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Breast Cancer

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ABSTRACT
Cancer is a malignant tumor that is caused by abnormal proliferation of any type of cell in the body. Breast cancer is the leading cause of mortality for women where the main tumor itself metastases to other parts of the body causing a majority of death. This review describes the epidemiological studies, signs and symptoms, variants of breast cancer, various drugs that have been employed for breast cancer, and also screening and prevention of breast cancer. This review also focused on how graphene-based nanomaterials (GBNs) have been used for the treatment of breast cancer. GBNs improve cell adhesion, trap breast cancer cells, and have inherent anticancer characteristics. It also has good biological safety for use in the detection and treatment of cancer.

Keywords - Breast cancer, Triple-negative breast cancer, Abemaciclib, Cyclophosphamide, Graphene-based nanomaterials

I. INTRODUCTION

A tumor is defined as any abnormal cell proliferation, whether benign or malignant. Cancer is a malignant tumor caused by the abnormal multiplication of any type of cell in the body [1]. It gets its name from Hippocrates' discovery more than 2,300 years ago that the long, swollen veins that shoot out from some breast tumors resemble crab limbs. This observation gave rise to the terms karkinoma in Greek and, later, cancer in Latin [2]. Depending on the severity and type cancer cells can spread to neighboring organs and can also travel through the bloodstream or lymph to other parts of the body [3].

Early Epidemiological Studies About Cancer [4]

Year	Event
1713	**Bernardino Ramazzini** observed that nuns suffered from high rates of breast cancer which he attributed to their celibate life.
1761	**John Hill** reported that immoderate use of tobacco snuff was associated with the occurrence of nasal cancer.
1775	**Percivol Pott** documented that chimney sweeps developed cancer of the scrotum which he deduced to be caused by their heavy exposure to soot.
1875	**Richard von Volkmann** diagnosed three cases of scrotal cancer among coal tar distillers in **Germany,** which was quickly followed by similar reports by other physicians.
1876	**Joseph Bell** described two cases of scrotal cancer among shale oil workers in **Scotland** and commented that the cancer was quite common among shale oil workers.
1879	**Harting and Hesse** documented that the miners in the **Black Forest regions of Schneeberg in Germany** and **Joachimsthal in Czechoslovakia** suffered fromhigh mortality due to lung cancer.
1881	**Sir Jonathan Hutchinson** observed that patients who used a tonic that contained arsenic for extended durations frequently developed keratosis lesions which sometimes progressed to skin cancer.
1895	**Ludwig Rhen** reported that long-term dye workers in **Germany** frequently perished of bladder cancer **Wilhelm Conrad Rontgen** discovered X-rays which were heralded as a phenomenal discovery because they permitted the painless visualization of bones. The early radiologists routinely tested the performance of their equipment by exposing their hands. Then a few days after prolonged exposure, an extremely painful skin condition termed radiodermatitis developed. A decade after the discovery of X-rays, case reports began emerging from many diverse of the world that radiologists were succumbing to

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	skin cancer.

Breast Cancer

In women, breast cancer is the leading cause of mortality [5]. In addition to the main tumor itself, metastases to other body organs contribute to the majority of breast cancer mortality [6]. Breast cancer is characterized by erratic cell growth and proliferation that begins in the breast tissue. The breast is made up of two different types of tissues: glandular tissue and stromal tissue. Glandular tissue contains the milk-producing glands and ducts, whereas stromal tissue contains the breast's fatty and fibrous connective tissues. Tumors can form in a variety of areas of the breast. Most breast cancers start in the cells that line the ducts, but some start in the cells that line the lobules, and a few start in other tissues.Breast cancer is the most common type of cancer and the leading cause of cancer death in women. The majority of breast cancer deaths are caused not only by the primary tumor but also by metastasis to other organs in the body.[7.8]

The following data table shows breast cancer incidence in womenin 2020. Belgium had the highest rate of breast cancer followed by the Netherlands[9]. Here the ASR indicates age standardized rate. The age-standardized rate is the summary rate that would have been observed, given the schedule of age-specific rates, in a population with the age composition of some reference population, often called the standard population.

RANK	COUNTRY	NUMBER	ASR/100,000
1.	Belgium	11,734	113.2
2.	The Netherland	15,725	100.9
3.	Luxembourg	497	99.8
4.	France	58,083	99.1
5.	France,New Caledonia	185	99.0
6.	Denmark	5,083	98.4
7.	Australia	19,617	96.0
8.	New Zealand	3,660	93.0
9.	Finland	5,228	92.4
10.	United State	2,53,465	90.3

Signs & Symptoms[10]

- A change in breast size or shape
- A lump or thickening
- Redness or rash on the skin or around the nipple
- Changes in skin such as puckering or dimpling
- Nipple discharge
- Inversion or change in position or shape
- Underarm swelling
- Constant pain in the breast or armpit

Types Of Breast Cancer

Based on their immunohistochemical (IHC) characteristics, breast cancers are clinically divided into three basic types and they are hormone-receptor positive (HR+), human epidermal growth factor receptor-2 positive (HER-2 positive), and triple-negative breast cancer[11].

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1. Hormone Receptor-Positive:

Hormone receptors including the progesterone receptor and estrogen receptors are expressed by over 70% of human breast cancers[12]. Tumor Infiltrating Lymphocytes (TILs) counts are often lowest in HR+ malignancies[13]. In general, women with advanced estrogen receptor-positive breast cancer and non-life-threatening illness who are too old for intensive chemotherapy are treated with hormone therapy[14].

2. Human Epidermal Growth Factor Receptor-2 Positive (Her-2 +):

The epidermal growth factor receptor family has two members, the second of which is the HER-2/neu oncogene. Breast, ovarian, lung, stomach, and oral cancers are only a few of the several human tumors in which it is overexpressed. Repression of HER-2/neu decreases the malignant phenotypes of cancer cells that overexpress HER-2/neu, as numerous studies have demonstrated clearly. These results strongly imply that HER-2/neu may be an attractive target for the development of anticancer drugs tailored for cancer cells that overexpress HER-2/neu. In tissue culture, the development of HER-2/neu overexpressing human breast cancer cells can be selectively inhibited by tyrosine kinase inhibitor[15].

3. Triple-Negative Breast Cancer

Due to its aggressive behavior, relatively poor prognosis, and lack of targeted medicines, which leaves chemotherapy as the cornerstone of treatment, triple-negative breast cancer has specific clinical and pathologic features and is a clinical concern. Although the majority of triple-negative tumors belong to the basal-like molecular subtype of breast cancer, the words are not entirely identical. A higher histologic grade, an increased mitotic count, sparse stromal material, central necrosis, pushing borders of invasion, a stromal lymphocytic response, and numerous apoptotic cells are common features of triple-negative tumors. Histologically, they are primarily ductal, but some rare histologies, such as metaplastic atypical or typical medullary, or adenoid cystic carcinomas, are also overrepresented[16].

Treatment of Breast cancer

Drug	Description	Mechanism of Action	Adverse effects
Abemaciclib	Abemaciclib has been authorized for the first line and subsequent treatment of hormonereceptor-positive advanced/metastatic breast cancer (HR+ ABMC), both alone and in combination with antiestrogen activity. Eli Lilly and Company is working on the cyclin-dependent kinase 4 and 6 inhibitor abemaciclib, which is taken orally. In combination with fulvestrant, abemaciclib has been licensed in the USA for the treatment of advanced or metastatic breast cancer in women whose illness	Abemaciclib has been demonstrated to reduce the development of cancerous cells both in vitro and in vivo. It is a reversible, ATP-competitive, kinase inhibitor that is selective for CDK4 and CDK6 (cyclin-dependent kinase 4 and cyclin-dependent kinase 6, represent the driving force of tumorigenesis in several cancer types).This anticancer effect is caused by preventing Rb's (retinoblastoma) phosphorylation, which in turn prevents the advancement of the tumor cell cycle into the G1/S phase[19].	Diarrhea (most common), neutropenia (low neutrophil count)[20]

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	has progressed after endocrine therapy and who do not express the human epidermal growth factor receptor 2 (HER2)[17,18].		
Ado Trastuzumab Emtansine	Ado-trastuzumab emtansine was granted FDA approval on February 22, 2013, to be used as a single agent for treating patients with metastatic breast cancer that is HER2-positive and who have previously treated either trastuzumab alone or in combination with a taxane. Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that combines trastuzumab's HER2-targeting and therapeutic characteristics with DM1 (mertansine) cytotoxic action[21]	Ado-trastuzumab emtansine is made up of the cytotoxic maytansinoid DM1 and the humanized monoclonal antibody trastuzumab, which are joined by the stable thioether linker 4-[N-maleimidomethyl]-cyclohexane-1-carbonyl (MCC). The ADC is guided to HER2-overexpressing cancer cells by the trastuzumab component, which binds to the extracellular receptor domain and stimulates cellular endocytosis of the receptor-ADC complex there. The active metabolite, lysine-MCC-DM1, a microtubule polymerization inhibitor that interrupts the cell cycle during the G2-M phase and ultimately leads to apoptosis, is produced when ado-trastuzumab emtansine is internalized and goes through lysosomal proteolytic breakdown[22].	Fatigue, diarrhea, anemia, increased transaminases, and mild-to-moderate hemorrhagic effects, which are likely to be connected to induced thrombocytopenia, are the most prevalent adverse effects of T-DM1[23]
Abraxane (Paclitaxel Albumin Stabilized Nanoparticle Suspension)	The oncologist will have a wide range of successful treatment choices for patients due to the availability of new therapies like Abraxane in combination with other conventional and unconventional drugs (new anti-cancer agents and targeted molecules). ABI-007 is a brand-new, albumin-bound, 130-nm paclitaxel formulation that is solvent-free. For the treatment of advanced	Microtubule inhibition is the basis of Abraxane's therapeutic activity. By avoiding depolymerization, Abraxane encourages the construction of microtubules from tubulin dimers and stabilizes these microtubules. This stabilization inhibits the division, motility, and intracellular transport of cancer cells by preventing microtubules from correctly rearranging and retaining their normal shape during mitosis[25].	dose-limiting bone marrow depression, peripheral neuropathy, and hypersensitivity responses which might include flushing, rash, dyspnea, hypotension, chest discomfort, and angioedema. Alopecia, arthralgia, myalgia, mucositis, bradycardia, alterations in the ECG, nail dystrophies, and elevated liver enzyme readings are some other side effects [26]

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	ovarian, breast, and lung cancers, paclitaxel, a naturally occurring complex substance derived from the bark of the western yew (Taxus brevifolia), is frequently used[24].		
Cyclophosphamide	One of the most effective anticancer substances ever created is cyclophosphamide. Cyclophosphamide was synthesized 50 years ago, yet it is still often employed as a chemotherapeutic drug and in mobilization and conditioning treatments for bone marrow transplants today (BMT)[27]. Breast cancer, sarcoma, and multiple myeloma are among the neoplasms that are managed and treated with the help of the drug cyclophosphamide. Nitrogen mustard known as cyclophosphamide works against cancer by alkylation[28].	Cyclophosphamide's main mode of action is DNA alkylation, which inhibits DNA synthesis and causes cell death as a result[29].	Cyclophosphamide is known to have hemorrhagic cystitis as a side effect, which may also be what prevents more people from using it[30].
Doxorubicin	A methodical investigation of the most effective chemical species among a collection of physiologically active microbial metabolites, namely the anthracycline glycosides, led to the successful creation of doxorubicin as a wide-spectrum antitumor antibiotic[31].	Doxorubicin's main method of action is its capacity to intercalate among DNA base pairs, breaking DNA strands and inhibiting the creation of both DNA and RNA. Topoisomerase II is inhibited by doxorubicin, which results in DNA damage and the activation of apoptosis[32].	fatal cardiotoxicity and dose-restricted myelosuppression[33].

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Graphene-based nanomaterials (Gbns)

Over the past few decades, nanotechnology has been rapidly developed and widely used. Carbon nanomaterials have been widely used in the detection, prevention, and treatment of various chronic diseases. Graphene is a two-dimensional sheet of hexagonally organized carbon atoms segregated from the three-dimensional parent material graphite that has the distinct characteristics of being extremely thin, having a high surface area, having strong electrical conductivity, having outstanding optical performance, having good mechanical qualities, and more. GBNs can improve cell adhesion, trap breast cancer cells, and have inherent anticancer characteristics. It also has good biological safety for use in the detection and treatment of cancer. [34-36]

Screening and Prevention

Breast cancer prevention begins with early detection. Primary prevention includes dietary modification, exercise, tobacco & alcohol, exogenous use of estrogens and progestins, and so on, Mammography is a screening technology that uses low-energy X-rays to produce high-resolution images of the breast.Another common screening method for breast cancer is magnetic resonance imaging (MRI). In high-risk women, it is more sensitive than mammography, particularly in detecting invasive ductal carcinoma. The development of biological prophylaxis to enhance the quality of life for breast cancer patients is best known as the monoclonal antibodies for the disease. The first HER2-targeted medication to receive FDA approval is a recombinant humanized monoclonal antibody called trastuzumab (Herceptin) [37,38].

II. CONCLUSION

This review gathers information about the various types, epidemiological studies and many drugs that are used for the treatment of breast cancer and also their screening and prevention. This review also includes about graphene-based nanoparticles (GBNs) and their role in treatment of breast cancer.

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