogenous estrogen levels are just as likely as women to develop breast cancer. Expression of the androgen receptors impedes the treatment of the disease. Also, mutations in *BRCA1* and *BRCA2* are connected with an increased risk of breast cancer. A large number of breast cancers in males are ductal cancers which are invasive. The diagnosis of breast cancer in men is done with the help of mammography and ultrasound, as well as a confirmation using a biopsy [84]. Tumor characterization relies heavily on immunohistochemistry, which shows the expression of hormone receptors (PR and ER) and HER2/neu. In men, hormone receptor expression is nearly exclusively positive while HER2/neu expression is negative. The main treatments used in breast cancer are surgery, hormone therapy, radiation therapy, chemotherapy, targeted therapy, and gene therapy. Surgery: Surgery can be of two types, mastectomy (removal of the breast), or lumpectomy (removal of the lump along with some of the surrounding tissue) [85]. Hormone Therapy: In hormone-positive tumors, tamoxifen is used to lower the possibility of recurrence than aromatase inhibitors in men. In the case of androgen receptor positivity, tamoxifen would be less effective. Chemotherapy can be used in advanced tumors. Targeted Therapy: Trastuzumab can be used as targeted therapy in case of HER2-positive tumors Gene Therapy: This treatment can be used in breast cancers with specific genetic

mutations like poly-ADP-ribose polymerase inhibitors or molecules that can target androgen receptors. The treatments mentioned above can be given as a monotherapy or in combination with other therapies. The size and other characteristics of the lump that has formed, the patient's health status, and the cancer stage must all be taken into consideration while choosing the appropriate treatment plan. The prognosis for males with breast cancer differs according to the stage of diagnosis. There hasn't been a discernible increase in survival in recent years. Early detection results in survival rates that are similar to those of females [86]. However, because of ignorance and a delayed diagnosis, the prognosis may be worse in advanced stages. There is no discernible difference in terms of survival in advanced stages (IV), even though men typically have a worse prognosis due to advanced clinical stage diagnosis and more aggressive tumors; however, there is a discernible difference in the clinicopathological features and pattern of metastasis between the two genders. Exposure to Environment The risk of acquiring MBC has been linked to a number of occupational hazards, such as exposure to chemical substances like combustion products, hot working environments, and ionizing and electromagnetic radiation. These results, however, have only been applied to case series and case reports. It is generally known that FBC is associated with mutations in the tumor suppressor genes BRCA1 and BRCA2, which are involved in DNA repair. These autosomal dominant variants are linked to 10-15% of FBC and carry a cumulative 45–65% lifetime risk [87, 88].

In Females

All females are at the risk of breast cancer. Factors contributing to breast cancer other than sex include age, females above the age of 40, family history, reproductive factors like early menarche and late menopause, age of first pregnancy, hormones like endogenous and exogenous estrogen and lifestyle like excessive alcohol consumption. The most common symptom of breast cancer is breast lumps [89]. There are many other symptoms reported in females. Some of them include breast pain, nipple abnormalities, breast ulceration, breast skin abnormality, chest pain and weight loss. Breast tumors are developed from the increased proliferation of ducts which is a result of carcinogens. This can further contribute to metastatic cancer by the persistent exposure to carcinogens and the ignorance of the symptoms [90]. The tumor microenvironment plays a crucial role in the advancement of breast cancer. Macrophages in the tumor microenvironment have the ability to induce mutagenic inflammatory microenvironment. This contributes to angiogenesis and further immune escape for the cancer cells. DNA methylation in the tumor microenvironment can contribute to carcinogens [91]. Any breast cancer can progressively develop as random mutations where these mutations can accumulate to form tumor cells. The treatments involved in breast cancer are surgery, radiotherapy, chemotherapy, targeted therapy, and vaccines. Surgery: There are mainly two types known as mastectomy usually followed by breast reconstruction and lumpectomy Radiation: High-energy radiations are applied on the part of the tumor or the whole breast. Radiation therapy just before surgery can increase the efficiency of the treatment and the survival of the patient. Chemotherapy: It includes the use of different cytotoxic drugs like alkylating agents and antimetabolites [92, 93]. Chemotherapies can be used for both adjuvant and non-adjuvant systems. Targeted therapy: Targeted therapies can be used for HR-positive metastatic breast cancer by targeting the estrogen receptor or the estrogen synthesis. Targeted therapy can be done using aromatase inhibitors, and antibodies targeting *HER-2* like pertuzumab and trastuzumab. Vaccines: Vaccinations can be used as an immunotherapy to prevent the recurrence of the cancer in high-risk cancer patients [94]. Triple-negative breast cancers are the most aggressive type of breast cancer and vaccines can be used against their recurrence. PPV or Personalized peptide vaccines are used according to the immunity of the patient, for instance, PVX-410 vaccines. A complex mix of hereditary, environmental, and lifestyle factors can contribute to breast cancer. Women going through menopause are more vulnerable, and genetics is a major contributing factor. Physical inactivity, obesity, drunkenness, smoking, and hormone therapy are examples of modifiable factors. Male breast cancer risk is influenced by hereditary factors and hormonal changes associated with testicular illness. Age, genetic mutations, radiation, hormone exposure, family history, and liver cirrhosis are risk factors. Delays in detection in males often result in advanced stages of diagnosis. Breast cancers in men are typically more aggressive than those in women [95, 96, 97]. Oncogenes have been overexpressed and mutated in breast tumors. Immunohistochemistry for HER2/neu and hormone receptors (PR and ER) is used in the diagnosis processes in males. Common therapies include hormone therapy, chemotherapy, targeted therapy, gene therapy, and surgery (mastectomy or lumpectomy) [98]. The prognosis is dependent upon the diagnosis stage, with higher survival rates associated with early discovery. Age, family history, reproductive characteristics, hormones, and lifestyle choices are among the many variables that put all women at risk. Increased ductal proliferation, which results in metastatic cancer, is a function of carcinogens in females. The tumor microenvironment is important, as macrophages provide an inflammatory milieu that might cause mutations [99]. The target of targeted therapy is HER-2 or hormone receptors in females. Vaccines can be used in female breast cancer as immunotherapy to prevent recurrence, such as personalized peptide vaccines.

Conclusion

Breast cancer is a type of cancer that is diagnosed both in men and women. Even though there are more similarities in male and female breast cancers, minor differences are also seen among two genders. It is the second most common cancer in women while breast cancer is a rare disease in men. Male breast cancer constitutes 1.4% of all cancers of the breast. The expected age of a female to be diagnosed with breast cancer is above 40, while that of a male is above 60. In men, a higher stage of disease is usually shown during diagnosis due to the lack of awareness. As we approach Breast Cancer Awareness Month, it's important to discuss breast cancer and how it impacts males as well. Breast cancer is not simply a disease that affects women. Even though male breast cancer is uncommon, there may be a cultural stigma associated with men discussing physical issues that prevents them from learning about this illness. This truism applies to men's health in general, and there is a perceived stigma around topics like male breast cancer [100]. However, this illness is a serious issue. Breast cancer in men can be fatal. It's crucial to heed the warning signals.

According to the American Cancer Society, like past years, 2,800 males will receive a breast cancer diagnosis in 2023, and 530 of those men will pass away from the illness. By contrast, according to the same figures, roughly 297,790 women will receive a diagnosis and 43,170 will pass away in 2023. Less than 1% of cases of breast cancer in men are diagnosed with the disease. In a man's lifetime, about one in 833 will get breast cancer. Male breast cancer is particularly difficult since it is so uncommon, even while the statistic—one in eight males will receive a diagnosis in their lifetime—may not seem as scary as the equivalent for women. Some differences in the outcomes of breast cancer in males compared to women have been observed in recent studies [101]. This is likely due to a lack of research and knowledge among men and physicians. Male breast cancer patients have a 19% higher death rate than female breast cancer patients, according to a 2019 study by Vanderbilt University researchers using mortality data from 16,025 men and 1.8 million women who had breast cancer. In a 2023 study that was published in the Journal of the National Cancer Institute, a number of investigators from the BCRF and other organizations discovered that, in contrast to breast cancer in women, male breast cancer survival rates had not increased noticeably during the previous 30 years [102]. Men are often undertreated for breast cancer, according to groundbreaking research by Dr. Fatima Cardoso and the International Male Breast Cancer Program, which is funded by the BCRF. In comparison to women with identical breast cancers, males were less likely to have endocrine therapy for ER-positive illness or breast-conserving surgery for early-stage breast cancers, according to her 2018 study of 1,482 men with the condition. Male breast cancers differ from female breast cancers in terms of biology and molecular makeup, according to research conducted by Dr. Cardoso and her associates. This finding emphasizes the need for additional study. 2019 saw the analysis of data from over 10,000 males in the National Cancer Database by Mayo Clinic researchers. The prognosis of male breast cancer is worse than that of females. Klinefelter's syndrome can be one of the causes of breast cancer in males. Male cancer has more estrogen receptor-positive tumors. The overexpression of *p53* and *Erb-B2* is seen in females and not in males. Early-onset breast cancer is seen in women more than in men, caused by hormone exposure or reproductive factors. In the field of treatment, hormone replacement therapy is an option for female breast cancers but not in males.

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102. All images are created with BioRender.com templates: https://www.biorender.com