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Novel Approaches for Breast Cancer Screening and Treatment: A Review

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Abstract

Latest statistics proved breast cancer being the second leading cause of death in women in the world, which has led to an increase in public awareness for early screening and detection in order to reduce breast cancer death cases. Since the last two decades, many advances have emerged regarding its screening and treatments resulting in more efficient, less toxic results, and fewer death rates. This review paper highlights the different types of breast cancer, its different screening strategies such as mammography the gold standard technique and biosensors a new emerging device, and the different kind of treatments such as surgery, radiotherapy (non-drug therapy), chemotherapy, nanotechnology integration, or gene replacement therapy (drug-therapy).

Keywords: Breast cancer; Screening; Surgery; Radiotherapy; Chemotherapy; Nanotechnology; Gene replacement therapy

Introduction

Breast cancer accounts for more than 1 in 10 new cancer diagnosis each year and is the leading cause of cancer death in women. The breast is formed from many tissues, within this tissue is a network of lobes each lobe consists of small tube-like structures called lobules that contain milk glands. Small ducts connect the glands, lobules, and lobes carry the milk from the lobes to the nipple. Blood and lymph vessels also run throughout the breast tissues. Cancer starts when healthy cells in the breast grow uncontrollably, a tumor can be malignant or benign. The cancer that spreads to different parts of the body is called malignant and cancer that can grow but will not spread is benign [1].

Similar but not identical DNA/RNA to organism cells, cancer cells are often undetectable if the immune system is weak or if the mutated cells are too high to be eliminated by the immune system; this is caused by a number of factors such as toxic environment (exposition to radiations, pollutants), poor diet [1], genetic predisposition [2], and age (people 80 years and above) [3].

Diagnostic at early stages and thus decreased death risk especially in younger women has improved because of the public awareness and the different screening techniques. This article addresses the various types of breast cancer, the different screening techniques including some very recent advances, and the approaches for both drug therapy such as gene therapy and chemotherapy and non-drug therapy including radiation and surgery.

Types of Breast Cancer

Breast cancer is highly diverse, this diversity is further classed into three categories tumor grade, morphological classification, and molecular classification [4].

The most common is the morphological classification that evaluates the morphological properties of the tumor from the normal cells, this classification is also known as the Nottingham Prognosis index that is very important for prognosis with a main issue of this index is its reproducibility. The two principal morphological umbrellas are Breast cancer's invasiveness and its place of origin [5].

Non-invasive breast cancer: cancer cells remain in the ducts and do not spread into the surrounding fatty and breast tissues. 90% of non-invasive breast cancer are ductal carcinoma in situ, however, some are lobular carcinoma in situ and are considered as a marker for an increased risk of breast cancer development in the future [1]. Noting that the term in situ means that the cancer did not spread from the area where it initially started.

Invasive breast cancer: cancer cells cross the lobular and ductal wall and spread into the fatty and breast tissues. However, the cancer can be invasive without spreading into different organs [1].

Invasive ductal carcinoma: accounts for 80% of breast cancer cases. It firstly starts in the ducts and spread through the surrounding breast cancer tissues with a possibility of other body parts spread [1].

Medullary carcinoma: accounts for 5% of invasive breast cancer diagnosis that forms a recognizable boundary between normal and tumor tissues [1].

Mutinous carcinoma: it is formed by the mucus-producing cancer cells and is a very rare type of breast cancer [1].

Inflammatory breast cancer: it is very rare accounting for only 1% of breast cancer cases but this type is growing rapidly. In this type, cancer cells block the lymph vessels which causes the inflammation of the breasts and the appearance of thick ridges [1].

Paget's disease of the nipples: accounts for only 1% of breast cancer diagnosis its onset is the milk ducts spreading into the nipple and areola [1].

Regarding its molecular classification breast cancer is divided into two subcategories estrogen receptor positive and estrogen receptors negative; these two subcategories can also be divided into many subcategories found in Table 1[6].

In addition to these subcategories, we note the triple-negative breast cancer where there are no immunohistochemical traces of progesterone, estrogen, and human epidermal receptor 2 (HER2), hence the name [7].

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Molecular subcategories	PR	ER	HER2	Histological grade	Basal marker	Proliferation cluster
Basal-like	-	-	-	High	+	High
Molecular apocrine	-	-	+/-	Intermediate	+/-	High
Luminal A	+	+	-	Low	-	Low
Luminal B	+/-	+/-	+/-	High	-	High
Claudine low	-	-	-	High	High	High
HER+/ER-	+/-	-	+/-	High	+/-	High
PR: progesterone receptor, ER: estrogen receptor, HER2: human epidermal receptor 2						

Table 1: Breast cancer molecular classification and prognosis.

Screening Techniques For Breast Cancer

There are several techniques for breast cancer diagnosis, I will be briefly talking about mammography the traditional technique, and the techniques that are still under development such as "biosensors".

Mammography

Mammography is currently the gold standard technique that uses X-rays in order to provide images that help the screening of the asymptomatic and the diagnosis of breast cancer [8].

Even though this technique has some limitations such as false positives and overdiagnosis, it is important to light on its importance in early detection and thus in saving lives. However, this technique is not cost-effective for people living in poor healthcare communities which leads to many awareness programs on the clinical breast examination for early signs [9].

Biosensors

A biosensor is a machine that measures biological or chemical reactions of the analyte by generating proportional signals to its concentration. Biosensors are used in many applications such as disease monitoring, new drug research, and biomarker indicating the presence of the disease in the body fluids like blood, urine, saliva [10].

A recent study showed the successful detection of 10 pg/mL human epidermal receptor 2 (HER2) in the saliva using the standard addition methods (Y=0.0118X + 0.1282/ R2=0.9876), this biosensor showed sensitivity and specificity; this gives hope for the sensitive detection of breast cancer biomarkers for the future in an easy sensitive and cost-effective way [11].

Breast Cancer Management

After being diagnosed with breast cancer there are many approaches for managing the disease such as surgery, radiation therapy, chemotherapy, gene therapy, etc.

Surgery

Lumpectomy (lump removal), mastectomy (removal of the whole breast) are performed depending on both the stage and the type of breast cancer. During the surgery the surgeon must have tissue margins clear from cancer. Nowadays sentinel lymph node technique that requires the removal of fewer lymph nodes, thus fewer side effects, is emerging [1].

There are two main breast cancer surgeries:

-Breast-preserving surgery where only cancer and some of its surrounding tissues are removed, this surgery is divided into two subcategories lumpectomy where only small amounts of the surrounding breast tissues are removed, and quadrantectomy where almost a quarter of the breast tissue is removed.

-Mastectomy: all breast tissues are removed.

The different surgery types are represented in Figure 1[1].

Radiation therapy

Radiation therapy is used after surgery or directly at a tumor site in order to destroy cancer cells or the remaining cancerous cells after surgery, treatments by this technique are performed 5 times a week for almost fifteen minutes for a five to six-week period of time. In order to effectively kill the cancerous cells, strong radiation doses are used such as X-rays or Gamma rays [1].

Chemotherapy

This technique requires anti-cancerous drugs usage in order to treat cancer cells. The drugs are prescribed based on many factors such as age (menopause or not), weight, medical history, cancer stage, etc. in order to provide a specific and effective treatment.

Chemotherapy can be also used before surgery as it reduces the tumor size and the surgeon might go from mastectomy to lumpectomy or quandrantectomy [1].

The most commonly used chemotherapy agents are classed regarding their mode of action such as antimetabolites, DNA alkylating agents, antimitotic agents, immunologic therapy, endocrine therapy, and metal ions as mentioned in Figure 2 [12].

Immunologic therapy

This therapy is used to treat HER2 overexpressed tumors that consist of 20% of metastatic breast cancer [13]. HER2 is normally an inactive monomer, once activated by dimerization with HER3 a phosphorylation cascade reactions are activated by tyrosine kinase receptors which cause the development of cancer due to excessive cellular proliferation, angiogenesis, metastasis, and apoptosis [14,15]. Immunological antibodies block tyrosine kinase receptors thus prevent cancer development, however, acquired drug resistance is still a major limitation for these drugs [16].

The immunologic therapy consists of monoclonal antibodies such as Herceptin which was the first humanized antibody to be used in the HER2 + breast cancer. Herceptin works by binding on HER2 juxtamembrane tyrosine kinase receptor, thus preventing the dimerization process which affects many signaling pathways strength such as MAP and PI3 kinase signaling pathways responsible for tumor development in case of abnormal amounts of signals [17,18], and of antibody-drug conjugates such as ado-trastuzumab considered to be the newest drug for immunological therapy, this drug is formed of two parts a cytotoxic drug-releasing a toxin into the cancerous cell and monoclonal antibody trastuzumab that is very specific to cancerous

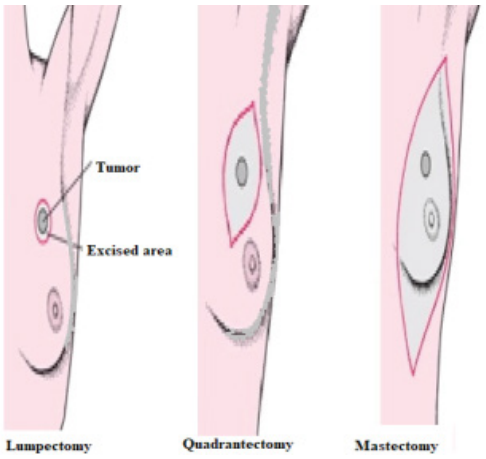

Figure 1: Different surgery types applied for breast cancer.

cells [16,19]. When trastuzumab binds to HER2 its prompts its cellular endocytosis and the complex is then destroyed inside the lysosome [16]. In addition, the cytotoxic drug is released into the cell and interacts with its microtubule stopping the polymerization process which results in cell cycle arrest and apoptosis along with the disruption of intracellular trafficking of HER2 [16,20].

Hormonal therapy

Hormonal therapy is the golden method of treatment in both pre and post-menopausal women expressing hormone-positive receptors (estrogen-positive and or progesterone positive) [21]. In the case of estrogen-positive breast cancer, hormonal therapy uses anti-estrogens in order to block estrogen receptors or aromatase inhibitors to downregulate estrogen synthesis [22].

The hormonal therapy consists of Anti-Gonadotrophin releasing hormone (GnRH) therapy such as Gosereline drug which is the synthetic product of GnRH that has a role in the production of and the suppression of both follicle-stimulating hormones (FSH) and luteinizing hormone (LH), this treatment is the golden treatment for pre-menopausal women as it suppresses LH responsible for the production of both estrogen and progesterone [23]. Also, anti-estrogens consisted of estrogen receptor antagonists and aromatase inhibitors.

Estrogen receptor antagonists such as Tamoxifen are used as a first-line treatment in both pre and post-menopausal women by binding on the estrogen receptors and thus blocking estrogen fixation on its receptor resulting in the inhibition of estrogen signaling pathway [24,25].

As for the aromatase inhibitors, they act by blocking cytochrome p450; aromatase enzyme responsible for the synthesis of estrogen [26]. These inhibitors are firstly used in post-menopausal women as they block the transformation of adrenal androgens into estrogen in many tissues including the breast which results in undetectable plasma levels of estrogen [27].

Ion modulators

Bone cancer is induced by almost 30% of metastatic breast cancer patients. Pamidronatebisodium binds to hydroxyapatite crystals of the bone which causes the reduction of the bone resorption, it also lowers osteocytic lesions caused by breast cancer metastasis [28,29].

DNA alkylating drug treatment

Developed in 1940, DNA alkylating agents work by stopping the cell cycle, thus preventing the cancerous cell division by blocking DNA transcription.

DNA alkylating agents are classified into platinum compounds such as Gisplatin, this anti-cancer drug binds into the guanine base of the DNA and creates lesions, thus stops its replication [30]. However, the use of this anti-cancer drug has been limited due to its serious side effects such as nephrotoxicity, blindness, etc[31]; Nitrogen mustard such as cyclophosphamide that selectively binds into cancerous cells and express high amounts of phosphoamidases to nitrogen mustard which undergoes many cyclization reactions that creates an unstable etheyleneimine cation that binds covalently into the DNA and thus stops its transcription [32]; and organophosphorus compounds such as thiotepa that is a prodrug for aziridine that interacts with the DNA causing a ring-opening and a DNA scission [33].

Antimitotic agents

These drugs modify the microtubule function which is a fundamental element in chromosome segregation during mitosis, this will alter the cell cycle leading to apoptosis [34-36]. These antimitotic agents consist of synthetic compounds such as Ixabepilone this drug binds to the microtubules and leads to tubulin dimerization which result in the mitotic arrest of cancerous cells [37]; and natural compounds that are further classified into marine compounds such as Eribulinmesylate that stops the microtubule growth leading to cell cycle arrest between metaphase or anaphase [38], and plant compounds such as taxanes (microtubule-stabilizing agents) or alkaloids (microtubule-destabilizing agents); taxanes bind to beta-tubulin and blocks microtubule growth and elongation causing cell cycle arrest and activating apoptosis [35], as for alkaloids they work as inhibitors of the tubules polymerization resulting in cell cycle arrest in metaphase [39].

Antimetabolites

Antimetabolites inactivate intracellular enzymes or they produce a new product lacking normal intracellular functions. Antimetabolites are either active or inactive products for the latter ones they must undergo the biotransformation process to be activated; they work cooperatively with 5-Fluorouracil.

Antimetabolites are subcategorized regarding the target enzyme noting dehydrogenase inhibitors such as methotrexate which is a competitive inhibitor for the enzyme that transforms dihydrofolate into tetrahydrofolate, dihydrofolate reductase; this leads to cell cycle arrest as folate which is essential during purine synthesis will be accumulated and inhibit DNA synthesis [40,41]; Nucleoside inhibitors such as Capecitabine, 5-Fluorouracil (prodrug requires activation through many enzymatic processes), contend with DNA and RNA replication. Capecitabine has higher specificity and sensitivity to cancerous cell as 5-fluorouracil as well as lower toxicity [42]; Topoisomerase II inhibitors such as doxorubicin that inhibit topoisomerase II action and thus affects DNA repair, it also generates free radicals that cause damage to cancer cells membrane and proteins, however, the use of this drug is limited due to its cardiotoxic effects [43].

The Integration of Nanotechnology in Breast Cancer Treatment

As mentioned previously, anti-cancer drugs have severe side effects as they are generally hydrophobic, untargeted, and toxic [44]. However, nanotechnology has fewer side effects because of the limitation of drug degradation, thus a higher amount of drug will target cancerous cells

[45]. Also, it targets and eliminates breast cancer stem cells which is an important factor of chemotherapy resistance [46]. This technique works by binding a nanoparticle into the anti-cancer drug, many nanoparticle-anticancer drugs based are approved by the U.S Food and Drug Administration (FDA) and many others are still under trial.

Liposome based nanoparticles

Liposomes are constituted of an aqueous heart and a membrane lipid layer, hydrophobic drugs consisting most of the anti-cancer drugs can be integrated into the lipid layer, and the hydrophilic ones will be in the core of the liposome, this will reduce the toxic effects of these drugs, and give them a higher circulation time. Also, to enhance their selectivity to cancerous cells, liposomes are bioconjugated with selective ligands such as antibodies, aptamer, etc.

The first FDA-approved lysosome-based drug is Doxil®, it intercalates between the DNA base pairs and leads to DNA synthesis and transcription inhibition [47].

Polymeric nanoparticles

Similar but not identical to liposomes, polymer nanoparticles encapsulate the hydrophobic anti-cancerous drug inside their core, and the hydrophilic anticancer drugs are attached to the outer shell of the polymer via covalent, electrostatic, etc. bonding. In order to specifically target cancer cells, peptides, and antibodies are attached to the polymers [48]. However, polymers are stable in case of temperature, pH, external stimulus, etc. [47].

Under Phase II trials, Genexol®-PM is proved to be able to deliver the antimitotic agent Paclitaxel in a higher dose (300 mg/m2) and within less toxicity when compared to the traditional chemotherapy (175 mg/m2) [49,50].

Nab paclitaxel

Paclitaxel is one of the first approved FDA drugs for the treatment of breast cancer. Belonging to the taxanes family, this drug has poor water solubility, thus it is administered with another drug Cremophor EL which causes serious dose-dependent toxicity that might lead to death. In order to limit its usage, Nab Paclitaxel has been developed and approved by the FDA. This drug was prepared by the reversible linkage of albumin which is a carrier of hydrophobic molecules to paclitaxel under high pressure. Nab paclitaxel granted the safe administration of Paclitaxel in much higher doses without any serious side effects [47].

Gene Therapy

Many cancers are developed because of many complex mutations in the genes, this has led to the rise of gene therapy for cancer such as oncogene inactivation and tumor suppressor genes [51].

Oncogene inactivation

Many oncogenes are being associated with different types of cancer including breast cancer noting ErB2 (Erb-B2 Receptor Tyrosine Kinase 2), PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha. Antisense is the most popular advent in clinical trials for oncogene inactivation. In addition, the use of adenoviral gene to inhibit the transcription of ErB2 oncogene which is a very good strategy for cancers expressing this oncogene such as breast cancer [51].

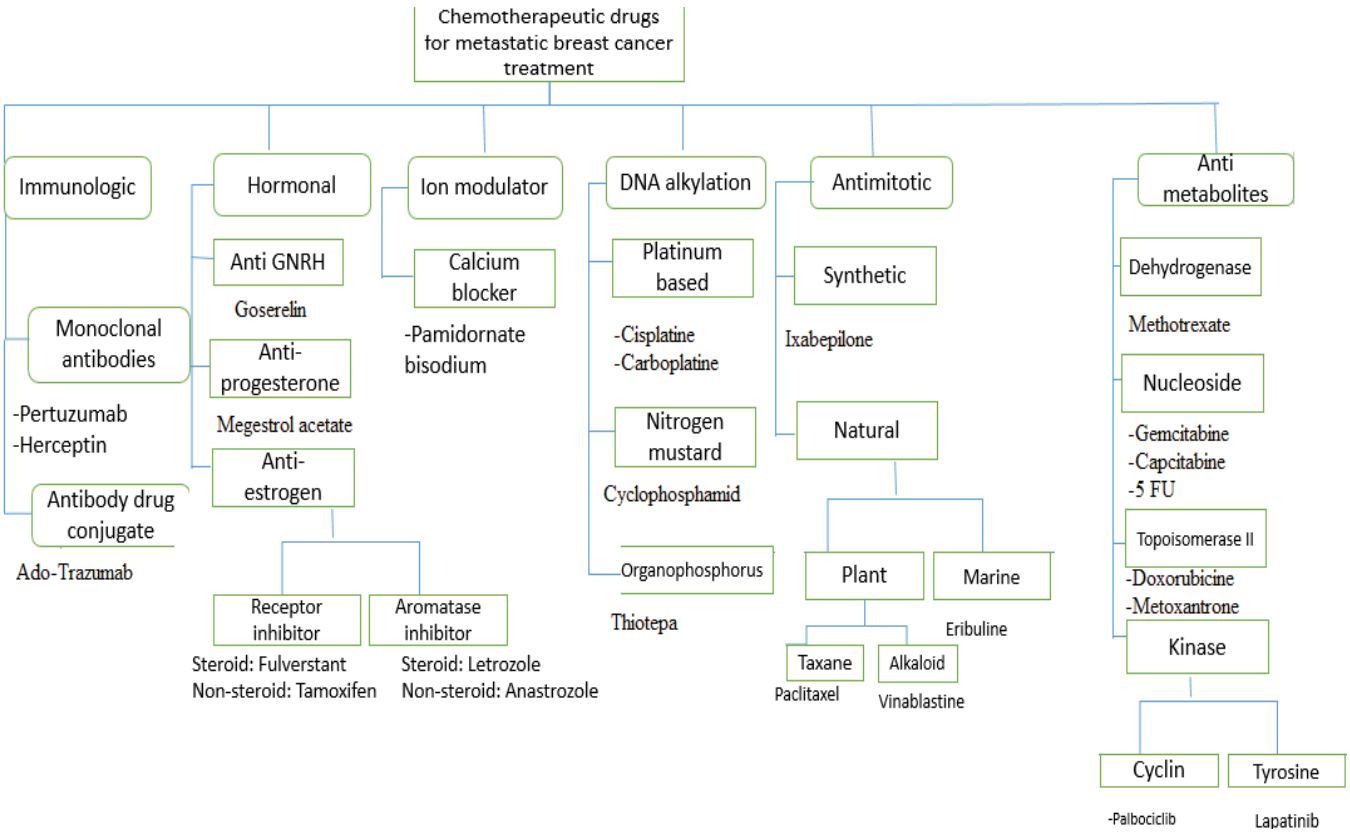

Figure 2: Different classes of chemotherapeutic drugs based on their mode of action.

Tumor suppressor gene augmentation

Mutations in many tumor suppressor genes have been associated with different types of cancer, which led many trials trying to use adenoviral vectors in order to augment p53 numbers. In addition, viral vectors are being used to introduce the breast cancer gene BRAC1 into ovarian cancer. However, these approaches might fail for the sole reason that the mutated gene has a dominant effect on the normal gene [51].

Conclusion

Breast cancer became a worldwide issue as it has taken many women lives, symptoms such as nipple discharge, breast skin changes shall not be underestimated, and screening must be done each year as early diagnosis is a very important step to prevent breast cancer death. Nowadays, scientists are working hard to give new approaches in both screening and treatment, biosensor devices may be a positive changing point in breast cancer diagnosis in the near future, as for the treatments, new technologies are being used to reduce the traditional techniques serious effects such as nanotechnology combined with chemotherapy, and gene replacement therapy, not to forget to mention the importance of traditional therapies such as surgery and radiotherapy. With the advances mentioned, death rates are decreasing and 90% of the diagnosed patients will survive for at least five years with the hope that the treatments, and the screening techniques that are still under trial increase more the survival rate.

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