Chapter

The Future Perspectives of Drug Repurposing and Treatment for the Drug Resistant Breast Cancer: A Review

Panneerselvam Theivendren, Selvaraj Kunjiappan, Yashoda Mariappa Hegde, Kaveena Ravi, Sivakumar Vellaichamy, Murugananthan Gopal and Manimekalai Pichaivel

Abstract

Breast cancer is a major health concern as it is the second leading cause of death from cancer. There are several well-known risk factors that contribute to breast cancer. Despite the various treatment options available, complete cure is still difficult due to heterogenicity of BC subtypes. As a result, identifying BC subtypes is critical for determining the optimal treatment approach. Over the last several years, new drugs targeting particular therapeutic targets have resulted in significant advances in the treatment of breast cancer. Nonetheless, resistance to treatment is the "major" issue, and a significant increase in survival rates has been the main focus for researchers. The purpose of this review article is to provide a broad overview of the molecular basis of drug resistance in breast cancer, as well as a detailed assessment of current treatment options, potential new treatment methods for drug-resistant breast cancer and repurposed drugs used for treatment. The possibility of non-cancer drugs being studied for breast cancer in the future, as well as the obstacles and bottlenecks of drug repurposing, is also highlighted. Finally, we go through present problems and future prospects in drug-resistant breast cancer therapy.

Keywords: Breast Cancer, Endocrine Resistance, Oestrogen Receptor Modulation, Drug Repurposing

1. Introduction

Breast cancer is the most frequent disease among women, according to the World Health Organisation (WHO), and it is the second leading cause of death from cancer, after lung cancer. It is considered a severe health concern that affects patients' quality of life as well as their psychological well-being, It is the main cause of death among women aged 45 to 55 years old. The incidence of breast cancer is expected to grow by 85 per 100.000 women by 2021 [1]. Experts estimate that by 2050, there will be approximately 3.2 million new BC cases each year worldwide,

based on population increase. Although there is no single risk factor for the majority of breast cancer patients, there are a number of well-known risk factors, including obesity, lack of physical activity, consumption of alcohol, hormone replacement therapy, increased breast density, and inherited genetic susceptibility due to mutations in autosomal dominant genes, which contribute for 5–10% of all breast cancer cases in the United States [2]. Treatment for BC is difficult since it is a heterogeneous illness with various subtypes that have different but distinct clinical and biochemical characteristics. As a result, identifying BC subtypes is critical for determining the optimal treatment approach [3]. Breast cancer may be in situ or invasive, with in situ tumours being the easiest to cure. Invasive breast cancers, especially invasive ductal carcinoma (which accounts for 80% of all invasive breast cancers), are a major source of concern. While receptor-specific therapy is used to treat the first two types of breast cancer, chemotherapy remains the mainstay of TNBC treatment [4]. BC is characterised as basal-like or non-basal-like according on the cell type of origin (luminal or basal/myoepithelial cell compartment). The aforementioned, also referred to as "triple-negative," contributes approximately 10% of all BCs. Understanding the etiological heterogeneity of BC subgroups will aid in directing therapy, predicting survival, and impacting preventive measures due to the complexity of biology [5]. With the standardisation of systemic chemotherapy as the gold-standard method for most cancer types and the moderate increase in both survival rates and toxicity reduction, targeted therapy has undoubtedly garnered the greatest scholarly attention and financing from the pharmaceutical sector. Nonetheless, resistance to treatment is the "major" issue, and a significant increase in survival rates is still a pipe dream for researchers. It is important to note that tremendous progress has been achieved in the area of breast cancer research during the last decade. The 'battle' against this mysterious and aggressive form of cancer, however, is still ongoing [6]. The purpose of this review article is to provide a broad overview of the molecular basis of drug resistance in breast cancer, as well as a detailed assessment of current treatment options and potential new treatment methods for drug-resistant breast cancer. Finally, we go through present problems and future prospects in drug-resistant breast cancer therapy.

2. Breast cancer risk factors

BC is associated with the following epidemiological risk factors: (a) a younger age at the first menstrual cycle and during the first birth, (b) pre-menopause is the prime factor in most BC patients, (c) civilization is an unavoidable outcome of increased risk for BC fatalities, (d) socio - economic background is an unbiased predictor of sophisticated extent at assessment in breast cancers, and (e) obesity and higher BMI are epidemiological risk factors for BC (**Figure 1**).

3. Pathogenesis

Breast cancers typically begin as ductal hyperproliferation and progress to benign tumours or even metastatic carcinomas as a result of continuous stimulation by carcinogenic agents. Breast cancer initiation and progression are influenced by tumour microenvironments such as stromal effects and macrophages. When only the stroma, not the extracellular matrix or the epithelium, was exposed to carcinogens, the mammary gland of rats may be driven to neoplasms. Macrophages may create a mutagenic inflammatory microenvironment, allowing cancer cells to avoid immune rejection and increase angiogenesis. The normal and tumour-associated

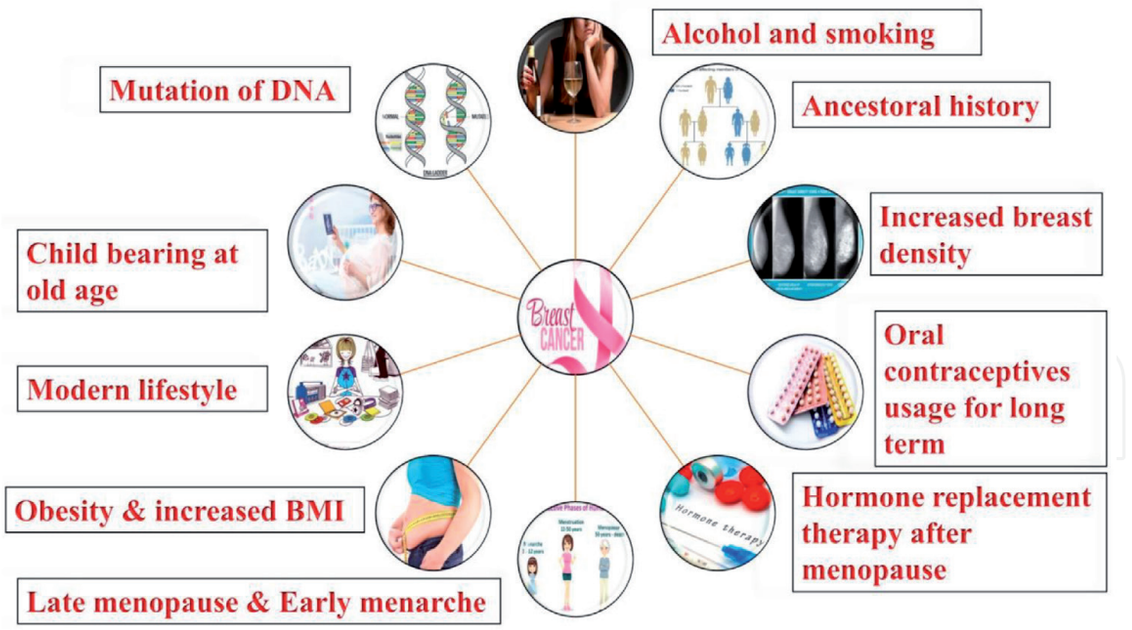

Figure 1.
The risk factors of breast cancer.

microenvironments exhibit different DNA methylation patterns, suggesting that epigenetic changes in the tumour tissue may promote tumorigenesis. Cancer stem cells (CSCs), a new type of malignant cell seen in tumours, have been linked to tumour genesis, migration, and relapse. This minor group of cells can auto renew and is resistant to chemotherapy and radiation. They may be produced from stem

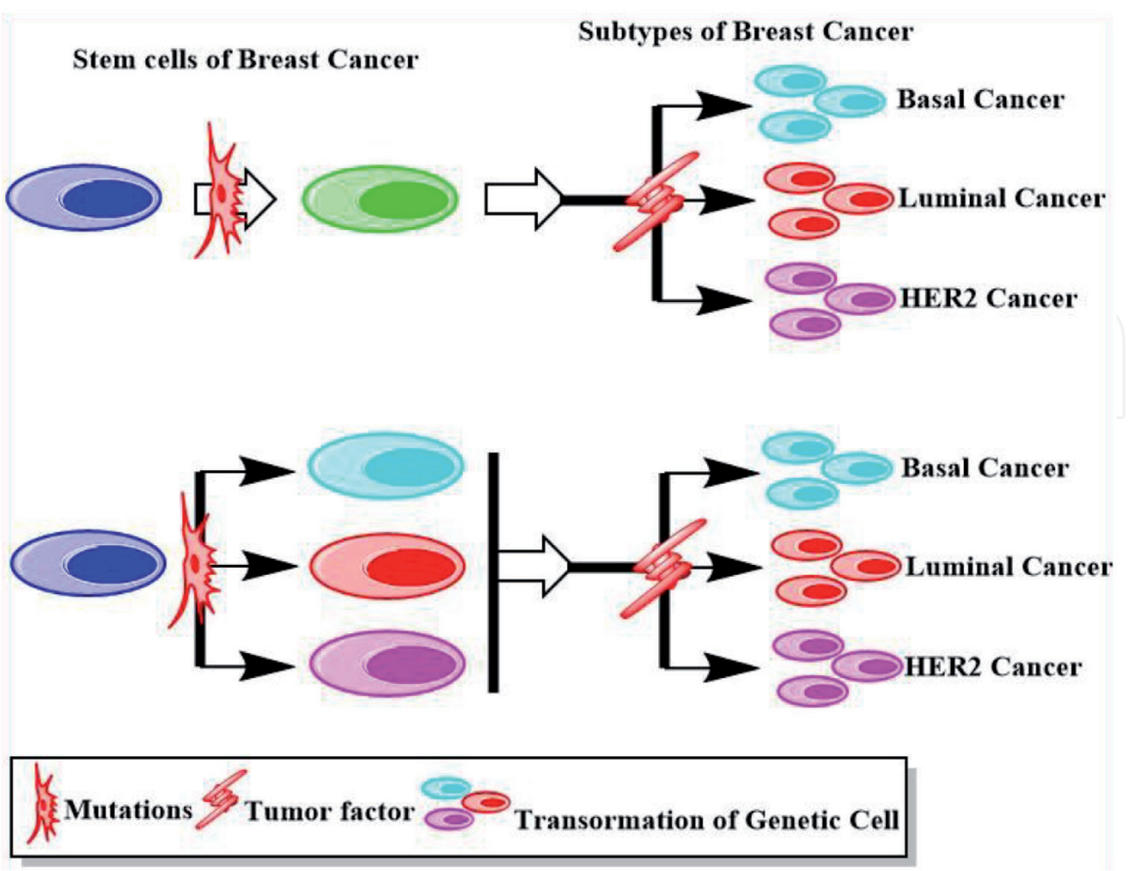

Figure 2.
The possible hypothesis for onset and development of breast cancer.

cells or progenitor cells in normal tissues. Ai Hajj was the first to identify breast cancer stem cells (bCSCs), demonstrating that as few as 100 bCSCs can create new tumours in infected mice. Luminal epithelial progenitors are more likely than basal stem cells to give rise to bCSCs. Wnt, Notch, Hedgehog, p53, PI3K, and HIF are all signalling pathways involved in the auto-renewal, multiplication, and migration of bCSCs. However, more research is needed to fully comprehend bCSCs and create ingenious ways for their eradication. The cancer stem cell theory and the stochastic theory are two distinct hypotheses for breast cancer initiation and progression. All tumour subtypes, according to the cancer stem cell theory, are derived from the same stem cells or transit-amplifying cells (progenitor cells). Various tumour features will result from acquired genetic and epigenetic alterations in stem cells or progenitor cells (**Figure 2**). According to the stochastic theory, each tumour subtype begins from a single type of cell (stem cell, progenitor cell, or differentiated cell) (**Figure 2**). Any breast cell can acquire random mutations over time, eventually transforming it into a tumour cell if enough mutations are accumulated. Despite the fact that both theories are backed up by evidence, neither can adequately explain the origins of human breast cancer [7].

4. Types of breast cancer

According to a review, breast cancer is divided into invasive and noninvasive breast cancers **Figure 3.**

4.1 Non-invasive breast cancer

It's a malignancy that has not spread beyond the lobule or ducts in which it's found [8]. Ductal carcinoma in situ is an example of a kind of non-invasive breast cancer. Ductal carcinoma in situ develops when abnormal cells form inside the milk ducts but do not spread to nearby tissue or to the outside. The term "in situ" means "in place." Atypical cells may develop and mature into invasive breast cancer even if they have not spread beyond the lobules or ducts.

4.2 Lobular carcinoma in situ (LCIS)

Breast lobules form as a result of this kind of breast cancer. Outside of the lobules, the breast cancer has not spread into the breast tissue. Non-invasive breast cancer is typically diagnosed as lobular carcinoma in situ.

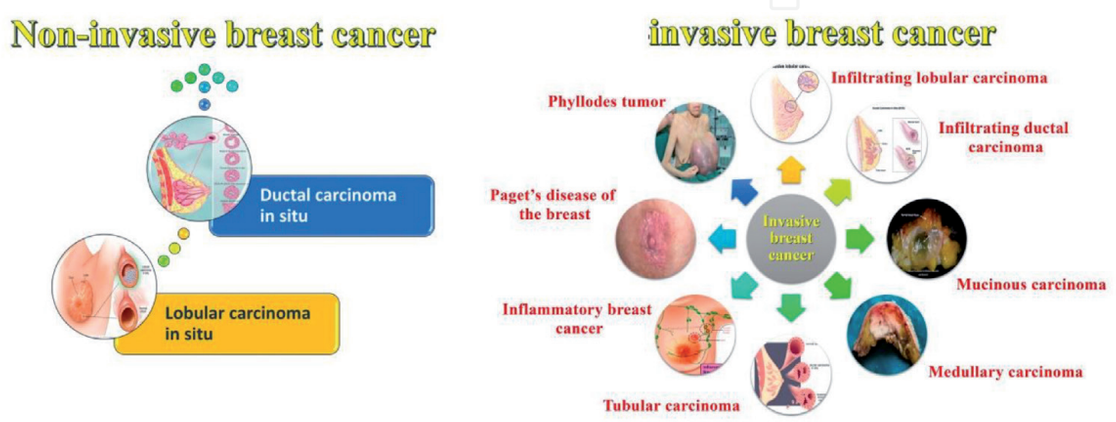

Figure 3.
Types of breast cancer.

4.3 Ductal carcinoma in situ

It is the most common type of non-invasive breast cancer, because it only affects the breast duct. Ductal comedocarcinoma is an example of ductal carcinoma *in situ*.

4.4 Invasive breast cancer

When abnormal cells from the lobules or milk ducts break off and come into contact with breast tissue, this condition occurs. Through the immune system or the systemic circulation, cancer cells may spread from the breast to other areas of the body. They may migrate early in the formation of the tumour, when it is small, or later, when it is large. Invasive breast cancer is the most common kind of cancer in women. Metastatic breast cancer is defined as invasive breast cancer that has spread to other parts of the body. The brain, bones, lungs, and liver are the most frequent organs to which these cells travel. These cells separate and grow irregularly once again, resulting in new tumours. Although new forming cells are appearing in many parts of the body,but still remains to be breast cancer cells [9, 10].

4.5 Infiltrating lobular carcinoma (ILC)

Invasive lobular carcinoma is another name for infiltrating lobular carcinoma. ILC begins in the breast milk glands (lobules), but it may spread to other parts of the body.

4.6 Infiltrating ductal carcinoma

Invasive ductal carcinoma is also known as infiltrating ductal carcinoma. IDC begins in the breast milk ducts and spreads to the duct wall, infecting the fatty tissues of the breast and perhaps other areas of the body.

4.7 Medullary carcinoma

Invasive breast cancer with a distinct normal and medullary tissue border is known as medullary carcinoma.

4.8 Mucinous carcinoma

Mutinous carcinoma, sometimes called colloid carcinoma, is an uncommon kind of breast cancer characterised by cancer cells that produce mucus. Females who have mutinous carcinoma have a better prognosis than those who have other kinds of invasive carcinoma.

4.9 Tubular carcinoma

Tubular invasive breast carcinomas are a form of invasive breast carcinoma. Tubular carcinoma had a better prognosis than other forms of invasive carcinoma.

4.10 Inflammatory breast cancer

Inflammatory breast cancer causes swollen (red and heated) breasts with bulges and/or broad ridges, which happens when cancer cells block lymph arteries or channels in the skin surrounding the breast. Inflammatory breast cancer is an uncommon kind of cancer that rapidly spreads. Throughout treatment,

all multidisciplinary techniques, including as radiation therapy, surgery, chemotherapy, and imaging, must be carefully integrated. Since the first publication on this subject, neoadjuvant chemotherapy has resulted in a substantial increase in overall survival and has taken the place of locoregional treatments like radiation and surgery, resulting in long-term improvements in this disease [11, 12].

4.11 Paget's disease of the breast

It's an uncommon kind of breast cancer that produces visible changes to the breast's nipple. Red itchy rashes around the nipple, which may occasionally spread to the rest of the body, are among the symptoms. Paget's disease of the breast differs from other skin problems like eczema and psoriasis in that the other skin problems usually affect both breasts and can start at the areola rather than the nipple of the breast, whereas Paget's disease of the breast usually affects only one breast and starts at the nipple of the breast rather than the areola. Men and women are equally affected by Paget's disease, which contributes for 1–3% of all breast malignancies.

4.12 Phyllodes tumour

Tumours caused by Phyllodes may be benign or malignant. Phyllodes tumours grow in the breast's connective tissues and may be surgically removed. Phylloides tumours are very rare; in the United States, less than 10 women die of this kind of breast cancer each year [13–15].

4.13 Triple-negative breast cancer

Breast cancer is now well understood to be a diverse disease with several subforms characterised by their distinct clinico-pathological features, prognosis, and treatment responses. The absence of progesterone receptor, human epidermal growth factor receptor 2, and oestrogen receptor expression characterises triple-negative breast cancer. This kind is primarily destructive, and it is more frequent in premenopausal females. It accounts for 10–15 percent of cases in white females, with a higher frequency.

5. Stages of breast cancer

5.1 Stage 0

This is a non-invasive tumour stage in which both cancerous and non-cancerous cells are enclosed within the boundaries of the breast part where the tumour begins to grow, with no evidence of their invasion into the surrounding tissues of that part; ductal cell carcinoma in situ (DCIS) is an example of this tumour stage [16].

5.2 Stage 1

Invasive breast cancer is described as this stage, and microscopic invasion is conceivable. It is divided into two stages: 1A and 1B. Te category 1A refers to a tumour that is up to 2 cm in diameter and does not include any lymph nodes, while stage 1B refers to a tiny collection of cancer cells bigger than 0.2 mm discovered in a lymph node [17].

5.3 Stage 2

Stage 2 is divided into two categories: 2A and 2B. The tumour is detected in axillary lymph nodes or sentinel lymph nodes in Stage 2A, but there is no tumour in the breast. The tumour may be 2 cm in diameter or 5 cm in diameter. Stage 2B, on the other hand, defines a tumour that is bigger than 5 cm in diameter but does not reach the axillary lymph nodes [18].

5.4 Stage 3

It's broken down into four sections: 3A, 3B, and 3C. Stage 3A refers to a tumour that has caused swelling or ulceration on the breast skin and has spread to up to 9 axillary lymph nodes or sentinel lymph nodes, whereas stage 3B refers to a tumour of any size that has caused swelling or ulceration on the breast skin and has spread to up to 9 axillary lymph nodes or sentinel lymph nodes. Because it has progressed to 9 axillary lymph nodes or sentinel lymph nodes, stage 3B breast cancer is deemed inflammatory. Tumour spread to 10 or more axillary lymph nodes, as well as lymph nodes above and below the clavicle, is classified as stage 3C [19].

5.5 Stage 4

This is the late and metastatic stage of cancer, in which the disease has spread to other internal organs including the lungs, bones, liver, and brain **Figure 4** [20].

6. Clinical breast cancer diagnosis techniques

The assessment methods and popular imaging techniques that will aid physicians in providing better care to patients and advancing clinical diagnosis are discussed below.

1. History and physical examination of breast cancer

   The clinical history of breast cancer patients is used to assess the risk of developing cancer and to show the existence or absence of breast disease symptoms [21]. Age at menarche, menopausal status, prior pregnancies, and usage of hormone replacement therapy or oral contraceptives beyond menopause are all factors to consider. Personal as well as family history should be carefully investigated. Breast soreness, weight loss, bone pain, tiredness, and nipple discharge are just a few of the symptoms to check into. During a physical examination, doctors look at the breasts, the area around the neck and collarbone, and the armpits (axillae). Any anomalies in the breasts, such as lumps or other breast cancer signs, are investigated. Lymph nodes, which are often enlarged in breast cancer patients, are also assessed [22, 23].

2. Self examination

   The value of breast self-examination is debatable since no benefit in terms of decreased mortality has been demonstrated. Most doctors teach women to do monthly self-examinations in order to get familiar with their normal structure and to give them authority over their own healthcare. Self-examination may reveal irregularities in breast size and form. Sreedharan et al. performed research at hospitals in the United Arab Emirates. A self-administered structured questionnaire was utilised to look at self-examination and knowledge practises. This research [24] produced satisfactory outcomes. These studies have

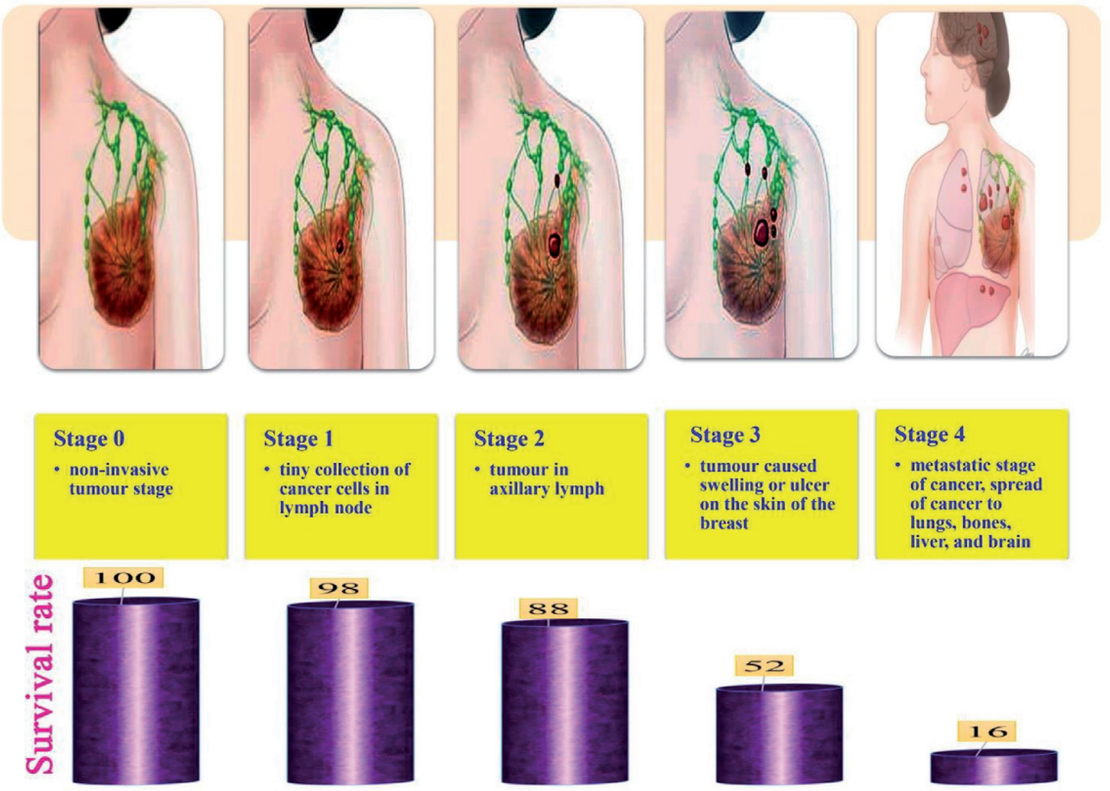

Figure 4.
Stages in development of breast cancer.

demonstrated that a continuous breast cancer education programme may help people become more aware of the disease. Ceber et al. performed research on Turkish women's breast self-examination and health attitudes, concluding that early detection of breast cancer may avoid physical diseases and early mortality. He further claimed that just one out of every seven patients with breast cancer receives a timely diagnosis [25].

3. Mammography

Mammography (MG) is the recommended method for screening and detecting breast cancer, and it aids physicians in gathering clinic data on BC patients. The data indicates that early MG screening may decrease the death rate of BC patients by 30 percent to 40 percent [26]. Meanwhile, only 4 percent –10 percent of BC patients have MG as a positive diagnostic finding. With the passage of time, MG continues to grow. The two primary methods for diagnosing BC patients in clinic are contrast-enhanced mammography (CEM) and digital breast tomosynthesis (DBT) [27, 28]. Age, ethnicity, personal history, radiologist expertise, and technique quality all influence mammography sensitivity. In high-density breasts in premenopausal women, sensitivity may be decreased. Mammography has a number of disadvantages, including the use of ionising radiation, inability to diagnose thick breasts, high false-positive and false-negative rates, and an unpleasant examination.

4. Ultrasonography

Breast ultrasonography is a low-cost and commonly available screening method that detects malignancies by rebounding acoustic waves off breast tissue. To identify the anatomy of the human breast, an ultrasonic transducer

is utilised to detect the acoustic waves reflected off it. Although less efficient than mammography, breast ultrasonography increases cancer detection rates in high-risk women and helps in the identification of cysts and solid masses. For women at high risk of breast cancer, pregnant women, and those who are unable to undergo mammography, breast ultrasonography has been recommended as a supplement to mammography. When breast ultrasonography and mammography are used together, the sensitivity of the imaging increases at the cost of specificity and biopsy rates. Because the reverberant characteristics of healthy and malignant tissues are so similar, breast ultrasonography fails to identify many tumours. It also necessitates the employment of qualified radiologists, which has a big impact on sensitivity and specificity [29].

5. Magnetic resonance imaging

   MRI creates pictures at different cross-sections by mixing a strong magnetic field with RF signals. Breast MRI is suggested for high-risk women, but not for the general population because of its high rate of inaccuracy, higher expense, time commitment, insufficient number of units, requirement for trained radiologists, and lack of therapeutic effect. The American Cancer Society (ACS) has published recommendations for utilising MRI as a complement to mammography, and for specific demographic groups, such as BRCA mutation carriers and those at higher risk of complications, annual MRI scans are advised. In women at high risk of breast cancer, MRI is less specific but more sensitive than mammography and ultrasound in identifying small lesions [30].

6. Nuclear medicine

   It is a kind of molecular imaging in which a person is administered a radioactive substance, and the radiation released by the radiopharmaceutical is shown by sensitive emission detectors such as gamma cameras and PET detectors located outside the patient's body. The combination of a CT scanner and a gamma camera, as well as a CT scanner and a PET scanner, is a significant advance in the identification and localization of disease.

7. Single photon emission computerised tomography (SPECT)

   This method employs single photon radionuclides that produce gamma rays, such as gallium-67, iodine-131, and technicium-99. It's a fast and precise scan for the organ of concern. It may be used over the whole body, is quite safe in terms of radiation dose, and is effective in detecting both primary and metastatic tumours. The abbreviation PET/CT refers to positron emission tomography. PET/CT is also low-radiation since it utilises positron-emitting radionuclides including oxygen-15, fluoride-18, and carbon-11 to produce positrons. In positron emission tomography, a radioactive version of glucose, such as [18F] fuoro-2-deoxy-d-glucose, is a typical tracer. Tissues with greater metabolic needs, such as developing cancer cells, absorb the tracer more readily, which is seen on the scan. Using a combination of CT and PET, significant information about a range of situations impacting the different organs of the body may be readily mapped. PET/CT is extremely sensitive and accurate for predicting opaque and distinct areas of loco-regional lymph nodal extent and/or far-away metastases that are not apparent on conventional imaging, with up to 25% of patients having their staging changed. This technique is used to plan management by describing the primary disease's spread. It's also utilised in re-staging and treatment follow-up after a return of a managed disease [31].

8. Tumour markers

Tumour markers should be examined at all stages of breast cancer therapy, diagnosis, and screening, including metastasis prediction, treatment, and diagnosis, according to Porika et al. Thirteen distinct breast cancer tumour indications are investigated, six of which are new to the guideline. The different variations have been proven to be therapeutically useful and are recommended for use in clinical practice [32]. In order to avoid over- or under-interpreting the therapeutic potential of a few studies, the physician must be aware of the limits in the combined specificity and sensitivity of each sign. With these restrictions in mind, submitting tissue, germ-line, and soluble tumour markers for clinical trials may assist individuals who are at risk for or have breast cancer get back on track with their treatment.

9. Breast biopsy

Breast biopsies are the most effective way to find out whether you have breast cancer. Biopsies of the breast occur in a range of sizes and forms. To enhance diagnosis accuracy and remove as many false negative results as possible, breast imaging, breast self - examination, and biopsy are all performed at the same time (triple test).

a. Fine needle aspiration

A thin prickle is used to extract cells from an abnormal area or a breast nodule. Ultrasound may be used to guide the prickle. A local anaesthetic may be used to anaesthetize the region where the prickle will be inserted.

b. Core biopsy

A larger prickle is used to extract a core of tissue from the abnormal region or breast lump. It is usually performed under a limited anaesthesia, so the breast is unaffected, and the patient may feel no pain or discomfort depending on when the anaesthetic is administered. For the length of the core biopsy, an MRI, ultrasound, or mammography may be utilised to guide the procedure.

c. Vacuum-assisted stereotactic core biopsy

Different small tissue samples are obtained through a single tiny incision in the skin using a prickle and a suction-type device in this core biopsy. It is done with the use of a local anaesthetic. To guide the prickle into place, an MRI, ultrasound, or mammography may be used. During the procedure, the patient may feel a bit uneasy.

d. Surgical biopsy

A surgical biopsy is performed if the abnormal site is too small to be biopsied by another technique or if the biopsy result is unclear. A guide wire may be inserted into the breast prior to the biopsy to aid the medical practitioner in locating the abnormal tissue. A local anaesthetic may be administered, and the wire can be guided into place using MRI, ultrasound, or mammography. After that, a general anaesthesia is used to perform the biopsy. Along with the wire, a little region around the breast tissue and lump is removed.

7. Treatment methods

The goal of breast cancer treatment is to maintain quality of life while extending life expectancy. Breast cancer treatment methods vary based on the stage of the disease, its size, location, whether it has spread to other organs of the body, and the individual's physical state. Targeted treatments, hormone treatment, radiation therapy, and surgery are being used to treat breast cancer.

1. Surgery

   This is the most common treatment option for people with breast cancer that has not spread to other parts of the body, and it's also a viable option for those with more advanced stages of the disease. The amount of tissue removed with the cancer varies according on the cancer's features, whether it has spread, and the patient's particular emotions. The following are a handful of the most common types of surgery:

   a. Lumpectomy (breast conserving surgery)

      According to the American Cancer Society [33], a lumpectomy, also known as a selective mastectomy, is a practice that requires removing the portion of the breast that contains the malignant tumour, as well as some healthy tissues and lymph nodes around it, while leaving the rest of the breast preserved as much as possible. This operation is often performed on women in the early stages of cancer, but in addition to the surgery, the patient will need additional treatments such as radiation, chemotherapy, or hormone replacement therapy. Most surgeons and patients, particularly if the woman is going to lose her breast, prefer a lumpectomy over a full breast removal at first. Tenderness, transient inflammation, sclerosis, and a change in the look of the breast are all possible side effects of a lumpectomy.

   b. Mastectomy

      The purpose of a mastectomy is to reduce the chance of developing breast cancer. Bilateral preventive mastectomy reduces the risk of getting breast cancer but does not fully remove it. Aromatase and tamoxifen are more effective than contra-lateral preventive mastectomy in reducing the risk of contra-lateral breast cancer. Mastectomy is the most efficient treatment for a disseminated instance of breast cancer in whom a lumpectomy was ineffective. Nonetheless, most women experience feelings of asexuality, loss of self-image, and melancholy as a result of breast loss [34].

   c. Reconstructive surgery

      Females who have had a mastectomy might consider having their breasts renovated, either immediately or later. It is used to improve the appearance of the breast after tumour surgery. All ladies who have had a mastectomy should be given the choice of reconstructive surgery [35]. Mastectomy is a very straightforward surgical procedure that usually requires 1–2 days in the hospital. Breast mass deficiency alters the patient's appearance and makes it difficult to wear certain types of clothes. The use of an external prosthesis to address these issues may be uncomfortable and abrasive, especially for women with large breasts. The most serious side effect after mastectomy is the psychological impact of the physical and cosmetic changes, which may include anxiety,

sorrow, and poor effects on body image and sexual activity [36]. Females with breast cancer who are unable to get breast-conserving therapy or who have a higher genetic risk of breast cancer often seek breast reconstruction. Breast reconstruction methods now available are varied and may include the use of a prosthetic implant, an autologous tissue flap, or both. Cancer may recur in the rebuilt breast regardless of the technique used; furthermore, in autologous tissue flaps repaired breasts, minor complexity such as fat necrosis may occur. Breast reconstruction, according to studies, restores body representation, demonstrates vitality, femaleness, and sexuality, and has a positive impact on the patient's emotions of comfort and life quality [37].

2. Ovarian ablation as adjuvant therapy for breast cancer

Breast cancer patients have been treated with ovarian ablation. Radiation-induced ovarian ablation, surgical removal of the ovaries, and long-term use of luteinizing hormone-releasing hormone (LHRH) analogues are all options for ovarian ablation. Furthermore, there are a few theories that cytotoxic chemotherapy may help premenopausal women with breast cancer by causing ovarian ablation. Many of the case studies and clinical trials of ovarian excision conducted in the past had methodological flaws. A meta-analysis of randomised clinical trials found that women who had ovarian ablation as an adjuvant therapy had a significant improvement in overall survival and disease-free survival compared to those who did not. According to a study of the literature, ovarian ablation may be used as an alternate treatment for breast cancer [38].

3. Breast cancer therapy by class

Various classes of therapeutic agents are employed for breast cancer treatment:

a. Alkylating agent: cyclophosphamide (nitrogen mustard)

b. Anti-metabolite: methotrexate (folic acid analogue), 5-fluorouracil &capacitabine (pyramidine analogues)

c. Natural product: vinorelbine (vinca alkaloid), paclitaxel (taxane), doxorubicin (antibiotic)

d. Hormone and antagonist: tamoxifen (anti oestrogen), letrozole&anastrazole (aromatase inhibitors)

e. Miscellaneous: trastuzumab (monoclonal antibody), lapatinib (Protein tyrosine kinase inhibitor)

4. Chemotherapy

Chemotherapy is the process of eliminating cancer cells with the help of specific medications. It may be administered both before and after surgery, depending on the patient's health. Docetaxel, Paclitaxel, Platinum agents (cisplatin, carboplatin), Vinorelbine (Navelbine), Capecitabine (Xeloda), Liposomal doxorubicin (Doxil), Cyclophosphamide (Cytoxan), Carboplatin (Paraplatin), and other drugs are included in chemotherapy, according to the American Cancer Society [39]. However, it has a number of negative side effects. The following are some of the most frequent breast cancer treatment regimens.

Cyclophosphamide is used to treat breast cancer metastases by preventing DNA replication and cell division. This prodrug is converted into active metabolites by hepatic intracellular enzymes (i.e. 4 hydroxy cyclophosphamide, aldophosphamide, acrolein and phosphor amide mustard). The medication has been utilised in the treatment of breast cancer as an adjuvant therapy in conjunction with CMF or an anthracycline.

Platinum compounds such as **Carboplatin and Cisplatin** are used to treat breast cancer as monotherapy or in conjunction with other cancer treatments. Platinum compounds have been investigated for their effect on DNA structure and stability, and a variety of platinum-DNA adducts have been discovered in vivo and in vitro. The impact of these different lesions on DNA replication, their potential to introduce mutations, and their susceptibility to DNA repair methods have all been measured in the early studies. Platinum (IV) compounds may cause further DNA damage, perhaps as a result of the cell's conversion to platinum (II) compounds. About 20–35 percent of patients with metastatic breast cancer who were receiving monotherapy responded to carboplatin treatment. The medicines Gemcitabine and Taxanes are often used in conjunction with Platinum compounds.

Capecitabine is a fluoropyrimidine oral prodrug that, when converted to 5-FU by the thymidine phosphorylase enzyme, has comparable effects as 5-FU infusion. It has been used in conjunction with taxanes to treat metastatic breast cancer that has progressed.

Gemcitabine (also known as difluorodeoxycytidine) is a pyrimidine nucleotide that inhibits RNA synthesis and DNA replication and is used to treat malignancies of the lung, bladder, and breast. Weekly IV injections of gemcitabine are well tolerated.

Vinorelbine binds to tubulin, causing mitotic metaphase to be disrupted. According to several studies, this medication has shown encouraging effects in advanced breast cancer.

Although metastatic or secondary breast cancer is difficult to cure, it may be managed for years. Chemotherapy may be used to control metastatic breast cancer and slow or stop its progression. It may also be used to reduce the severity of certain symptoms. Other treatments may be started before to or concurrently with chemotherapy.

5. Aromatase inhibitors

These are compounds that target aromatase, the enzyme complex that is responsible for the last step in the synthesis of oestrogen, in order to reduce oestrogen formation. Letrozole, exemastane, and anastrozole are examples of third-generation aromatase inhibitors that are currently used. A randomised clinical study that looked at the efficacy of these chemicals in treating women with advanced breast cancer found that they are quite beneficial. Females treated with aromatase inhibitors had a lower risk of developing contralateral breast cancer than women treated with tamoxifen, according to a clinical trial [40].

6. Anti–angiogenesis drugs

Antiangiogenic therapy for breast cancer has a lot of potential and several ongoing studies are attempting to better understand the optimal care settings and mediator selection. Research suggests a link between endocrine resistance and cancer dependency on angiogenic networks in patients with oestrogen receptor positive tumours, suggesting a possible therapeutic benefit in combining endocrine treatment with antiVEGF mediator. Results from randomised clinical trials highlight the wide range of responses to antiVEGF therapy, indicating that a better selection of patient subgroups is needed to maximise the benefits of these treatments. The identification

of biomarkers for treatment response is a single area of intense interest, however most studies to far have failed to find a correlation between cancer-associated indicators such as cancer mutations and EGF expression and scientific response.

7. Radiation therapy

Radiation treatment is beneficial in early breast cancer patients, according to Zhou et al. This research looked at 143 women who had breast conserving surgery and received either regular or intraoperative radiation treatment. There was substantial local control of the tumour after 54 months of follow-up. Radiation treatment uses high-energy beams to destroy cancer cells. Only the cells that are treated are affected by this treatment. After breast cancer surgery, radiation treatment may be used to eliminate any residual cells in the chest region [41].

a. Brachytherapy

It's a type of radiation treatment. Accelerated partial breast irradiation is a term that comes to mind. It just focuses radiation in the general region where the cancer was discovered. This might potentially eliminate the need for whole-breast radiotherapy. The number of management sessions is also reduced.

8. Protein tyrosine kinase inhibitor

Lapatinib is an orally active, reversible EGFR and HER2 tyrosine kinase inhibitor whose primary mechanism of action tends to be driven by HER2. When trastuzumab-treated HER2-positive breast cancer developed, lapatinib was authorised for use in combination with capecitabine; it's also utilised as a first-line treatment for HER2-positive metastatic breast cancer in combination with letrozole. Lapatinib and chemotherapy combined achieved a 22 percent response rate and a 27 percent clinical value rate in patients who had previously been treated with trastuzumab, and as prophylaxis, it achieved 12.4 percent to 25 percent clinical value rates; however, constrained resistance to lapatinib was observed in some cases [42, 43].

9. Gene therapy for carcinoma of the breast

Gene therapy is a kind of treatment that attempts to correct particular molecular defects related to breast cancer growth and progression. Cancer development is linked to mutated BRCA1 and p53 genes, which have been identified as cancer genetic markers. [44]. Cancer gene modification techniques may allow for selective targeting without presenting substantial hazards to non-cancer cells since cancer cells are the only ones that suffer mutational inactivation of gene activity in these circumstances. Even BRCA1 and p53 have been found to limit tumour cells without mutations in these genes, suggesting that so-called gene modification methods may be more effective than previously believed. These and other genes have been discovered as possible targets for gene substitution therapy as cancer genetics has become more well-known. Early patient investigations using BRCA1 and p53 gene therapy have shown a lot of encouraging indications of effectiveness, but they have also highlighted areas where additional clinical trials are required before these treatments may be widely utilised in breast cancer patients.

10. Cancer stem-cell therapy for breast cancer

The cancer stem-cell idea is based on recent breast biology studies. According to two key aspects of this theory, cancer arises in progenitor cells or mammary

stem cells as a result of a dysregulation of the normally tightly controlled mechanism of self-renewal. As a result, cancers contain a cellular component that retains basic stem-cell functions including self-renewal, differentiation, and tumorigenesis while also being accountable for cellular heterogeneity. Advances in the stem-cell field have assisted the identification of stem cells in both normal and malignant breast tissue. The finding of these stem cells has assisted in identifying the origins of human breast cancer's genetic complexity. In the early diagnosis, prevention, and treatment of human breast cancer, the cancer stem-cell hypothesis is critical. Dysregulation of stem cell renewal pathways is linked to both sporadic and hereditary breast cancers. These abnormal stem cells might be utilised to create novel cancer prevention methods. Moreover, because breast cancer stem cells may be resistant to chemotherapy and radiation, efficient targeting of this cell type may be required for the development of novel effective treatments for breast cancer.

11. Monoclonal antibodies

Trastuzumab is a physiologically active, humanised monoclonal antibody that acts against the extracellular domain IV of HER2 and has increased survival rates in HER2/neu positive breast cancer patients. This monoclonal antibody is clinically safe and effective when used in a three-week cycle, and it may also be used in conjunction with paclitaxel, gemcitabine, vinorelbine, or carboplatin.

12. Immunotherapy

To combat cancer cells, it makes use of the body's immune system. One of the examples is a cancer vaccination. Vaccines are made using cancer cell parts or cancer cells themselves. These cells activate the immune system, which aids in the attack and destruction of cancer cells. Immunotherapy has become an important component in the treatment of breast cancer. At the moment, HER2 targeted treatment is a significant element of HER2 over expressing breast tumour therapy.

Trastuzumab, in combination with the newer additions of pertuzumab and TDM1, provides significantly better breast cancer prediction.Immunotherapies are progressing in the field of development, with several FDA-approved antibody treatments being utilised in adjuvant and metastatic situations. Current gains in targeted treatments, robust specific immunotherapy, and grip ensure that general endurance in the adjuvant context will continue to improve. The very precise and focused vaccination treatment method not only avoids the side effects of contemporary standard of care medicines, such as active and passive immunotherapies like ipilimumab, but also provides a remedial strategy for those who are not HER2-overexpressing. Despite the fact that vaccinations for breast cancer have been mostly unsuccessful in previous clinical studies, the majority of these studies were done in the setting of advanced age metastatic disease, which is an unfavourable environment for medicines designed to halt, rather than manage disease. Immunogenicity is now showing a connection with medical response in adjuvant situations, according to current clinical research.

8. Drugs used for breast cancer

FDA approved and clinical status of investigational drugs for breast cancer treatment is listed in **Table 1** [45].

Anticancer agent	Target & application	Clinical status	Type
5-fluorouracil	Palliative treatment of breast cancer	Approved	Treatment
Abemaciclib	HR^+ and $HER2^-$ advanced/metastasized cancer	Approved	Treatment
Abemaciclib (LY2835219)	Rb^+ TNBC that is recurrent,locally advanced,metstatic or cannot be removed by surgery	Phase II	Treatment
Ado-Trastuzumab emtansine	$HER2^+$ metastasized and recurrent cancer has already been treated with trastuzumuab and a taxane	Approved	Treatment
Alisertib with or without fulvestrant	Locally advanced ot metastatic, endocrine – resistant breast cancer	Phase II	Treatment
Anastrozole	Postmenopausal women early stage, HR^+ metastatic breast cancer advanced breast cancer that has gotten worse after treatment with tamoxifen citrate	Approved	Treatment
Anastrozole or letrozole	HR^+ stage II-III breast cancer that can be removed by surgery	Phase I	Treatment
Cabozantinib with or without fulvestrant	HR^+ metastatic stage cancer with bone involvement	Pilot phase II	Treatment
Capecitabine	Metastasized cancer whose dieases has not gotten better with other chemotherapy *metastatic breast cancer	Approved *phase II	Treatment
Cyclophosphamide	Breast cancer *mesothelin-targeted T-cells after treating patients with metastatic, mesothelin expressing, $HER2^-$ breast cancer	Approved *phase I	Treatment
Dendritic cell vaccine + gemcitabine hydrochloride	Metastatic breast cancer	Pilot early phase I	Treatment
Docetaxel	Locally advanced or metastasized breast cancer that is node –positive and can be removed by surgery	Approved	Treatment
Docetaxel + carboplatin	Neoadjuvant treatment of stage II-III TNBC	Phase II	Treatment
Doxorubicin hydrochloride	Adjuvant therapy for braest cancer that has spread to the lymoh nodes after surgery	Approved	Treatment
Epirubicin hydrochloride	After whose cancer has spread to the lymph nodes under the arm	Approved	Treatment
Eribulin mesylate	Metastasized breast cancer who have already been treated with anthracycline and taxane *brain metastases from breast cancer	Approved *phase II	Treatment
Eribulin mesylate or paclitaxel	Recurrent stage IIIC-IV breast cancer	Randomised phase III	Treatment
Eribulin mesylate with or without pembrolizumab	HR^+ and $HER2^-$ stage IV breast cancer	Phase II	Treatment

Anticancer agent	Target & application	Clinical status	Type
Everolimus	Advanced $HR^+/HER2^-$ and has not gotten better after treatment with letrozole or anastrozole	Approved	Treatment
Exemestane	Early stage and ER^+; postmenopausal women who have already been treated with tamoxifen citrate –postmenopausal with stage 0-II ER^+ breast cancer before surgery	Approved *randomised phase IIb	Treatment
Fulvestrant	Postmenopausal women with HR^+ and $HER2^-$ advanced cancer	Approved	Treatment
Gemcitabine hydrochloride	Metastasized breast cancer that has gotten better with other chemotherapy	Approved	Treatment
Goserelin acetate	Premenopausal and perimenopausal women with advanced breast cancer	Approved	Treatment
Ixabepilone	Advanced metastasized who have not gotten better with other chemotherapy	Approved	Treatment
Lapatinib ditosylate	$HR^+/HER2^+$ breast cancer	Approved	Treatment
Letrozole	Early stage, HR^+ / $HER2^+$ advanced metastatic breast cancer	Approved	Treatment
Megestrol acetate	Palliative treatment of advanced disease in breast cancer	Approved	Treatment
Methotrexate	Breast cancer *breast cancer and leptomeningeal metastasis	Approved *phase II	Treatment
Neratinib	Stage IV $HER2^+$ breast cancer	Phase II	Treatment
Olaparib	Metastatic breast cancer with certain mutations in the BRCA1 or BRCA2 genes whose have $HER2^-$*triple negative non-metastatic breast cancer who have completed definitive local treatment and chemotherapy**metastatic breast cancer with DNA repair gene mutation	Approved *randomised Phase III**phase II	Treatment
Paclitaxel	Breast cancer	Approved	Treatment
Paclitaxel albumin-stabilised nanoparticle formulation (Abraxane)	Recurred (come back) or metastasized cancer	Approved	Treatment
Palbociclib (Ibrance)	HR^+ and $HER2^-$advanced or metastasized cancer	Approved	Treatment
Pamidronate sodium **Raloxifene hydrochloride**	• Invasive breast cancer in postmenopausal women who have osteoporosis • Selective benzothiopene oestrogen receptor modulator (SERUM) with lipid lowering effects and activity against osteoporosis • Oestrogen receptor	Approved	Treatment

Anticancer agent	Target & application	Clinical status	Type
Ribociclib	HR^+ / $HER2^-$ metastasized cancer who has not been treated with hormone therapy *ER^+ breast cancer	Approved *randomised phase II	Treatment
Tamoxifen citrate	Metastasized (spread to other parts of the body) breast cancer	Approved	Treatment
Thiotepa	Breast cancer	Approved	Treatment
Toremifene	Metastasized breast cancer and postmenopausal with ER^+ or ER^-	Approved	Treatment
Trastuzumab	Breast cancer that is $HER2^+$	Approved	Treatment
Trastuzumab emtansine	HER2 amplified or mutant advanced cancer	Phase II	Treatment
Vinblastine sulfate	Breast cancer that has not gotten better with other treatment	Approved	Treatment
Combination therapy **AC** **A = doxorubicin hydrochloride(Adriamycin)** **C = cyclophosphamide**	Primary, recurrent and metastatic breast cancer	Approved	Treatment
AC-T **A = Doxorubicin hydrochloride (Adriamycin)** **C = cyclophosphamide** **T = paclitaxel**	Adjuvant treatment of breast cancer	Approved	Treatment
CAF **C = cyclophosphamideA = Doxorubicin hydrochloride (adriamycin)** **F = fluorouracil**	Adjuvant treatment of nonmetastatic breast cancer alone for treatment of metastatic breast cancer	Approved	Treatment
CMF **C = cyclophosphamide** **M = methotrexate** **F = fluorouracil**	Adjuvant setting for the treatment of nonmetastatic breast cancer or alone for the treatment of metastatic breast cancer	Approved	Treatment

Anticancer agent	Target & application	Clinical status	Type
FEC **F = fluorouracil** **E = epirubicin hydrochloride** **C = cyclophosphamide**	Adjuvant setting and also for the treatment of recurrent and metastatic breast cancer	Approved	Treatment
TAC **T = docetaxel (Taxotere)** **A = Doxorubicin hydrochloride (adriamycin)** **C = cyclophosphamide**	Adjuvant treatment for breast cancer	Approved	Treatment

Table 1.
List of FDA approved and clinical status of investigational drugs for breast cancer treatment (source: NH-NCI, U.S).

9. Endocrine resistance for breast cancer

ER is expressed in around 70% of breast malignancies and plays an important role in their genesis and progression. Because of the involvement of ER in ER+ breast cancer, endocrine treatments such as aromatase inhibitors (AIs), selective oestrogen receptor modulators (SERMs), and selective oestrogen receptor degraders are commonly used to treat these tumours (SERDs). While hormone treatments have been successful in avoiding recurrence, about 20% of these tumours acquire resistance to hormone therapies and will return.

10. Drugs that block oestrogen receptors

These medicines operate by preventing oestrogen from driving the growth of breast cancer cells.

1. Selective oestrogen receptor modulators (SERMs)

The "selective" in the acronym SERMs alludes to the unique regulation of the oestrogen receptor and the downstream effect on ER signalling that happens inside various organs. Tamoxifen, for example, is known to have anti-proliferative (or antagonistic) effects in breast tissue while having agonistic or partial agonistic effects on the uterus, bone, and heart. In both the usage of SERMs and the creation of new medicines, the ratio of therapeutic benefit to negative tissue-specific effects has been an essential factor to address [46].

a. Tamoxifen

Tamoxifen has been effectively used to treat breast cancer in both premenopausal and postmenopausal women at all stages. It's utilised as a palliative treatment for those who have advanced cancer, as well as an adjuvant treatment after surgery for node-negative or positive cancer. Tamoxifen has consistently prolonged disease-free intervals as a postsurgical adjuvant therapy for early breast cancer with a low frequency of side effects. It is possible to achieve a 20% decrease in 5-year mortality, with the reduction being most noticeable in women over 50. Tamoxifen is used to reduce the risk of breast cancer and invasive breast cancer in women who are at high risk for the disease, as well as those who have ductal carcinoma in situ. Negative oestrogen receptor tumours do not respond to treatment [47].

b. Role of tamoxifen:

For individuals with oestrogen receptor (ER)-positive breast cancer, anti-oestrogen tamoxifen has been the endocrine therapy of choice. Tamoxifen decreases the risk of recurrence following surgery when used as an adjuvant treatment. Tamoxifen provides an objective clinical response in half of the individuals with recurrent illness. The cancer, on the other hand, will eventually become hormone-independent, meaning it will no longer respond to tamoxifen. Despite significant research, resistance mechanisms remain mostly understood [48].

Tamoxifen's hopeful profile spurred a slew of clinical studies and decades of anti-oestrogen research, which revealed new details about ER biology and its link to ER-dependent malignancies. There have been several randomised studies of adjuvant tamoxifen in early breast cancer patients. Before recurrence, information on

every woman in any randomised study of adjuvant tamoxifen versus no tamoxifen that began before 1990 was sought in 1995. The overall effects of tamoxifen proved to be minor among these women, therefore following studies of recurrence and total mortality are limited to the remaining women [49].

The effects of 1–2 years of tamoxifen and around 5 years of tamoxifen in the studies comparing tamoxifen vs. no adjuvant tamoxifen are summarised in Tamoxifen versus No Tamoxifen. The studies are separated by ER status, which is categorised as ER-poor, ERpositive, and ER-unknown, according to the recognised importance of the original tumour's hormone receptor status. Current and future assessments of receptor state may be more predictive of response as procedures for assessing receptor status advance. ER measures were, on average, extremely significant predictors of response to 5 years of adjuvant tamoxifen, despite the fact that it may be difficult to characterise the receptor assays employed in these studies many years ago. Many of the effects and side effects of tamoxifen in ER breast cancer patients are random [50].

2. Selective oestrogen receptor degraders (SERDs)

A selective oestrogen receptor degrader or downregulator (SERD) is a medication that binds to the oestrogen receptor (ER) and causes the ER to be degraded and therefore downregulated in the process. They're utilised with earlier types of medicines including selective oestrogen receptor modulators (SERMs) and aromatase inhibitors to treat oestrogen receptor-sensitive or progesterone receptor-sensitive breast cancer.

Selective oestrogen receptor degraders (SERDs) are oestrogen receptor antagonists that also cause proteasome-mediated ER degradation. Fulvestrant is a therapy for ER+ advanced breast cancer that has been authorised by the FDA [51].

a. Fulvestrant

Fulvestrant is an oestrogen receptor antagonist that inhibits and destroys oestrogen receptors. This medication is not a SERM; rather, it works as an anti-oestrogen throughout the body. It's referred to be an oestrogen receptor degrader that's selective (SERD). Fulvestrant is at least as effective and safe as comparator endocrine treatments in postmenopausal women with advanced hormone-sensitive breast cancer. Fulvestrant is a safe and effective systemic medication that can be regarded as a viable therapeutic option for postmenopausal women with hormone-sensitive advanced breast cancer in the treatment sequence [52].

Fulvestrant is a steroidal ER antagonist that was developed for its lack of agonism in almost all types of tissues studied, but it was subsequently shown to be a SERD that causes ER to be ubiquitinated and destroyed by the proteasome. It is, in fact, the only FDA-approved treatment for postmenopausal women who have relapsed on hormone therapy and have advanced ER-positive breast cancer. Fulvestrant, on the other hand, has an unfavourable pharmacokinetic profile and requires a painful intramuscular injection to be administered (500 mg dose). Stable-state plasma concentrations require 3–6 months to achieve, even with improved loading-dosage regimens (500 mg dose on days 1, 15, and 29). Its overall therapeutic efficacy is limited by the poor ER turnover seen in patient cases (less than 50%), compared to complete receptor downregulation shown in in-vivo breast cell line investigations. As a result, there is still an unmet medical need for a potent orally available SERD capable of reaching higher levels of malignant exposure [53].

b. Mechanism associated with ER Suppression:

Resistance to oestrogen suppression or inactivation of ER by other methods (SERMs/SERDs) is linked to and/or caused by mechanisms. Although the phrase "endocrine resistance" technically refers to resistance to oestrogen suppression, we use it here to refer to oestrogen or ER suppression resistance.

In ER+ metastatic breast cancer, endocrine resistance is an unavoidable outcome (MBC), As a result, when CDK4/6 inhibitors (e.g., palbociclib, ribociclib, abemaciclib) are added to antiestrogens, progression-free survival in patients with ER+ MBC is significantly increased compared to antiestrogens alone. The addition of CDK4/6 inhibitors to antiestrogens abrogates some of the resistance mechanisms. However, in early-stage cancers, they might still be important drivers of hormone resistance. The **Figure 5** was indicating that the activation of HER2, EGFR, FGFR, and Other RTKs Promotes Endocrine Resistance, RTK activation is augmented by PI3K and MAPK signalling, which induces ER phosphorylation and promotes ligand-independent ER activation (most often by mutation or amplification). NF1 loss-of-function mutations activate Ras in a constitutive manner, which can activate the PI3K and MAPK pathways as well. In a ligand-independent way, ER phosphorylation increases transcription of ER-regulated genes. ER and oncogenic RTK signalling both target CCND1, the gene that encodes cyclin D1. RTKs activate additional transcription factors

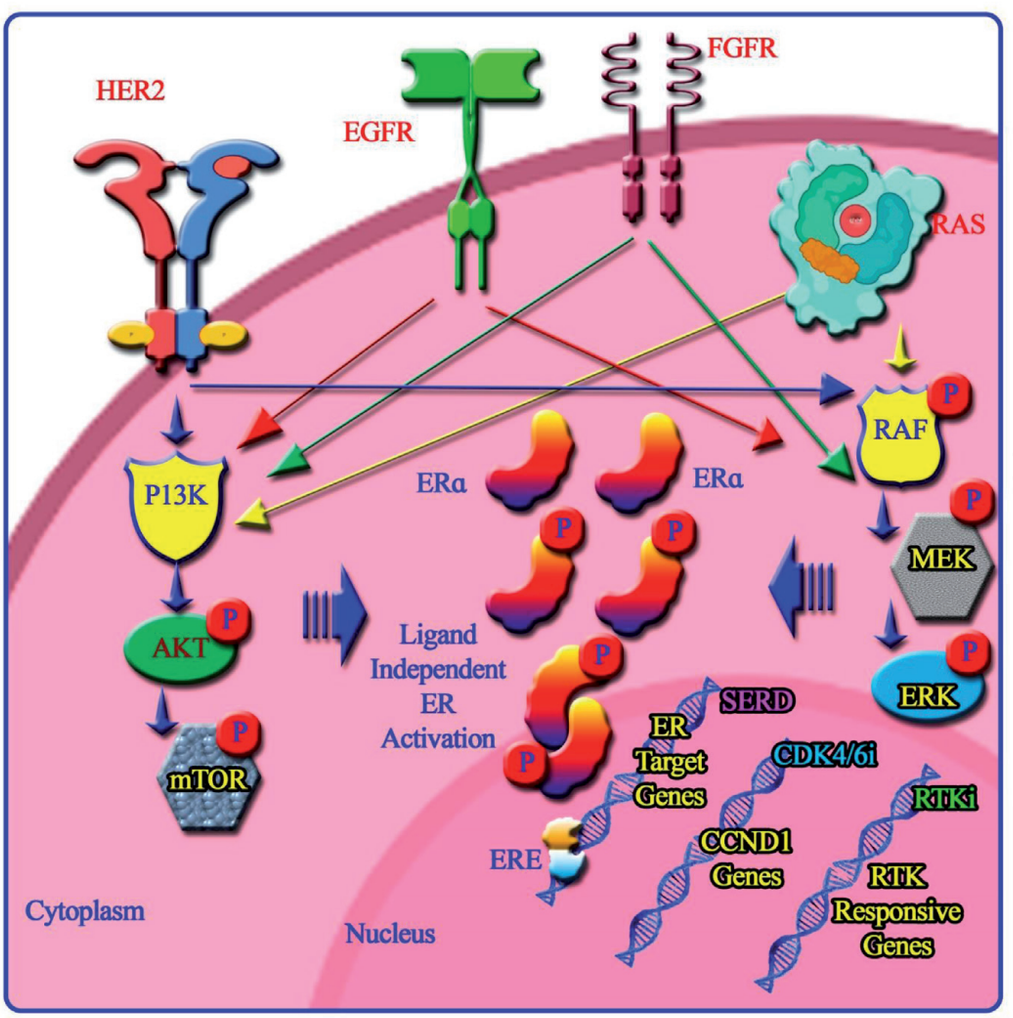

Figure 5.
Activation of HER2, EGFR, FGFR, and other RTKs.

that promote ER-independent survival in addition to ER. The combination of an ER antagonist with the appropriate RTK inhibitor CDK4/6 inhibitor might potentially overcome RTK-mediated endocrine resistance. Sensitivity to endocrine treatment and resistance to it in ER+ breast cancers are similar to other hormone-dependent malignancies including prostate cancer and endometrial cancer [54, 55].

11. Concept of selective oestrogen receptor modulation

SERMs are estrogenic and antiestrogenic molecules that have a wide range of effects. Two SERMs are now accessible in clinical trials: tamoxifen for breast cancer prevention and raloxifene for osteoporosis prevention. Tamoxifen was first created as an antiestrogen to treat breast cancer. Tamoxifen's widespread use as a therapy for all stages of ER-positive breast cancer in men and women has been assisted by its low risk of adverse effects. Concerns about the effects of an antiestrogen on bone density and the risk of CHD were raised when the strategy of testing long-term (5 years) tamoxifen therapy in ER-positive, lymph node-negative women and the proposed testing of tamoxifen as a preventive agent in high-risk women were proposed in the mid-1980s. Tamoxifen, on the other hand, is not a pure antiestrogen; it has antiestrogenic as well as estrogenic properties [56]. According to laboratory studies, tamoxifen is a selective oestrogen in areas like bone but an antiestrogen in breast tissue, preventing carcinogenesis and tumour development. Laboratory investigations dating back to the 1980s [57, 58] have confirmed raloxifene's SERM activity.

11.1 Mechanisms of action

Even though exact molecular mechanism of oestrogen or SERMs at the ER is unknown, two ERs govern oestrogen activity in target tissues: 1) ER, the traditional ER [59]; and 2) ER, which controls the action of ER and decreases tamoxifen's oestrogen-like effects [60, 61]. Although the crystal structure of the whole ER has yet to be determined by x-ray crystallography, data on the ligand-binding domains conjugated with estrogens and SERMs has been published. The outer forms of oestrogen and SERM complexes have been better understood as a result of this information. Oestrogen receptors (ERs) are nuclear transcription factors that bind estrogens, dimerize, and form a transcription complex with coactivators and other molecules to help unwind DNA. At oestrogen-responsive genes, RNA polymerase produces messenger RNA. SERM–ER complexes appear to alter the signal transduction route to oestrogen-responsive genes (through oestrogen response elements [EREs]) by binding a corepressor protein or activating fewer or different coactivators. This is, however, a simplistic model of oestrogen and antiestrogen action that overlooks the nuances of SERM function.

12. Drugs repurposed for breast cancer treatment

The commercially approved drugs that were originally used for diseases other than breast cancer are discussed in the following section. These medicines, on the other hand, are now being used or researched for breast cancer treatment. The drug candidates repurposed for breast cancer are divided into categories based on how they work (**Table 2**).

Drug	Chemical name	Mechanism	Original indication
Alkylating agent	Cyclophosphamide	Inhibits DNA replication by damaging genetic material of the cell	As immuno-modulator in autoimmune diseases
	Thiotepa		Immunosuppressant
Anthracyclins	Doxorubicin	DNA intercalation	Antibiotic from *Streptomyces peucetius* bacterium
	Capecitabine		Colon cancer
Antimetabolite	Fluorouracil	False building block incorporation during cell growth	Keratoacanthomas, actinic keratosis, and skin warts
	Gemcitabine		Anti-viral drug
	Methotrexate		Leukaemia
CDK 4/6 inhibitor	Palbociclib, Palbonix	Interferes with cell cycle	CDK 4/6 inhibitor
	Tamoxifen		Albright syndrome, ovulation induction
HT-SERM	Toremifene	Binds to ER	Infertility with an ovulatory disorders
	Raloxifene		Osteoporosis in postmenopausal women
HT-Aromatase inhibitor	Letrozole	Lowers oestrogen amount	Induction of ovulation
	Anastrazole		Induction of ovulation

Table 2.
A list of repositioned drugs approved for breast cancer treatment.

13. Executive summary

Breast cancer is still a significant public health problem, even though it was first reported more than 3500 years ago. This is particularly true in light of most societies' substantial and harmful lifestyle changes. At both the epidemiological and molecular levels, breast cancer is diverse. Many significant breast cancer risk factors have been discovered by clinical and epidemiological data, including age, family history, early menarche, and medical history; variables that are intangible or beyond our control. However, about 70% of breast cancers nowadays are caused by risk factors that may be altered or avoided. Obesity, lack of exercise, smoking, drinking, and nutrition, as well as other variables that may have a detrimental impact on a woman's hormonal environment, are among them. These important rate-limiting measures in the battle against breast cancer should not be ignored. As discussed in this review, significant advances in cancer biology have led to significant advancements in cancer early detection, therapy, and prevention in recent years. The growing emphasis on personalised treatment, as well as the combination of targeted and immunological therapies with current therapeutic techniques, holds potential for the cure of breast cancer. Drug resistance in breast cancer is a complicated clinical condition caused by a variety of molecular changes. Because chemotherapy is often used in conjunction with targeted treatments for the ER+ or HER2+ subtypes in clinical practice, targeted therapy-induced resistance may lead to chemo-resistance and vice versa. Treatment methods and therapeutics must be specially developed to address each distinct resistance mechanism in various clinical circumstances in response to every particular resistance mechanism. Early clinical trials are looking for drugs that target each route individually. Clinical studies

investigating tailored medication delivery methods are also underway in the meanwhile. These therapeutic agents may enter cells through receptor-mediated endocytosis, thereby bypassing typical drug resistance mechanisms such as drug efflux pumps, cell surface docking site mutations, and so on, allowing them to overcome drug resistance. The heterogeneity of breast cancer cells, on the other hand, poses major difficulties in terms of treatment response and may be a contributing factor in drug resistance. Tamoxifen, a selective oestrogen receptor modulator, is claimed to be used as a therapy for all stages of oestrogen receptor (ER)-positive breast cancer in men and women, thanks to its low risk of adverse effects. Notwithstanding major investments in prevention and treatment, breast cancer remains the primary cause of cancer mortality in women throughout the world. The existing therapeutic options are both expensive and have serious negative effects.

Drug repurposing, or finding new applications for existing therapies, has arisen as an unique drug development strategy. Repositioning existing, off-patent non-cancer medicines with established targets into newer indications is like repurposing outdated weaponry for a new war. The process of medication repurposing has been made easier thanks to developments in genomics, proteomics, and information computational biology. The repositioning method not only speeds up the medication development process, but it also results in more effective, less expensive, and safer medicines with fewer/known adverse effects. Alkylating compounds, anthracyclins, antimetabolites, CDK4/6 inhibitors, aromatase inhibitors, mTOR inhibitors, and mitotic inhibitors have all been repurposed for breast cancer therapy in the recent decade.

14. Conclusion and future perspectives

Medical experts are enthusiastic about the increasing management methods, but they are concerned that resources will be inadequate to get these therapeutics to advanced clinical trials. The difficulties are therefore to choose the most competent drugs to be examined, as well as the appropriate clinical trials to conduct such assessments. Over the last several years, new drugs targeting particular therapeutic targets have resulted in significant advances in the treatment of breast cancer. Resistance to systemic therapy (endocrine and others), expensive treatment, and limited availability of adequate cancer care in many countries remain challenges. We must continue to improve our available technology in order to provide proper guidance for those living with the disease, as well as those at high risk of developing it, and to develop new, more effective therapies in order to significantly improve the outcomes of breast cancer patients around the world. Individualising therapies offers the potential of helping patients through challenging treatment choices in order to enhance their long-term results. In this review, we have uncovered the most well-documented therapy options and potential technologies in the fight against breast cancer. We go through the benefits of medication repurposing for breast cancer treatment in depth in this article. We offered a number of medicines that were effectively repurposed for the treatment of breast cancer. Preclinical investigations have shown that a combination of chemotherapies and a medication repurposing strategy might produce promising results. The possibility of non-cancer drugs being studied for breast cancer in the future, as well as the obstacles and bottlenecks of drug repurposing, were also highlighted. As a result, we draw the conclusion that combining system biology and bioinformatics to select the most appropriate gene-protein-pathway-target-drug modelling has a high potential for providing more efficient, safer, and cost-effective chemotherapeutics for the treatment of even the most severe forms of breast cancer.

Author details

Panneerselvam Theivendren[1*], Selvaraj Kunjiappan[2], Yashoda Mariappa Hegde[3], Kaveena Ravi[3], Sivakumar Vellaichamy[4], Murugananthan Gopal[5] and Manimekalai Pichaivel[6]

1 Department of R and D, Swamy Vivekananda College of Pharmacy, Namakkal, Tamilnadu, India

2 Department of Biotechnology, Kalasalingam Academy of Research and Education, Krishnankoil, India

3 Department of Pharmaceutics, Swamy Vivekananda College of Pharmacy, Namakkal, Tamilnadu, India

4 Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, India

5 Department of Pharmacognosy, Swamy Vivekananda College of Pharmacy, Namakkal, Tamilnadu, India

6 Department of Pharmacology, Swamy Vivekananda College of Pharmacy, Namakkal, Tamilnadu, India

*Address all correspondence to: tpsphc@gmail.com

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