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ADVANCEMENTS IN UNDERSTANDING AND TREATMENT OF BREAST CANCER: A COMPREHENSIVE REVIEW

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Abstract:

Breast cancer, a complex disease driven by environmental, behavioral, and genetic factors, remains a significant health challenge. Carcinogenesis in breast cancer involves processes such as evasion of apoptosis, limitless proliferation, enhanced angiogenesis, resistance to anti-growth signals, and metastasis. Early detection and effective management are critical for improving survival rates, which vary significantly between high-income and low-income countries. Pathophysiology encompasses genetic and molecular alterations, including mutations in key pathways (P13K/AKT, RAS/MEK/ERK) and abnormal growth factor signaling, leading to uncontrolled cell division and tumor progression.

Diagnosis employs techniques such as mammography, MRI, ultrasonography, and biopsies, with mammography being the most prevalent screening method. Risk factors include age, hormonal status, reproductive history, diet, and genetic predispositions. Treatment strategies for non-metastatic breast cancer combine local (surgery, radiation) and systemic therapies (hormonal, chemotherapy, targeted therapies), tailored to tumor subtypes. Advances in systemic therapies, particularly for triple-negative breast cancer, include PARP inhibitors and immunotherapy. Non-coding RNAs also play a crucial role in cancer progression and treatment response.

Recent therapeutic advancements emphasize personalized approaches, genomic testing, and fertility preservation for young patients. The integration of multidisciplinary care and ongoing research into targeted and supportive therapies, such as bisphosphonates for bone metastasis, underscores the dynamic and evolving landscape of breast cancer treatment.

Keywords: Breast cancer, Screening methods, Genetic mutations, Treatment strategies, Triple-negative breast cancer

Introduction :

As a complex disease, breast cancer is primarily caused by environmental, behavioural, and hereditary variables in lifestyle choices. **[1]**

Carcinogenesis, which has six main characteristics, can happen in any type of cell, tissue, or organ and cause the degenerative changes that give rise to a large variety of cancers. The main processes that permit its advancement include apoptosis evasion, boundless ability to proliferate, increased angiogenesis, resistance to anti-growth signals and induction of self-growth signals, and the potential to spread. **[2]**

Australia, breast cancer is the most frequent cancer to strike women. According to a recent analysis of the best radiation therapy utilization rates, the percentage of breast cancer the percentage of patients for whom radiation therapy is advised is 87%. Patients who had radiation therapy following breast-conserving surgery (BCS) had a 7% likelihood of local recurrence at 5 years of follow-up, compared to 26% in patients who did

not receive radiation therapy, according to a sizable meta-analysis conducted by the Early Breast Cancer Trialists' Group . Furthermore, the data revealed that radiation therapy after BCS reduced the absolute risk of death attributable to breast cancer by 5.4% at 15 years following diagnosis when compared to BCS alone.**[3]**

Breast cancer begins in the cells of the breast. A tumour that is carcinogenic is a collection of cancer cells that can spread into and damaging the tissue in the vicinity. It can also spread across the entire body. Every now and then, breast cells experience modifications that keep them from developing or functioning correctly. These alterations may lead to atypical hyperplasia, cysts, and non-cancerous breast diseases. Furthermore, they could lead to benign malignancies such as intraductal papillomas. On the other hand, alterations to breast cells can sometimes lead to breast cancer. The cells lining the ducts, or the tubes that convey milk from the glands to the nipple, are where breast cancer usually starts. **[4]**

Currently, early detection of breast cancer and prompt treatment following diagnosis are the two main pillars that must be addressed for the illness to be managed effectively and preserve lives. **[6]**

The 5-year survival rate for breast cancer varies greatly between high-income and low-income countries, with the former having an estimated 80% survival rate and the latter having less than 40%.**[5]**

Pathophysiology:

In the past, women with breast cancer had similar rates to those who were not pregnant. Between 75 and 90 percent of the tumours in each category are ductal carcinomas. **[22]** The breast has undergone long-lasting histological and molecular changes as a result of pregnancy and lactation. The human breast exhibits a unique genetic signature following a full-term pregnancy, which sets it apart from nulliparous tissues and has been associated with the long-term preventive effect of pregnancy on the risk of breast cancer. **[26]**

Breast cancer primarily manifests as carcinomas, arising from breast epithelial elements. These carcinomas are broadly categorized into two major types: in situ carcinomas and invasive (or infiltrating) carcinomas.**[17]** Breast cancer is diagnosed histologically according to standardized criteria, with invasive ductal carcinoma being the most prevalent histology (50%-75% of cases), followed by invasive lobular carcinoma (5%-15% of cases).**[16]**In situ carcinomas develop within ductal or lobular epithelium but remain confined without invading the basement membrane, resulting in limited metastatic potential. Conversely, invasive ductal or lobular carcinomas extend beyond the basement membrane, leading to increased risks of metastasis and ultimately, mortality. **[17]**The pathophysiology of breast cancer encompasses several key mechanisms crucial for cancer initiation and progression. It involves a complex interplay of genetic, molecular, and cellular events. Mutations in key signalling pathways, such as the P13K/AKT and RAS/MEK/ERK pathways, are pivotal in driving uncontrolled cell division, a hallmark of cancer. These mutations, disrupt the normal regulatory mechanisms that balance cell proliferation and programmed cell death. **[9]**Abnormal growth factor signalling further amplifies cancer cell growth. This includes deregulated interactions between stromal (supporting) and epithelial (lining) cells in the breast tissue. These interactions contribute to the formation of a tumour microenvironment that supports tumour growth and progression. **[9]** Genetic mutations play a significant role in breast cancer pathogenesis. For instance, mutations in genes such as BRCA1 and BRCA2, impair DNA repair mechanisms. This leads to genomic instability, allowing for the accumulation of further mutations and promoting the development of cancerous cells.**[9]**The expression of estrogenic receptor alpha (ERα), regulated by GATA-3, is central to breast cancer pathophysiology and is addressed in the study. **[16]**ERα and progesterone receptor (PR) positivity guide hormonal therapy choices, while ERBB2 overexpression defines a subtype targeted by specific therapies like trastuzumab and pertuzumab,**[16]** Triple-negative breast cancer, characterized by the absence of ER, PR, and HER2 expression, poses unique challenges due to limited targeted therapy options, emphasizing the heterogeneous nature of breast cancer pathophysiology.**[16]**

Diagnosis:

1) Mammography

Diagnostic mammography is a low-radiation x-ray technique that produces an image of the breast. Use of it is for following up on unexpected results from a screening mammography or clinical breast examination. During a biopsy, mammography can also be used to detect an abnormal area. **[4]**

Recently, CE digital mammography has been utilized in addition to mammography as a breast screening method. CE digital mammography uses tumour angiogenesis as its means of detecting breast cancer. It

produces marginally more radiation than mammography and employs intravenous iodinated contrast injections. **[7]**

The MIAS, DDSM, and IN breast breast mammography datasets are commonly utilized. A total of 160 distinct patient data, comprising 322 images of the left and right breasts from mammograms, were as determined by the MIAS dataset. Digital mammography images have a resolution of 200μ and a pixel count of 1024 × 1024. The MIAS dataset included three categories for mammography images: fatty, glandular dense, and fatty glandular. The mediolateral oblique perspective is where the photos were taken. Access to the severity groups—normal and poor mammography—was made possible by the dataset. Each abnormal mammography picture was additionally classified as benign or malignant, along with specifics regarding the type of lesion, such as asymmetry, calcification, and mass. **[8]**

Mammography screening using approved, safe equipment, competent technologists, and experienced radiologists interpreting the results can reach an accuracy rate of 85% to 90% in identifying pre-clinical, non-palpable tumours<15 mm in size.38 As a result, mortality drops by 30% to 50%. **[23]**

2) Magnetic Resonance Imaging (MRI):

Using low-energy radio frequency waves and a magnetic field, MRI is a non-invasive, non-ionizing diagnostic imaging technique that provides detailed images of structures seen in the breast. In women who have received a prior diagnosis of breast cancer, magnetic resonance imaging (MRI) can be utilized to quantify the extent of the malignancy and search for spread malignancies. Accurate identification of tumours less than or equal to 2 cm has been achieved and quantified by magnetic resonance imaging. However, because aberrant breast tissue surrounds the real lesion, larger breast tumours are frequently exaggerated, which can result in higher rates of mastectomy. **[6]**

3)Breast thermography:

Using an infrared (IR) camera to detect the surface temperature of the breasts and picture post-processing to find areas of abnormal temperature is the idea behind breast thermography. Lawson provided one of the earliest indications in 1956 that breast cancer alters the breasts' typical temperature distribution. **[24]**

4)Ultrasonography:
US can precisely pinpoint the site of lesions and is used to observe the morphology and varying condition of tumour tissues. US is appropriate for everyone and does not pose a threat to humans. The US development history is as follows: Because of its poor resolution, the early grayscale US could only identify the presence of the tumour at the point of detection, making it challenging to differentiate between benign and malignant tumours. **[10]**

5)BIOPSY:

The worrisome breast lump is removed using three techniques. Fine-needle aspiration is one technique, however it is not able to distinguish between invasive cancer and ductal carcinoma in situ.**[9]**

A biopsy is the only procedure that can reliably identify breast cancer. A biopsy is performed to obtain tissues or cells from the patient's body for analysis in a lab. The report from the pathologist will ascertain whether or not the sample included cancer cells. Whether a lump is palpable, or something you can feel, or non-palpable, or something you can't, will determine the kind of biopsy that is done. The doctor may use mammography or ultrasound to locate the area that needs to be checked. The majority of biopsies are done in a hospital, and you can go home after they're finished. **[4]**

6)Screening:

The most crucial public health tactic to lower BC mortality is screening. Screening women over 50 has been shown to improve survival in multiple randomized controlled trials. Early screening is debatable, and a meta-analysis was the sole source of evidence supporting its benefits for people in the 40–50 age range. Approximately one in 350 people need to be screened in order to prevent one fatality. **[20]**

7)Breast self-examination:

Breast self-examination is a patient-centered, noninvasive treatment that helps women feel good about their bodies, which makes it appealing. The scope of current practice is estimated below, nevertheless. The estimated sensitivity of breast self-examination, which is done on a regular basis by around one-third of US women, is poor (20% to 30%).**[21]**

Risk factors:

Older age, female sex, early menarche, late menopause, nulliparity, not breastfeeding, positive family history, thick breast tissue, hormone therapy, and a history of chest radiation therapy are risk factors linked to breast cancer.

1)Menopause & Menarche:
The majority of risk factors for breast cancer are associated with endocrinological or gynaecological occurrences in the life of a woman. **[11]**

The risk of breast cancer rises with age, however after menopause there is a noticeable decrease in the pace of growing risk. For every year that the menopause takes longer to begin, the risk increases by 3%. **[12]**

2) Hormonal status:

The likelihood that a woman may get breast cancer appears to be significantly influenced by factors related to her hormonal condition. Numerous research' findings show that the length of time spent exposed to oestrogen increases the chance of acquiring breast cancer, which prolongs the early menarche, the late menopause, the first child's birth age, and the number of births .**[14]**

3)Testosterone:
In both premenopausal and postmenopausal women, elevated levels of endogenous sex hormone are associated with an increased risk of breast cancer. In postmenopausal women, high levels of circulating testosterone have been associated with an increased risk of breast cancer. **[5]**

4)Dietary factor: Excessive levels of blood cadmium, intake of total n-6 polyunsaturated fatty acids (PUFA), vitamin D deficiency or insufficiency, and excessive intake of salt, sugar, and saturated fat and oils were among the dietary variables linked to an elevated risk of BC. The trace metals lithium, cobalt, magnesium, copper, and cadmium were discovered in high concentrations in women with BC. **[15]**

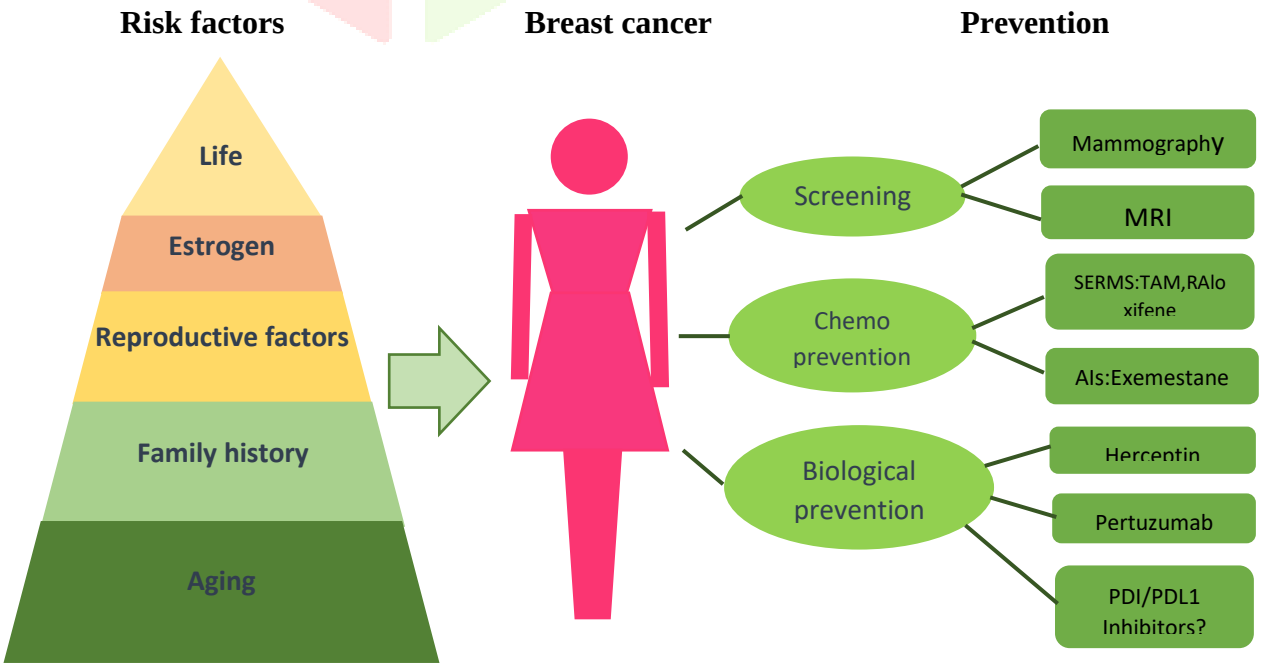

Fig No. 1 : Risk Factors and Prevention measure for breast cancer[18]

Treatment:

The primary goals of therapy for non metastatic breast cancer include removing the tumour from the breast and nearby lymph nodes and preventing its spread to other parts of the body. Treatment strategies involve a combination of local and systemic approaches.**[13]** Local therapy typically involves surgical removal of the tumour and nearby lymph nodes, along with potential postoperative radiation therapy. **[13]** Systemic therapy, administered either before (neoadjuvant) or after (adjuvant) surgery, targets specific breast cancer subtypes. Hormone receptor-positive (HR+) tumours are treated with endocrine therapy, sometimes combined with chemotherapy. ERBB2-positive (HER2+) tumours receive trastuzumab-based therapy in addition to chemotherapy (and endocrine therapy if HR+). Triple-negative breast cancer is managed with chemotherapy alone. In metastatic breast cancer, the focus shifts to prolonging life and managing symptoms, with systemic therapies tailored to the specific subtype. Local treatments like surgery and radiation may be used for symptom relief in metastatic disease. **[13]**

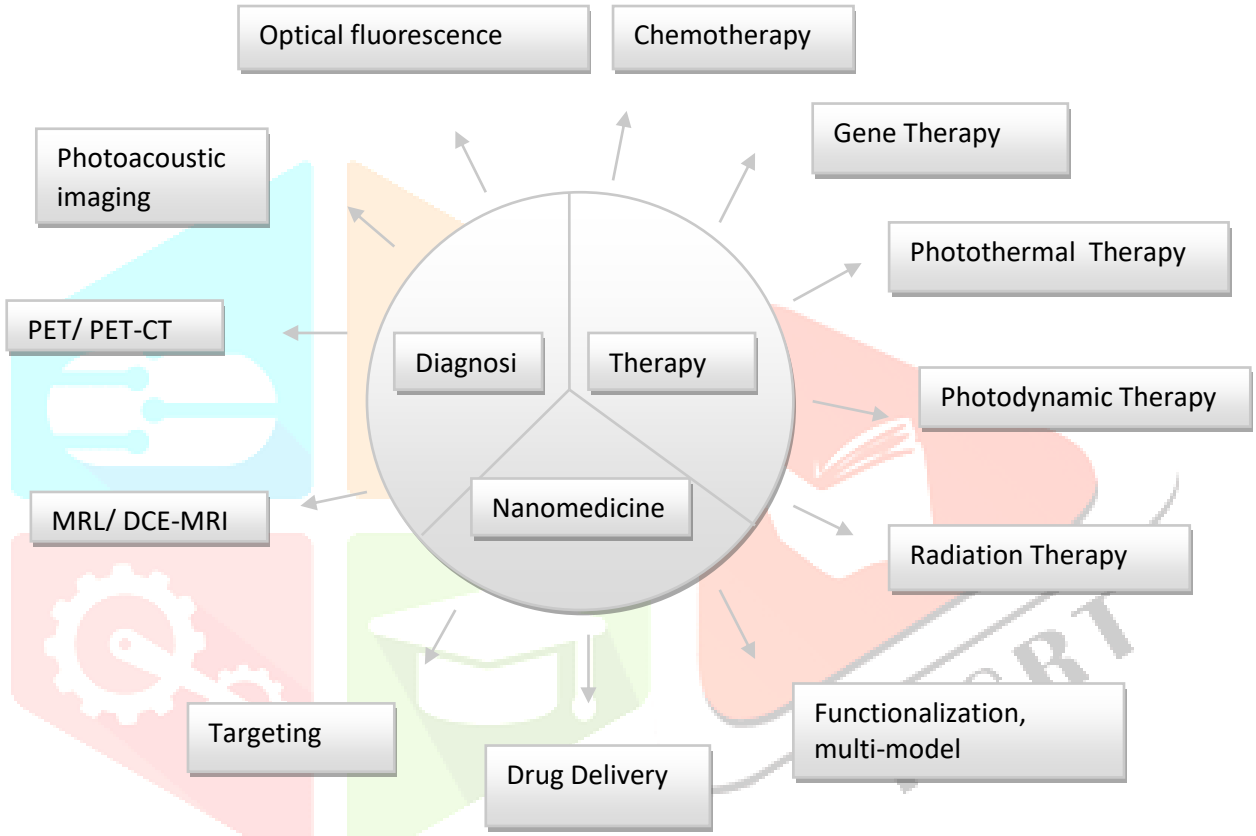

Fig No. 2: Approaches in breast cancer management **[6]**

The **management** of breast diseases:

1) Multidisciplinary Approach: Breast disease management involves various medical disciplines such as diagnostic imaging, pathology, surgery, radiation oncology, and medical oncology.
2) Breast Cancer Screening: Mammography screening is recommended starting at age 40 for women without a high risk of breast cancer. High-risk individuals may benefit from earlier screening and more sensitive imaging techniques like magnetic resonance imaging (MRI).
3) Treatment Based on Stage and Features: Treatment after a breast cancer diagnosis depends on factors like disease stage, receptor status, and tumour grade. Surgical resection and evaluation of lymph nodes are common procedures.
4) Advancements in Surgery: Lumpectomy followed by radiation therapy (breast conserving surgery) has shown equivalent outcomes to mastectomy in terms of local recurrence and overall survival. Sentinel lymph node biopsy reduces surgical morbidity
5) Adjuvant Therapy: Adjuvant therapy after surgery can reduce the risk of breast cancer recurrence significantly, especially for patients with a high risk of disseminated disease.
6) Neoadjuvant Therapy: Administered before surgery, neoadjuvant therapy may downstage tumours, making them operable, and allows for adjustments based on tumour response. Complete pathologic response to neoadjuvant therapy is associated with a good prognosis.

7) Advanced Breast Cancer: Patients with metastatic breast cancer have a median survival of around 2-3 years, with treatment focusing on palliative care. Some patients may achieve durable complete remissions, but survival improvements with chemotherapy are modest. **[27]**
8) Local Therapy: Surgical options for early-stage breast cancer in men include breast-conserving therapy and mastectomy. Most men undergo modified radical mastectomy, although some may prefer lumpectomy due to its lesser morbidity. Feasibility of sentinel node biopsy in men has been demonstrated, with studies showing differences in axillary node involvement compared to women. Post-surgical radiation criteria are often extrapolated from data in women, with considerations for factors like tumour size, lymph node involvement, and surgical margins.
9) Systemic Therapy: Limited data exist regarding systemic therapy in men with breast cancer. Adjuvant chemotherapy, particularly anthracycline-based regimens, shows potential benefits in node-positive disease. The efficacy of trastuzumab for HER2-positive disease in men is not well-studied, but providers often follow similar approaches used in women. Endocrine therapy, mainly tamoxifen, has shown benefits in terms of recurrence-free and overall survival, although studies have mixed results regarding its efficacy for ER-positive tumours in men. Treatment for metastatic disease in men includes endocrine therapy (orchiectomy, estrogen, tamoxifen) and aromatase inhibitors, with limited data on their effectiveness. **[13]**

Recent Treatments for Triple Negative Breast Cancer: Recent advancements in treating triple-negative breast cancer (TNBC) focus on targeted therapies like PARP inhibitors (e.g., olaparib, thalasoparib) and immunotherapy using checkpoint inhibitors such as atezolizumab and pembrolizumab. These treatments have shown promising results in improving progression-free survival (PFS) and overall survival (OS) in TNBC patients, particularly those with specific genetic mutations or PD-L1 expression.

The Role of Non-Coding RNAs in Breast Cancer: Non-coding RNAs, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play crucial roles in breast cancer progression and response to treatment. Altered expression of miRNAs like miR-21, miR-210, and miR-221 is associated with poor prognosis in TNBC, while lncRNAs like miR-200 family and miR-205 show potential as suppressors of metastasis and cell proliferation in breast cancer. Understanding the regulatory functions of these non-coding RNAs holds promise for developing targeted therapies and improving outcomes for breast cancer patients, including those with TNBC.**[14]**

Advances in systemic therapies for breast cancer:

1) Systemic Therapy Considerations: Young age alone should not prompt more aggressive systemic therapy. High-risk features in young women (TN, Her2 positive, high-grade tumours, nodal positivity) justify chemotherapy. Chemotherapy regimens in early breast cancer remain the same regardless of age, often taxane or anthracycline-based. Anthracycline-based chemotherapy shows a greater reduction in death rate in women under 50 compared to older age groups.
2) Targeted Therapies: Young patients with Her2 positive breast cancers benefit from targeted therapies like trastuzumab and pertuzumab, with no age-related changes in treatment.
3) Hormone Therapy: Adjuvant hormone therapy (HT) is crucial for hormone-sensitive breast cancers. Tamoxifen (TAM) is recommended for premenopausal women, while aromatase inhibitors (AIs) are for postmenopausal women. Extended use of HT to 10 years shows benefits in recurrence-free and overall survival. Combined therapies like ovarian suppression (OS) with TAM/AI are beneficial, especially in young, high-risk women.
4) Genomic Testing and Personalized Therapy: Genomic testing like the recurrence score helps in decision-making for adjuvant therapy. Intermediate recurrence scores (11-25) may not require chemoendocrine therapy in all cases, especially in premenopausal women. Clinical risk factors combined with genomic testing can further refine adjuvant therapy decisions. Race and age can also influence adjuvant therapy decisions, suggesting opportunities for personalized recommendations.
5) Fertility Concerns: Young breast cancer patients face unique challenges related to fertility, including infertility risk due to factors like age at diagnosis, ovarian reserve, and chemotherapy type. Fertility preservation options such as oocyte/embryo cryopreservation and GnRH agonist administration are discussed.
6) Chemotherapy and Infertility: Chemotherapy can cause temporary or permanent ovarian failure and amenorrhea, especially with alkylating agents, impacting fertility. The use of GnRH agonists alongside chemotherapy can improve pregnancy rates post-treatment.

7) Hormone Therapy (HT) and Pregnancy: Hormone therapy doesn't cause infertility but has teratogenic effects, necessitating caution during pregnancy planning. The POSITIVE trial is mentioned as relevant to the safety of pausing HT during pregnancy.
8) Psychosocial Concerns: Young women with breast cancer face unique psychosocial challenges due to their life stage, including concerns about fertility, career, and interpersonal relationships. Sexual dysfunction and reproductive concerns post-treatment are highlighted, along with the impact of early menopause on quality of life.**[19]**

"**Treatment" section:**

Breast cancer treatment evolved from early surgical interventions to targeted hormonal therapies, spurred by the discovery of endocrine signalling pathways in the late 19th century.

Targeted Hormonal Therapies:

- *Selective Estrogen Response Modulators (SERMs):* Tamoxifen has been a cornerstone in hormone receptor-positive breast cancer treatment for decades, reducing recurrence risk and mortality.

- *Aromatase Inhibitors (AIs)*: Third-generation AIs like anastrozole, letrozole, and exemestane show superior efficacy over SERMs in postmenopausal ER-positive breast cancer.

Adjuvant and Neoadjuvant Approaches: AIs demonstrate benefits in adjuvant settings, improving disease-free survival and reducing contralateral tumours. Neoadjuvant therapies with AIs are being studied for their efficacy compared to traditional treatments.

Other Endocrine Therapies: Fulvestrant, a "pure anti-estrogen," shows efficacy in tamoxifen-refractory and metastatic cases, offering an alternative in hormone-sensitive breast cancer.

Ongoing Research and Controversies: The role of endocrine therapy in locally advanced breast cancer and prevention remains debated, with ongoing studies focusing on optimizing AI use and understanding their preventive effects.

This condensed version provides a succinct overview of the advancements in breast cancer treatment through targeted hormonal therapies and ongoing research areas.

Chemotherapy

Research on breast cancer is now evaluating medications to lower the risk of the disease's early clinical development. Besides the anti-estrogens that are frequently prescribed to high-risk individuals, additional substances have also been tested. **[25]**
Chemotherapy is widely used in breast cancer treatment to relieve symptoms in advanced cases and lower recurrence risks in localized disease. Common drugs like anthracyclines (e.g., doxorubicin, epirubicin), fluoropyrimidines (e.g., 5-FU), cyclophosphamide, taxanes (e.g., paclitaxel, docetaxel), vinorelbine, and gemcitabine are employed. Anthracyclines inhibit topoisomerase II, while taxanes stabilize microtubules, blocking cell division. Strategies include sequential or combination regimens, with combinations often improving response rates but also causing more side effects. Clinical trials compare different regimens, assessing factors like time to treatment failure and overall survival. Chemotherapy's role extends to adjuvant and neoadjuvant settings, aiming to shrink tumours, prevent recurrences, and improve survival. Advances in drug formulations, such as capecitabine and nab-paclitaxel, enhance drug delivery and efficacy while minimizing side effects. Additionally, biologic therapies targeting receptor tyrosine kinases offer further avenues for tailored treatment approaches.

Supportive care with bisphosphonates for breast cancer metastasis:

1) Importance of Bone Metastasis: Bone is a common site of breast cancer metastasis, significantly impacting quality of life with complications like bone pain, fractures, hypercalcemia, and spinal cord compression.
2) Bisphosphonates as Standard Care: Bisphosphonates are considered standard for treating cancer-induced hypercalcemia and inhibiting osteoclast-mediated bone resorption.
3) Generations of Bisphosphonates: First-generation bisphosphonates (clodronate, etidronate) and second-generation bisphosphonates (pamidronate, ibandronate, zoledronic acid) have differing mechanisms and clinical effectiveness.

4) Reduction in Skeletal-Related Events: Studies show bisphosphonate treatment reduces the risk of skeletal-related events in breast cancer patients with bone metastasis.
5) Comparative Effectiveness: Trials comparing different bisphosphonates (pamidronate vs. zoledronic acid) demonstrate similar effectiveness in reducing skeletal-related events.
6) Adjuvant Therapy: Bisphosphonates like clodronate show potential benefits in reducing bone metastasis risk and improving overall survival, especially in advanced breast cancer without bone metastasis.
7) Ongoing Research: Ongoing trials are evaluating the use of second-generation bisphosphonates in adjuvant settings, with future studies expected to provide more insights into their roles and effectiveness.
8) Safety Considerations: While generally well-tolerated, bisphosphonate therapy can lead to serious complications like renal failure and osteonecrosis of the jaw, requiring careful monitoring and management.**[27]**

Conclusion:

Breast cancer continues to be a major health concern worldwide, with its complexity arising from a myriad of environmental, behavioral, and genetic factors. The multifaceted nature of carcinogenesis in breast cancer underscores the need for a comprehensive understanding of its pathophysiology, which involves key genetic mutations and abnormal signaling pathways driving tumor growth and progression. Early detection and timely intervention remain pivotal in managing the disease effectively, with diagnostic methods like mammography, MRI, and biopsies playing critical roles.

Despite advancements in screening and treatment, significant disparities in survival rates persist between high-income and low-income countries, highlighting the need for equitable access to healthcare resources. Treatment strategies have evolved to include a combination of local and systemic therapies, personalized based on tumor subtypes and genetic profiles. Innovations in systemic therapies, especially for challenging subtypes like triple-negative breast cancer, offer new hope with targeted approaches such as PARP inhibitors and immunotherapy.

The role of non-coding RNAs in breast cancer pathophysiology and treatment response opens new avenues for research and potential therapeutic interventions. Additionally, the integration of genomic testing and personalized therapy plans enhances treatment efficacy and patient outcomes, particularly for young patients facing unique challenges such as fertility preservation.

The ongoing advancements in breast cancer treatment, including the use of bisphosphonates for managing bone metastasis, underscore the importance of a multidisciplinary approach in improving patient care. Continued research and innovation are essential to address the unmet needs in breast cancer therapy, ultimately aiming to reduce mortality and enhance the quality of life for patients globally.

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