



Breast Cancer- The Serious Threat!

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Abstract:

Breast cancer is a complex and heterogeneous disease that arises from genetic mutations and environmental factors. It is classified into various subtypes based on histological characteristics, receptor status, and molecular features, impacting treatment strategies and prognostic outcomes. This review explores the current understanding of breast cancer pathophysiology, highlighting advances in early detection, targeted therapies, and immunotherapy. We also discuss challenges in managing advanced stages of the disease, the importance of personalized medicine, and ongoing research efforts aimed at improving survival rates and quality of life for patients. Understanding these factors is essential for developing effective treatment protocols and patient-centered care strategies. Breast cancer remains a leading cause of cancer-related morbidity and mortality among women worldwide. This review comprehensively examines the multifactorial etiology of breast cancer, including genetic predispositions, hormonal influences, and lifestyle factors. We detail advancements in screening methodologies, such as mammography and genetic testing, which have improved early detection rates. Furthermore, we explore the evolution of treatment options, focusing on targeted therapies, and personalized medicine that cater to the specific molecular profiles of tumors. This review aims to provide insights into current trends and future directions in breast cancer research and management.

Keywords:

Breast cancer, Genetic mutations, Targeted therapies, Immunotherapy, Advanced stages, Personalized medicine, Screening methodologies, Research, Management.

1. Introduction:

Breast cancer a serious threat isn't it? Listening to this what's the first thing came to your mind? So the answer comes is the microbes present in the gut. Scientists are discovering that the tiny organisms living inside us might be linked to breast cancer. In this article, we'll look at how these microbes could affect cancer and discuss practical steps to keep your gut healthy and improve your chances of fighting the disease.

Breast cancer starts when cells in the breast tissue grow abnormally. It's the second most common cancer in women in the U.S. after lung cancer, but men can also get it. More people are surviving breast cancer today because of early detection and improved treatments. Ongoing research is helping doctors make better treatment plans and offer more options to patients. Researchers are constantly working on new ways to treat breast cancer more effectively.

1.1 What does the Breast cancer mean and their types?

Cancer occurs when there's a change in the instructions that tell your cells how to work, grow, and reproduce. When a cell becomes cancerous, it starts growing and multiplying quickly and out of control. This rapid growth can lead to a tumor, and sometimes the cancer cells spread to other parts of the body this is called as metastasis. Cancer can affect any cell in your body, including those in your breasts. Most breast cancer cases are sporadic, meaning they occur randomly (90%-95%), with only 5%-10% of cases

linked to a known genetic mutation. The BRCA1 and BRCA2 genes are the most common genetic mutations associated with breast cancer.

The two main types of invasive breast cancer are invasive ductal carcinoma and invasive lobular carcinoma. The development of breast cancer results from a mix of genetic and environmental factors, hormone levels, and individual risk factors.

The molecular subtypes of breast cancer play a key role in determining how it develops, how it is treated, and the outlook:

1.1.1 Luminal A: Hormone receptor-positive, HER-2 negative.

1.1.2 Luminal B: Hormone receptor-positive, HER-2 positive.

1.1.3 Basal-like: Hormone receptor-negative, HER-2 negative.

1.1.4 HER-2 enriched: HER-2 positive, hormone receptor-negative

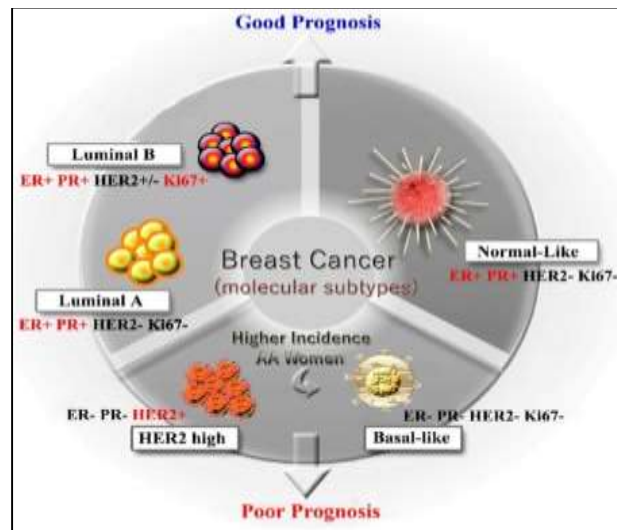


Fig 1.1 : Molecular subtypes of Breast cancer [39].

There are different types of breast cancer, and they show up in various ways. Some of the main types include: [12]

- ER-Positive Breast Cancer:** This type of cancer has cells with estrogen receptors, meaning the hormone estrogen helps the cancer grow.
- Triple-Positive Breast Cancer:** These cancer cells have receptors for estrogen (ER), progesterone (PR), and an excess of a protein called HER2. All three affect the cancer's growth.
- HER2-Positive Breast Cancer:** This type has too much of the HER2 protein, which speeds up cell growth and division.
- Triple-Negative Breast Cancer:** This form of cancer doesn't have receptors for estrogen progesterone, or HER2, so it's not influenced by these hormones.

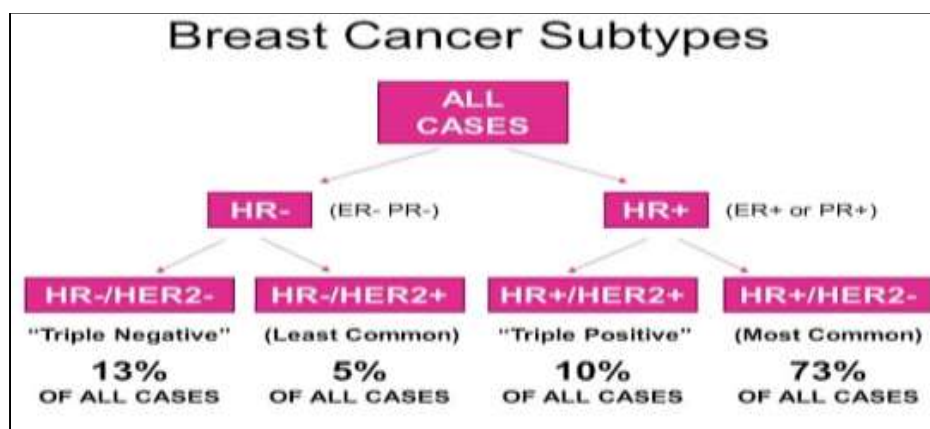


Fig 1.2 : Types of Breast cancer [40]

2. Epidemiology:

According to the World Health Organization, breast cancer is the greatest burden for women worldwide, accounting for an estimated 107.8 million life-altering disability years (DALYs), of which 19.6 million are due to cancer. Breast cancer is the most common cancer in women worldwide, with 2.26 million new cases in 2020 (95% UI, 2.24-2.79 million). Breast cancer alone accounts for approximately 29% of all new cancers in women in the United States. 2018 GLOBOCAN data show that the age-specific incidence rate (ASIR) of breast cancer has a positive association with the human development index (HDI). According to 2020 data, ASIR is highest in countries with a high Human Development Index (75.6 per 100,000 people), while in countries with a medium and low Human Development Index, ASIR is lower than 200% (75.6 per 100,000 people and 27.8 per 100,000 people and 36.1 per 100,000 people, respectively). Even though developed regions had the highest breast cancer rates, Asia and Africa accounted for 63% of total deaths in 2020. In high-income countries, most women survive breast cancer, but in low- and many middle-income countries, the outcome is often the opposite [1].

In 2022, there were 2.3 million global cases of breast cancer diagnosed in women leading to 670,000 deaths [2]. In 2024, it is projected that around 310,720 women and about 2,800 men will be diagnosed with invasive breast cancer [3].

3. Ethnicity:

Breast cancer diagnoses are more common among White women than among Black, Hispanic, and Asian women [4]. However, Black women tend to develop more aggressive forms of breast cancer, often at a younger age and in more advanced stages. Additionally, they have a higher likelihood of dying from breast cancer [6].

4. Mortality rate:

Across all countries, the average breast cancer mortality rate was 13.77 per 100,000 in 1990, with an overall increase of 0.7 per 100,000 in the mortality rate from 1990 to 2015. Due to limited information, inadequate awareness about cancer, insufficient healthcare facilities, and restricted access to treatment, along with delayed screening and diagnosis, breast cancer mortality rates are higher in developing countries [5].

5. Etiology:

5.1 Age :

Most of the breast cancer found and diagnosed in after age of 50 year in women. But now cancer can strike at any age. According to observed data cancer found at younger age between 18 year to 45 year this is called as early onset breast cancer. In 2012 and 2016 about 10 % women were diagnosed early onset breast cancer [7].

5.2 Family history/ heritable factor :

Having a first-degree family member with breast cancer significantly increases the risk of developing the disease. Studies show that a woman is twice as likely to get breast cancer if she has a first-degree relative (like her mother, sister, or daughter) with a history of the disease. If a woman has two first-degree relatives who had breast cancer, her risk is three times higher than a woman with no family history. Additionally, a large study of over 5,000,000 women found that those with a second-degree relative (like a grandmother, aunt, or niece) who had breast cancer, but no first-degree relatives with the disease, had a 20% higher risk [11].

5.3 Gender :

Each year, around 280,000 women and 3,000 men are diagnosed with breast cancer in the United States, indicating that women are about 100 times more likely to develop the disease than men. This higher rate in women is mainly due to increased stimulation from the hormones estrogen and progesterone. Studies have found that in post-menopausal women, higher levels of circulating estrogens and androgens are linked to an increased risk of breast cancer. In men, a higher ratio of estrogen to androgen—resulting from excess estrogen or low androgen levels—is also associated with a greater risk. Furthermore, both pre-menopausal and post-menopausal women experience more significant fluctuations in sex hormone levels throughout their lives compared to men, which contributes to their elevated breast cancer risk.

5.4 Endogenous Estrogen :

As women age, estrogen levels rise because fat cells in the breasts generate more of the enzyme aromatase, which facilitates estrogen production. Elevated estrogen can encourage the division and growth of breast tissue, potentially leading to mutations that cause cancer. Common understanding of estrogen's role in breast cancer is that it serves as a catalyst for tumor growth by promoting the division and proliferation of breast tissue, which increases the likelihood of mutations that can lead to cancer [40]. Estrogen, a strong stimulator of mammary cell growth, has been associated with the development of breast tumors for a long time [15].

5.5 Obesity:

Obesity is known to increase the risk of developing breast cancer [15]. Excess body weight is associated with a higher risk of postmenopausal breast cancer, and emerging evidence indicates that obesity may lead to a poorer prognosis in women who have been diagnosed with early-stage breast cancer [16].

5.6 Alcohol consumption :

The byproducts of alcohol metabolism are toxic and may cause changes to DNA that can lead to cancer. Recent studies have looked at genes that affect how quickly alcohol is metabolized. Genes that increase blood levels of acetaldehyde are thought to raise the risk of breast cancer [17].

6. What causes a normal cell to become cancerous?

A normal cell can turn into a cancer cell when its DNA is damaged. DNA plays a crucial role in controlling the cell's growth and death cycles, so any alterations or damage to it can significantly impact the cell's behavior. In healthy cells, when DNA is damaged, the cell typically either repairs the damage or undergoes programmed cell death. However, in cancer cells, the damaged DNA remains unrepaired, and this faulty genetic information is passed on to newly formed abnormal cells that arise from the original defective cell.

Damaged DNA can be inherited from parents or relatives through genetic mutations. Additionally, exposure to harmful substances, such as tobacco smoke and alcohol, can also lead to DNA damage [18].

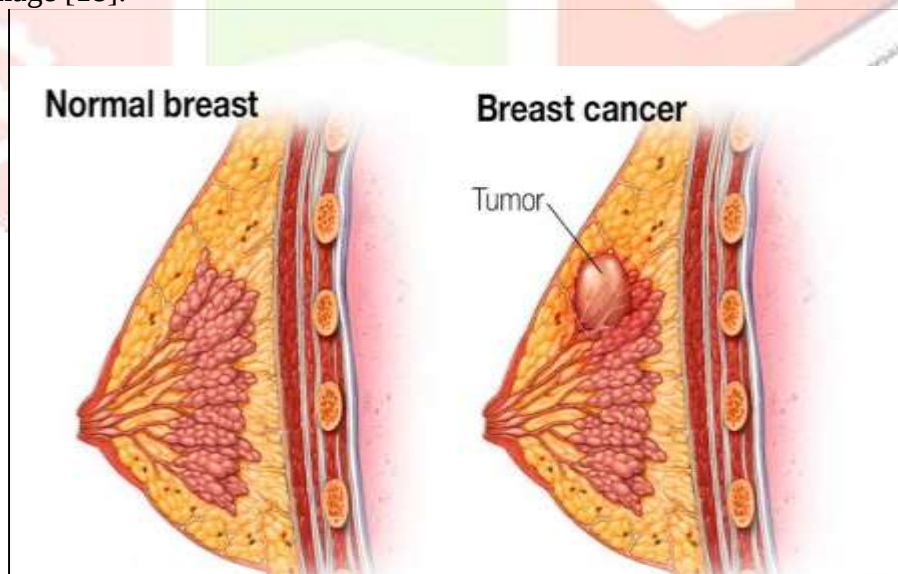


Fig 6: Normal breast v/s Cancerous breast [42]

6.1 In many cases there is occurrence of lumps, so what does this lumps in breast actually mean?

Breast lumps can be caused by various conditions, with most being non-cancerous or other medical conditions. Common causes include: [38]

- Fibrocystic breast condition, which makes breasts feel lumpy, tender, and sore.
- Cystic breast condition, which are fluid-filled sacs that can develop in the breast.

While lumps can be concerning, they aren't always linked to cancer.

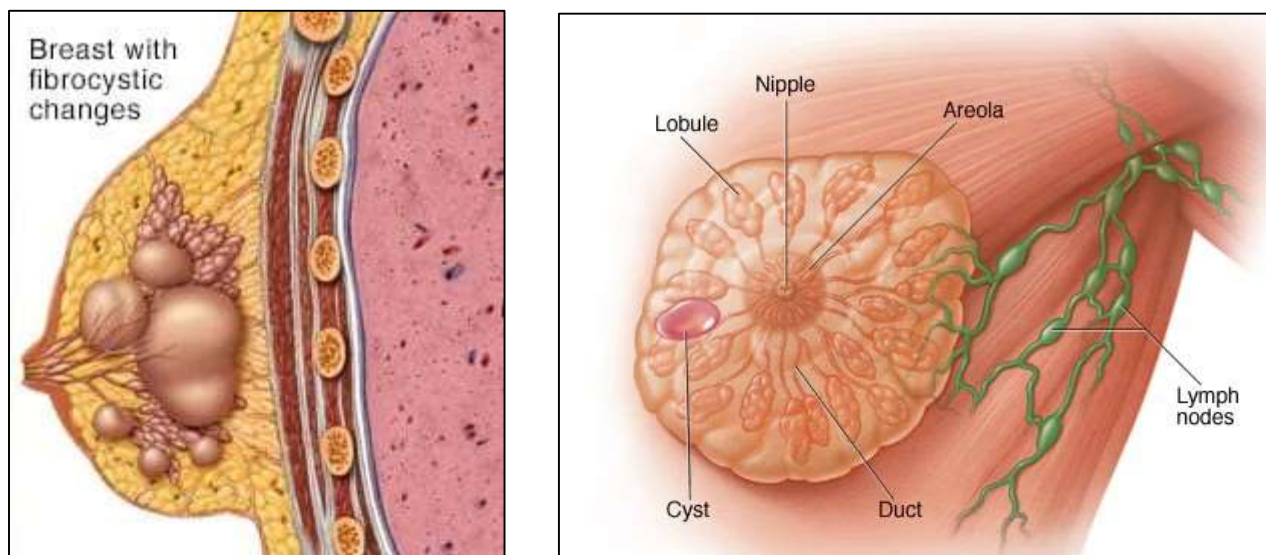


Fig 6.1 : Fibrocystic and Cystic breast condition [33]

7. Pathogenesis

The human body contains trillions of cells, each governed by a precisely regulated cell cycle that manages their growth, development, division, and death. In childhood, normal cells divide rapidly to support growth. Once a person reaches adulthood, cell division mainly occurs to replace aging cells and to heal injuries. This process of cell division and growth is regulated by the cell's genetic blueprint, which consists of DNA and genes located within the nucleus [18].

Breast cancer is a type of malignant tumor that originates in the breast cells. Like other forms of cancer, various factors can increase the developing breast cancer. DNA damage and genetic mutations, often linked to estrogen exposure, have been shown to contribute to the onset of breast cancer [18].

7.1 Step-by-Step Process of Pathogenesis in Breast Cancer

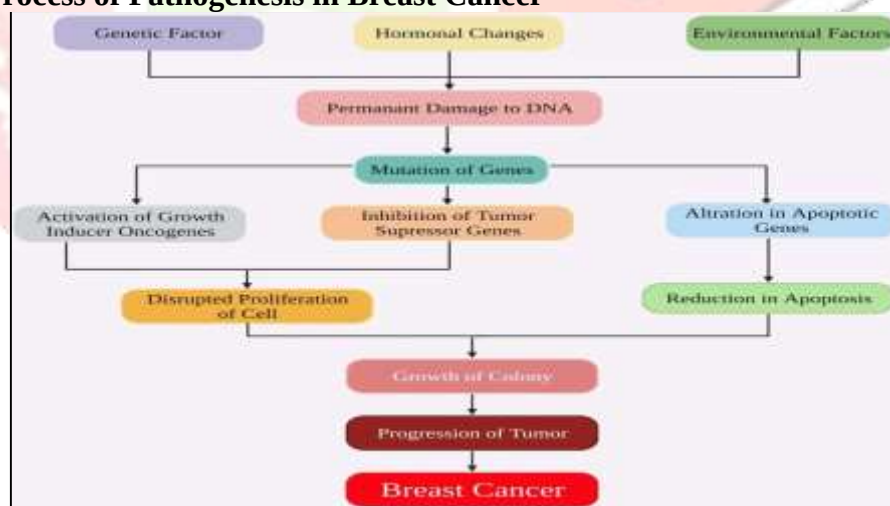


Fig 7.1: Step-by-Step Process of Pathogenesis in Breast Cancer [32]

7.1.1 Genetic Mutations :

The pathogenesis of breast cancer often begins with mutations in genes that regulate cell growth and division. Commonly mutated genes in breast cancer include BRCA1, BRCA2, TP53, and PIK3CA. These mutations can be inherited (germ line mutations) or acquired over time (somatic mutations) due to environmental factors like radiation, carcinogens, or hormones [19].

7.1.2 DNA Damage and Repair Mechanisms in a normal cell :

DNA damage is repaired by complex mechanisms such as homologous recombination. In cells with mutated BRCA1/BRCA2, these repair mechanisms are defective, leading to the accumulation of DNA damage. This unrepaired DNA damage contributes to further mutations and genomic instability [20].

7.1.3 Proliferation of Mutated Cells :

Once the DNA damage is no longer controlled, the affected breast epithelial cells begin to proliferate abnormally. Growth signals in breast cancer are often mediated by overexpression of receptors such as HER2 (human epidermal growth factor receptor) , which leads to increased cell division [21].

7.1.4 Avoidance of Apoptosis:

Cancer cells develop mechanisms to evade programmed cell death (apoptosis). In breast cancer, mutations in the TP53 gene, a tumor suppressor gene, lead to the loss of apoptotic control, allowing damaged cells to survive and proliferate [22].

7.1.5 Angiogenesis:

As the tumor grows, it requires more oxygen and nutrients. Cancer cells stimulate the formation of new blood vessels (angiogenesis) by producing growth factors such as VEGF (vascular endothelial growth factor). These new blood vessels supply the tumor, enabling further growth and metastasis [23].

7.1.6 Metastasis:

Breast cancer cells eventually acquire the ability to invade nearby tissues and spread (metastasize) to distant organs such as the lungs, liver, and bones. This process involves changes in the cell adhesion molecules, allowing cells to detach from the primary tumor and enter the bloodstream or lymphatic system [24].

7.1.7 Immune System Evasion :

Cancer cells can evade detection by the immune system by expressing immune checkpoint molecules like PD-L1. This allows them to avoid destruction by immune cells, further promoting tumor survival and growth [25].

8. Diagnosis:

8.1 Breast Ultrasound:

An ultrasound uses sound waves to create images of structures inside the body. A breast ultrasound helps doctors learn more about a lump in the breast, such as whether it's a solid mass or a fluid-filled cyst. This information helps determine what further tests might be needed [8]

8.2 Mammogram:

A mammogram is an X-ray that takes images of the breast. It is commonly used to screen for breast cancer. If a screening mammogram shows anything unusual, you may need a follow-up mammogram to examine the area more closely. This detailed test is called a diagnostic mammogram and is used to look closely at both breasts [8].

8.3 Breast Biopsy:

A biopsy is a procedure where a sample of breast tissue is removed for testing. A needle is inserted through the skin into the breast, guided by imaging such as X-rays or ultrasound. A small marker is often placed where the tissue was taken to help track the area in future tests [8].

8.4 Breast MRI:

An MRI uses a magnetic field and radio waves to produce detailed images of the breast. It can help spot other areas of cancer in the affected breast or check the other breast for cancer. Usually, a dye is injected before the MRI to enhance the clarity of the images [8].

8.5 Lab Testing of Biopsy:

The tissue sample from the biopsy is tested in a lab to determine if it is cancerous. Additional tests help identify the type of cancer and how fast it is growing. Special tests can also check for hormone receptors on the cancer cells, helping guide treatment decisions [8].

8.6 Staging Breast Cancer:

After a breast cancer diagnosis, further tests are done to determine the cancer's stage, which helps assess the outlook and plan treatment. Staging tests may include blood tests, bone scans, CT scans, MRIs, or PET scans. Full staging information might not be available until after surgery [8].

9. Who provides the breast cancer treatment?

Depending on your treatment plan, your medical team may include various specialists, such as,

9.1 A breast surgeon or surgical oncologist: a physician specializing in surgical treatment for breast cancer [26].

9.2 A radiation oncologist: A doctor focused on treating cancer with radiation therapy [26].

9.3 A medical oncologist: A breast surgeon or surgical oncologist: a physician specializing in surgical treatment for breast cancer [26].

9.4 A plastic surgeon: A doctor who focuses on reconstructive or reparative surgery for parts of the body affected by cancer treatment [26].

10. Prophylaxis:

10.1 Local treatment:

Certain treatments, such as surgery and radiation, are localized, targeting the tumor without impacting the rest of the body. The majority of women with breast cancer will undergo some form of surgery to remove the tumor. Based on the type and stage of breast cancer, additional treatments may be necessary either before, after surgery, or in some cases, both [26].

- Surgery for breast cancer.
- Radiation for breast cancer.

10.2 Systematic treatment

Medications used to treat breast cancer are classified as systemic therapies because they can target cancer cells throughout the body. These drugs may be taken orally, injected into a muscle, or administered directly into the bloodstream. The specific type of drug therapy used will depend on the kind of breast cancer and may include various options, such as [26].

- Chemotherapy for breast cancer
- Hormone therapy for Breast cancer
- Targeted drug therapy for Breast cancer.
- Immunotherapy for breast cancer

11. Current research and future findings:

Current research in breast cancer is focusing on several key areas, including improving early detection, understanding tumor biology, developing targeted therapies, and enhancing personalized treatment plans. These advances aim to increase survival rates, minimize side effects, and improve the quality of life for breast cancer patients.

11.1. Genomic Research and Precision Medicine:

Researchers are exploring the genetic changes and mutations that drive breast cancer. Genomics is beginning to transform breast cancer treatment, with advancements becoming increasingly impactful, particularly as treatment personalization evolves and new technologies are implemented. The impact of genomics in breast cancer treatment is still moderate. It mainly helps in deciding on adjuvant treatments for early-stage cancers and guiding therapy for HER2-positive breast cancers at any stage. However, since breast cancer is diverse and complex, treatments must be tailored to different molecular subtypes and driven by specific genetic changes [43].

11.2. Targeted Therapies:

Targeted therapy uses drugs to focus on specific molecules in or on cancer cells that help them grow and divide. By blocking these molecules, the drugs stop cancer cells from growing and spreading, while causing less damage to normal cells. This type of treatment is also known as molecular targeted therapy. Targeted therapies are designed to attack specific proteins or genes involved in cancer growth. Research on HER-2 positive breast cancer has led to therapies like trastuzumab (Herceptin) and pertuzumab, which significantly improve outcomes for this subtype. Ongoing studies are examining other targets, such as PI3K, CDK4/6 inhibitors (like palbociclib), and PARP inhibitors, which are particularly useful for cancers involving BRCA mutations [44].

11.3. Immunotherapy:

Immunotherapy uses medications to boost the immune system, helping it recognize and destroy cancer cells more effectively. It targets specific proteins in the immune system to strengthen its response against cancer. Some immunotherapy drugs, like monoclonal antibodies, work in different ways to control cancer cells. They can also be considered targeted therapy because they block specific proteins on cancer cells to stop them from growing. Trials are investigating immune checkpoint inhibitors, such as pembrolizumab, to treat triple-negative breast cancer (TNBC), which has fewer treatment options and a more aggressive course. Early results are promising, especially when combined with chemotherapy [45].

11.4. Liquid Biopsies:

Liquid biopsy, using blood samples to detect cancer DNA or cells, is being studied for early breast cancer detection, treatment monitoring, and relapse identification. It has improved breast cancer care by aiding in diagnosis, prognosis, and tracking disease progression. Liquid biopsy analyzes blood components like circulating tumor cells (CTCs), DNA (ctDNA), RNA, and exosomes, offering a less invasive way to manage the disease [47].

11.5 Hormonal Therapies and Resistance:

Research is ongoing to address resistance to hormonal therapies, such as tamoxifen or aromatase inhibitors, which are commonly used to treat hormone receptor-positive breast cancer. Research indicates that patients with estrogen receptor-positive tumors often benefit from tamoxifen, a medication approved by the FDA for several uses. These include:

- Treating breast cancer in both women and men
- Providing additional treatment after surgery and radiation (adjuvant therapy)
- Treating women with ductal carcinoma in situ (non-invasive breast cancer) after surgery and radiation to lower the risk of developing invasive breast cancer
- Reducing breast cancer risk in certain high-risk individuals [42].

11.6 Prevention and Risk Reduction:

Studies on lifestyle factors, such as diet, exercise, and alcohol consumption, aim to identify ways to reduce the risk of developing breast cancer. Additionally, researchers are investigating the use of medications, like tamoxifen and raloxifene, in high-risk populations for preventive purposes.

Current breast cancer research is moving toward more personalized, less invasive treatments, with a focus on understanding tumor biology, expanding targeted therapies, and utilizing the immune system to improve patient outcomes. These advances hold promise for better management of breast cancer in the future [46].

12. Some warning signs of breast cancer include



Fig 12: symptoms of breast cancer [32]

- 12.1 A Thickening or swelling in part of the breast[35]
- 12.2 Skin irritation or dimpling on the breast[35]
- 12.3 Redness or flaky skin around the nipple or breast[35]
- 12.4 Nipple pulling inward or pain in the nipple area[35]
- 12.5 Unusual nipple discharge, including blood[35]
- 12.6 Changes in breast size or shape[35]
- 12.7 Pain in any part of the breast[35]
- 12.8 A new lump in the breast or underarm [35]

13. Prevention:

13.1 Lifestyle modifications: Keep a healthy weight, engage in regular physical activity, and follow a nutritious diet. A plant-based diet high in whole grains, vegetables, fruits, and legumes is advised. Reduce consumption of red and processed meats, sugary beverages, and soft drinks [37].

13.2 Bilateral Risk-Reducing Mastectomy (BRRM): Bilateral Risk-Reducing Mastectomy (BRRM) lowers the chance of getting breast cancer by 90% in women at high risk, like those with BRCA gene mutations. It also helps improve survival rates specifically for BRCA1 carriers. Additionally, removing the ovaries and fallopian tubes (Bilateral Risk-Reducing Salpingo-Oophorectomy) can reduce the risk of breast cancer in premenopausal women with BRCA2 mutations [27].

13.3 Risk Perception and Communication: Improving how risk information is shared with women, helping them understand their chances of developing breast cancer [28].

13.4 Identification of High-Risk Women: Using tools like "Prevent! Online" to identify women at high risk [29].

13.5 Risk-Reducing Programs: Developing personalized, multi-level prevention programs based on individual risk factors [29].

13.6 Genetic screening for high risk individual [29].

13.7 Regular mammograms and self-examinations for early identification [29].

13. Complication:

14.1 Neuronal complication

Neurological issues were found in about half of the women receiving breast cancer treatment. The most frequent problems included nerve pain and chemotherapy-induced peripheral neuropathy. Cognitive problems either already present or developing during treatment, were also commonly seen in these patients [30].

14.2 Pregnancy in breast cancer

Currently, about one in 3,000 women giving birth are either diagnosed with or being treated for breast cancer. While it's uncommon, the number of cases of pregnancy-related breast cancer (PABC) is rising because more women are waiting until later in life to have children [31].

14.3. Co -morbidities -: other health issues [31].

14.4. Osteoporosis -: Weakened bones and nails [31].

14.5. Fatigue -: Persistent feeling of tiredness or exhaustion that doesn't improve [31].

14.6. Physical functioning challenges-: Difficulty in mobility and lack of strength [31].

14.7. Difficulty in Cognitive function -: Difficulty in focus and concentration, Memory issue, Problem solving and other aspect of thinking [31].

14.8. Nutritional concern-: Consumption of high fat diet [31].

14.9. Reduced physical function :- Difficulty in daily activities [31].**15. Conclusion:**

Breast cancer remains a critical health issue, necessitating a multifaceted approach to management and prevention. Early detection through regular screenings is vital for improving outcomes, while advancements in targeted therapies and personalized treatment strategies have revolutionized patient care. A multidisciplinary approach involving healthcare professionals ensures comprehensive support, addressing both medical and emotional needs. Additionally, tackling disparities in access to care is essential for equitable treatment across diverse populations. Future research will continue to enhance our understanding of the disease, leading to innovative therapies and improved prevention strategies. Collectively, these efforts aim to reduce the burden of breast cancer and enhance the quality of life for those affected.

References:

1. Łukasiewicz S, Czezelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. *Cancers (Basel)*. 2021 Aug 25; 13(17):4287. Doi: 10.3390/cancers13174287. PMID: 34503097; PMCID: PMC8428369
2. The world health Organization.(2022).breast cancer - <https://www.who.int/news-room/fact-sheets/detail/breast-cancer>.
3. BreastCancer.org. "Facts and Statistics." Accessed September 30, 2024.<https://www.breastcancer.org/facts-statistics>
4. BreastCancer.org. "Race and Ethnicity as Risk Factors for Breast Cancer." Accessed September 30, 2024. <https://www.breastcancer.org/risk/risk-factors/race-ethnicity>
5. Dr.Mettlin, Curtis. "Global Breast Cancer Mortality Statistics." *CA: A Cancer Journal for Clinicians* 49, no. 3 (1999): 138-144. [Google Scholar]
6. Breastcancer.org. (n.d.). Risk factors for breast cancer: Race and ethnicity. Retrieved September 30, 2024, from <https://www.breastcancer.org/risk/risk-factors/race-ethnicity>
7. Dr.Mettlin, C. (1999). Global breast cancer mortality statistics. *CA: A Cancer Journal for Clinicians*, 49(3), 138-144. <https://doi.org/10.3322/canjclin.49.3.138> [Google Scholar]
8. Mayo Clinic. (n.d.). Breast cancer - Diagnosis and treatment. Mayo Clinic. Retrieved September 30, 2024, from <https://www.mayoclinic.org/diseases-conditions/breast-cancer/diagnosis-treatment/drc-20352475>
9. Watson, S. (2023, July 12). Is stage 4 cancer curable? *Medical News Today*. Retrieved September 30, 2024, from <https://www.medicalnewstoday.com/articles/is-stage-4-cancer-curable>
10. National Center for Biotechnology Information. (n.d.). Etiology of breast cancer. In *Breast Cancer*. Retrieved September 30, 2024, from <https://www.ncbi.nlm.nih.gov/books/NBK583809/> .
11. National Cancer Institute. (n.d.). Breast cancer research. U.S. Department of Health and Human Services. Retrieved September 30, 2024, from <https://www.cancer.gov/types/breast/research/articles>
12. National Center for Biotechnology Information. (n.d.). Etiology of breast cancer. In *Breast cancer*. Retrieved September 30, 2024, from <https://www.ncbi.nlm.nih.gov/books/NBK583809/>.
13. Harvard Gazette. (2023, May 18). Estrogen: A more powerful breast cancer culprit than we realized. Retrieved September 30, 2024, from <https://news.harvard.edu/gazette/story/2023/05/estrogen-a-more-powerful-breast-cancer-culprit-than-we-realized/> .
14. Cleary, M. P., Grossmann, M. E., & Ray, A. (2010). Effect of obesity on breast cancer development. *Journal of Comparative Pathology*, 47(2), 2. <https://doi.org/10.1177/0300985809357753> .

15. Ligibel, J. (2011). Obesity and breast cancer. *Oncology*, 25(11),994-1000.https://scholar.google.com/scholar?hl=hi&as_sdt=0%2C5&q=Brest+cancer+obesity+can+cause&btnG=#d=gs_qabs&t=1727447376755&u=%23p%3Dr_aoKoVunPEJ [Google Scholar]
16. Coronado, G. D., Beasley, J., & Livaudais, J. (2011). Alcohol consumption and the risk of breast cancer. *Salud Pública de México*, 53(5), 440-447.https://scholar.google.com/scholar?hl=hi&as_sdt=0%2C5&q=breast+cancer+alcohol+consumption&oq=breast+cancer+al#d=gs_qabs&t=1727449049474&u=%23p%3DIN0TXfK6K6QJ [Google Scholar].
17. News-Medical. (n.d.). Breast cancer pathophysiology. Retrieved September 30, 2024, from <https://www.news-medical.net/health/Breast-Cancer-Pathophysiology.aspx>.
18. Fan XY, Yuan L, Wu C, Liu YJ, Jiang FL, Hu YJ, Liu Y. Mitochondrial toxicity of organic arsenicals: membrane permeability transition pore opening and respiratory dysfunction. *Toxicol Res (Camb)*. 2017 Dec 19;7(2):191-200. doi: 10.1039/c7tx00234c. PMID: 30090574; PMCID: PMC6061234 . [PubMed].
19. Depue BE, Burgess GC, Willcutt EG, Ruzic L, Banich MT. Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: evidence from deficits in individuals with ADHD. *Neuropsychologia*. 2010 Nov;48(13):3909-17. doi: 10.1016/j.neuropsychologia.2010.09.013. Epub 2010 Sep 21. PMID: 20863843; PMCID: PMC2979319. [PubMed].
20. Depue BE, Burgess GC, Willcutt EG, Ruzic L, Banich MT. Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: evidence from deficits in individuals with ADHD. *Neuropsychologia*. 2010 Nov; 48(13):3909-17. doi: 10.1016/j.neuropsychologia.2010.09.013. Epub 2010 Sep 21. PMID: 20863843; PMCID: PMC2979319. [PubMed].
21. Our New York Letter: Treatment of Typhoid Fever in the New York Hospitals-Dr. Spitzka's Experiments in the Production of Hydrophobia-A Successful Case of Laparotomy in Case of Gun-Shot Wound-Treatment of Varicocele, Etc. *Atlanta Med Surg J* (1884). 1886 Nov;3(9):569-571. PMID: 35827911; PMCID: PMC8927315. [PubMed].
22. Wang L, Jirka G, Rosenberg PB, Buckley AF, Gomez JA, Fields TA, Winn MP, Spurney RF. Gq signaling causes glomerular injury by activating TRPC6. *J Clin Invest*. 2015 May;125(5):1913-26. doi: 10.1172/JCI76767. Epub 2015 Apr 6. PMID: 25844902; PMCID: PMC4463190. [PubMed]
23. Li X, Krumholz HM, Yip W, Cheng KK, De Maeseneer J, Meng Q, Mossialos E, Li C, Lu J, Su M, Zhang Q, Xu DR, Li L, Normand ST, Peto R, Li J, Wang Z, Yan H, Gao R, Chunharas S, Gao X, Guerra R, Ji H, Ke Y, Pan Z, Wu X, Xiao S, Xie X, Zhang Y, Zhu J, Zhu S, Hu S. Quality of primary health care in China: challenges and recommendations. *Lancet*. 2020 Jun 6;395(10239):1802-1812. doi: 10.1016/S0140-6736(20)30122-7. PMID: 32505251; PMCID: PMC7272159. [PubMed]
24. Morgan EL, Macdonald A. Autocrine STAT3 activation in HPV positive cervical cancer through a virus-driven Rac1-NFκB-IL-6 signalling axis. *PLoS Pathog*. 2019 Jun 21;15(6):e1007835. doi: 10.1371/journal.ppat.1007835. PMID: 31226168; PMCID: PMC6608985.
25. American Cancer Society. (n.d.). Breast cancer treatment. Retrieved September 30, 2024, from <https://www.cancer.org/cancer/types/breast-cancer/treatment.html>
26. Thorat MA, Balasubramanian R. Breast cancer prevention in high-risk women. *Best Pract Res Clin Obstet Gynaecol*. 2020 May;65:18-31. doi: 10.1016/j.bpobgyn.2019.11.006. Epub 2019 Nov 21. PMID: 31862315. [PubMed].
27. Borgquist S, Hall P, Lipkus I, Garber JE. Towards Prevention of Breast Cancer: What Are the Clinical Challenges? *Cancer Prev Res (Phila)*. 2018 May;11(5):255-264. doi: 10.1158/1940-6207.CAPR-16-0254. Epub 2018 Apr 16. PMID: 29661853.[PubMed] .

28. Borgquist S, Hall P, Lipkus I, Garber JE. Towards Prevention of Breast Cancer: What Are the Clinical Challenges? *Cancer Prev Res (Phila)*. 2018 May;11(5):255-264. doi: 10.1158/1940-6207.CAPR-16-0254. Epub 2018 Apr 16. PMID: 29661853.[PubMed]
29. Pereira, S., Fontes, F., Sonin, T., Dias, T., Fragoso, M., Castro-Lopes, J. M., & Lunet, N. (2015). Neurological complications of breast cancer: A prospective cohort study. *Breast*, 24(4), 411-416. <https://doi.org/10.1016/j.breast.2015.05.006>
30. Asgeirsson KS. Pregnancy-associated breast cancer. *Acta Obstet Gynecol Scand*. 2011 Feb;90(2):158-66. doi: 10.1111/j.1600-0412.2010.01035.x. Epub 2010 Dec 2. PMID: 21241261.[PubMed].
31. Ganatra, H., Tan, J.K., Simmons, A. et al. Applying whole-genome and whole-exome sequencing in breast cancer: a review of the landscape. *Breast Cancer* (2024). <https://doi.org/10.1007/s12282-024-01628-9>
32. Conditions. (2024, January 9). Breast cysts. <https://www.altru.org/health-library/conditions/breast-cysts>.
33. Charan M, Verma AK, Hussain S, Misri S, Mishra S, Majumder S, Ramaswamy B, Ahirwar D, Ganju RK. Molecular and Cellular Factors Associated with Racial Disparity in Breast Cancer. IN *J Mol Sci*. 2020 Aug 18;21(16):5936. doi: 10.3390/ijms21165936. PMID: 32824813; PMCID: PMC7460595
34. Centers for Disease Control and Prevention. (2023). What are the symptoms of breast cancer?. Retrieved from <https://www.cdc.gov/breast-cancer/symptoms/index.html>
35. Hormonal Therapies: Mayo Clinic. (2022). Hormone therapy for breast cancer. Retrieved from <https://www.mayoclinic.org/tests-procedures/feminizing-hormone-therapy/about/pac-2038509>
36. UCSF Health. (n.d.). Breast cancer prevention tips. UCSF Health. <https://www.ucsfhealth.org/education/breast-cancer-prevention-tips>.
37. Cleveland Clinic. (n.d.). Breast lumps: Symptoms and causes. Cleveland Clinic. Retrieved October 1, 2024, from <https://my.clevelandclinic.org/health/symptoms/6906-breast-lumps>
38. Yedjou, C. G., Sims, J. N., Miele, L., Noubissi, F., Lowe, L., & Tchounwou, P. B. (2020). Molecular and cellular factors associated with racial disparity in breast cancer. ResearchGate. https://www.researchgate.net/publication/343725505_Molecular_and_Cellular_Factors_Associated_with_Racial_Disparity_in_Breast_Cancer
39. LP Information. (2020, November 6). HR+/HER2- breast cancer market size, share, development by 2025. Press release. <https://www.openpr.com/news/2173566/hr-her2-breast-cancer-market-size-share-development-by-2025>
40. Pesheva, E. (2023, May 17). Potential path to better testing in findings that identify hormone as 'a catalyst and a cause' in disease. HMS Communications. Retrieved from <https://news.harvard.edu/gazette/story/2023/05/estrogen-a-more-powerful-breast-cancer-culprit-than-we-realized/>.
41. Normal breast vs. Breast cancer image <https://images.app.goo.gl/BSh1oXX62t6ifXR09>

42. Quirke VM. Tamoxifen from Failed Contraceptive Pill to Best-Selling Breast Cancer Medicine: A Case-Study in Pharmaceutical Innovation. *Front Pharmacol.* 2017 Sep 12;8:620. doi: 10.3389/fphar.2017.00620. PMID: 28955226; PMCID: PMC5600945.
43. Hamdan D, Nguyen TT, Leboeuf C, Meles S, Janin A, Bousquet G. Genomics applied to the treatment of breast cancer. *Oncotarget.* 2019 Jul 30;10(46):4786-4801 doi: 10.18632/oncotarget.27102. PMID: 31413819; PMCID: PMC6677666
44. Canadian Cancer Society. (2024, March). Targeted therapy for breast cancer. Retrieved from [https://cancer.ca/en/cancer-information/cancer-types/breast/treatment/targeted-therapy#:~:text=Targeted%20therapy%20uses%20drugs%20to,back%20\(recurred\)%20after%20other%20tre atments](https://cancer.ca/en/cancer-information/cancer-types/breast/treatment/targeted-therapy#:~:text=Targeted%20therapy%20uses%20drugs%20to,back%20(recurred)%20after%20other%20tre atments)
45. American Cancer Society. (n.d.). Immunotherapy for breast cancer. Retrieved from <https://www.cancer.org/cancer/breast-cancer/treatment/immunotherapy.html>
46. Centers for Disease Control and Prevention. (n.d.). Breast cancer: Reducing risk. Retrieved from <https://www.cdc.gov/breast-cancer/prevention/index.html#:~:text=Steps%20you%20can%20take,ways%20to%20lower%20your%20risk>
47. Alimirzaie S, Bagherzadeh M, Akbari MR. Liquid biopsy in breast cancer: A comprehensive review. *Clin Genet.* 2019 Jun;95(6):643-660. doi: 10.1111/cge.13514. Epub 2019 Feb 27. PMID: 30671931.

