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"BREAST CANCER: A COMPREHENSIVE REVIEW"

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ABSTRACT

The objective of this study was to provide a concise overview of breast cancer, including its causes, risk factors, diagnosis, and treatment options both in India and around the world. Additionally, it offered a brief description of cancer and its various types. Breast cancer is recognized as the most prevalent cancer among women globally, with varying incidence rates across different regions. It ranks second in terms of incidence worldwide, following lung cancer. According to a 2012 survey by the World Health Organization, there were approximately 1.67 million new cases of breast cancer diagnosed globally, with an incidence rate of about 25.8 per 100,000 individuals in India. This disease has emerged as the most common cancer among women in both urban and rural areas of India. It is also noteworthy that breast cancer can affect men, although it occurs much less frequently, accounting for less than 1% of all cases, with only one in a thousand men expected to be diagnosed with the disease.

KEYTAKEAWAYS

- Early detection and screening are critical.
- Targeted therapies and immunotherapy show promise.
- Chemotherapy remains a cornerstone of treatment.
- Multidisciplinary care improves patient outcomes.
- Continued research is essential for advancements.

1) INTRODUCTION

Breast cancer is a common and serious tumor affecting women, influenced by various internal and external factors, including lifestyle, environment, and social-psychological

aspects.[1-3] Research shows that 5% to 10% of cases are linked to genetic mutations and family history, while 20% to 30% are due to modifiable risk factors.[4] It begins in breast cells, forming tumors that can invade surrounding tissues and metastasize. Abnormal growth can also lead to non-cancerous conditions like atypical hyperplasia and benign tumors such as intraductal papillomas.[5]

However, alterations to breast cells can sometimes lead to breast cancer. The cells lining the ducts, which are the tubes that transport milk from the body, are usually where breast cancer starts. to the nipple glands. The term "ductal carcinoma" refers to this particular form of breast cancer. The lobules' cells, which are groups of glands that produce milk; they can also provide develop into cancer.[6,7] This type of cancer is called lobular carcinoma of cancer. It is possible for lobular and ductal carcinomas to be in situ. It indicates that the cancer is still there where it initially appeared. emerged and hasn't reached nearby tissues. They might additionally be intrusive, signifying that they have infiltrated the surrounding tissues.[8]

Breast cancer can present in various less common forms, including triple-negative breast cancer, Paget's disease of the breast, and inflammatory breast cancer. Additionally, non-Hodgkin lymphoma and soft tissue sarcoma are rare types associated with breast cancer.[9] Although the overall incidence of breast cancer remains low, research indicates a steady increase in cases in China. By 2022, it is projected that the number of Chinese women diagnosed with the disease will exceed 100 per 100, 000, resulting in an estimated 2.5 million women aged 35 to 49 affected by breast cancer. Therefore, it is essential to investigate the risk factors associated with breast cancer to mitigate its incidence.[10] Globally, breast cancer is the most common cancer among women and the leading cause of cancer-related mortality in this demographic. In 2018, approximately 630,000 women succumbed to breast cancer, with around 2.09 million new cases diagnosed. While there are variations in incidence rates across different regions, the overall trend is an increase. Given China's vast population and the rising incidence of breast cancer, which has seen increases of 17.6% and 15.6% in recent years, it is noteworthy that the global incidence (36.1 per 100,000) and mortality rates (8.8 per 100,000) remain relatively low. Nevertheless, the growing burden of breast cancer is becoming a significant concern for public health worldwide.[11]

Breast cancer is a complex illness with significant behavioral/lifestyle, environmental, and genetic components. The goal of the present review was to look into the risk factors and epidemiology. causes of breast cancer worldwide to see how common it is and support early

detection. The primary causes of breast cancer risk genetic factors, particularly family history; nutrition; and obesity, as our nation's standard of living rises, women are becoming more and more obese, and they typically eat increasing fat content; drinking and smoking; the other is ionising radiation; menstruation in particular, bear, and if nursing, these elements may also have an impact on the incidence of breast cancer.

We should strive to stay away from using cosmetics that include oestrogen in our daily life in order to decrease the effect that exogenous hormones have on the body. There has been much discussion over these appeals. Therefore, it is crucial to carefully investigate the breast cancer risk variables employing clinical prevention and treatment using meta-methods.[12] We carried out a meta-analysis of risk variables for breast cancer in Chinese women in the present research by obtaining relevant literature between 2001 and 2021, notwithstanding the fact that Chinese academics already completed the task.[13]

Our objective was to give Chinese women basic knowledge about preventing breast cancer. A risk factor is something that increases your likelihood of developing cancer. The cause may be a disease, drug, or habit. Most malignancies are caused by a variety of risk factors. However, women can sometimes acquire breast cancer. who lack any of the following risk factors. Women have a higher risk of breast cancer than men do. Women are when exposed to oestrogen and progesterone, their breast cells are more prone to develop breast cancer.

These hormones, especially oestrogen, which has been connected to breast cancer, aid in the growth of some breast cancers. High-income, developed countries like the US, Canada, and several European countries are examples where breast Cancer is more common. Growing older increases the chance of obtaining breast cancer. Women in the 50–69 age range are the most prevalent group for breast cancer.[14] The breast is made up of 15 to 20 lobes arranged in a circular pattern. The size and shape of the breasts are affected by the adipose tissue surrounding the lobes. Each lobe contains lobules that contain the glands responsible for milk production when stimulated by hormones. The development of breast cancer is often subtle, with many patients discovering their condition during routine screenings. Others may notice symptoms such as nipple discharge, changes in breast shape or size, or an incidental lump. Mastalgia is also a common experience. Diagnosing breast cancer requires a physical examination, imaging technique especially mammography and a tissue biopsy.[14]

Early detection greatly improves survival rates. The risk of a poor prognosis and the likelihood of distant metastasis are linked to the tumour's ability to spread via lymphatic and haematogenous pathways. This highlights the critical role of breast cancer screening programs.[15] A risk factor is any element that raises the chances of developing cancer, which can include lifestyle choices, substances, or medical conditions. Most cancers result from a combination of various risk factors. Breast cancer is more common in women than in men, especially when breast cells are exposed to estrogen and progesterone. The incidence of breast cancer is particularly high in wealthy, developed countries like Canada, the United States, and certain European nations. These hormones, particularly estrogen, are connected to the disease and promote its progression. Furthermore, the risk of developing breast cancer increases with age, with the majority of diagnoses occurring in women aged 50 to 69 years.[14]

2) Epidemiology

Breast cancer ranks as the most commonly diagnosed cancer and is the leading cause of cancer-related fatalities among women globally. In 2018, breast cancer represented 2.08 million of the 18.08 million new cancer cases worldwide, resulting in an incidence rate of 11.6%. Additionally, it accounted for 626,679 of the 9.55 million cancer-related deaths, which corresponds to 6.6% of all such fatalities.[16,17] In India, breast cancer has overtaken cervical and oral cancers to become the predominant cancer type and the primary cause of cancer deaths. That same year, there were 162,468 new breast cancer diagnoses, making up 27.7% of all new cancer cases among women in India and 11.1% of all cancer-related deaths.[18,19]

The epidemiological characteristics of breast cancer in Indian women exhibit notable differences when contrasted with those in Western populations.[20,21] In the Western context, the median age for breast cancer diagnosis is around 61 years, with the highest incidence occurring between the ages of 60 and 70. Conversely, in India, a significant number of breast cancer patients are premenopausal, with the peak incidence occurring between the ages of 40 and 50.[22,23] This trend raises concerns, as early-onset breast cancer tends to be more aggressive and associated with a worse prognosis compared to cases diagnosed later in life.[24] Additionally, in the United States, 60% to 70% of breast cancer patients are identified at stage 1, whereas only about 1% to 8% of Indian women are diagnosed at this early stage. While approximately 10% of women in the United States present with stage IV disease, this

figure ranges from 6% to 24% in India, with around 29% to 52% of Indian women diagnosed at stage III. Lastly, despite a global increase in breast cancer incidence, mortality rates are declining in Western countries, whereas they are on the rise in India.[25]

Risk factors

The definitive cause of carcinogenesis remains unidentified; however, various risk factors associated with the onset of breast cancer have been recognized. Among the most significant factors, as highlighted by the aforementioned epidemiological data, are gender, age, and the level of economic development within a specific country. Hormonal influences, particularly those related to the duration of estrogen exposure, are equally critical, alongside reproductive factors such as the number of children, the age at which the first child is born, and breastfeeding practices. Genetic predispositions, the use of hormone replacement therapy, poor dietary habits, and resultant obesity are also considered to play a substantial role in the development of breast cancer. Additionally, hormonal contraception, alcohol intake, and exposure to ionizing radiation during youth are noted as significant risk factors for breast cancer.

i. Sex

Women are the ones who get breast cancer in 99 percent of cases. Men only make up 1% of instances of this malignant tumour, which has a 0.4/105 standardised incidence rate in Poland. Annually, no more than 100 instances are documented.[26] But the Similar to women, men's breast cancer incidence is steadily rising, which is probably linked to increased longevity and obesity.[27]

ii. Age

One of the most significant risk factors for breast cancer is age. All age categories have shown an increase in the prevalence of breast cancer worldwide, with women under fifty years old.[27] Despite being uncommon in this age range, this malignant tumour is still a serious social and clinical issue, as a result of its worsening course—many research show that young women's breast cancer has a higher histological malignancy, Steroid receptors' weak expression, the HER-2 receptor's frequent overexpression, or happens as a "basal-like" (or "triple negative") molecular biological subtype.[28] Additionally, Premenopausal women are increasingly developing breast cancer; within 30 years, it has nearly doubled in size.[26]

iii. Degree of economic development

The relationship between the incidence and mortality rates of breast cancer and a country's economic development has been highlighted in the epidemiology section. Numerous studies have documented this correlation.[29,30,31]

Globally, the incidence of breast cancer is on the rise, driven by population growth and an ageing demographic.[30] Developed nations report the highest incidence rates, a trend attributed to the "Western lifestyle" previously discussed. It is anticipated that developing countries will soon experience a similar increase in morbidity rates. As these nations progress economically, access to public healthcare improves, leading to the implementation of prevention and screening programs that enhance detection rates, alongside reductions in maternal, infant and child mortality decrease.[31] Conversely, factors that contribute to breast cancer development are becoming more significant, including delayed first childbirth, fewer births, hormone replacement therapy usage, obesity, sedentary lifestyles, and poor dietary habits. Presently, however, lower middle- and low-income countries exhibit higher breast cancer mortality rates compared to developed nations, despite having lower incidence rates.[29,30,31,34]

iv. Hormonal status

A woman's chance of developing breast cancer appears to be significantly influenced by factors connected to her hormonal condition. Numerous research' findings show that the longer a person is exposed to oestrogen, the higher their chance of acquiring breast cancer. delays the onset of early menarche, late menopause, the first child's birth age, and the number of offspring.[35,30-33] According to Brinton et al., the first menstrual cycle that started at or after the age of Compared to the first, 15 was linked to a 23% lower incidence of breast cancer. early menarche, or menstruation before the age of twelve.[36]

v. reproductive and hormonal risk factors in breast Cancer

Estrogens are significantly implicated in the pathogenesis of breast cancer development.[37] This malignancy is classified as a hormone-dependent tumour, where heightened estrogen levels and prolonged exposure to this hormone correlate with an increased risk of occurrence.[37] Epidemiological research substantiates that both endogenous and exogenous estrogen exposure elevates the likelihood of developing breast cancer.[38] In postmenopausal women, elevated serum estrogen concentrations are linked to a greater risk of breast cancer.[38] It is evident that both hormonal and reproductive factors play a crucial role in

augmenting this risk. The length of estrogen exposure and the impact of pregnancy, influenced by factors such as the age at which menstruation begins, the age of first pregnancy (notably in women who have their first child after 30), null parity, and the age at which menopause begins, all contribute to the individual risk of breast cancer.[39] An early onset of menstruation at 12 years and a late cessation at 50 years can double the risk compared to women who experience a later onset at 15 years and an earlier cessation at 40 years.[40]

Childlessness and delayed first pregnancies after age 30 are associated with increased estrogen exposure and a 2 to 5 times higher illness risk. Miscarriages lack the protective benefits of full-term pregnancies, potentially increasing risk due to reduced progesterone. The link between exogenous estrogen and breast cancer is still debated and needs more research.[41,42] Hormone Replacement Therapy (HRT) is a major breast cancer risk factor. Concerns about HRT began in the 1990s, with a 1997 meta-analysis showing a 2.7% increase in breast cancer risk for each year of use.[43] A 2019 follow-up found that HRT with both estrogens and progestogens significantly raised risk, especially with daily progestogen use.[43] Even short-term HRT (1 to 4 years) increased risk, particularly for steroid receptor-positive cancers. Risk decreased if HRT started after age 60 and was lower in obese women using estrogen-only HRT.[43]

vi. Genetic factors family occurrence

5–10% of breast cancer cases are linked to genetic factors, primarily mutations in the BRCA1 and BRCA2 genes.[43] The BRCA1 gene, located on chromosome 17, acts as a tumour suppressor and is crucial for genomic stability, working with other proteins to influence DNA repair and transcription. The BRCA2 gene, found on chromosome 13, also plays a key role in repairing double-strand DNA breaks.[44] Mutations in BRCA1 and BRCA2 are found in only 3–5% of breast cancer patients, but those with these mutations face a tenfold increased risk of developing the disease. The cumulative risk of breast cancer by age 70 exceeds 60%, with lifetime risks ranging from 41% to 90%. BRCA1 mutations are associated with triple-negative breast cancer, while BRCA2 mutations are linked to estrogen receptor-positive breast cancer, highlighting the need for preventive health programs for affected individuals.[45-47] Certain suppressor genes, such as TP53 (linked to Li-Fraumeni syndrome) and PTEN (associated with Cowden syndrome), have high-penetration mutations that significantly elevate breast cancer risk. Women with Li-Fraumeni syndrome have a 54% risk of breast cancer by age 70, while those with Cowden syndrome face a 25% to 50% lifetime

risk. Both syndromes are rare.[48, 50] Mutations in ATM, BRIP1, CHEK2, and PALB2 genes also moderately increase breast cancer risk by 2 to 3 times.[50] Less than 10% of breast cancer cases are inherited.[51] over 90% arise from sporadic mutations. Women with a close relative who had breast cancer double their risk, which can rise to three to six times if two close relatives are affected, though this risk decreases with the relative's age at diagnosis.[16]

vii. Mild breast changes

Benign changes in the mammary glands can significantly increase breast cancer risk. Lesions like atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) raise the risk by four to five times, while proliferative lesions without atypical can double the risk. A study by Hartmann et al.[47] found an overall relative risk of 1.56 for developing breast cancer among patients with benign lesions.[51] lasting for 25 years post-biopsy. For non-proliferative benign lesions, the risk was 1.27, and for mild proliferative lesions without atypia, it rose to 1.88. The highest risk, 4.24, was seen in women with atypical hyperplasia. Earlier detection of benign changes (before age 55) correlates with a higher risk.[51] and women with atypical hyperplasia and a family history of breast cancer may face up to nine times greater risk.[52]

viii. Alcohol consumption

Research shows a link between alcohol consumption and increased breast cancer risk. Alcohol raises estrogen levels by impairing liver metabolism and converting androgens to estrogens. It also suppresses the immune system and DNA repair, promoting cell proliferation. Moreover, alcohol metabolites are carcinogenic. Each daily intake of 10 grams of pure alcohol is associated with a 9% rise in breast cancer risk.[53-58]

ix. Diet

Research indicates that dietary choices significantly affect cancer progression. A low-variety diet high in saturated fats, particularly from animal sources, is linked to an increased risk of colorectal cancer.[59] The connection between diet and breast cancer risk is less clear. A review by Dandamudi et al. found that out of seventeen studies from 2013 to 2017, ten identified harmful dietary components—such as sugary drinks, processed juices, red and processed meats, trans fats, and refined grains—associated with higher breast cancer risk, especially red and processed meats and sodium. In contrast, diets rich in vegetables, fruits, fish, legumes, and healthy oils are linked to a lower risk of breast cancer.[60] While nutrition may influence breast cancer prognosis, current evidence is insufficient for definitive dietary guidelines. Promoting a balanced diet is essential for reducing mortality rates.[61] A nutritious

diet with whole grains, vegetables, fruits, nuts, and olive oil, along with limited saturated fats and red meat, may enhance survival rates post-breast cancer diagnosis. Additionally, patients undergoing chemotherapy or radiation often seek nutritional interventions to improve their quality of life. The relationship between breast cancer and diet is complex and nonlinear. Traditional epidemiological studies have shown inconsistent results regarding dietary habits and breast cancer risk, except for alcohol consumption. This inconsistency may stem from the multifaceted nature of breast cancer, which is both histologically and molecularly diverse. Nutrigenomics and related fields could improve our understanding by revealing the molecular mechanisms of breast cancer and supporting personalized treatment approaches.[62]

x. Nicotinism

Research on chronic nicotine use and breast cancer risk shows mixed results. However, a 2017 study by Jones et al. found that smoking during early adolescence is linked to a moderate increase in breast cancer risk, especially in those with a family history.[63] Nicotine also promotes breast cancer metastasis by activating N2 neutrophils and creating a pre-metastatic environment in the lungs.[64] Additionally, nicotine contributes to chemo resistance in breast cancer cells, highlighting its negative impact on treatment.[65]

3) Breast Cancer of Classification

3.1) Invasive breast cancers (IBC)

It include various tumors with differing clinical presentations, behaviors, and morphologies. The World Health Organization (WHO) recognizes at least 18 histological types, with invasive breast cancer of no special type (NST), formerly invasive ductal carcinoma, being the most common, accounting for 40–80% of cases.[66,67] About 25% of IBCs have distinct growth patterns, leading to specific subtypes like invasive lobular carcinoma and mucinous carcinoma.[68]

IBC can also be categorized into molecular subtypes based on mRNA gene expression. In 2000, Perou et al. identified four molecular subtypes: Luminal, HER2-enriched, Basal-like, and Normal Breast-like, with the latter later excluded due to contamination concerns.[69] The Cancer Genome Atlas Project (TCGA) further profiled over 300 tumors, confirming four primary intrinsic subtypes: Luminal A, Luminal B, HER2-enriched, and Basal-like, and identified a fifth subtype, claudin-low breast cancer, in 2007.[70,71]

In 2009, Parker et al. created the PAM50, a 50-gene signature for classifying breast cancer subtypes, achieving 93% accuracy.[72] PAM50 is now used globally in clinical practice via the NanoString nCounter®, forming the basis of the Prosigna® test. This test combines the PAM50 assay with clinical data to evaluate the risk of distant relapse in postmenopausal women with hormone receptor-positive, early-stage breast cancer, aiding adjuvant chemotherapy decisions.[73,74,75]

3.2. Luminal Breast Cancer

Luminal breast cancers, which are estrogen receptor-positive, account for nearly 70% of cases in Western populations.[76] They typically present as invasive breast cancer of no special subtype but can also manifest as invasive lobular and mucinous carcinomas. Luminal-like tumors are classified into Luminal A and B subtypes based on proliferation-related and luminal-regulated pathways, correlating with different clinical outcomes. Luminal A tumors are ER and/or PR positive, HER2 negative, and characterized by low proliferation-related gene expression, making them low-grade, slow-growing, and associated with a favorable prognosis.[77,78]

In contrast, Luminal B tumors are higher grade with a poorer prognosis, being ER positive, possibly PR negative and/or HER2 positive, and showing increased expression of proliferation-related genes like MKI67 and AURKA.[79-81] They have reduced luminal epithelium marker expression while maintaining similar ER levels to Luminal A tumors, aiding in the distinction between luminal and non-luminal diseases.

3.3 HER-2 Enriched breast cancer

The HER2-enriched subgroup represents 10–15% of breast cancer cases, marked by high HER2 expression and lack of estrogen (ER) and progesterone receptors (PR). This subtype mainly expresses proliferation-related genes like ERBB2/HER2 and GRB7, with mutagenesis linked to APOBEC3B-induced cytosine mutations.[81-83]

HER2-enriched cancers grow faster than luminal cancers and historically had poor prognoses before the advent of HER2-targeted therapies. It's crucial to differentiate this subtype from clinically HER2-positive breast cancer, as many ER-positive, HER2-positive tumors are classified as luminal Additionally, around 30% of HER2-enriched tumors may appear clinically HER2-negative based on IHC and FISH techniques.[84]

3.4 Basal-Like/Triple-Negative Breast Cancer

Triple-Negative Breast Cancer (TNBC) is a diverse group of breast cancers that lack estrogen, progesterone, and HER2 receptors, accounting for about 20% of cases. It is more common in women under 40 and African-American women, with approximately 80% of BRCA1-related breast cancers classified as TNBC. Known for its aggressive nature and poorer prognosis, TNBC typically presents as infiltrating ductal carcinoma but can appear in other forms.[84-85]

While often linked to basal-like characteristics, not all TNBC cases fit this profile. Gene expression profiling has identified six TNBC subtypes: basal-like (BL1 and BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), luminal androgen receptor (LAR), and an unspecified group (UNS). The clinical significance of these subtypes is still unclear, highlighting the need for further research on their treatment implications.[86-87]

4) SYMPTOMS

Many patients with breast cancer, especially in the early stages, experience no symptoms at all. For this reason, routine screening mammograms are crucial. One kind of X-ray called a mammogram can find tiny tumours before you can feel them. In order to understand what is and is not normal for you, you should also get to know your breasts because mammography isn't always accurate. Be mindful of any changes you notice in your breasts, especially these potential red flags.[88-91]

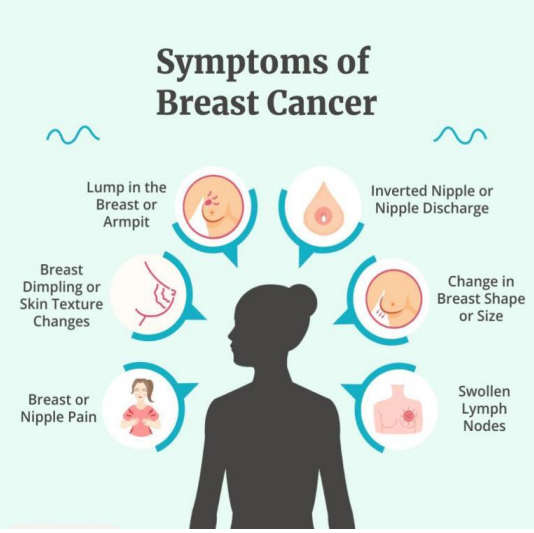


Fig: symptoms of breast cancer.

i. A recent growth in the armpit or breast.
ii. alterations to the breast's size or form, such as swelling, thickness, or shrinkage.
iii. Skin that is pitted or dimplified (like an orange peel). Thicker, flaky, dry, or red skin on the breasts or nipples.
iv. A painful nipple or one that turns inward the nipple's milky or bloody discharge enlarged lymph nodes around the collarbone or beneath the armpit
v. Pain in the breast nips.

5) STAGES OF BREAST CANCER

According to the Breast Cancer.org report Breast cancer stages are determined by the tumor's size, kind, and degree of tumour cell penetration. the tissues of the breast. In contrast, stage 0 explains the stage 4, which denotes the invasive type, and non-invasive tumour. These tumour phases are described as follows:

Stage 0

This stage indicates a non-invasive tumor, with both cancerous and non-cancerous cells confined to the breast area of origin, without invasion into surrounding tissues. An example is ductal carcinoma insitu (DCIS).

Another name for stage 0 breast cancer is ductal carcinoma in situ (DCIS). If the cancer is hormone-receptor-positive, doctors treat DCIS with hormone treatment, such as tamoxifen. Doctors may prescribe aromatase inhibitors, such as exemestane (Aromasin) and anastrozole (Arimidex), to postmenopausal women.

Following surgery, using these drugs for five years may help lower the chance of cancer recurring.

Stage 1: Characterized as invasive breast carcinoma, Stage 1 is divided into 1A and 1B. Stage 1A involves tumors up to 2 cm with no lymph node involvement, while 1B indicates small clusters of cancer cells larger than 0.2 mm in the lymph nodes. Before or after surgery and radiation therapy, patients with stage 1–3 breast cancer may get medication therapy.

Stage 2: Stage 2 is split into 2A and 2B. Stage 2A shows tumors in axillary or sentinel lymph nodes without breast tumors, with sizes ranging from under 2 cm to over 5 cm. Stage 2B involves tumors larger than 5 cm that do not affect the axillary lymph nodes. *

Stage 3: Divided into three subcategories:

i. 3A: No tumor in the breast, but cancer in 4 to 9 axillary or sentinel lymph nodes.

ii. 3B: Tumor of varying size with swelling or ulceration of the breast skin, affecting up to 9 lymph nodes; often classified as inflammatory breast cancer.
iii. 3C: Tumor spread to 10 or more axillary lymph nodes and lymph nodes above and below the clavicle.

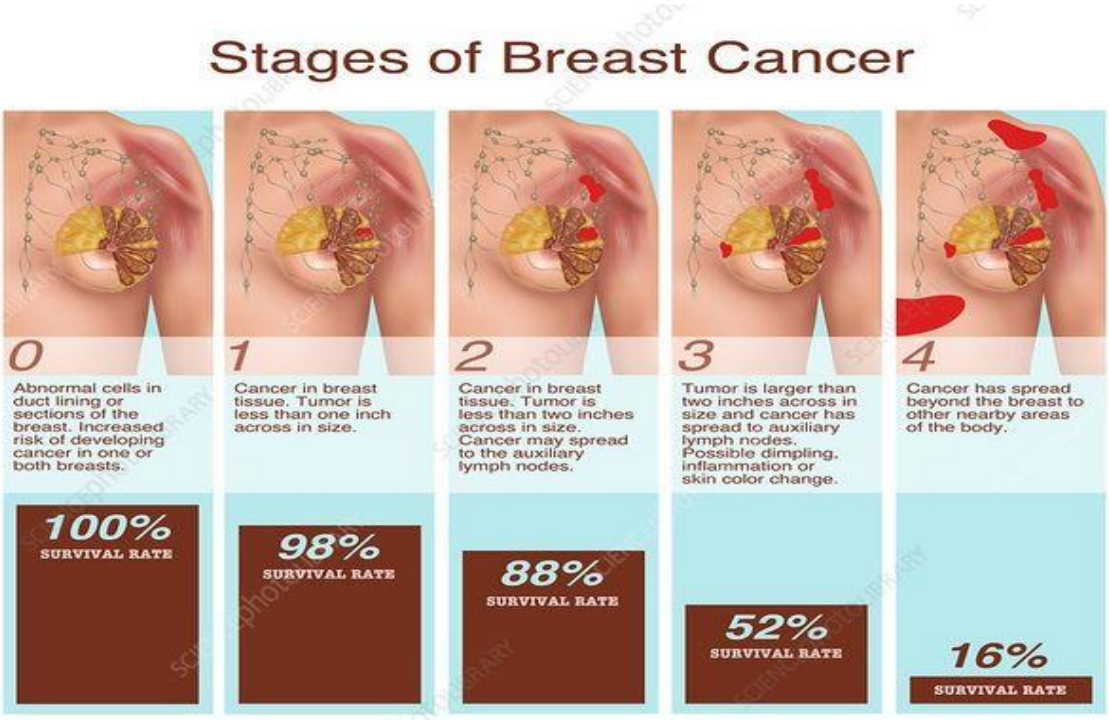
Before or after surgery and radiation therapy, patients with stage 1–3 breast cancer may get medication therapy. Among the medication therapy that may be used are: Drugs used in hormone therapy, like tamoxifen, immunotherapy, such pembrolizumab, and targeted therapy, like trastuzumab (Herceptin), pertuzumab (Perjeta), abemaciclib (Verzenio), and olaparib (Lynparza) chemotherapeutic medications, such as doxorubicin (Adriamycin) and epirubicin (Ellence), which are anthracyclines Carboplatin(Paraplatin),capecitabine(Xeloda),and5-fluorouracil(5-FU)Cytoxan, or cyclophosphamidetaxanes, such as paclitaxel (Taxol) and docetaxel (Taxotere)

Stage 4:- Represents advanced, metastatic cancer that has spread to other organs, including the lungs, bones, liver, and brain. Depending on the type of cancer, stage 4 breast cancer may require different types of drugs, such as the following:

- **Positive for hormone receptors:** A physician might recommend: Inhibitors of aromatase and tamoxifen CDK4/6 inhibitors, such as palbociclib (Ibrance) and amemaciclib
- **Medications that target therapy:** It including everolimus (Afinitor) and ribociclib (Kisqali)

  PI3K inhibitors, like Piqray's alpelisib
- **Hormone receptor-negative:** Chemotherapy medications may be prescribed by a physician, including:

  eribulin (Halaven), capecitabine, vinorelbine (Navelbine), gemcitabine (Gemzar), ixabepilone (Ixempra), and platinum agents like cisplatin (Platinol) and carboplatin taxanes, such as docetaxel paclitaxel, albumin-bound paclitaxel (Abraxane), and anthracyclines, such as doxorubicin, liposomal doxorubicin (Doxil), and epirubicin (Pharmorubicin).



6) Chemotherapy of drug

1) Aromasin: Exemestance, marketed as Aromasin, is an aromatase inhibitor used to treat breast cancer by blocking estrogen production, which is essential for the growth of estrogen receptor-positive (ER-positive) tumors. Exemestane is available as Aromasin and generic exemestane as 25 mg oral tablets that are taken by mouth.

Pharmacodynamic:- Exemestane is an oral steroidal aromatase inhibitor used to treat estrogen receptor-positive breast cancer, particularly in post-menopausal women, often alongside surgery or radiation. In post-menopausal women, estrogen is produced by converting androgens via the aromatase enzyme. Exemestane irreversibly inactivates aromatase by mimicking 4-androstenedione, leading to permanent estrogen production inhibition through "suicide inhibition," unlike non-steroidal inhibitors such as anastrozole and letrozole. Research indicates that exemestane can reduce estrogen levels in young adult males by 35% for estradiol and 70% for estrone.[92-94]

Pharmacokinetic: The gastrointestinal system absorbs exemestane rapidly, although the liver experiences substantial first-pass metabolism. Plasma levels in healthy individuals peak about 2.9 hours after treatment, whereas in breast cancer patients, they peak at around 1.2 hours. Two to three days are needed to get the highest level of aromatase inhibition. The medication attaches itself to plasma proteins in about 90% of cases. The 17-keto group is

changed into an alcohol by aldo-keto reductases, whereas the methylidene group at position 6 is oxidised by the liver enzyme CYP3A4. Within a week, just 1% of urine excretion is the parent chemical; the remaining 40% of metabolites are eliminated in faeces and 40% in urine. 24 hours is the terminal half-life of exemestane.[93,95,96]

Mechanism of action: Exemestane, which shares structural similarities with the natural substrate androstenedione, is an irreversible steroidal aromatase inactivator. The aromatase enzyme uses it as a fake substrate, and it is converted into an intermediate that attaches to the enzyme's active site permanently. Resulting in its deactivation, a phenomenon commonly referred to as "suicide inhibition.

“According to clinical studies, women who switched to Aromasin after taking tamoxifen for two to three years had a 31% reduced chance of breast cancer recurrence and a 14% lower mortality rate than those who stayed taking the medication for five years.

Side effect: Common side effects reported in over 10% of patients include hot flashes and sweating due to estrogen deficiency from exemestane, along with insomnia, headaches, and joint pain. Nausea and fatigue are mainly seen in those with advanced breast cancer.

About 20% of patients on Aromasin experience reduced lymphocyte counts, particularly those with a history of lymphopenia.

Exemestane may cause androgenic side effects like acne and weight gain, especially at doses above the therapeutic range.[97-99]

2) Anastrazole: Anastrozole, marketed under various brand names including Arimidex, is an antiestrogen medication utilized as a supplementary treatment for breast cancer. It is particularly indicated for cases of hormone receptor-positive breast cancer. Additionally, it has been employed as a preventive measure for individuals at elevated risk of developing breast cancer. The medication is administered orally**.**

Pharmacodynamic

Anastrozole inhibits the aromatase enzyme, blocking the conversion of androgens to estrogens through competitive inhibition. At a daily dose of 1 mg, it achieves a 96.7% to 97.3% inhibition rate, while 10 mg results in 98.1% inhibition. Thus, 1 mg is the minimum effective dose for optimal aromatase suppression, leading to at least an 85% reduction in

estradiol levels in postmenopausal women, without affecting corticosteroids or other adrenal steroids.[100-102]

Pharmacokinetc: The bioavailability of anastrozole in humans is not fully established, but animal studies indicate effective absorption. In humans, absorption is linear for daily doses of 1 to 20 mg, with minimal food impact. Peak plasma concentrations occur within 2 to 12 hours, typically around 3 hours, and steady-state levels are reached after 7 to 10 days, with a 3.5-fold accumulation. Maximal estradiol suppression occurs within 3 to 4 days of starting therapy.

Research suggests that P-glycoprotein may limit anastrozole's entry into the central nervous system in rodents, indicating potential peripheral selectivity in humans, though this remains unconfirmed. Anastrozole is expected to lower central nervous system estradiol levels, as estradiol can cross the blood-brain barrier. The drug has a plasma protein binding of about 40%.

Anastrozole is metabolized through N-dealkylation, hydroxylation, and glucuronidation, with aromatase inhibition attributed to the drug itself. Its elimination half-life is 40 to 50 hours, allowing for once-daily dosing. It is primarily metabolized in the liver (83-85% of elimination), with 11% excreted unchanged by the kidneys, mostly in urine.[100-107]

Side effects: Common side effects of anastrozole (occurring in 10% or more of patients) include hot flashes, fatigue, arthritis, joint pain, hypertension, depression, nausea, skin rashes, osteoporosis, bone fractures, back pain, insomnia, headaches, peripheral swelling, coughing, shortness of breath, pharyngitis, and lymphedema. Serious but rare effects (less than 0.1%) may involve skin lesions, allergic reactions (swelling of the face, lips, tongue, or throat), and abnormal liver function tests or hepatitis.[104]

3) Transtuzamab: Trastuzumab is a biologic antineoplastic drug that received FDA approval in 1998, positioning it among the earliest "targeted" chemotherapy options. Trastuzumab deruxtecan is a conjugate of trastuzumab that delivers its cytotoxic agents upon binding to and penetrating HER2-expressing cells, thereby providing effective treatment for HER2-positive gastric, lung, colorectal, and metastatic breast cancers.

Mechanism of action: Trastuzumab is a monoclonal antibody that targets the HER2 receptor, inhibiting its signaling and enhancing antibody-dependent cellular cytotoxicity

against HER2-expressing cells. Trastuzumab deruxtecan (T-DXd) is a third-generation antibody-drug conjugate (ADC) that links trastuzumab to a cytotoxic topoisomerase I inhibitor (DXd) via a cleavable linker, featuring a high drug-to-antibody ratio of 8:1. In contrast, trastuzumab emtansine (T-DM1) is a second-generation ADC that combines trastuzumab with the cytotoxic agent emtansine.

Adverse effect: Trastuzumab can cause common side effects like flu-like symptoms, nausea, and diarrhea. A more serious concern is its potential to affect cardiac health, with 2–7% of patients experiencing cardiac dysfunction, including congestive heart failure. Regular cardiac evaluations, such as MUGA scans or echocardiograms, are standard during treatment, and any decline in ejection fraction is usually reversible.

Trastuzumab works by downregulating neuregulin-1 (NRG-1), which is essential for cardiomyocyte survival and function. NRG-1 activates key pathways that maintain cardiac integrity, so trastuzumab may contribute to cardiac issues. Additionally, it poses risks to a developing fetus.

4) Pertuzumab: The monoclonal antibody pertuzumab, marketed under the Perjeta brand, is used in conjunction with trastuzumab and docetaxel to treat metastatic HER2-positive breast cancer. It is also used as a neoadjuvant in cases of early HER2-positive breast cancer.[4]

Mechanism of action: HER2 is an extracellular receptor and receptor tyrosine kinase that, when activated, promotes cell proliferation. Overexpression, due to ERBB2 gene amplification, leads to HER2-positive breast cancer in 15-30% of cases. HER2 requires dimerization with another protein to function, forming either homodimers or heterodimers, with the HER2/HER3 combination being the most effective for signaling.

Pertuzumab inhibits HER2/HER3 dimerization, blocking associated signaling, while trastuzumab binds to the domain where HER2 interacts with itself. Together, these monoclonal antibodies effectively prevent HER2 from functioning.[108-110]

Adverse effect: In clinical trials of a three-agent combination therapy for metastatic breast cancer, over half of participants reported adverse effects such as diarrhea, alopecia, and neutropenia, with more than 10% experiencing neutropenia with fever and leukopenia. After discontinuing docetaxel, common side effects included diarrhea (28.1%), upper respiratory infections (18.3%), rashes (18.3%), headaches (17.0%), and fatigue (13.4%). In neoadjuvant

trials, over 50% reported hair loss and neutropenia. Additionally, more than 10% experienced other adverse effects like anemia, allergic reactions, infusion-related reactions, reduced appetite, insomnia, altered taste, oral inflammation, constipation, nail disorders, and myalgia.[111]

5) Abemaciclib: Abemaciclib, marketed under the brand name Verzenio among others, is a pharmaceutical agent utilized in the management of advanced or metastatic breast cancer. Developed by Eli Lilly, it functions as a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). In October 2015, the United States Food and Drug Administration (FDA) recognized it as a breakthrough therapy for breast cancer. Subsequently, in September 2017, the FDA granted approval for its use in the treatment of specific types of breast cancer within the United States.

Mechanism of action: Abemaciclib, like palbociclib and ribociclib, inhibits cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), which are essential for phosphorylating and inactivating the retinoblastoma protein. This inhibition prevents cells from progressing from the G1 to the S phase of the cell cycle, leading to apoptosis. Additionally, in vitro studies suggest that abemaciclib may also induce a non-apoptotic form of cell death characterized by cytoplasmic vacuoles from lysosomes, indicating an alternative mechanism of action.[112-114]

Pharmacokinetc: After oral administration, abemaciclib has an absolute bioavailability of 45%. Peak blood plasma concentrations occur around 8 hours post-dose, ranging from 4.1 to 24.0 hours. In the bloodstream, 96.3% of abemaciclib binds to plasma proteins. The liver enzyme CYP3A4 primarily metabolizes it into N-desethylabemaciclib (M2), along with smaller amounts of hydroxy derivatives (M18, M20) and another metabolite (M1), all of which also bind strongly to plasma proteins. Abemaciclib is mainly eliminated through feces (81%), with only 3% excreted in urine, and has an average elimination half-life of about 18.3 hours.[112]

Side effects: Adverse effects reported in 20% or more of participants in clinical studies included diarrhea, nausea, and vomiting, as well as leukopenia (reduced white blood cell count), which encompasses neutropenia, anemia (decreased red blood cell count), and thrombocytopenia (reduced platelet count). Additional side effects comprised abdominal pain, infections, fatigue, diminished appetite, and headaches.[112,115]

6) Olaparib: Olaparib, branded as Lynparza, is a PARP inhibitor used for maintenance therapy in advanced ovarian cancer patients with BRCA mutations. It blocks the enzyme poly ADP ribose polymerase (PARP), essential for DNA repair. Approved in December 2014 by the EMA and FDA, it is effective against cancers linked to hereditary BRCA1 or BRCA2 mutations, including certain ovarian, breast, and prostate cancers.

Mechanism of action: Olaparib functions as an inhibitor of the enzyme poly ADP ribose polymerase (PARP), categorizing it as a PARP inhibitor. Individuals with BRCA1/2 mutations may possess a genetic predisposition to certain types of cancer and may exhibit resistance to various cancer therapies. Nevertheless, these cancers often display a distinct weakness, as the cancer cells depend heavily on PARP for DNA repair, which allows them to persist in their division. Consequently, medications that specifically inhibit PARP could prove advantageous for cancers that are responsive to this form of treatment.[116-117]

Side effects: Adverse effects may encompass gastrointestinal issues, including nausea, vomiting, and decreased appetite; fatigue; pain in muscles and joints; as well as reduced blood cell counts, such as anemia, with rare occurrences of leukemia. Additionally, somnolence was occasionally observed in clinical trials that administered doses exceeding the approved regimen.[118,119]

7) Palbociclib: Palbociclib, marketed under the brand name Ibrance, is a pharmaceutical agent developed by Pfizer for the management of HR-positive and HER2-negative breast cancer. It functions as a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6. Notably, palbociclib was the inaugural CDK4/6 inhibitor to receive approval for use in cancer treatment.

Mechanism of action: It serves as a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6.During the G1 phase of the cell cycle, mammalian cells must navigate a critical checkpoint known as the restriction point "R" to successfully complete the cell cycle and undergo division. The complex formed by CDK4 and CDK6 with Cyclin D facilitates the phosphorylation of the retinoblastoma protein, Rb, thereby enabling the cell to surpass the restriction point and commit to division. In numerous cancers, the regulation of one or more proteins associated with this checkpoint is compromised. By inhibiting CDK4/6, palbociclib effectively prevents the cyclin D-CDK4/6 complex from phosphorylating Rb, thereby

obstructing the cell's ability to pass the restriction point and exit the G1 phase, which ultimately halts its progression through the cell cycle.[120-125]

Side effect: A significant proportion of patients undergoing treatment with palbociclib develop neutropenia, characterized by an unusually low count of neutrophils. This adverse effect compromises the immune system and is likely a contributing factor to the second most prevalent side effect, which is infection. Additionally, leukopenia and anemia are commonly observed in individuals receiving palbociclib. Over 10% of patients report experiencing other side effects, including fatigue, nausea, diarrhea, respiratory infections, headaches, thrombocytopenia, vomiting, and reduced appetite. The FDA advises patients to remain vigilant for any indications of pulmonary embolism. Furthermore, the FDA warns that women should be cautious, as the medication may adversely affect a developing fetus, and therefore, it is contraindicated during pregnancy.[123-125]

8) Amemociclib: Abemaciclib, marketed under the brand name Verzenio, is a pharmaceutical agent utilized in the management of advanced or metastatic breast cancer. Developed by Eli Lilly, this medication functions as a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). In October 2015, the United States Food and Drug Administration (FDA) recognized it as a breakthrough therapy for breast cancer. Subsequently, in September 2017, the FDA granted approval for its use in the treatment of specific types of breast cancer within the United States.

Mechanism of action: Abemaciclib, like palbociclib and ribociclib, inhibits cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), which are essential for phosphorylating and inactivating the retinoblastoma protein. This inhibition prevents cells from progressing from the G1 to the S phase of the cell cycle, leading to apoptosis. Additionally, in vitro studies suggest that abemaciclib may also induce a non-apoptotic form of cell death characterized by cytoplasmic vacuoles from lysosomes, indicating an alternative mechanism of action.[126-128]

Side effect: In clinical studies, adverse effects reported in 20% or more of participants included diarrhea, nausea, vomiting, and leukopenia (a decrease in white blood cell count), which includes neutropenia, as well as anemia (a reduction in red blood cell count) and thrombocytopenia (a decrease in platelet count). Other side effects included abdominal pain, infections, fatigue, loss of appetite, and headaches.[126-129]

9) Everolimus: Everolimus, sold as Afinitor, Zortress, and Certican, is an immunosuppressant used to prevent organ transplant rejection and as a targeted therapy for renal cell carcinoma and other cancers. It also helps reduce restenosis in drug-eluting stents. Chemically, it is a derivative of sirolimus that inhibits the mTOR pathway. Everolimus is included in the WHO's List of Essential Medicines and is available as a generic.

Mechanism of actio: Everolimus has higher water solubility and greater selectivity for the mTORC1 complex than rapamycin, with minimal effects on mTORC2. This selectivity may hyper-activate AKT kinase due to disrupted negative feedback from mTORC1, enhancing cell survival and significantly impacting cell growth and proliferation.

Inhibiting mTORC1 with everolimus normalizes tumor blood vessels, increases tumor-infiltrating lymphocytes, and enhances adoptive cell transfer therapy. It may provide benefits similar to rapamycin while reducing glucose intolerance and immunosuppression.

Loss or inactivation of the tumor suppressor genes TSC1 and TSC2 leads to mTORC1 activation. Everolimus binds to FKBP12, inhibiting mTORC1 and altering mRNAs related to the cell cycle and glycolysis, ultimately suppressing tumor growth.[130-133]

10) Ribociclib: Ribociclib, marketed under the brand name Kisqali, is a pharmaceutical agent utilized in the treatment of specific types of breast cancer. It functions as a kinase inhibitor and was developed through a collaboration between Novartis and Astex Pharmaceuticals.

Pharmacodynamic: Cyclin-dependent kinases (CDKs) 4 and 6 promote cell division in both healthy and cancerous cells, with many cancer cells showing increased CDK activity that can inactivate tumor suppressor genes. Ribociclib, when used with other drugs like ALK or MEK inhibitors, enhances therapeutic responses due to "crosstalk" among signaling pathways. Inhibiting multiple pathways reduces the tumor's ability to adapt and survive, leading to a stronger anti-tumor effect and helping to prevent treatment resistance.[134-135]

Pharmacokinetic: The gastrointestinal absorption percentage of ribociclib is unknown. Peak plasma concentrations occur within 1-4 hours post-administration, with steady-state levels reached after about 8 days of continuous dosing. Food does not affect absorption, and approximately 70% of ribociclib binds to plasma proteins. Ribociclib is mainly metabolized by CYP3A4 into several metabolites, including CCI284, LEQ803, and M1, which have minimal clinical activity. The drug has a slight accumulation in the body, with an average

half-life of 32 hours. It is primarily eliminated through feces (69%) and urine (23%), with unchanged drug accounting for 17% of fecal and 12% of urinary excretion, while the remainder consists of metabolites.[138-139]

Side effect: Main side effects in clinical studies included reduced blood cell counts, especially neutropenia (75% vs. 5% placebo) and anemia (18% vs. 5%). Gastrointestinal issues were prevalent, with nausea in 52% (29% placebo) and diarrhea in 35% (22% placebo). Alopecia affected 33% of patients compared to 16% in the placebo group. The medication also prolonged the QT interval and increased liver enzymes. Common side effects included infections, headaches, cough, nausea, vomiting, diarrhea, constipation, fatigue, hair loss, and rashes. Severe side effects often involved infections, decreased blood cell counts, vomiting, abnormal liver function tests, and hypophosphatemia.[138-140]

7) Diagnosis

Medical professionals use various tests to identify breast cancer. As of May 2024, the U.S. Preventive Services Task Force recommends that cisgender women and individuals assigned female at birth have biennial mammograms starting at age 40.[141]

Common diagnostic procedures include:[142-143]

i. Comprehensive physical examination:-A healthcare professional reviews your health changes and medical history.
ii. Blood analysis:-Assesses organ and tissue function through blood sample analysis.
iii. Breast examination:- Inspects breasts for lumps or changes.
iv. Mammography:-An X-ray procedure to detect potential breast cancer indicators.
v. Ultrasound imaging:- Visualizes tumors to determine if they are malignant or benign.
vi. Magnetic resonance imaging (MRI):-Produces detailed images of organs and tissues, typically for high-risk women.
vii. Biopsy: Extracts a breast tissue sample for cellular examination.

After confirming a diagnosis, a medical professional will perform more tests and procedures to find the cancer's spread sites, assess the disease's stage, and find characteristics of your specific cancer that could help direct treatment. These could consist of:

- Extra imaging examinations
- Measurement of progesterone and oestrogen receptors in malignant tissue using bone scan laboratory tests

- HER2 gene and HER2 protein levels in malignant tissue are measured in a lab.
- Finding gene mutations associated with an increased risk of breast cancer by multigene testing (BRCA1, BRCA2, PALB2).

8) Treatment/Management

Breast cancer treatment is complex and tailored to factors like disease stage, pathology, patient preferences, and available resources. It is generally categorized into three types: early, locally advanced, and metastatic breast cancer.

- **Early Breast Cancer:** is defined by tumors under 5 cm and no clinically positive lymph nodes. Treatment options include surgery, chemotherapy, radiation, and hormonal therapy, based on the cancer's stage and molecular characteristics.
- **Surgical options:** involve breast-conserving surgery (like lumpectomy) or total mastectomy. Axillary lymph node management:- includes sentinel lymph node biopsy; if 2 to 3 nodes are microscopically positive without extra nodal extension, further surgery may not be needed. However, completion axillary dissection or radiation is required for more than three positive nodes or extra nodal extension.
- **Chemotherapy:** The use of systemic chemotherapy depends on the disease stage and tumor characteristics. For hormone receptor-positive tumors, chemotherapy initiation is based on genomic profiling risk assessment (e.g., Oncotype Dx). High-risk patients benefit from chemotherapy alongside hormonal treatment. All HER2-positive tumors over 1 cm should receive targeted anti-HER2 therapy, and triple-negative tumors larger than 1 cm are recommended for systemic chemotherapy.
- **Radiation:** Patients who have breast-conserving surgery (BCS) must receive radiation therapy to reduce local recurrence risk. In contrast, mastectomy patients typically do not need radiation unless specific conditions are met, such as tumors over 5 cm or multiple positive lymph nodes.
- **Hormonal Therapy:** Anti-estrogen or aromatase inhibitors are advised for all hormone receptor-positive patients. Neoadjuvant chemotherapy is increasingly used for early-stage triple-negative and HER2-positive tumors, offering benefits like assessing tumor response and improving the likelihood of breast-conserving surgery.
- **Locally Advanced Breast Cancer (LABC):** LABC is defined by tumors larger than 5 cm or with clinically positive lymph nodes. Most LABC patients will receive neoadjuvant therapy, followed by surgery and radiation.

- Chemotherapy protocols are customized based on tumor pathology (e.g., hormone receptor-positive, HER2-positive, triple-negative), patient age and health, and local resources. The main goals of initial chemotherapy are to reduce tumor size, eliminate micrometastatic disease, and assess tumor behavior through treatment response. After chemotherapy, imaging is performed to evaluate treatment response and guide further management, which may include:
- **Surgical intervention:** Options include breast-conserving surgery (BCS) or total mastectomy. BCS is not suitable for large tumors, chest wall or skin involvement, multifocal disease, inability to undergo radiation, or disproportionate tumor size.
- **Axillary lymph node management:** Patients with a clinically positive axilla require axillary dissection, regardless of chemotherapy response. For those with a clinically negative axilla, a sentinel lymph node biopsy is performed, collecting at least three nodes. Patients with residual disease may need completion axillary dissection or radiation.
- **Systemic chemotherapy:** Patients with residual disease may be eligible for additional chemotherapy based on the tumor's molecular profile.
- **Radiation therapy:** Criteria for radiation therapy are similar to those for BCS.
- **Hormonal therapy:-**Anti-estrogen or aromatase inhibitors are recommended for all hormone receptor-positive tumors.
- Metastatic breast cancer is mainly treated with systemic therapies, including chemotherapy, targeted therapy, immunotherapy, and hormonal therapy, chosen based on the cancer's molecular characteristics and the patient's health. Palliative radiation may be used for significant tumors and metastases in the brain, bones, and lungs. Surgery is typically avoided unless it alleviates symptoms or serves palliative.

9) Future Directions

1. Personalized medicine approaches.
2. Immunotherapy and combination regimens.
3. Liquid biopsies and biomarker development.
4. Improved understanding of breast cancer subtypes.
5. Enhanced survivorship and quality of life strategies.

10) CONCLUSION

Breast cancer is a significant global health concern, affecting millions worldwide. Understanding its epidemiology, classification, staging, diagnosis, and treatment options is

crucial for effective management. Advances in chemotherapy, targeted therapies, and early detection strategies have improved survival rates and quality of life for patients. Multidisciplinary approaches, including surgery, radiation, and systemic therapies, offer personalized care. Ongoing research aims to optimize treatment outcomes, reduce resistance, and improve prognosis. Breast cancer management has made significant strides, but challenges persist. Continued research and collaboration are crucial to addressing disparities, improving outcomes, and advancing personalized medicine. Emerging therapies, innovative diagnostic tools, and enhanced supportive care will further improve patient experiences.

The fight against breast cancer requires a multifaceted approach, integrating:

1. Advanced early detection methods
2. Targeted therapies and precision medicine
3. Interdisciplinary collaboration
4. Continuous education and updates
5. Innovative research and clinical trials.

By prioritizing these areas, we can improve Asurvival rates, enhance quality of life, and ultimately overcome breast cancer.

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