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Review Paper

Decoding Breast Cancer: Molecular Classification, Therapeutic Advances and Prevention

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ABSTRACT

Breast cancer is a heterogeneous malignancy and remains a major global health concern. Its development involves complex interactions among genetic susceptibility, hormonal exposure, lifestyle, environmental factors and the tumour microenvironment. Molecular characterization based primarily on estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and proliferation markers such as Ki-67 has improved understanding of tumour biology and facilitated more individualized treatment. Major molecular groups include Luminal A, Luminal B, HER2-enriched and triple-negative breast cancer (TNBC), each demonstrating distinct biological characteristics, prognosis and therapeutic responses [1]. Management includes surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy and immunotherapy. Prevention focuses on modification of avoidable risk factors and identification of individuals at increased risk [1-3]. This review summarizes epidemiology, risk factors, pathogenesis, molecular classification, diagnosis, treatment and prevention, with emphasis on therapeutic advances and future perspectives

INTRODUCTION

Breast cancer is one of the most frequently diagnosed malignancies worldwide and represents a major cause of cancer-related morbidity and mortality among women. It is characterized by considerable biological heterogeneity, which influences tumour development, metastatic potential, treatment response and clinical outcomes [1,4]. Advances in early diagnosis, molecular characterization and personalized treatment have improved outcomes, particularly in non-metastatic disease. However, metastatic breast cancer remains a major therapeutic challenge. Development is influenced by genetic, hormonal, lifestyle and environmental factors, including susceptibility genes such as BRCA1 and BRCA2, hormonal exposure, obesity, alcohol

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consumption and physical inactivity [1,4]. Breast cancer is not a single disease but comprises biologically distinct subtypes. Assessment of ER, PR and HER2, together with proliferation markers such as Ki-67, contributes to molecular classification and therapeutic decision-making [1,4]. Treatment has progressed beyond conventional surgery, chemotherapy and radiotherapy to include endocrine therapy, HER2-targeted agents, immunotherapy and other molecularly directed approaches [1,3].

2. EPIDEMIOLOGY

Breast cancer is the most frequently diagnosed cancer globally and represents an important cause of death among women. The burden varies geographically, with differences related to risk factors, early diagnosis, screening, treatment availability and healthcare infrastructure [1,4]. In India, breast cancer represents an important public health problem. The supplied literature describes breast cancer as the leading cancer diagnosed among Indian women and reports differences between urban and rural incidence [1]. Male breast cancer is considerably less common and accounts for fewer than 1% of cancers in men, although genetic and hormonal factors can influence risk [2].

3. RISK FACTORS

Breast cancer has a multifactorial aetiology. Risk factors include genetic, hormonal, reproductive, lifestyle, environmental and histopathological factors [1,2,4].

3.1 Genetic factors

BRCA1 and BRCA2 are among the best-characterized genes associated with hereditary breast cancer. They participate in DNA double-strand break repair through homologous recombination. Germline pathogenic variants can impair DNA repair and contribute to genomic instability and malignant transformation [1]. Other susceptibility genes include TP53, PTEN, PALB2, ATM and CHEK2. Genetic counselling can help identify individuals with hereditary susceptibility and guide surveillance and preventive management [1,2].

3.2 Hormonal and reproductive factors

Estrogen and progesterone play important roles in breast development and carcinogenesis. Prolonged hormonal exposure may increase cellular proliferation and the probability of replication errors. Factors associated with increased exposure include early menarche, late menopause, nulliparity and certain hormone replacement exposures [1,4]. Reproductive factors such as parity, age at first full-term pregnancy and breastfeeding can also influence risk [2].

3.3 Lifestyle factors

Obesity, physical inactivity, alcohol consumption and smoking are important lifestyle-related factors. Obesity has been associated with increased risk of some breast cancer subtypes, including certain ER-negative cancers and TNBC [2]. Regular physical activity is associated with reduced risk; the prevention review cites a meta-analysis reporting a 12% reduction among physically active individuals compared with inactive individuals [2].

3.4 Environmental factors

Environmental exposures discussed in the recent literature include ionizing radiation, endocrine-disrupting chemicals, air pollutants and occupational or persistent organic pollutants. Proposed mechanisms include hormonal dysregulation, oxidative stress, DNA damage and epigenetic changes [1].

4. PATHOGENESIS

Breast cancer pathogenesis involves genetic alterations and complex interactions between malignant cells and the tumour microenvironment (TME). The TME contains cancer cells together with stromal and immune components. Chronic inflammation, extracellular matrix remodelling, hypoxia, angiogenesis, immune suppression and metabolic changes can contribute to tumour growth and progression [1]. Accumulation of genetic abnormalities can disrupt cellular proliferation, DNA repair, apoptosis and genomic stability. BRCA1/2 alterations are important examples of abnormalities affecting DNA repair [1]. Tumour-associated macrophages, regulatory T cells and myeloid-derived suppressor cells can contribute to an immunosuppressive environment, whereas tumour-infiltrating lymphocytes may be associated with improved prognosis and treatment response in some subtypes [1]. Rapid tumour growth can result in hypoxia. HIF-1α can promote expression of angiogenic factors such as VEGF, supporting tumour progression and metastasis. Cancer stem cells and metabolic reprogramming may also contribute to tumour initiation, recurrence, metastasis and treatment resistance [1].

5. MOLECULAR CLASSIFICATION

Molecular classification is central to modern breast cancer management. Clinical classification commonly incorporates ER, PR, HER2 and Ki-67, while gene-expression profiling can provide additional molecular information [1,4].

5.1 Luminal A

Luminal A is generally characterized by ER and PR positivity, HER2 negativity and a low Ki-67 proliferation index. These tumours tend to grow more slowly and generally have a favourable prognosis and good response to endocrine therapy [1].

5.2 Luminal B

Luminal B generally demonstrates higher proliferation and Ki-67 and lower PR expression than Luminal A. Some tumours may also be HER2 positive. These tumours are generally more aggressive and may require endocrine therapy combined with chemotherapy or targeted treatment depending on their characteristics [1].

5.3 HER2-positive disease

HER2-positive breast cancers demonstrate increased HER2 expression and may exhibit aggressive biological behaviour. HER2 signalling activates downstream pathways including MAPK and PI3K/AKT, promoting cellular proliferation and survival. Anti-HER2 agents such as trastuzumab, pertuzumab and ado-trastuzumab emtansine have substantially changed treatment [1,3].

5.4 Triple-negative breast cancer

TNBC lacks expression of ER, PR and HER2. It is generally considered an aggressive and heterogeneous subtype and has historically had fewer targeted treatment options. TNBC remains an important area for chemotherapy, immunotherapy and emerging targeted approaches [1,3].

6. DIAGNOSIS

Diagnosis involves clinical assessment, imaging, tissue biopsy, histopathological examination and molecular characterization. Common approaches include mammography, ultrasonography, MRI and biopsy. Immunohistochemical determination of ER, PR and HER2 is particularly important because receptor expression directly influences

treatment selection [1,4]. Liquid biopsy approaches, including circulating tumour DNA and tumour-derived exosomes, are also being investigated for less-invasive molecular characterization and monitoring [1].

7. TREATMENT

Breast cancer treatment requires a multidisciplinary approach. Selection depends on disease stage, tumour burden, lymph-node status, hormone receptor status, HER2 status, molecular characteristics and patient factors [1,3].

7.1 Surgery

Surgery is a major component of treatment for early breast cancer. Principal approaches include breast-conserving surgery (BCS) and mastectomy, with or without reconstruction. BCS followed by radiotherapy is an established approach for appropriate patients. Neoadjuvant systemic therapy may reduce tumour size and facilitate breast conservation in selected patients [3].

7.2 Chemotherapy

Chemotherapy may be administered as neoadjuvant, adjuvant or salvage therapy. Neoadjuvant chemotherapy can reduce tumour size, facilitate breast-conserving surgery and address micrometastatic disease. It is particularly important in selected patients with large tumours, extensive nodal involvement and aggressive subtypes such as TNBC and HER2-positive disease [3].

7.3 Radiotherapy

Radiotherapy provides local and regional disease control and remains an important component following breast-conserving surgery. Whole-breast, hypofractionated and partial-breast approaches may be selected according to patient and disease characteristics [3].

7.4 Endocrine therapy

Endocrine therapy is a major component of treatment for hormone receptor-positive breast cancer. Tamoxifen and aromatase inhibitors are important options, with selection influenced by menopausal status and clinical circumstances [3].

7.5 HER2-targeted therapy

The introduction of anti-HER2 therapy significantly changed the prognosis of HER2-positive breast cancer. Trastuzumab was the first widely used anti-HER2 targeted drug, followed by additional targeted agents that expanded therapeutic options [1,3].

7.6 Immunotherapy

Immune checkpoint inhibition has become an important area of treatment, particularly in selected TNBC. Pembrolizumab and other checkpoint inhibitors are among the developments described for early and metastatic TNBC [1,3].

8. PREVENTION

Breast cancer prevention aims to reduce disease probability by addressing modifiable risk factors and identifying individuals at increased risk. Not all risk factors can be modified; therefore, prevention should be individualized [2].

8.1 Lifestyle modification

Maintaining a healthy body weight, regular physical activity, minimizing alcohol consumption, avoiding tobacco and avoiding unnecessary ionizing radiation are among approaches discussed for risk reduction [2]. Breastfeeding may also be associated with lower risk in some populations [2].

8.2 Risk assessment and genetic counselling

Risk assessment can incorporate clinical, histopathological and genetic factors. The Gail and Tyrer-Cuzick models are examples discussed in the prevention literature. Genetic counselling is important for individuals with suspected hereditary cancer susceptibility [2].

8.3 Chemoprevention

Tamoxifen, a selective estrogen receptor modulator, reduced invasive breast cancer incidence by approximately 49% in the Breast Cancer Prevention Trial cited by Sauter. Potential adverse effects include endometrial cancer and thromboembolic events, requiring individualized risk-benefit assessment [2]. Raloxifene is another SERM used for risk reduction in selected postmenopausal women. Aromatase inhibitors such as exemestane and anastrozole have also been investigated for chemoprevention in postmenopausal high-risk women [2].

8.4 Risk-reducing surgery

Risk-reducing bilateral mastectomy may be considered in selected women carrying high-risk pathogenic variants, including BRCA1, BRCA2, TP53, PALB2, CDH1 and PTEN. Bilateral salpingo-oophorectomy may also be considered in selected genetically high-risk premenopausal women [2]. These procedures are intended for selected high-risk populations and are not routine prevention for the general population.

9. RECENT THERAPEUTIC ADVANCES AND FUTURE PERSPECTIVES

The treatment landscape is moving increasingly toward precision and personalized medicine. Genomic sequencing can identify potentially targetable alterations and support treatment selection based on tumour biology [1]. Artificial intelligence and machine learning are being investigated for analysis of mammograms, histopathological slides, clinical information and multi-omics data, with potential applications in diagnosis, prognosis and treatment decision-making [1]. Other emerging approaches include antibody-drug conjugates, immune checkpoint inhibitors, gene therapy, microRNA-based therapies, cancer vaccines and cellular therapies such as CAR-T-cell approaches. Several remain investigational and require further clinical evidence [1,3].

CONCLUSION

Breast cancer is a complex and heterogeneous disease arising from interactions among genetic, hormonal, lifestyle, environmental and tumour-microenvironmental factors. Molecular classification using ER, PR, HER2 and proliferation markers such as Ki-67 provides important information for prognosis and therapeutic selection [1,4]. Treatment has progressed from conventional surgery, chemotherapy and radiotherapy toward individualized treatment incorporating endocrine therapy, HER2-targeted therapy, immunotherapy and other molecularly directed approaches [1,3]. Prevention requires a risk-adapted approach involving lifestyle modification, physical activity, healthy body weight, minimizing alcohol and appropriate management of high-risk individuals. Selected high-risk women may benefit from chemoprevention, while risk-reducing surgery may be considered for individuals with specific high-risk genetic alterations [2]. The future of breast cancer management lies increasingly in precision medicine, molecular profiling, immunotherapy, targeted treatment, artificial intelligence and innovative cellular and genetic therapies [1]. Continued research and improved access to early diagnosis and effective treatment

will be essential for reducing the global burden of breast cancer.

Table 1. Major molecular subtypes of breast cancer

Subtype	Major characteristics	General therapeutic implication
Luminal A	ER+, PR+, HER2-, low Ki-67	Strong role for endocrine therapy
Luminal B	Higher proliferation; may be HER2+	Endocrine therapy ± chemotherapy/targeted therapy
HER2-positive	HER2 overexpression	HER2-targeted therapy ± chemotherapy
TNBC	ER-, PR-, HER2-	Chemotherapy; selected patients may receive immunotherapy

Table 2. Major treatment modalities

Treatment	Main role	Examples/notes
Surgery	Local tumour control	Breast-conserving surgery; mastectomy
Chemotherapy	Systemic cytotoxic treatment	Neoadjuvant/adjuvant therapy
Radiotherapy	Local/regional control	Whole-breast or partial-breast irradiation
Endocrine therapy	Hormone receptor-positive disease	Tamoxifen; aromatase inhibitors
HER2-targeted therapy	HER2-positive disease	Trastuzumab; pertuzumab; ado-trastuzumab emtansine
Immunotherapy	Selected TNBC	Pembrolizumab and other checkpoint inhibitors
Emerging therapies	Precision/investigational approaches	Gene therapy; vaccines; cellular therapies

Table 3. Breast cancer prevention strategies

Strategy	Target/role
Healthy body weight	Modifiable metabolic risk
Physical activity	Lifestyle-related risk reduction
Minimize alcohol	Modifiable risk factor
Avoid tobacco	General cancer risk reduction
Breastfeeding	Potential reduction in breast cancer risk.
Genetic counselling	Hereditary/high-risk individuals
Tamoxifen	Chemoprevention in selected high-risk women
Raloxifene	Chemoprevention in selected postmenopausal women
Exemestane/anastrozole	Selected high-risk postmenopausal women
Risk-reducing surgery	Selected individuals with very high genetic risk

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