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RECENT ADVANCES IN BREAST CANCER TREATMENT: INNOVATIONS AND ONGOING RESEARCH

Sugra Begum*(Pharm-D) and Afeefa*(Pharm-D)

Prathap Narender Reddy College of Pharmacy.

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***Corresponding Author**
Sugra Begum
Prathap Narender Reddy
College of Pharmacy.

ABSTRACT

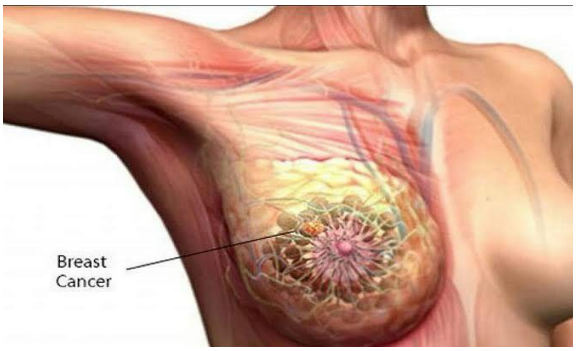
Breast cancer is the most commonly diagnosed cancer among women worldwide, with approximately 2.3 million new cases reported annually, accounting for about 1 in 8 cancer diagnoses globally, according to the World Health Organization. These statistics are based on 2022 data, which recorded 2.3 million diagnoses and 670,000 deaths from breast cancer. While nearly 99% of breast cancer cases occur in women, 0.5-1% affect men. Several factors increase the risk of developing breast cancer, including advancing age, obesity, excessive alcohol consumption, family history, prior radiation exposure, reproductive history (such as age at menarche and first pregnancy), tobacco use, and postmenopausal hormone therapy. Inherited high-penetrance gene mutations, particularly in BRCA1, BRCA2, and PALB2 genes, significantly elevate the risk. Women with mutations in these genes may opt for risk-reducing strategies, such as prophylactic mastectomy or chemoprevention. The management of breast cancer in men follows the same treatment principles as in women. This chapter explores the etiology of breast cancer, alongside the latest innovative research on its associated risk factors.

KEYWORDS: Breast cancer, Etiology, Vaccine, Therapies, Treatments.

INTRODUCTION

Breast cancer is a disease in which abnormal breast cells grow out of control and form tumours. If left unchecked, the tumours can spread throughout the body and become fatal. Breast cancer cells begin inside the milk ducts and/or the milk-producing lobules of the breast. The earliest form (in situ) is not life-threatening and can be detected in early stages. Cancer cells can spread into nearby breast tissue (invasion). This creates tumours that cause

lumps or thickening. Invasive cancers can spread to nearby lymph nodes or other organs (metastasize). Metastasis can be life-threatening and fatal.



Treatment is based on the person, the type of cancer and its spread. Treatment combines surgery, radiation therapy and Medicines. In 2022, there were 2.3 million women diagnosed with breast cancer and 670 000 deaths globally. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life.

Global estimates reveal striking inequities in the breast cancer burden according to human development. For instance, in countries with a very high Human Development Index (HDI), 1 in 12 women will be diagnosed with breast cancer in their lifetime and 1 in 71 women die of it.

In contrast, in countries with a low HDI; while only 1 in 27 women is diagnosed with breast cancer in their lifetime, 1 in 48 women will die from it.

BREAST CANCER TYPES

1. Ductal carcinoma in situ (DC/S)

It is a non-invasive cancer where abnormal cells have been found in the lining of the breast milk duct.

The atypical cells have not spread outside of the ducts into the surrounding breast tissue.

Ductal carcinoma in situ is very early cancer that is highly treatable, but if it's left untreated or undetected, it can spread into the surrounding breast tissue.

2. Invasive ductal carcinoma

The abnormal cancer cells that began forming in the milk ducts have spread beyond the ducts into other parts of the breast tissue IDC is the most common type of breast cancer, making up

nearly 70-80% of all breast cancer diagnoses. IDC is also the type of breast cancer that can most commonly affects men.

3. Inflammatory Breast Cancer

Inflammatory Breast Cancer is an aggressive and fast-growing breast cancer in which cancer cells infiltrate the skin and lymph vessels of the breast.

It often produces no distinct tumour or lump that can be felt and isolated within the breast. But when the lymph vessels become blocked by the breast cancer cells, symptoms begin to appear.

4. Angiosarcoma of the breast

Angiosarcoma is a rare cancer that starts in the cells that line blood vessels or lymph vessels. It is often a complication of previous radiation treatment to the breast. It can happen 8-10 years after getting radiation treatment to the breast. Angiosarcoma of the breast is an exceedingly rare disease that may occur as a primary neoplasm or as a complication of radiation + therapy after breast conservation. Only about 20% of angiosarcomas are primary sarcomas. The incidence of primary breast angiosarcoma is about 17 new cases per million women.

NEW INNOVATIVE TREATMENTS FOR BREAST CANCER

Role of oncoplastic multidisciplinary team meeting (mdt)

According to the Association of Breast Surgeons (ABS) and the British Association of Plastic, Reconstructive and Aesthetic Surgeons guidelines (BAPRAS), oncoplastic breast surgery should be considered in all patients with breast cancer.

These discussions include volume replacement techniques, such as level 2 oncoplastic procedures and perforator flaps, and discussing the role of other reconstruction methods, such as implant-based or autologous flaps following mastectomy, as an immediate or delayed procedure. Breast Implant Registry.

Following the publication of Keogh's Review of Regulations of Cosmetic Interventions in the United Kingdom, the Breast and Cosmetic Implant Registry (BCIR) was opened in 2016. The registry records the details of any individual who has breast implant surgery for any reason and can now be traced in case of a product recall or safety concerns relating to a specific type

of implant. It also allows the identification of possible trends and complications relating to a specific type of implant.

Surgical considerations

Implementing the Enhanced Recovery Programme in breast surgery has revolutionized breast surgery and improved its outcomes. Using a perforator flap for reconstruction and infiltration of local anaesthesia for flap harvesting, techniques such as quilting to reduce dead space and using Tranexamic acid to reduce hematoma/bruising, are among various strategies that can reduce complication rates. The reduced dependence on opiates in breast surgery has also facilitated early discharge, thereby performing most procedures as day-cases.

The use of novel oncoplastic techniques to reduce mastectomy rates wherever possible has provided good cosmetic outcomes and has been the mainstay of surgical treatment for breast cancer recently. The use of techniques such as mammoplasties and local advancement perforator flaps such as lateral thoracic artery perforator (LTAP), lateral intercostal arteries (LiCAP), anterior intercostal arteries (AiCAP), thoracodorsal artery perforator (TDAP), and medial intercostal arteries (MiCAP) have all now become new standards in oncoplastic breast surgery, providing patients with more options for treatment and enabling breast conservation. In patients where breast conservation is not an option, mastectomy is indicated, such as high-risk/BRCA genetic patients, and the choice of breast reconstruction is offered where feasible. Newer techniques, such as Prepectoral breast reconstruction using Acellular Dermal Matrix], such as Braxon® and Verita, can provide immediate reconstruction with an implant. This has enabled surgeons to perform the procedure in the prepectoral space without disrupting the pectoralis muscle, which causes less post-operative pain and shoulder problems and provides good cosmetic outcomes. However, with the increased use of implants and adoption of newer cohesive breast implants, the risks of breast implant illness and low-grade anaplastic lymphoma (BIA-ALCL), with an estimated risk of 1:25,000 to 30,000 have now been added to the list of complications with the use of breast implants. These patients are informed about this while deciding on surgery.

With the increased use of breast reconstruction, modifications in the management of implant handling during surgery to reduce surgical site infection complications have also become paramount. Using theatre checklists for implants has become a standard of care in hospitals carrying out implant-based reconstruction.

Chemotherapy and immunotherapy

A combination of immunotherapy and chemotherapy has recently emerged as a novel treatment option, with encouraging results observed with the combination of immune checkpoint blockade with diverse biological agents, including anti-HER2 agents, cyclin-dependent kinase (CDK) 4/6 inhibitors, and PARP inhibitors. Currently, three selective CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) have been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating HR-positive, HER2-negative metastatic breast cancer . Treatment with CDK4/6i in combination with endocrine therapy is generally safe and well tolerated. Haematological toxicity is commonly seen with all three inhibitors, but some haematological adverse events (AEs) are more frequent with palbociclib and ribociclib rather than abemaciclib . Toxicities are easily treatable and can be managed with dose adjustment and supportive care.

FUTURE OF BREAST CANCER TREATMENT

Role of Artificial Intelligence (AI)

The evolution of AI in breast surgery had progressed from the early stages, when researchers and clinicians started exploring the potential of AI in analysing medical images, such as mammograms, to aid in breast cancer diagnosis and screening. Basic machine learning algorithms were used for image analysis and feature extraction, but the applications were limited. As technology advanced, more sophisticated deep learning algorithms, such as convolutional neural networks (CNNs), showed promise in detecting breast lesions and classifying breast cancer subtypes more accurately. These advances led to more applications of AI in breast surgery, including image-guided surgery, surgical planning, and prediction of treatment outcomes. Currently, numerous studies and clinical trials are exploring the use of AI in various aspects of breast surgery, including image analysis, surgical planning, decision support, and prediction of patient outcomes. AI-powered tools, such as computer-aided detection (CAD) systems, are increasingly used in clinical practice to assist radiologists in breast cancer screening and diagnosis. Virtual reality (VR) and augmented reality (AR) technologies are also being utilized to enhance surgical visualization and training.

The ongoing research and development pave the way for the availability in the near future of automated histopathology analysis, prediction of treatment response, and patient-specific treatment planning and optimized surgical approaches.

To resurface from the suspension of breast cancer screening during the COVID-19 infection, various centres across the United Kingdom have opted to participate in or conduct clinical trials into using AI as a screening aid for detecting breast cancer. One such centre in England, Leeds, recently announced the use of AI software as a LIBRA study . The aim is to generate evidence for AI's benefits and investigate if it could increase detection rates, reduce patient recalls, and ease workforce pressures.

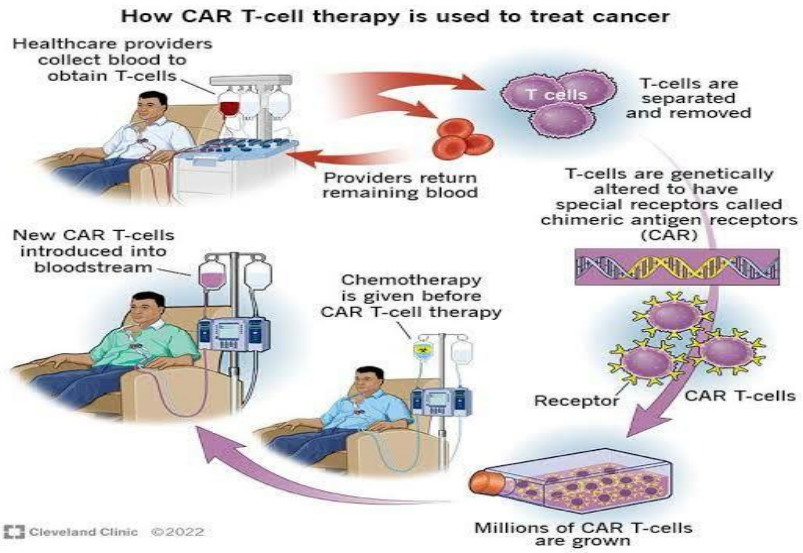
Reliance on AI will likely proceed through stages. It will involve careful attention to mitigate its limitations and challenges around patient privacy, accountability, bias, informed consent, and economic and social justice.

Similarly, in digital pathology, transforming histopathology slides into digital images using whole-slide scanners and subsequent analysis of these digitized images by using AI appears promising. It can help speed up the diagnostic process with a limited workforce.

Chimeric Antigen Receptort T cell therapy

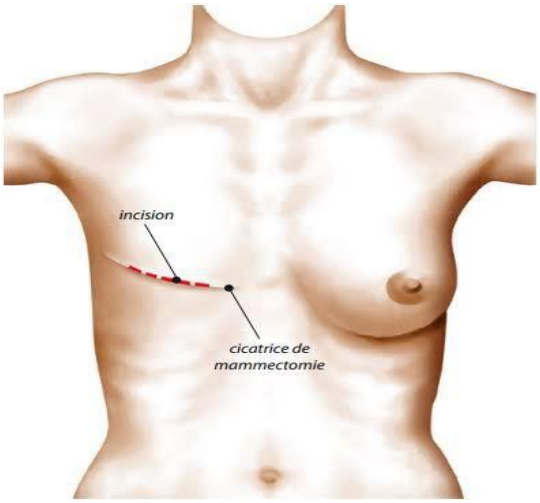
Doctors nowadays are leading a clinical trial that uses a type of immunotherapy — chimeric antigen receptor (CAR) T cell therapy — that was developed on-site to treat patients with HER2-positive breast cancer that has spread to the brain.

For this trial, patients' T cells are collected and then reengineered in a laboratory to actively seek out and destroy cancerous cells. More specifically, the T cells are genetically engineered to express a CAR that allows these immune cells to target and eradicate HER2-positive cancer cells.



3D Nipple Areolar Complex Tattooing

Mastectomy (surgical removal of one or both breasts) is a common and effective procedure for breast cancer patients, but it can also negatively impact a woman's body image. The procedure often involves the removal of the nipple and areola, which can dramatically change the appearance of the breast. To help mastectomy patients rebuild their self-confidence and improve their self-image, hospitals offers advanced surgical techniques that help reconstruct the look and feel of the breast.



For patients who have had their nipple and areola removed during a mastectomy, surgeons are now offering 3D nipple areolar complex tattooing, a reconstructive procedure that restores a more natural appearance to the area. While 3D nipple areolar tattoos are not actually three-dimensional, this innovative surgical technique uses multiple shades of nontoxic ink, as well as expert techniques founded on an understanding of skin tone, shadows and highlights, to create a more realistic appearance to the nipple and areola.

Previous nipple-tattooing methods typically used only one or two colour to create concentric circles on the breast after nipple reconstruction. 3D nipple tattoos appear more authentic and do not require an additional reconstructive surgical procedure.

"A few years ago, some really smart tattoo artists designed tattoos of the nipple that make it look three dimensional. So that means no surgery, but literally a tattoo — but a complex tattoo to give you the illusion that there's something there," explained Wai-Yee Li, M.D., Ph.D., an associate clinical professor in City of Hope's Division of Plastic Surgery.

A shot to replace chemotherapy

For patients with metastatic HER2-positive breast cancer, a combination of Herceptin and Perjeta (two immune targeted therapy drugs) is a first-line treatment. Administered by IV alongside chemotherapy, this drug combination is quite effective, but the process is time consuming, and can last up to 2.5 hours.

TYPES OF VACCINES

Cancer vaccines are medicines that belong to a class of substances known as biological response modifiers. Biological response modifiers work by stimulating or restoring the immune system's ability to fight infections and disease.

Two broad types of cancer vaccines

• Preventive (or prophylactic) vaccines prevent cancer from developing in healthy people.

• Treatment (or therapeutic) vaccines treat an existing cancer by strengthening the body's natural defences against the cancer. Antigen vaccine

• These use tumour-specific antigens - proteins displayed on a tumour cell - to stimulate the immune system.

• By injecting these antigens into the cancerous area of the patient, the immune system will produce an increased amount of antibodies or cytotoxic T lymphocytes, also known as killer T cells, to attack cancer cells that carry that specific antigen. Dendritic cells break the antigens on the cancer.

Dendritic cell

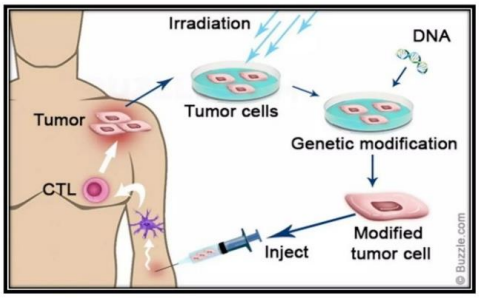
cell surfaces into smaller pieces.

• The dendritic cells then act as most-wanted posters for the immune system, displaying those antigen pieces to the killer T cells. This combination of dendritic cells and antigens is then injected into the patient and the dendritic cells work to program the T cells. Tumour Cell Vaccines (Autologous /Allogeneic).

Tumor cells

• Autologous and allogeneic tumour cells were one of the first types of tumour vaccines to be used.•A second advantage is that tumour cell-based immunization allows the development of cancer vaccines without knowing the specific antigens.

TUMOR CELL VACCINES:



DNA vaccines

• Bits of DNA from the patient's cells are injected into the patient, which instructs the other cells to continuously produce certain antigens.

• This DNA vaccine increases production of antigens, which forces the immune system to respond by producing more T cells.

CANCER VACCINES WHICH ARE CURRENTLY UNDER CLINICAL TRIALS:

• Onyvax: (a monoclonal antibody 105AD7 anti-idiotype vaccine)

• It is used for the treatment of advanced colorectal adenocarcinoma.

• The vaccine is administered endemic together with the BCG vaccine or intramuscularly together with the alum adjuvant.

• OncoVAX

• Autologous vaccine for Stage Il colon cancer.

• Received fast-track status from FDA in 2006.

• STUDY: 254 patients received either

OncoVAX or placebo.

• Improves 5-year survival and recurrence-free interval.

• 57.1% relative risk reduction.

CANCER VAX

• It is being used together with the surgical treatment in the treatment of melanoma Ill stage.

• In order to increase the cellular immune response, this vaccine is given together with the BCG Vaccine.

NY-ESO-1 Peptide Vaccine

• It is used endermic in the treatment of Soft tissue Sarcoma Stage II-IV expressing NY-ESO-1, LAGE antigen NY-ESO-1 or LAGE antigen .

• Granulocyte-macrophage colony stimulating factor (GM- CSF) is to be injected, subcutaneous, in additional to this vaccine

GP100 AND MART-1

• A vaccine therapy using Tyrosinase, GP100 and MART-1

peptides together with the alum adjuvant is being used for the treatment of the patients with lIB IIC, Ill, or IV cutaneous melanoma OR stage Ill or IV ocular or mucosal melanoma.

• Interleukin-12 and the granulocyte-macrophage colony-stimulating factor (GM-CSF) are also used beside the vaccine.

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VG-1000 VACCINE

• This vaccine is most beneficial in treating carcinomas and melanomas.

• Patients subjected to chemotherapy or radiation respond more slowly to VG-1000 as they have a depressed immune system, however, patients who have had neither radiation nor chemotherapy respond favourably indicating it as first-line treatment for persons with recently diagnosed cancers

HSPPC-96, OR ONCOPHAGE

• The vaccine is a heat-shock protein, a class of compounds that has shown activity as autologous therapy

• The therapeutic agent is derived from and tailored to the tumors of individual patients.
• The HSPPC-96 vaccine contains antigens extracted from melanoma.
• Some of these antigens, like MART-1 and GP100, are unique to melanoma.

SIPULEUCEL-T

• Dendritic cell vaccine approved for treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer.
• Target-prostatic acid phosphatase (PAP), which is found in 95% of prostate cancers.

HPV VACCINE

• Gardasil: The FDA approved Gardasil for people ages 9 to 26 years to prevent:
• Cervical, vaginal, and vulvar cancers in girls and women
• Anal cancer in women and men
• Genital warts in men and boys
• The vaccine protects against the human papillomavirus (HPV).
• Cervarix: This vaccine also protects against HPV infection. The FDA approved it for the prevention of cervical cancer in girls and women ages 9 to 25 years.
• The first HPV vaccine became available in 2006.

CONCLUSION

Cancer is a disease characterized by abnormal cell growth that can spread to other parts of the body. Treatment options include surgery, chemotherapy, radiotherapy, and palliative care.

Key conclusions regarding cancer include:

- Early Detection: Early diagnosis significantly increases the chances of effective treatment and better outcomes.
- Treatment Options: A range of treatment strategies, including surgery, chemotherapy, radiotherapy, and palliative care, are available, each playing a role in managing the disease.
- Quality of Life: Addressing quality of life concerns is essential throughout cancer treatment, ensuring the well-being of patients during and after treatment.
- Survival Rates: Early detection and timely treatment are critical in improving survival rates.
- Functional Deficits: Cancer can lead to physical, cognitive, and psychosocial challenges, which may become more pronounced over time.

- Clinical Trials: Participation in clinical trials plays a crucial role in advancing treatment options, improving survival rates, and minimizing treatment-related toxicity.
- Cancer Awareness: Increased awareness and education about cancer are vital for reducing its burden on individuals and society as a whole.

In summary, a comprehensive approach involving early detection, effective treatment, attention to quality of life, and ongoing research through clinical trials is crucial for improving cancer outcomes and reducing its impact.

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