UMYU Scientifica, Vol. 4 NO. 1, March 2025, Pp 217 – 231
https://doi.org/10.56919/usci.2541.022
ISSN: 2955 – 1145 (print); 2955 – 1153 (online)
*A periodical of the Faculty of Natural and Applied Sciences, UMYU, Katsina*

REVIEW ARTICLE

# Molecular Subtypes and Biomarker-based Detection of Breast Cancer: Challenges and Future Perspectives

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## ABSTRACT

Breast cancer remains a serious global health challenge, being the leading cause of cancer-related death in women. Its prevalence is still rising despite improvements in diagnostic techniques and awareness efforts. However, disparity exists due to its complex molecular heterogeneity and limited access to advanced diagnostics. Genetic and epigenetic changes such as DNA methylation, histone modification, non-coding RNAs, alterations in tumor suppressor genes, immune system interactions, and hormonal and growth factor signaling pathways contribute to breast cancer pathogenesis. Racial discrimination and socioeconomic determinants of health can also affect prognosis, even though biological differences by ethnicity may be partially responsible for the observed discrepancies. This review highlights the continued challenges and opportunities in enhancing the prognosis of breast cancer worldwide, in addition to bringing into light the molecular mechanisms, molecular subtypes, and innovative approaches to early detection and treatment of breast cancer.

**ARTICLE HISTORY**

Received December 18, 2024
Accepted March 18, 2025
Published March, 23 2025

**KEYWORDS**

Breast cancer, Molecular subtypes, Screening, Treatment, Survivorship



## INTRODUCTION

Despite available diagnostic methods, in addition to continuous campaigns on breast self-examination, breast cancer remains the main cause of cancer-related deaths among women globally (El Masri & Phadke, 2022; Kawiak, 2024). Estimates indicate that in 2022, there will be 51,400 new cases of ductal carcinoma in situ (DCIS) and 287,850 newly diagnosed cases of invasive breast cancer in the US. Additionally, it is anticipated that 43,250 deaths in that year will be related to breast cancer (Siegel et al., 2022). Second only to lung cancer in terms of mortality, breast cancer is the most commonly diagnosed cancer among women in the United States. The timely detection of breast cancer is crucial since it can greatly impact the available treatments and increase the chance of survival. There is a 90% likelihood of surviving for five years if cancer is detected in its early stages, but if the diagnosis is made at a more advanced stage, the survival rate drops to 25% in the same period (Li et al., 2025). In Nigeria, the prevalence of breast cancer is increasing. In 2020, the International Agency for Cancer Research (IARC) reported 28,380 new cases of breast cancer in Nigeria, which accounted for the largest percentage of all cancer types and 22.7% of new cancers. Nigeria has the highest age-standardized breast cancer mortality rate in Africa and among the highest in the world. According to a recent sub-Saharan African study, out of the six nations examined, Nigeria had the lowest three-year survival rate for breast cancer patients (36%), followed by Uganda (44%), Zambia (47%), Namibia (56%), and South Africa (59%) (McCormack et al., 2020). Unlike other cancers, breast cancer incidence is gradually increasing, possibly due to increased alcohol consumption, obesity in postmenopausal breast cancer, and the advent of more sensitive imaging techniques (Agurs-Collins *et al.*, 2019).

The most likely explanation for the increased incidence and mortality rate of breast cancer is that our understanding of its biological heterogeneity is incomplete. Importantly, the primary clinical parameters and pathological markers, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2), which are frequently employed in the clinic to group patients for prognostic predictions, choose treatments, and enroll patients in clinical trials, do not adequately capture this complexity. This underscores the need for understanding the molecular mechanisms of breast cancer to ensure proper management and improve the implementation of personalized treatment approaches.

The combination of cutting-edge imaging methods, genetic testing, and interdisciplinary approaches has transformed the treatment of breast cancer. However, the limitations of the available diagnostic and therapeutic

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**How to cite**: Kabir I. M. (2025). Molecular Subtypes and Biomarker-based Detection of Breast Cancer: Challenges and Future Perspectives. *UMYU Scientifica*, 4(1), 61 – Pp. https://doi.org/10.56919/usci.2541.022

approaches highlight the necessity of more investigation into less well-known histological and molecular subtypes and the creation of affordable screening techniques. This review highlights the continued challenges and opportunities in enhancing the prognosis of breast cancer worldwide, in addition to bringing into light the molecular mechanisms, molecular subtypes, and novel approaches to early detection of breast cancer.

## METHODS

A search was conducted in PubMed using keywords 'breast cancer', 'molecular mechanism', 'molecular subtypes' and 'detection methods' from 2000 to 2025. Article not in English language and those without full text were excluded. Review articles, studies that reported empirical findings, and clinical trials focusing on molecular mechanisms and diagnosis of breast cancer were reviewed for relevance.

### Risk factors for breast cancer

It is believed that one in eight women worldwide will develop breast cancer, of which 5-10% of the cases are due to genetic alterations, and 90-95% are associated with lifestyle and environmental factors (Kolak *et al.*, 2017). Modifiable factors such as alcohol consumption, diet, hormone therapy, obesity, lack of physical activity, and non-modifiable factors like early menarche, late age of first labour, late menopause, dense breast, genetic mutation, family history and previous chest irradiation for the treatment of other ailment increases the risk of recurrence and morbidity (El Masri & Phadke, 2022; Kolak *et al.*, 2017).

A healthy diet is essential in the prevention of cancer and helps maintain proper body weight. It should be rich in vegetables, legumes, and fruits and should contain less red meat, trans-fatty, calories, sweet and alcoholic beverages, and little salt. A study by Aune *et al.* (2012) demonstrated a negative correlation between the frequency of tumor prevalence and the amount of fiber in the diet in a meta-analysis of 16 prospective studies on the relationship between fiber consumption and breast cancer risk (Aune *et al.*, 2012). Also, there exists a link between the reduction in the risk of breast cancer morbidity and the levels of lutein, beta-carotene, and alpha-carotene. Consuming carrots, broccoli, and other fresh, green vegetables is most closely associated with levels of alpha and beta-carotene, as well as lutein and zeaxanthin, according to epidemiological studies, while citrus fruit influences the blood lutein concentration.

There is no doubt that cancer risk is increased by alcohol consumption and by biological mechanisms. Three mechanisms have been suggested to explain the link between alcohol consumption and breast cancer. These include impact on ER, level of estrogen, and by-products of alcohol metabolism. By activating aromatase, alcohol also affects the estrogen pathway. By reducing the frequency and changeability of cycle duration, it can also have an impact on the menstrual cycle. While excessive alcohol use on weekends is linked to extremely high blood levels of estrogen, heavy alcohol use is linked to heightened luteal phase estrogen levels. According to one theory, alcohol may have an effect on mammary gland cancer development by elevating endogenous estrogen levels (Kolak *et al.*, 2017). Alcohol also influences the menstrual cycle by decreasing the cycle length (Liu *et al.*, 2015).

High calorie consumption causes weight gain, obesity and increases the risk of cancer development. (Orecchioni *et al.*, 2015). The body mass index (BMI) is a frequently used determinant of underweight, overweight, and obesity. Numerous studies have demonstrated that calorie restriction slows the progression of neoplasia. Hyperinsulinemia and insulin resistance, elevated insulin-like growth factor (IGF) production, altered sex hormone metabolism, chronic inflammation, altered fatty tissue adipocytokine and vascular endothelial growth factor (VEGF) production, oxidative stress, and immune response alterations are some of the mechanisms linking obesity to cancer risk.

The association between breast cancer and physical activity is greater in postmenopausal women who have no family history of breast cancer, have a normal body weight, and have at least one healthy child. Epidemiological studies suggest that women who engage in exercise have about 10-15% less risk than those who do not. Although the exact workout plan needed to prevent this malignancy is not established, a decrease in risk is noted in tandem with increased physical activity (Lahart *et al.*, 2015).

### Molecular mechanisms of breast cancer

*Genetic and epigenetic alterations*

A variety of changes in genetic and epigenetic components can influence the complex chain of events that leads to breast cancer development. Through a thorough examination of genetic data, including DNA copy numbers, exon sequencing, mRNA arrays, DNA methylation, reverse-phase protein arrays, and microRNA sequencing, the Cancer Genome Atlas Network has discovered three highly mutated genes (TP53, PIK3CA, and GATA3) that are frequently present in different types of breast cancer (Garrido-Sánchez et al., 2012). Furthermore, significant mutant genes that had not previously been connected to breast cancer, including PTPN22, TBX3, AFF2, RUNX1, SF3B1, PTPRD, CBFB, PIK3R1, NF1, and CCND3, have recently been found. Variations exist in the types and frequency of genetic alterations in the several intrinsic mRNA categories of breast cancer, including HER2-enriched subtypes, basal-like/TNBC, luminal A, and luminal B. For example, the luminal A and B groups had a larger percentage of TP53 mutations that resulted in minor alterations to the protein structure, while the basal-like group had a higher frequency of TP53 mutations that led to altered or non-functioning proteins. Also, different forms of mRNA show discrepancies in the number of copies of proteins expressed. Patients treated with aromatose inhibitors showed a higher percentage of mutation in the gene responsible for regulating estrogen levels, ESR1 (Li et al.,

2025). These genetic changes can activate transcription without a ligand, resulting in reduced receptor sensitivity to common treatments, including fulvestrant, RU-58,688, AZD9496, and GDC-0810.

Tumor suppressor genes are essential players in genetic and epigenetic alterations in breast cancer. BRCA1, situated on chromosome 17, was initially identified in 1990 in families with suggestive pedigrees by linkage analysis and related to breast cancer, specifically triple-negative breast cancer (TNBC). BRCA1 controls DNA repair through interaction with DNA repair proteins, cell cycle regulators, and tumor suppressors (Daniyal et al., 2021). The BRCA1 C-terminal domain and ring structure found in the BRCA1 protein prevents tumor development, particularly in breast and ovarian cancer. The interaction between the BRCA1 C-terminal domain and phosphoproteins is crucial for BRCA1's tumor suppressor activity at DNA damage sites. Consequently, the disruption of double-stranded DNA damage and the subsequent development of breast cancer are caused by mutations in these domains. It is unclear exactly what the zinc finger domain of the BRCA protein does. Breast, ovarian, and uterine malignancies have been found to contain mutations in the BARD1 gene, and missense mutations in the BRCA1 ring domain (such as C61G) interfere with the BRCA1:BARD1 interaction. The BARD1 regulates RNA processing during transcription and DNA repair by interacting with and inhibiting the activity of an RNA polyadenylation factor (Cst-50) (Sarhangi et al., 2022). A TP53 mutation frequently coexists with a BRCA1 gene mutation, increasing the risk of breast cancer (Han et al., 2020). Furthermore, epigenetic silencing via promoter hyper-methylation, which results in the downregulation of the BRCA1 gene, may be linked to BRCA1 deficiency (Daniyal et al., 2021).

BRCA2 gene has a bigger open reading frame of 10.3 kb compared to BRCA1. It encodes a nuclear protein that is 384 kDa in size located on chromosome 13q12-13 and also provides instructions necessary for coding a protein that acts as a tumor suppressor. This protein is a transcription factor with a protected helix domain at the C-terminal and a DNA binding domain in the N-terminal. Additionally, two nuclear localization signals (NLS) are found in the BRCA2's C-terminal region. Important biological processes carried out by the BRCA2 protein include transcriptional control, embryonic development, and DNA damage repair. By guiding the RAD51 protein to the locations (Daniyal et al., 2021) of double-strand breaks, the BRCA2 protein primarily aids in homologous recombination, which repairs DNA damage. More than 1,800 BRCA2 mutations, which are categorized as insertion, deletion, frame change, and nonsense mutations, have been found, resulting in premature protein and an increase in the risk of breast cancer development (Sarhangi et al., 2022)

TP53 is another tumor suppressor gene mutated in different cancers, including breast cancer. Its protein, P53, is involved in various mechanisms such as DNA repair, cell growth, and apoptosis. Its activation occurs in response to cellular stress. For individuals with breast cancer, particularly those with the triple-negative subtype, TP53, and its mutant state are both a potential biomarker and therapeutic target because of their high prevalence. A variety of genes that are either directly or indirectly regulated by the p53 transcription factor exhibit altered expression when the TP53 gene is mutated. Various TP53 gene mutations, especially in intron 3 and exon 4, have been reported in TNBC, with missense mutations being the most common seen in advanced stages of cancer (Daniyal et al., 2021).

The intricate and adaptable processes of epigenetics impact the transcription and translation of genetic information into proteins, which in turn impacts health and illness. Epigenetic changes are believed to be reversible and comprise chemical alterations to DNA (or DNA-associated chromosomal proteins called histones) that occur independently of a change in the DNA sequence, as opposed to genetic modifications, which result in a change in the DNA base sequence of DNA. Epigenetic mechanisms such as histone modifications, DNA methylation, microRNA (mRNA), and long non-coding RNA can be passed on by generational inheritance (meiotically) or through cell division (mitotically). Epigenetics has emerged as a key link between genes and the environment, being a molecular mechanism that explains individual diversity in the biological response to environmental factors (Agurs-Collins et al., 2019; Li et al., 2025).

DNA methylation involves the addition of a methyl group to the DNA sequence between cytosine and guanine base pairs. DNA methyltransferases are responsible for the majority of this methylation that takes place at the CpG islands. Promoter DNA methylation attracts methyl-binding proteins that alter histones, which normally cause chromatin compaction and gene silencing and interfere with the binding of transcription factors (Agurs-Collins et al., 2019). It is believed that DNA methylation variations, regulated by particular enzymes known as DNMTs and TETs, are responsible for the DNA mutations found in breast cancer patients (Barrios-Rodríguez et al., 2020). Other proteins, such as GADD45, AID, and APOBEC, have also been connected to the development of breast cancer due to their function in modifying gene expression. It has been shown that the GADD45 and BRCA1 genes may be linked to the development of breast cancer because they may be involved in the repair of damaged nucleotides. Also, DNA methylation, which may aid in the development of malignant tumors, can be actively removed by AID proteins(Fucito et al., 2008). Furthermore, the process of APOBEC mutagenesis has been connected to the progression of breast cancer. Interestingly, it can also set off immunological reactions that prevent the development of malignant growths. Abnormal DNA methylation may suppress HOXA5, TMS1, p16, RASSF1A, and BRCA1 genes that help prevent tumor growth (Li et al., 2025). These genes are essential for physiological functions such as estrogen sensing, cell division and death, cell proliferation regulation, and DNA repair.

Histone proteins, which are important in chromatin organization, can be modified by adding or removing certain chemical groups, a process termed histone modification. Histone acetylation, a type of histone modification, can disrupt the interaction between histones and DNA, loosening the chromatin structure and increasing gene expression. Specialized proteins known as histone acetyltransferases (HATs) and histone deacetylases (HDACs) oversee the control of this process. On the other hand, histone methylation alters gene activity by modifying the presence of methyl molecules on particular lysine and arginine amino acids. Changes in histone methylation, which is controlled by enzymes such as methyltransferases (KMTs) and demethylases (KDMs), have been linked to the development of breast cancer (Joshi et al., 2022). Epigenetic changes significantly impact breast cancer and are essential in regulating important genes linked to various biological functions. These changes play a major role in the initiation and development of breast cancer. Therefore, a deep understanding of these mechanisms will provide possibilities for effective breast cancer treatment.

Most of the human genome consists of RNAs that do not play a role in forming proteins. This consists of long non-coding RNAs, circular RNAs, small nucleolar RNAs, and tiny microRNAs. Several studies have shown that a large number of non-coding RNA molecules do not function properly in breast cancer and other cancer types. Important biological processes that impact breast cancer, including cellular motility, development and differentiation, angiogenesis, apoptosis, invasiveness, and response to therapy, are significantly influenced by non-coding RNAs. Several studies have been conducted to use non-coding RNAs as markers for detecting and treating breast cancer (Dsouza et al., 2021; Zhang et al., 2021).

*Hormonal and growth factor signaling pathways*

The PI3K/AKT/mTOR pathway activation occurs in various cancers. This pathway integrates extracellular signals that activate G-protein-coupled receptors (GPCRs) and tyrosine kinase receptors. AKT is activated by PDK1 mTORC2, and Tuberous sclerosis complex 2 (TSC2), a negative regulator of mTOR that triggers downstream mitogenic signaling, is phosphorylated and disinhibited by the activated AKT. PI3K needs several inputs for complete activation, including binding by Ras and membrane-bound tyrosine kinase receptors. Numerous factors, such as PIK3CA and AKT oncogene mutation, RTK overexpression, and PTEN tumor suppressor loss of function, contribute to cellular and tumor dependence on the PI3K pathway (Vasan et al., 2019). PIK3CA oncogenic mutations are the most prevalent PI3K pathway alterations in ER+ breast cancer, although PIK3CA gene amplification without mutation is rather uncommon. Constitutive enzymatic activity is caused by PIK3CA mutations, which are seen in up to 40% of ER+ primary and metastatic tumors that are HER2-negative. The preclinical justification for examining combination anti-HER2 therapy with PI3K pathway inhibition was provided by a study conducted in HER2-positive (HER2+) BC that revealed PIK3CA mutations predict decreased overall survival, indicating additivity between upstream RTK signaling and PIK3CA mutation (Zardavas et al., 2018). The most common PIK3CA mutations are the hotspot single amino acid substitutions in the kinase (H1047R in exon 20), and helical (E542K and E545K in exon 9) domains, each having a distinct mechanism of activation. The activation of the H1047R is Ras-independent and increases lipid membrane binding, while E545K activation is Ras-dependent and is similar to activation by tyrosine kinase receptor-phosphopeptides. The PIK3CA gene also has a lot of less common mutations, most of which cause partial activation in cellular and biochemical models. Upstream mutation or overexpression of tyrosine kinase receptors can activate the PIK3 pathway. Examples are HER2 mutations and overexpression, and ERRB2 amplification (Barzaman et al., 2020; Vasan et al., 2019).

PIK3R1 mutations were also reported to activate the MAPK pathway. For example, MKK4 activates both JNK, p38, and MAPK, but MKK7 only activates JNK. Both $PIK3R1^{R348*}$ and $KRAS^{G12D}$ enhanced phosphorylated MKK1/2 (p-MKK1/2), which phosphorylates ERK, in accordance with their distinct effects on MAPK phosphorylation. Among the naturally occurring mutations of PIK3R1, $PIK3R1^{R348*}$ and $PIK3R1^{L370fs}$ are distinct because they activate both the PI3K and certain MAPK pathway components. $PIK3R1^{R348*}$ and $PIK3R1^{L370fs}$ activate the MAPK pathway independently of PIK3R1's role in PI3K signaling. The functional effects of MAPK signaling are determined by signaling specificity, which includes activation strength, duration, and location (Cheung et al., 2014). A lower tumor-infiltrating lymphocytes (TIL) phenotype in triple-negative breast cancer (TNBC) is predicted by increased Ras-MAPK activation and to a lesser extent, by cell-cycle pathway activity. Ras-MAPK activation can enhance PD-L1 and MEK activity while suppressing inflammatory responses including IFN-γ production and MHC expression (Bates et al., 2018).

In order to control transcription, ER is recruited to the cis-regulatory regions of its target genes when estrogen binds to it, causing receptor dimerisation. The activity of this complex network depends on the recruitment of additional collaborating transcription factors and chromatin regulators, which are brought about by ER binding to its target genes (also known as the classical genomic signaling pathway) (Lupien et al., 2008). Estrogen genomic signaling causes the production or activation of proteins crucial for tumor growth, including insulin-like growth factor I receptor (IGF-IR) and insulin growth factor II (IGFII), in addition to downregulating genes like EGFR and HER2; therefore, the ER antagonist tamoxifen, the aromatase inhibitor letrozole, and exemestane, or the ER degrader fulvestrant are used to clinically suppress ER. The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) phase III clinical trial provided one of the earliest clinical pieces of evidence supporting the close interaction between the PI3K pathway and ER signaling. It demonstrated an improvement in progression-free survival (PFS) in ER+

BC patients treated with the mTOR inhibitor everolimus in conjunction with aromatase inhibitor exemestane (Baselga et al., 2012). Because the ER and PI3K pathways are so intricate, they interact at several levels. Results show that oncogene-mediated signaling can phosphorylate ER and its coregulators. Also, preclinical data has also suggested that ER uses nongenomic estrogen signaling pathways to control cellular processes apart from its classical transcriptional action. A part of the crosstalk between ER and the PI3K pathway occurs in a little pool of ER at the plasma membrane resembling growth factor ligands. Plasma membrane-bound ER initiates the activation of several signaling molecules rapidly, including IGF-1R/InsR, EGFR, HER2, PI3K, MEK, and Src, and raises the levels of second messengers such cyclic AMP. Several membrane ER isoforms that activate oncogenic kinases to promote endocrine resistance have been identified, including ERα, splice variants of ERα (ER-36, ER-46), ERβ, and GPR30 (Vasan et al., 2019; Wang et al., 2006)

*Tumor microenvironment and immune system interaction*

The perception of breast cancer's low immunogenicity is strengthened by the fact that the cells themselves are skilled manipulators and immune destruction evaders, and their methods are not fully known. It is essential to identify their immune evasion mechanisms in order to develop more potent treatments. The expression of immune inhibitory co-stimulatory receptors PD-1, cytotoxic T lymphocyte-associated protein (CTLA)-4, lymphocyte activation gene (LAG)-3, the infiltration of suppressive immune cells such as regulatory T cells (Tregs), the presence of tumor-derived immunosuppressive factors such as TGF-β, IL-10, IDO, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) in the microenvironment, in addition to altering the functions of the NK cells are the best-characterized mechanisms describing breast cancer's ability to evade the immune destruction (Bates et al., 2018). Particularly in TNBC and HER2-amplified breast cancer, tumors with higher immunogenicity and immune cell infiltration typically respond well to treatment and have a good prognosis. Any molecular subtype of breast cancer that have more than 50–60% lymphocytes in the tumor or stroma often indicates a good prognosis (Kroemer et al., 2015). Nonetheless, the composition of the tumor infiltrate may play contradictory and seemingly illogical functions in fostering an environment that either promotes or inhibits tumor growth. Although recent studies have clarified the importance of TILs and may show immune cell-specific significance, this is another characteristic of breast cancer that might contribute to its perception as an immunologically "silent" tumor (Bates et al., 2018).

Fibroblasts are mesoderm-derived cells that can easily adapt to the ex vivo growth of tissue cultures. Fibroblasts contribute to connective tissue physiology; however, their complex and dynamic functions in the pathological response associated with tissue injury recovery are yet to be fully understood. This is especially relevant to carcinomas, as the presence of cancer-associated fibroblasts (CAFs) in tumors indicates that CAFs play a role in the development of tumors, potentially providing different targets for cancer management, including breast cancer (Becker et al., 2020; LeBleu & Neilson, 2020). Different protein markers can be used to identify the varied population of mesenchymal cells that make up breast CAFs. Studies report that CAFs have both pro- and anti-tumor activities, highlighting their complicated biology in cancer (Kalluri, 2016; Monteran & Erez, 2019). The precise functional role of CAFs in the beginning and advancement of cancer is being investigated. As demonstrated by admixing experiments involving cancer cells and cultivated CAFs, which always result in faster-growing tumors as compared to cancer cells injected alone or in combination with normal fibroblasts (NFs), the in vitro proliferation of CAFs enriches for CAFs that promote cancer.

CAFs function as metabolic support cells for proliferating cancer cells. But regardless of the availability of oxygen, highly proliferative cancer cells exhibit increased glycolytic rates, converting glucose to lactate (Warburg effect). The increased need for biosynthetic products required for the growth and proliferation of cancer cells is supported by enhanced glycolysis (Vander Heiden & DeBerardinis, 2017). Similarly, it has been suggested that CAFs engage in a lactate shuttle with cancer cells that promote tumor growth and undergo metabolic reprogramming towards aerobic glycolysis (reverse Warburg effect) (Roy & Bera, 2016). Hypoxia and hypoxia-inducible factor 1 alpha (HIF-1α) cause glycolytic reprogramming, which directly triggers the transcription of glycolytic enzymes and is a crucial aspect of metabolic reprogramming in tumors. Moreover, the hypoxia response element in the HIF1A promoter region may become auto-transactivated if it is demethylated. Elevated HIF-1α is linked to a developing hypoxic tumour and may affect CAFs' secretome and glucose metabolism. It was discovered by CAFs and NFs that dynamic variations in oxygen levels probably cause epigenetic modifications (such as hypomethylation of the HIF1A promoter) that regulate metabolic reprogramming in CAFs towards elevated glycolysis (Becker et al., 2020).

A study reported that PI3Kβ is required for immune evasion. Using genetically engineered mice with deletion of Pik3ca (p110α) or Pik3cb (p110β), they generated primary tumor cells for transplantation experiments showing p53, PTEN, and PI3K isoform ablation. The Pik3ca (p110α)-deficient tumor cells express undetectable levels of E-cadherin and high levels of vimentin, while the Pik3cb (p110β)-deficient tumor cells express high levels of E-cadherin and very low levels of vimentin. However, the control group expressed intermediate levels of E-cadherin and vimentin, thus indicating notable heterogeneity in mesenchymal and epithelial phenotypes that may be a factor in variations in the disease progression among the groups (Bergholz et al., 2023). The same study also reported that using bulk RNA-seq analysis, STAT3 signaling was the top-downregulated canonical pathway. Thus, numerous genes involved in immune responses, including cytokines, regulators of antigen processing, immune stimulation, Toll-like receptor (TLR), and TNFα

signaling, were upregulated in the Pik3cb (p110β)-deficient cells, while tumor suppressor genes were downregulated. Also, IL6-JAK-STAT3 was downregulated, while TNFα signaling was upregulated via NF-ϰB signatures in the Pik3cb (p110β)-deficient tumor cells. These findings indicate the immune-suppressing function of PI3Kβ via STAT3.

Another crucial Strategy used in cancer treatment is the prevention of angiogenesis. The vascular endothelial growth factor (VEGF) receptor family is a significant angiogenesis mediator. In order to prevent angiogenesis, a monoclonal antibody called bevacizumab was also utilised in this instance to move the ligands to the VEGF receptor. Remarkably, bevacizumab was employed either alone or in combination with other chemotherapeutics in phase I/II clinical trials that treated patients with resistant metastatic breast cancer (Cobleigh et al., 2003). Furthermore, in a phase III clinical trial, 462 patients with metastatic breast cancer received bevacizumab in addition to capecitabine (Cobleigh et al., 2003).

**Histological and molecular subtypes**

Understanding the cellular mechanisms governing the development of breast tumors has been made possible by developments in molecular research, which has helped discover new therapeutic approaches and identify diagnostic markers. Breast cancer heterogeneity is determined by the complexity of the molecular processes that control tumor initiation and progression.

Regardless of the histological type, the terminal duct-lobular unit is the site of origin for the majority of invasive breast tumors and their precursors. The terms "ductal" and "lobular" carcinoma do not in any way indicate the origin or histogenesis of the disease within the ductal system of the breast. However, these are identified by their distinct immunohistochemical profiles, cytological characteristics, and architectural patterns.

Perou and colleagues worked toward the pioneer molecular classification at the start of this century. They first described a group of 65 breast cancer surgical specimens from 42 patients using complementary DNA microarrays that represented 8102 human genes. They discovered that the tumors could be categorized based on significant prevalent differences in gene expression profiles (Perou *et al*., 2000). Following more research and improvement, the authors' categorization system separated breast cancer into four intrinsic molecular subtypes: basal-like/TNBC, v-erb-b2 (ERBB2)/HER2 gene-overexpressing (HER2þ), luminal A, and luminal B. The expression of the ER and fluctuating cell proliferations are characteristics of luminal carcinomas. ERBB2-overexpressing tumors are characterized by HER2 overexpression (Zhang, 2023).

Hierarchical cluster analysis of genes that differ between tumours from different patients revealed that the cluster dendrogram was divided into ER-positive and ER-negative breast cancer, and additionally, there are four molecular subtypes of breast cancer: luminal, normal breast-like, HER2-enriched, and basal-like/TNBC (Weigelt *et al*., 2010). The ER-positive luminal tumors were first defined as tumors exhibiting patterns of expression similar to those of the mammary gland's normal luminal epithelia, such as low molecular weight cytokeratins 8/18, ER, and genes linked to an active ER pathway. They are categorized into Luminal A from Luminal B groups, with the group A showing elevated levels of ER-activated genes expression, decreased levels of proliferation-related genes, and mostly of low histological grade and good prognosis. While Group B has a high histological grade, showing poor prognosis and higher proliferation rates.

The ER-negative luminal tumours are classified into three subtypes: normal breast-like, basal-like/TNBC, and HER2-enriched. The normal breast-like was shown to be enriched for genes expressed in adipose tissue and clustered with normal breast samples and fibroadenoma. The clinical importance of these tumors has not yet been established, and their characteristics are currently lacking. According to the proponents of this molecular categorization, the normal breast-like subtype might only be an artifact of sample representation, meaning that it has an abnormally high amount of normal tissue contamination. Aggressive clinical behavior is linked to the HER2 and basal-like/TNBC molecular subtypes (Abd El-Rehim *et al*., 2004). HER2 and genes linked to its pathway and/or the HER2 amplicon on 17q12 are overexpressed in HER2 tumors. Instead of belonging to the HER2-microarray subtype, a sizable portion of HER2-amplified, ER-positive tumors really belong to the luminal B subtype (Klingbeil *et al*., 2010).

The basal-like/TNBC subtype was given its name because the neoplastic cells of the tumors express genes commonly found in the breast normal myoepithelial/basal cells, such as P-cadherin, caveolins 1 and 2, high molecular weight cytokeratins 5 and 17, CD44, and EGFR. However, these tumors may express genes characteristic of luminal epithelia at lower levels than luminal carcinomas. In addition, high mitotic indices, necrotic zones in the center, pushing boundaries, noticeable lymphocytic infiltration, atypical/typical medullary features, and metaplastic features are all characteristics of basal-like/TNBC carcinomas, which are typically of high histological grade, and associated with distinct risk factors. Furthermore, they are more prevalent among young women of Hispanic and African origin and to show a high response to local chemotherapy (Weigelt *et al*., 2010).

Although, current breast cancer molecular taxonomy asserts that it offers realistic representations of the disease that take into account its diversity, histological types have not been thoroughly studied, most likely because of the low prevalence and limited availability of frozen or fresh samples. Only invasive ductal carcinoma of no special type (IDC-NSTs) and two invasive lobular carcinomas were examined by the study; therefore, believing that these pictures could accommodate all characters is therefore debatable (Weigelt *et al*., 2010).

Interestingly, analyses comparing special types of a certain molecular subtype with IDC-NSTs of the same molecular

subtype have indicated significant differences in the genome and transcriptome despite the possibility that special kinds of breast cancer may be categorized into molecular subgroups. For example, DNA repair pathways such as the BRCA1 DNA damage response pathway, PTEN linked to chemotherapy resistance, and the molecular target of anthracyclines (TOP2A), were significantly downregulated in metaplastic breast carcinomas relative to basal-like IDC-NSTs (Weigelt *et al.*, 2009). Furthermore, it was discovered that, in contrast to IDC-NSTs of the basal-like/TNBC molecular subtype, metaplastic tumors exhibited noticeably greater gene expression linked to myoepithelial development and epithelial-to-mesenchymal transition (Lien *et al.*, 2007; Weigelt *et al.*, 2009). Also, activation of the Wnt pathway and mutations in the b-catenin gene were found to be higher in metaplastic breast cancer.

Adenoid cystic carcinomas, despite having a basal-like/TNBC phenotype, possess unique morphological characteristics, clinical presentation, and downregulation of genes linked to immune response, cell migration, and proliferation. These characteristics and low histological grade may explain their good prognosis (Azoulay *et al.*, 2005). In addition, secretory carcinomas have a painless clinical presentation with a basal-like/TNBC phenotype. Thus, this histological type of breast cancer has a balanced chromosomal translocation, leading to t(12;15)(p13;q25) ETV6-NTRK3 fusion transcripts.

*Luminal A and Luminal B subtypes*

These are classified as subtypes of hormone-receptor-positive breast cancer. The hormone-receptor-positive breast cancer is the type of breast cancer that expresses ER and/PR, and can occur at any age but more common in post-menopause. The expression of two principal biological processes (proliferation/cell cycle-related and luminal/hormone-regulated pathways) distinguishes the luminal A form luminal B subtypes. Luminal B tumors express more proliferation/cell cycle-related genes or proteins (like MKI67 and AURKA) than Luminal A tumors do. They also express fewer luminal-related genes or proteins, like progesterone receptor (PR) and FOXA1, but not the ER, which is expressed similarly in both luminal subtypes and can only be used to differentiate luminal from non-luminal disease (Prat et al., 2015).

Luminal A is the most prevalent subtype. About half of all breast cancers have low expression of HER2 genes, proliferation-related genes, including Ki-67 protein, and HR-related genes (ER+/PR+ with a low proliferation index). The luminal A subgroup responds better to endocrine therapy, such as aromatase inhibitors or anti-estrogens, and has a better prognosis than the luminal B subgroup. In luminal A, PIK3CA (45%), MAP3K1, GATA3, TP53, CDH1, and MAP2K4 are the most prevalent mutations. The luminal A subtype should be treated with hormone therapy and chemotherapy. Histology shows these tumors are low-grade and frequently non-invasive (Tsang & Tse, 2020).

Luminal B comprises about 20% of all breast cancers. Its prognosis is also relatively worse than luminal A. It is composed of two groups; the first group is characterized by a higher degree of Nottingham (ER+/PR+ with a high proliferation index), HER2-overexpressing (HER2+ disease), and higher expression levels of genes related to proliferation. The second group differs from the first group in that PR is negative, while HER2 is positive. Consequently, this group may exhibit lower levels of hormone expression than the others. Additionally, genes linked to proliferation, including the Ki-67 protein, exhibit fluctuating levels of expression. Completely diverse genetic alterations are frequently present in the TP53 and PIK3CA genes in luminal B malignancies. Compared to Luminal A, Luminal B tumors are more aggressive (Vuong et al., 2014).

*HER-2-enriched*

This is another kind of hormone receptor breast cancer that accounts for 20% of all cases and has a poor prognosis. This group is associated with the expression of the HER2 gene. Therefore, tumor cells contain large amounts of the HER2 protein, which causes growth signaling molecules to increase, aids in the rapid growth of tumors, and speeds up the progression of breast cancer. There are two types of HER2-positive breast cancer: hormone-receptor-positive and hormone-receptor-negative. Therefore, HER2-negative breast cancers are those that have few copies of the HER2 gene and/or no or low amounts of the HER2 protein (Iqbal & Iqbal, 2014). In contrast to luminal subtypes, HER2-positive breast cancers exhibit elevated expression of proliferation-related genes, including Ki-67 protein, and a high prevalence of TP53 (72%) and PI3K (39%) mutations. HER2-positive breast cancer is very invasive, with a very high chance of recurrence that can happen at any time but typically happens within five years of therapy. With the advent of targeted therapy, the likelihood of recurrence is much lower now than it was in the past (Sarhangi et al., 2022).

*Triple-negative breast cancer/Basal-like breast cancer*

This is a heterogenous cancer that is negative for both ER, PR, and HER2 (thus its name), and presents with distinct metastatic patterns, aggressive biological behavior and have poor prognosis It accounts for 15 to 20% of breast cancer and is common among all ethnicities (Wang et al., 2018). However, it is more common among premenopausal and black women (Yin et al., 2020). The TNBC subtype has the highest incidence of BRCA1/BRCA2, despite the BRCA1/BRCA2 gene mutation being linked to a high lifetime incidence of all breast cancers. A BRCA1/BRCA2 germline mutation is estimated to have been present in 20% of TNBC patients. Therefore, experts advise testing for BRCA1/BRCA2 gene mutations in all individuals with TNBC, particularly those under 50 (Yin et al., 2020). TNBC's molecular features give it a unique clinical manifestation. It is characterized by early recurrence (often within three years), absence of bone metastases, and distant metastases to the brain and viscera. TNBC has a poorer prognosis,

is less curable, and is linked to aggressive clinical behavior that spreads to adjacent tissues more quickly (Anders & Carey, 2008).

**Screening and early detection methods for breast cancer**

***Conventional diagnostic approaches***

The significant contribution of the conventional clinical/pathological variables is sometimes overlooked in light of the new emphasis on molecular prognostic testing. The most commonly utilized metrics are tumor size, grade, and number of regional lymph nodes with metastases (Table 1) (Nicolini *et al.*, 2018). The most important predictor of breast cancer outcome remains the presence and number of axillary node metastases. In fact, there is a clear correlation between the risk of metastasis and the number of metastatic axillary lymph nodes. The size of the tumor is free of this association, but its measurement is also crucial for determining the prognosis of breast cancer. Thus, independent of the number of lymph node metastases, the chance of metastasis formation rises with increasing tumor size.

In addition, prognosis is determined by the tumor grading for breast cancer patients (Cianfrocca & Goldstein, 2004). This depends on evaluating the microscopic similarity between breast cancer cells and normal breast tissue based on the number of dividing cells, gland or tubule formation, and nuclear pleomorphism (Rakha *et al.*, 2008).

**Table 1: Biomarkers for breast cancer diagnosis**

| Biomarker | Prognosis | | Prediction of | |
|---|---|---|---|---|
| | Worse | Good | Response | Resistance |
| Tumor grade* | 2-3 | 1 | - | - |
| Lymph nodes | Positive[a] | Negative[a] | - | - |
| Tumor size | > 2cm | ≤ 2cm | - | - |
| PR | Negative | Positive | Positive[b] | Negative[b] |
| ER | Negative | Positive | Positive[b] | Negative[b] |
| HER2/neu | Positive | Negative | Positive[c] | Negative[c] |
| Ki67 | > 25% | < 10% | - | - |
| Mammaprint | High risk | Low risk | High risk[d] | Low risk[d] |
| CTCs | ≥ 1/7.5 mL[e] | < 1/7.5 mL[e] | - | - |
| | ≥ 5/7.5 mL[f] | < 5/7.5 mL[f] | - | - |

*Nottingham score, [a]Correlation with involved lymph nodes, [b]To anti-estrogens, [c]To anti-HER2 mAbs/TKIs, [d]High-risk scored patients (adjuvant setting), [e]>1 tumor cell/7.5 mL of blood (adjuvant setting_, [f]>5 tumor cells/7.5 mL of blood (metastatic setting), CTCs: circulating tumor cells.

The most frequent pathways to a breast cancer diagnosis are either by breast self-examination (BSE) or clinical examination of a lump, nipple discharge or retraction, rash, or the finding of an anomaly on a screening mammography. In whatever case it presents itself, imaging and follow-up mammogram with or without ultrasound is recommended. But if upon examination or imaging, the abnormality is suspicious, a biopsy is carried out i.e., the triple assessment pathway (Karim *et al.*, 2020).

Although breast self-examination as a self-method is insufficient, it is nevertheless a crucial component in the early detection of cancer. It is a low-cost, widely accessible technique that doesn't require any sophisticated technological knowledge and may be done at home. Women can learn about healthy breast features through BSE, which aids in the detection of unusual lesions in the breast tissue.

Fine needle aspiration cytology (FNAC) is the first stage for pathologic examination. This involves the collection of cellular materials from a lump with a fine needle and the subsequent processing of the cells to evaluate malignant changes. After a pathologic examination of the biopsy samples confirms breast cancer, biomarker testing is carried out. These indicators, which are determined by immunohistochemistry, include HER2, PR, and ER (Figure 1). These biomarkers are prognostic and treatment-predictive, hence providing data that, when combined with other variables, can be utilized to assess a patient's prognosis and forecast how they will react to specific therapies like trastuzumab or endocrine therapy (Allison, 2021). In addition to biomarker testing, tumor grade, presence of in situ carcinoma, lymphovascular invasion and cell proliferation rate are also considered in making a definitive diagnosis.

To achieve this, the staging evaluation must then be completed. This involves locoregional staging using an axillary ultrasound and potentially an MRI of the breast. A computed tomography scan, nuclear bone scan, PET scan, and/or brain MRI may also be necessary for systemic staging if a patient has a sign of metastasis or a locally advanced tumor that has reached the axillary lymph nodes) The American Joint Committee on Cancer (AJCC) (9th edition) is the staging system in use today (El Masri & Phadke, 2022). It provides a more accurate prognostication by taking into account additional criteria in addition to the conventional TNM approach. This stage is crucial in determining the treatment modality of the patient and may have implications for both local and systemic treatment recommendations.

Since a positive genetic test may affect a patient's choice of surgery, genetic testing has emerged as a significant factor in the preoperative assessment of new breast cancer. To lower their risk of developing another breast cancer, patients with a BRCA1/BRCA2 mutation, for instance, can opt for a bilateral mastectomy rather than a lumpectomy. While some professional groups have

recommended that patients with breast cancer get genetic testing, obtaining a thorough family history is crucial for deciding if a patient should have genetic testing (Manahan *et al.*, 2019). To help with decision-making, referral to a certified genetic counselor is advised if one is available. While for premenopausal patients intending to preserve their fertility, a reproductive endocrinologist should be consulted prior to the commencement of chemotherapy to have an option of either embryo cryopreservation, oocyte cryopreservation, or using gonadotropin-releasing hormone agonist during chemotherapy.

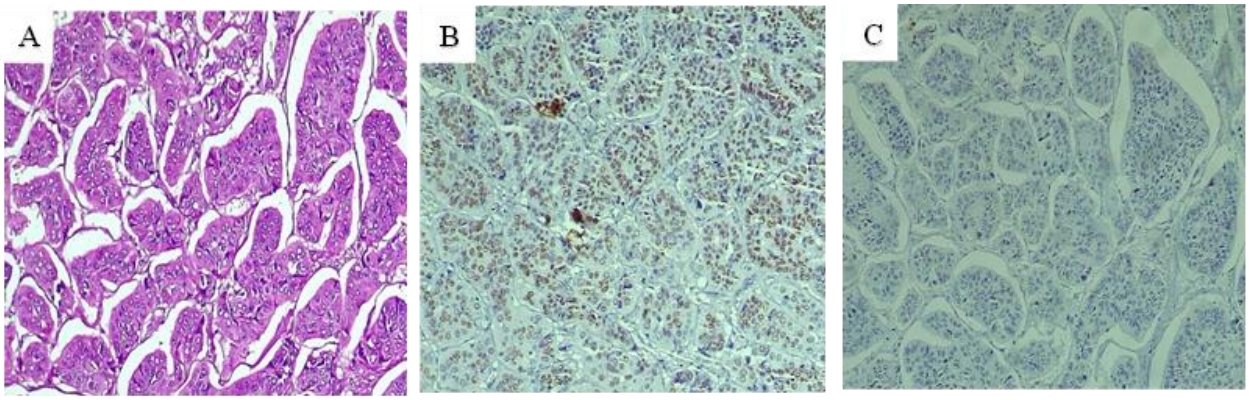


**Figure 1: Excisional biopsy of a left breast swelling, (A) a diagnosis of invasive carcinoma, H and E. Immunohistochemistry after Tamoxifen therapy revealed (B) a strong ER positivity, and (C) HER2 negativity, thus indicating positive response to therapy (Magnification ×10) (Kabir *et al.*, 2024)**

***Molecular and biomarker-based detection***

Molecular profiling/genomic assays are prognostic biomarkers employed to assess risk of recurrence and pathogenic changes in multiple relevant genes simultaneously. Several genomic assays have been developed and some are still been investigated. They include Oncotype DX, MammaPrint, BleuPrint, Prosigna Gene Signature, EndoPredict, PAM, 21-Gene Recurrence Score, etc.

Oncotype DX was first biomarker test for breast cancer treatment invented in 2004, launched for clinical trial in 2007, and made generally accessible in 2011 (Vieira & Schmitt, 2018). The Oncotype DX genomic assay uses real-time PCR to assess the probability of breast cancer recurrence in patients with invasive breast cancer, those who receive tamoxifen within five years, those who are hormone receptor-positive, and those who test negative for HER2 and lymph nodes. Patients have been categorized as low-, intermediate-, or high-risk groups based on their recurrence score. For any gene linked to cancer, this algorithm calculates its function, correlated expression, or both. A higher expression of a particular gene linked to cancer is necessary for an increased chance of recurrence. It should be noted that a recurrence score of less than 18 indicates low risk, a score of greater than 31 indicates high risk and a score between 18 and 31 indicates intermediate risk (Sarhangi et al., 2022).

MammaPrint is a microarray-based predictive signature test that examines 70 genes' activity in early-stage breast cancer. It is designed for patients with stage I or II, ER-positive or ER-negative, and HER2-negative breast cancer whose tumor size was less than 5 cm and who had up to three positive lymph nodes in order to predict the probability of tumor recurrence or metastasis within 5 to 10 years after surgery. The recurrence score is used to categorize patients into high-risk and low-risk groups. Adjuvant chemotherapy may be beneficial for high-risk patients. The Microarray in Node-negative Disease may Avoid Chemotherapy trial (MINDACT); other trials have validated this assay (Zhang, 2023).

BluePrint is a molecular subtype profile test that measures mRNA expression levels in 80 genes. These genes categorize tumors into three distinct molecular subtypes: Her2-type, Basal-type, and Luminal-type. When used in conjunction with MammaPrint, a better prognostic estimation and better choice of treatment is achieved. Thus, this approach stratifies patients into luminal subtype A/MammaPrint Low Risk, luminal subtype B/MammaPrint High Risk, HER2-type, and Basal-type. Luminal A is classified as low-risk due to its MammaPrint expression of less than 14%, while luminal B is classified as high-risk due to its MammaPrint expression of more than 14% (Mittempergher et al., 2020).

Prosigna Gene Signature, also known as prediction analysis of microarray of 50 genes (PAM50), is intended for postmenopausal women who have up to three positive lymph nodes and early-stage ER-positive breast cancer within ten years. It was designed to forecast the likelihood of tumor distant metastases following five years of conventional postoperative hormone therapy as well as the long-term benefits of hormonal therapy. Based on the nodal status, it creates the Prosigna risk of recurrence scores, which categorize patients into low-, intermediate-, or high-risk groups. There are fewer patients in the intermediate category than with Oncotype DX, providing a better risk classification (Pu et al., 2020).

EndoPredict is an RT-PCR-based prognostic multigene assay that measures the expression levels of 12 genes that have been divided into three gene entities. The first entity consists of eight genes linked to cancer, while three RNA reference genes and one DNA reference gene are present in the second and third entities (Sarhangi et al., 2022). It distinguished between low and high-risk tumor recurrence. The EndoPredict assay uses clinical

characteristics such as tumor size and the number of affected lymph nodes (EPclin) to calculate and predict the (EP) risk score. Patients with an EPclin-score of more than 3.3287 are classified as high-risk or low-risk. These statistics are typically used to make treatment decisions about CT and 6-hormonal therapy (Ovcaricek et al., 2019).

### *Advanced imaging techniques*

*AI and Machine learning in radiological diagnosis of breast cancer*

Artificial intelligence has greatly influenced medical research, particularly breast imaging, as it has been demonstrated to increase breast cancer detection rates in digital breast tomosynthesis, full-field mammography, breast ultrasound, and breast MRI (Lotter et al., 2021). Furthermore, assessing external and diverse data sets is essential to verifying the potential performance of AI systems across various demographics. Gaining practitioners' trust requires delivering comprehensive, patient-oriented solutions (Witowski et al., 2022). Additionally, it generates data that makes it possible to translate findings into future research and, eventually, clinical practice.

Artificial Intelligence (AI) is based on the idea that, with the right instruction, computers can learn to analyze a wide range of data in order to make predictions and enhance their performance. Traditional radionics and machine learning (ML) and deep learning (DL) are two methods that can be used for this. Traditional radiomics and machine learning extract quantitative imaging data to identify a phenotypical fingerprint, or "radiomics signature,". Expert readers or automatic software annotate the cancer to reflect the distribution of pixels at various levels of complexity. The radiomics pipeline typically consists of several steps for machine learning investigations, such as segmentation, image pre-processing, radiomics feature extraction and selection, and ML algorithm execution (Stanzione et al., 2022).

DL uses a complex network modeled after the human brain's structure to create its own features. Convolutional neural networks (CNN), which are made up of several processing layers intended to optimise millions of variables, known as weights and biases, to extract hierarchical patterns, retain the most crucial information, and use them for classification, are currently used in medical image analysis by DL algorithms (Reig et al., 2020). Most DL models employ supervised learning, where training is carried out with a large number of labelled examples that may be on various levels (exam, breast, pixel). Large datasets are necessary for DL studies, which must learn features from the data, although they are not always necessary for ML systems. As a result, depending on the architecture and dataset size, DL software requires a significant amount of computing time and cost to run (Romeo et al., 2023).

Despite the high sensitivity of MRI, the potential to apply AI to non-invasively distinguish benign from malignant breast tumours, in addition to determining the molecular profile of breast cancer, is appealing and has recently been investigated utilising various imaging modalities. A combined MRI and PET technique may be useful for simultaneously providing tumor diagnosis, profiling, and staging in highly suspicious breast lesions. ML was used in 2018 by Huang et al. to extract a total of 84 radiomics features of 113 patients using an unsupervised clustering based on PET and MRI radiomics features. They identified three groups that are significantly associated with tumor stage, grade, subtypes, and disease recurrence status. According to this report, both MRI and PET may be able to interpret the biological behaviour of breast cancer and provide imaging biomarkers that predict the recurrence of tumors (Huang et al., 2018). Another study developed an ML-based model for breast cancer diagnosis using a combination of quantitative diffusion and perfusion parameters, radiomic features, and PET parameters and obtained an area under the curve (AUC) of 0.983 (Romeo et al., 2022). Thus, combining MRI and PET could yield morphological tumor information in addition to functional and histological data, making it a "one-stop-shop" tool for a thorough diagnosis and staging of breast cancer.

Such an approach would significantly impact the management of patients. In fact, performing a "virtual biopsy" would significantly lessen patient discomfort while enabling a thorough evaluation of whole-lesion heterogeneity and tracking of changes in tumor features during PST, which would be used to gauge tumor resistance and development.

### Treatment approaches and novel therapies.

Patients with invasive breast cancer and lymph node involvement should undergo further radiologic investigation, such as a thoracic CT scan the abdomen and pelvis evaluate evidence of metastases. The most crucial test for visualizing and characterizing abnormalities is radiological imaging. An ultrasound scan enables a targeted analysis of a clinically palpable anomaly, while mammography screens the remaining breast tissue and provides additional information about the area of concern. Digital breast tomosynthesis enhances the results of mammography by producing 3D X-ray images of the breast tissue (Katsura *et al.*, 2024). Some patients will require contrast MRI to help them make decisions, like whether to have conservative breast surgery, to measure the size of the tumor when different imaging modalities show different sizes, or to track how the patient is responding to neoadjuvant chemotherapy.

Both tissue and cellular specimens are evaluated histopathologically. The AJCC grouping is used for disease staging. As earlier mentioned, it involves anatomical staging by tumor size, regional lymph node involvement, and evidence of metastasis (Table 2), and prognostic staging involving the former, in addition to the expression of estrogen receptors, EGFR-2 receptors, and progesterone receptors as established in the Nottingham prognostic index.

**Table 2: Anatomical staging system of breast cancer**

| | | |
|---|---|---|
| Tumor | Tis | Carcinoma in situ |
| | T1 | Tumor size < 2 cm |
| | T2 | Tumor size 2-5 cm |
| | T3 | Tumor size > 5 cm |
| | T4 | Tumor extended to the skin or chest wall |
| Lymph node | N0 | No regional lymph node involvement |
| | N1 | Homolateral movable axillary lymph node involvement |
| | N2 | Homolateral, immovable lymph node involvement or movable homolateral internal mammary lymph nodes |
| | N3 | Homolateral supraclavicular or infraclavicular lymph nodes, or homolateral internal mammary lymph nodes in combination with axillary lymph nodes |
| Metastases | M0 | No distant metastasis |
| | M1 | Distant metastasis |

Clinical staging is the initial step in the breast cancer diagnosis process. A patient-centered discussion about available treatments is then done in front of a clinical nurse specialist who can help the patient at every stage of their therapy. Surgeons, oncologists, pathologists, radiologists, psychologists, physiotherapists, and geneticists should all be part of the multidisciplinary team that provides treatment. Treatment is determined by the results of the diagnosis and usually includes a combination of endocrine treatments, radiation, chemotherapy, surgery, and targeted therapies (NHS England Breast Cancer Advisory Group, 2016).

Surgery is performed purposely for the removal of cancer, pathological staging, and good postoperative appearance. A breast-conserving surgery in which the tumor is removed along with a margin of macroscopically healthy tissue that has been histologically inspected for invasive cells is termed wide local excision. After this breast-conserving surgery, radiotherapy is highly advised to lower the chance of tumor recurrence. Alternatively, mastectomy may be done when this is not possible due to high tumor/breast ratio, poor cosmetic outcomes, patient choice, or when radiotherapy is contraindicated (Katsura *et al.*, 2024).

Patients who test positive for the BRCA/BRCA2 genes are frequently advised to consider more radical surgical options, like unilateral or perhaps contralateral risk-reducing mastectomies. Neoadjuvant chemotherapy may be used for masses that cannot be surgically removed, with the main goal being to make locally advanced masses resectable. Depending on the biology of the tumor or if locally advanced features exist at the time of diagnosis, neoadjuvant chemotherapy is also employed in some situations. Sentinel lymph node biopsy involving the injection of an intraoperative dye or radionucleotide into the areola is done if preoperative suspicion of axillary lymph node involvement does not exist. This is done by identifying the sentinel lymph node and examining for metastasis. An axillary lymph node dissection is then performed on such patients in order to minimize lymphatic dissemination guide prognosis, and subsequent treatment (Cardoso *et al.*, 2019). There is a 14% chance that an axillary lymph node dissection will result in upper limb lymphoedema (Johnson *et al.*, 2019).

The goal of adjuvant systemic therapy is to get rid of micro-metastases that could progress to metastatic illness. Risk stratification, which is influenced by tumor biology (including grade, hormone receptor, and HER2 status) and disease load (amount of positive lymph nodes and tumor size), determines therapeutic selection. In order to lower the chance of cancer recurrence, adjuvant radiotherapy is done either after breast-conserving surgery or, in the presence of high-risk characteristics, such as involvement of many lymph nodes, after a mastectomy. The anti-HER2 monoclonal antibody trastuzumab or other medications that are known to target HER2 are used as supplemental biological therapy for patients whose tumors test positive for these receptors (Cardoso *et al.*, 2019). Neoadjuvant therapy is used for large breast lesions prior to surgical intervention.

For triple-negative breast cancer, however, treatment options are surgery, chemotherapy and radiotherapy only because this cancer type does not express ER, PR, and HER2, hence resistant to both endocrine and biological therapies.

**Disparities in outcome and quality of life**

Several studies have revealed that disparities exist in breast cancer survival by socioeconomic status, insurance, race, geography, and rurality (Gerend & Pai, 2008; Richardson *et al.*, 2016). For instance, compared to white women, black women have a 40% higher mortality risk and are more likely to have malignant breast tumors that are detected earlier in life (Mootz *et al.*, 2020; Richardson *et al.*, 2016). Also, racial discrimination and socioeconomic determinants of health may affect prognosis, even though some studies indicate genetic variations related to ethnicity be partially responsible for the discrepancies (Gerend & Pai, 2008; Stringer-Reasor *et al.*, 2021). Underinsured or uninsured patients with low resources are less likely to receive treatment that is in line with guidelines and to be diagnosed at a later stage, both of which can have an impact on survival results (Mootz *et al.*, 2020). To bridge the differences in cancer outcomes for patients, more funding for research is desperately needed to pinpoint the causes and discover answers for these disparities in breast cancer.

For different people, being a breast cancer survivor might have different meanings. Breast cancer survivorship starts with diagnosis and continues during treatment to the remainder of one's life. Following surgical resection that effectively clears the body of cancer, a patient is deemed "cancer-free." Adjuvant radiotherapy and systemic therapy are intended to keep the patient "cancer-free" for the rest of their life. At this stage, the focus of care moves from active treatment to monitoring and health maintenance (Valente & Roesch, 2024). Patients with recurrent/metastatic breast cancer who are actively coping with the illness are also regarded as survivors.

Anthracycline chemotherapy and HER2-directed therapy are two examples of oncologic systemic medications that may be linked to cardiotoxicity and result in a lower left ventricular ejection fraction. When both drugs are administered together, this effect is increased. A cardiovascular evaluation of the body systems and collaboration with the primary care physician for a routine lipid check and suitable risk factor adjustments should be part of the follow-up for breast cancer patients.

One of the few proven strategies for overcoming fatigue is exercise. Aerobic and resistance training have been linked to improved quality of life and reduced cancer-related fatigue. Resistance training may also help with chronic pain and cardiorespiratory fitness (Boing *et al.*, 2020; Hasenoehrl *et al.*, 2020).

Survivors of breast cancer are more likely to experience chemotherapy-induced peripheral neuropathy, anxiety, sexual dysfunction, and a reduction in neurocognitive function (Carreira *et al.*, 2018). To assist control these consequences and improve quality of life, a multidisciplinary team composed of psychiatrists, psychotherapists, gynecologists, social workers, patient support groups and physical therapists is recommended.

## CONCLUSION

Given the rising incidence of breast cancer worldwide, diagnostic, prognostic, and treatment approaches must be continuously improved. Even while improvements in imaging and genetic profiling technology have transformed patient treatment, disparities in access to these advancements still remain a problem. It is crucial to prioritize early detection through affordable screening and awareness initiatives, especially in environments with limited resources. To close the gap between scientific discoveries and practical implementation, future studies should concentrate on understudied histological and molecular subtypes, creating scalable early detection methods and novel therapies, investigate innovative technologies, integrate artificial intelligence for non-invasive diagnostic approaches, and reiterate the importance of multidisciplinary cooperation to ensure an equal and successful outcome in the global battle against breast cancer. In addition, to close the differences in cancer outcomes and enhance outcomes for all patients, more funding for research is desperately needed to pinpoint the causes and discover answers for these disparities.

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