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Breast Cancer: Detection, Etiology, And Therapeutic Itinerary

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KEYWORDS

Breast cancer, chemotherapy, medicinal plants, new drug discovery, anti-HER-2 drugs.

ABSTRACT:

Women are frequently diagnosed with breast cancer, which ranks second in the world in terms of cancer-related deaths. The number of cases of breast cancer has sharply increased during the last forty years. In 2020, there were more than 2.3 million new cases of breast cancer recorded worldwide. Most breast tumors are benign and can be surgically removed, however 25% of breast cancers are latent and sneaky, meaning they start slowly but spread swiftly. The activity examines the etiology, subtypes, and treatment modalities of breast cancer using plant-based medicines, multiple therapies, allopathic pharmaceuticals, and new developments in the field of drug discovery.

1. Introduction

Most cases of breast cancer occur in women. Although 25% of breast cancers are latent and sneaky, meaning they form slowly but spread swiftly, the majority of breast tumors are benign and can be cured surgically [1]. The main issue that arises during breast cancer treatment is that the disease is diverse (heterogeneous disease) [2]. The cases of breast cancer have rapidly increased during the last 40 years. In 2020, there were more than 2.3 million new cases of breast cancer worldwide; the disease also claimed the lives of roughly 6,85,000 people, with large regional variations. High-income nations account for a larger share of breast cancer fatalities. By 2040, it is anticipated that there would be more than 3 million cases of breast cancer and more than 1 million annual deaths from the illness [3]. Breast cancer (BC), historically thought to be low immunogenic, was not initially well studied for immunotherapy susceptibility [3]. With the use of the immune histological technique, invasive breast cancer is categorized into four primary molecular subtypes based on the expression of the HER2, PR, and ER receptors [4]. The first subtype is luminal A BC which indicates that 60% of breast cancer [5]. Luminal B BC indicates 30% of breast cancer [6]. The third subtype HER2 BC indicates a 10% seizure [7]. The last subtype is TNB C (triple -ve breast cancer) which indicates 15 to 20% of BC [8].

Detection of breast cancer: Research indicates that educating healthcare professionals in CBE might lead to more early breast cancer detection, whereas if we talk about available data, it is questionable. More studies are required to evaluate its effect on other outcomes, such as the accuracy with which CBE is conducted and spread awareness and its effect on breast cancer-related fatalities [10]. Tree-based machine-learning techniques work well in predicting the metastasis of breast cancer to axillary lymph nodes. These techniques are trained using patient and tumor data that are gathered via routine pre-operative/pre-NST examinations. These models can help with more precise diagnosis and treatment planning, particularly for NST patients whose sole means of assessing lymph nodes are frequently radiological and clinical observation [11]. In order to get early knowledge of breast cancer datasets with four magnifications are used to diagnose histopathological

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images 40x, 100x, 200x, and 400x [12]. Research has led to the creation of

TYPE	ER	HER2	Ki-67	PR
Luminal A	+ve	-ve	Low	High
Luminal B	+ve	-ve	High	Low
HER2-positive	-ve	Over	uncle ar	-ve
Triple-negative	-ve	-ve	uncle ar	-ve

Table 1- Classification of breast cancer [9].

a dual-modal sensor that has great promise for its treatment, With the use of this sensor, exosomal surface protein profiling may be done in-depth, offering a useful diagnostic tool for breast cancer [13]. The DOB-scan probe may help identify breast cancer sooner when combined with ensemble learning techniques [14]. when it comes to identifying breast cancer in its early stages, Microwave Breast Imaging (MBI) has promise as a supplementary or substitute method to X-ray mammography, which is currently the gold standard. To increase the efficacy and precision of MBI, the development of microwave imaging algorithms and measuring system systems is essential [15]. Research on AI development and assessment will continue, in addition to qualitative studies that close important knowledge gaps about the acceptability of using AI in breast cancer screening services and the many ethical, social, and legal implications of their use in healthcare. Additionally, taking the big picture into account, the benefits and drawbacks of population breast cancer screening will need to be reevaluated to take into account additional benefits and drawbacks, like the unexpected results of replacing human image interpretation with artificial intelligence (AI) [16].

ETIOLOGY OF BREAST CANCER: Age, genetics, and family history are among the factors that are being examined for breast cancer, but the cause of the disease is still unknown. One in ten females receives a diagnosis of breast cancer, which is the second most deadly disease worldwide.[18]. Alcohol and tobacco use have a strong correlation, but published findings about their link to breast cancer have occasionally failed to account for the potential for confounding between these exposures. More than 80% of the data on alcohol and tobacco use and breast cancer was gathered, verified, and evaluated centrally. A total of 95,067 controls and 58,515 invasive breast cancer patients from 53 trials were analyzed [19]. A 1982 study by Janerich and Hoff found that women who have never given birth (parous women) have a higher risk of developing breast cancer before the age of 40 compared to women who have never given birth (nulliparous women) [20]. Hormones that change progesterone, estrogen, and androgen levels—both endogenous and exogenous—have a major impact on the development of breast cancer. When it comes to endogenous hormones, women who have high levels of prolactin before and after menopause, as well as high levels of estrogen and testosterone after menopause, are associated with a higher risk of developing breast cancer. [21 -24]. An increased level of physical activity has been linked to a lower risk of breast cancer, according to numerous study studies. Women who regularly exercise, such as those who practice yoga, meditation, or other physical activities, have a lower risk of developing breast cancer than those who do not, according to a thorough meta-analysis of millions of controls and over 230,000 cases of breast cancer. Exercise is a preventive measure against breast cancer development for all women, regardless of whether they have a family history of the disease or not [26]. Since the 1920s, a large number of studies undertaken worldwide have shown that women are around two to three times more likely to develop breast cancer than controls if one or more of their mothers, sisters, or other close relatives have had the disease [27]. It is well recognized that miRNAs exhibit abnormal expression in cancer, particularly breast cancer (BC). Depending on the gene or the pathway they control, certain RNAs can operate as suppressors of tumors and act as pathogenic miRNAs, or oncogens. The way that genes, transcriptional coactivators, tumor suppressors, and transcription factors are expressed that code for carcinogenic proteins can all be impacted by aberrant miRNA expression, which can then cause normal cells to change into tumor cells and spread to other locations [28],[30]. According to the etiological model studies, the number of sensitive cells which, in turn, rely on factors that affect early life or even pregnancy raises the risk of breast cancer by varying amounts of relevant stem cells. After a first full-term pregnancy, susceptible cells become refractory; subsequent pregnancies and breastfeeding complete this process. Mamotropic hormones, especially

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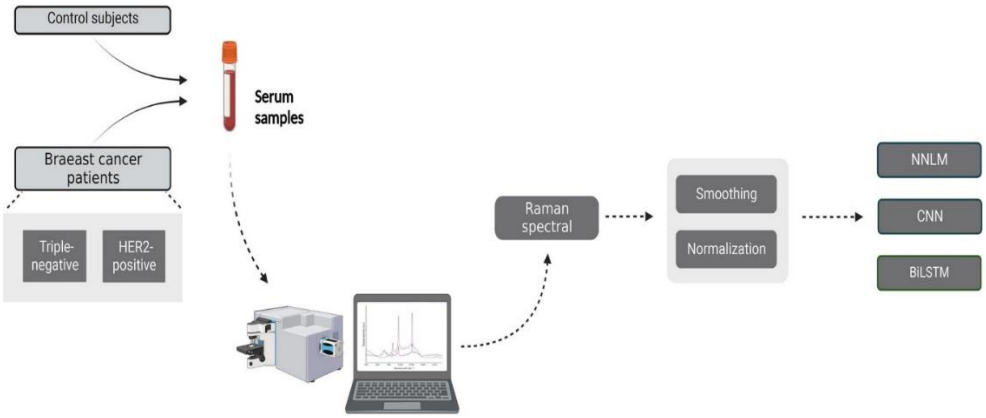

Fig.1- convolutional neural networks with serum Raman spectroscopy for quick detection of triple-negative and HER2-positive breast cancer [17]**.**

estrogen and their receptors influence the natural history of breast cancer in both the pre- and post-initiation phases [31].

TREATMENT: Treatment options for early-stage breast cancer include surgical resection, radiation, endocrine therapy, neoadjuvant/adjuvant chemotherapy, and anti-HER2 therapy. Systemic therapy, which consists of cytotoxic chemotherapy, target therapy, and endocrine therapy, is advised for metastatic breast cancers [32-33]. The therapy approaches were determined by taking into account several elements, including illness stages and genetics. Most cancer patients have surgery in the early stages of the disease, but when the tumor cells spread and metastasize, chemotherapy is frequently used [34], [35].

DNA methylation inhibitors: Inhibition of DNA methylation is the cause of endogenous retrovirus (ERV) production, which is related to the immunological checkpoint blockade (ICB) response. Therefore, by combining DNMTi, therapeutic ways to treat breast cancer might be created [36]. T cell function is significantly impacted by DNA methylation inhibitors, such as azacitidine and decitabine, which also improve T cell rejuvenation. This is why it's critical to research how well azacitidine and decitabine, respectively, work in combination with pembrolizumab and durvalumab to treat breast cancer cases. [37]

Histone de-acetylation inhibitors: It has been demonstrated that when histone deacetylases (HDACis) increase the production of MCH molecules on tumor cells, tumor-specific antigens are expressed [38]. The HDACis that have received FDA approval include belinostat, panobinostat, romidepsin, and vorinostat [39]. HDAC inhibitors inhibit the development of tumors and apoptosis, with little effect on normal tissue. HDAC inhibitors are capable of breaking down and condensing non-histone proteins' acetylation state in addition to the histone-DNA complex [40].

Histone demethylation and methylation inhibitors: The demethylation of H3K4 and H3K9 is controlled by LSD1, also known as KDMA1. LSD1 inhibitors transform genes (STING) that KDM5B and KDM5C connected to intratumor CD8+T cells are epigenetically repressed, resulting in immunological latent states because of methylation on H3K4 and H3K9 [41]. Inhibition of EZH2, an oncogenic histone methyltransferase, may cause a surge in myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment and lower antitumor immunity. But no research has been done to evaluate this strategy for breast cancer [42].

Bromodomain and extraterminal inhibitor: BET inhibitors usher in a new era of epigenetic medications for the treatment of breast cancer. Clinical information from inhibitor phase1/2 trails is progressively becoming accessible. Even yet, BET inhibitors demonstrated strong anticancer effects in mouse xenograft models and breast cancer cell lines [43]. Using the pan-BET inhibitor JQ1 and a thalidomide derivative as an E3 ligase handle, the first BET PROTAC, known as dBET1, was created. This

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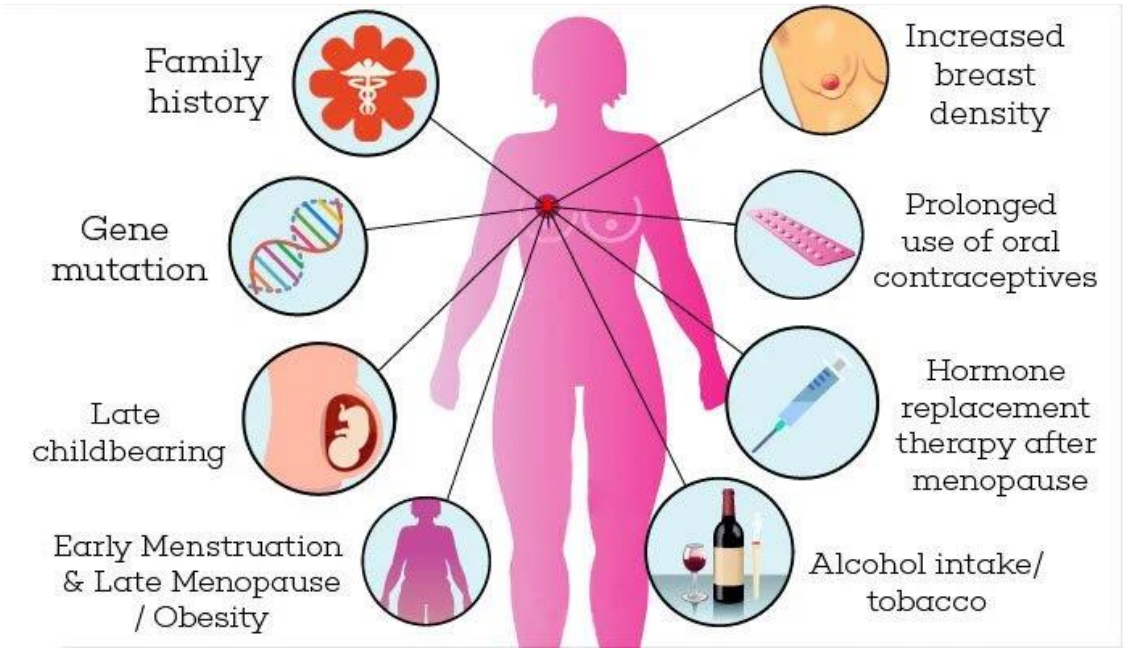

Fig.2- certain factors investigated for the cause of breast cancer [25].

resulted in the effective and selective degradation of all BET family members expressed in leukemic cells (BRD2-4) as well as a significant abrogation of MYC levels [44]

A - Endocrine Therapy: For pre/perimenopausal luminal-like early BC, monotherapy with tamoxifen for at least five years is one of the possible alternatives [45]. Tamoxifen reduces the chance of BC recurrence over the course of the first ten years of use and reduces the probability of BC death by about one-third during the first fifteen years from the start of ET when taken consistently. This advantage is not shown in ER-negative illnesses but is seen in malignancies with limited ER expression [46-48]. Even if AIs effectively reduce estrogen levels and SERMs block ER by altering ER structure and cofactor recruitment, the presence of ER itself can allow a tumor to escape from ET and activate the ER signaling pathway. [49]

Anti-HER2 Therapy: Human epidermal growth factor receptor, or HER2/neu, is a transmembrane tyrosine kinase [50]. Because of its similarity to the epidermal growth factor receptor (EGFR), the HER2/neu protein is known as the "Human Epidermal Growth Factor Receptor" Human chromosome 17's long arm, or 17q21-q22, contains the ERBB2 gene, a recognized proto-oncogene that encodes the HER2/nue protein [51], [52]when compared to individuals with HER2-negative BC [53], [54], patients with HER2-positive malignancies who might benefit from anti-HER2 targeted treatment can be identified by the physicians by the predictive function of HER2, as stated in ASCO/CAP recommendations. The prognosis of HER2-positive BC has been dramatically altered by targeted medicines such as trastuzumab, pertuzumab, lapatinib, and emtansine (T-DM1), which can bind to HER2 and inhibit downstream signaling [50], [55], [56].

B - Cytotoxic chemotherapy: chemotherapy's effect on $P16^{INK4a}$ expression has been verified in a separate, cross-sectional group of patients with metastatic breast cancer [58]. The mainstay of BC chemotherapy regimens, anthracyclines are an originator or potentiator of the ICD (immunologic cell death) process by activating the NLRP3 inflammasome [59]. It has also been demonstrated that docetaxel and doxorubicin enhance the expression of parts of the antigen-processing machinery, which increases the loading of MHC-1 molecules in BC cells [60]. There have also been reports of increased MHC-II and CD86 expression in the TNBC cell line, which is mediated by a novel chemotherapeutic compound MDA-MB-231 [61].

C - MEDICINAL PLANTS IN THE TREATMENT OF BREAST CANCER: The development of novel anti-

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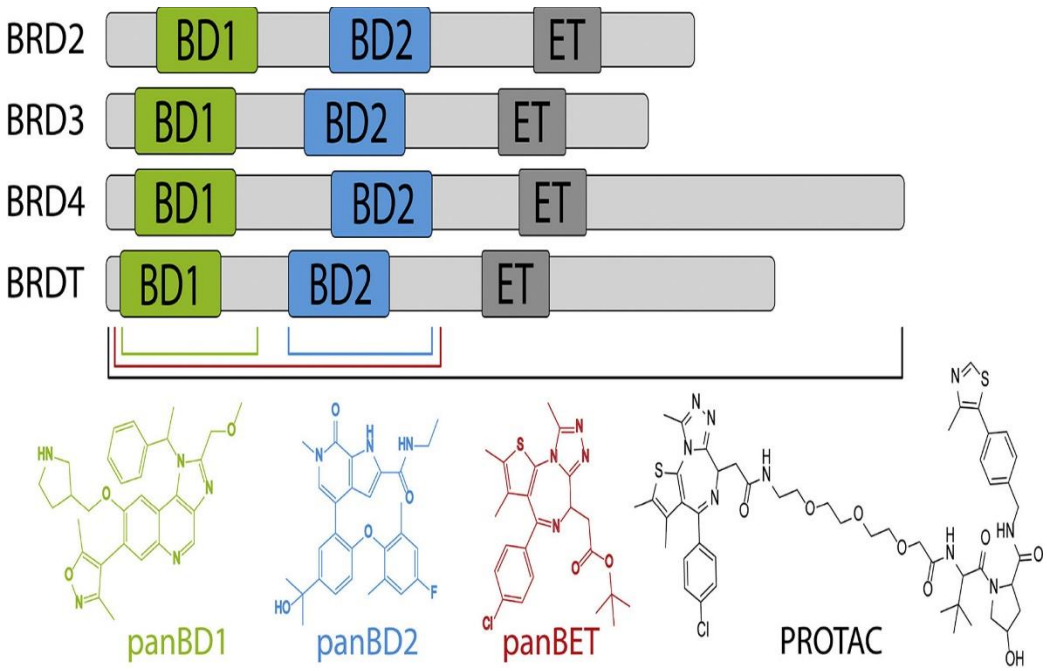

Fig.3- Mechanism of BET inhibitors [44].

cancer medications that may offer long-term cancer management with negligible side effects can be greatly aided by the identification of natural compounds [63]. Anticancer medications have a lot of major side effects and are largely ineffective in treating human cancers. In the traditional medical system, these herbs are frequently utilized as breast cancer treatments. Numerous documented studies suggest that medicinal plants have anti-cancer properties due to their active components and using these plant extracts can reduce malignancies [64]

There are thousands of medicinal plants with anticancer properties and the above table illustrates a few of them which are recently been recognized for possessing anticancer activity.

D - NEWLY DISCOVERED DRUGS: The US Food and Drug Administration (FDA) has authorized ORSEDU (elacestrant) for the treatment of postmenopausal women and adult males with ER+, HER2-, or ESR1-mutated advanced or metastatic breast cancer that has progressed following at least one line of endocrine therapy [75]. Trastuzumab (Herceptin) has been used to treat breast cancer for a long time. In June 2020, the FDA approved a new trastuzumab formulation containing docetaxel, according to a reliable source. Docetaxel is an enzyme that aids in the body's trastuzumab absorption. Atezolizumab (Tecentriq) was authorized by the FDA in March 2019 (reliable source). Atezolizumab is approved for use in individuals with locally advanced or metastatic triple-negative breast cancer (TNBC) that is not curable with surgery or whose tumors express the PD-L1 protein. Additionally, it is used with paclitaxel. datopotamab deruxtecam (Dato-DDd), a novel antibody-drug combination, for advanced estrogen receptor-positive. Triple-negative breast cancer with metastases [76] and early triple-negative cancer (TNBC) [77]. On April 17, 2020, the FDA authorized tucatinib, an orally accessible HER2 tyrosine kinase inhibitor, to treat patients with advanced, incurable, or metastatic breast cancer when combined with trastuzumab and capecitabine [78]. Palbociclib received approval in 2016 to treat breast cancer with HER+/HER2- metastatic diseases. Everolimus was authorized by the U.S. FDA on July 20, 2012, for the treatment of advanced HR+/HER2- in women who have completed menopause, [79], [80]. An FDA-approved medication for rheumatoid arthritis, auranofin exhibits strong antitumor activities against a variety of cancer cell types, encompassing cells from breast cancer [81].

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MONOCLONAL ANTIBODIES	
Trastuzumab	Binds to the HER2 receptor, inhibit proliferation of HER2 cells.
Pertuzumab	Binds to subdomain 2 of HER2 receptor.
Margetuximab	Target HER2 receptor.
TYROSINE KINASE INHIBITOR	
Lapatinib	Inhibits HER1 and HER2 tyrosine kinase receptors.
Tucatinib	Binds selectively to HER2 tyrosine kinase.
Neratinib	Irreversibly inhibits tyrosine kinase of HER1, HER2, and HER4
Pyrotinib	Irreversible dual pen-HER receptor tyrosine kinase inhibitor.
ANTIBODY-DRUG CONJUGATE	
Trastuzumab ematansine	Delivers cytotoxic drugs directly into cancer cells
Trastuzumab deruxtecam	Cytotoxic topoisomerase 1 inhibitor.

Table 2- Classification of Anti-HER2 drugs and their mechanism [57]

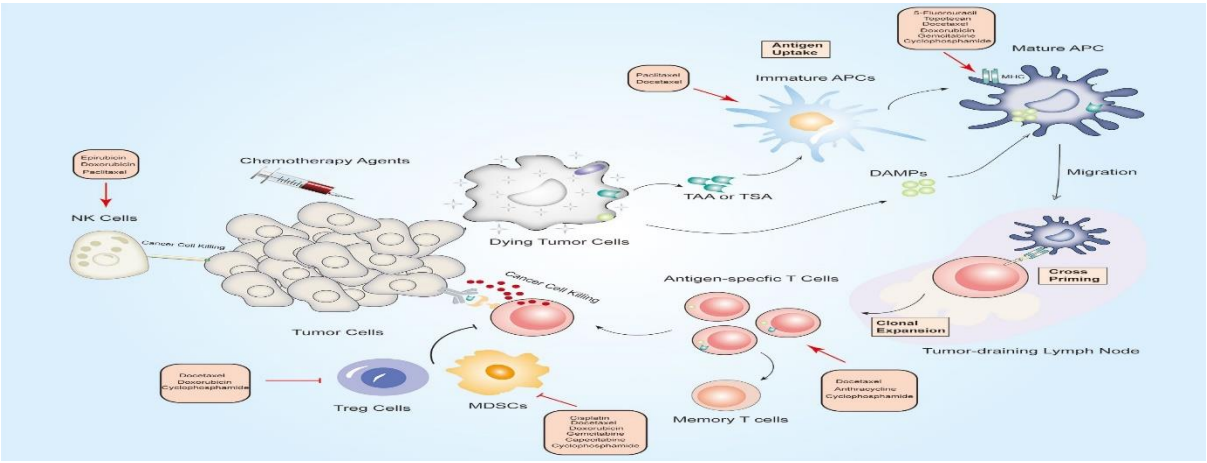

Fig.4 - An overview of chemotherapy immunostimulatory effects in breast cancer [62]

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S.no	BIOLOGICAL NAME	LOCAL NAME	OUTCOMES	REFERENCES
1	***Peperomia Pellucida***	Ketumpangan air	Active against Breast adenocarcinoma.	[65], [66]
2	***Urticamembranaceae***	Membranous nettle	Examined their effect against breast cancer, lung cancer, colon, and prostate.	[67]
3	***Mangifera Indica***	Mango	Proliferation of cells, reduction in cell viability, growth and migration	[68]
4	***Andrographis Paniculata***	Hempedu bumi	Induces apoptosis in the mutant p53	[69], [70]
5	***Persicaria Hydropiper***	Water pepper	Antitumor action on the MCF-7 breast cancer cell line	[71]
6	***Rhizoma Amorphophalli***		Inhibits breast cancer cell metastasis	[72]
7	***Dillenia Suffruticosa***	Simpoh Air	Reduces MDA MB-231 cell viability	[73]
8	***Sophora flavescens***	Shrubby Sophora	Reduces breast cancer cell motility	[74]

Table 3- Some medicinal plants with anticancer properties

CONCLUSION: The paper evaluation went into detail into breast cancer, a potentially fatal condition that primarily affects women and infrequently affects men. The review centres on the causes, symptoms, and different techniques to treating breast cancer. It also discusses the potential adverse effects of chemotherapy treatment for breast cancer and the anti-breast cancer properties of a number of medicinal plants. Also highlighted about the newly discovered compounds that show activity against breast cancer. Now it is very easy to detect and treat breast cancer through several screening techniques, therapies, and drugs.

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