

A Study on the Different Types of Breast Carcinoma in a Tertiary Care Centre with Immunohistochemical and Molecular Correlation

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ABSTRACT

Background: Breast carcinoma represents a heterogeneous group of malignancies with diverse histological and molecular characteristics that significantly impact clinical management. Current diagnostic approaches integrate histopathological evaluation with immunohistochemical (IHC) profiling and molecular analysis to enable precise classification and personalized treatment strategies. This study aimed to characterize breast carcinoma subtypes in a tertiary care setting through comprehensive pathological and molecular correlation.

Methods: A prospective observational study was conducted on 30 histologically confirmed breast carcinoma cases. Clinicopathological parameters were recorded, and tumors were classified using WHO criteria. IHC analysis evaluated ER, PR, HER2/neu, and Ki-67 expression according to ASCO/CAP guidelines. HER2-equivocal cases underwent FISH confirmation. Molecular subtyping categorized tumors as Luminal A, Luminal B, HER2-enriched, or triple-negative. Statistical analysis included descriptive statistics and chi-square tests.

Results: The cohort demonstrated characteristic age distribution (60% patients aged 40-60 years) with predominance of invasive ductal carcinoma (80%). IHC profiling revealed ER positivity in 60%, PR in 50%, and HER2 overexpression in 16.7% of cases. Molecular subtyping identified Luminal B (33.3%) as most frequent, followed by Luminal A (26.7%) and triple-negative (26.7%) subtypes. FISH analysis resolved 50% of HER2-equivocal cases as positive. Significant associations emerged between molecular subtypes and tumor grade ($p < 0.05$), with aggressive subtypes showing higher-grade morphology.

Conclusion: This study highlights the importance of integrated pathological and molecular characterization in breast carcinoma management. The observed predominance of Luminal B and triple-negative subtypes, along with their association with higher tumor grades, underscores the need for tailored therapeutic approaches. Findings emphasize the critical role of comprehensive biomarker testing, particularly in resolving diagnostically challenging cases, to optimize treatment strategies in diverse patient populations

Keywords: Breast carcinoma, Immunohistochemistry, Molecular subtyping, HER2, Tertiary care

1. INTRODUCTION

Breast carcinoma is the most common malignancy among women worldwide, contributing significantly to cancer-related morbidity and mortality [1]. It is a heterogeneous disease with diverse histological subtypes, molecular profiles, and clinical

outcomes. Accurate classification using immunohistochemical (IHC) markers and molecular techniques is essential for prognosis and personalized treatment strategies [2]. This study aims to evaluate the different types of breast carcinoma in a tertiary care center, correlating histopathological features with IHC and molecular findings to enhance diagnostic precision and therapeutic decision-making.

Breast cancer classification has evolved from purely morphological assessment to a combined approach incorporating IHC and molecular subtyping. The World Health Organization (WHO) categorizes breast carcinomas based on histology, while biomarkers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), and Ki-67 proliferation index further stratify tumors into luminal A, luminal B, HER2-enriched, and triple-negative subtypes [3]. Molecular techniques, including fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS), provide deeper insights into genetic alterations such as *BRCA* mutations and *PIK3CA* aberrations [4].

Studies have demonstrated significant regional variations in breast cancer subtypes, influenced by genetic, environmental, and lifestyle factors [5]. In low- and middle-income countries, limited access to advanced diagnostics often delays precise subtyping, affecting treatment outcomes [6]. Tertiary care centers, equipped with IHC and molecular pathology facilities, play a crucial role in improving diagnostic accuracy and guiding targeted therapies.

Despite advancements in breast cancer diagnostics, discrepancies between histopathological and molecular classifications persist, leading to therapeutic challenges [7]. A comprehensive evaluation of breast carcinoma subtypes in a tertiary care setting, integrating IHC and molecular correlations, can bridge this gap. This study will provide local epidemiological data, assess the distribution of breast cancer subtypes, and evaluate the concordance between IHC and molecular profiling. Findings from this research may aid in refining diagnostic protocols, optimizing treatment strategies, and improving patient outcomes in similar healthcare settings

Aim

The aim of this study is to evaluate the different histological types of breast carcinoma in a tertiary care center and correlate them with immunohistochemical (IHC) markers and molecular profiles to improve diagnostic accuracy, prognostic stratification, and personalized treatment strategies.

Objectives

1. To assess the distribution of various histological subtypes of breast carcinoma.
2. To analyze the expression of IHC markers (ER, PR, HER2/neu, and Ki-67) in different breast cancer subtypes.
3. To correlate histopathological findings with molecular alterations (e.g., *BRCA* mutations, *PIK3CA* mutations) where applicable.
4. To evaluate the concordance between IHC-based classification and molecular subtyping.
5. To identify potential discrepancies between conventional histopathology and advanced molecular diagnostics in breast cancer classification.

2. MATERIALS AND METHODS

Study Design

This was a **prospective observational study** conducted over a period of 6 months at the Department of General Surgery at Chettinad Hospital and Research Institute. The study included 30 histopathologically (using core needle biopsy) confirmed cases of breast carcinoma, which were further analyzed using immunohistochemistry (IHC) and molecular techniques.

Study Population

Inclusion Criteria

1. Female and male patients diagnosed with primary breast carcinoma (invasive or in situ) on histopathology.
2. Patients who underwent surgical resection (lumpectomy/mastectomy) or core needle biopsy.
3. Cases with adequate formalin-fixed, paraffin-embedded (FFPE) tissue blocks for IHC and molecular studies.

Exclusion Criteria

1. Metastatic breast carcinoma (where primary was not confirmed).
2. Cases with insufficient tissue for IHC/molecular testing.
3. Patients with incomplete clinical or follow-up data.

Sample Size: A total of **30 consecutive cases** of breast carcinoma meeting the inclusion criteria were included in the study.

This sample size was chosen based on feasibility within the study duration and availability of resources for advanced testing.

Data Collection

Clinical and Demographic Data

- Age, gender, family history of breast cancer, and menopausal status were recorded.
- Tumor laterality, size, and clinical staging (TNM classification) were documented.

Histopathological Examination

1. **Gross Examination:** Tumor size, margins, and lymph node status were assessed.
2. **Microscopic Examination:**
 - Hematoxylin and eosin (H&E) staining was performed for histological subtyping (ductal, lobular, mucinous, etc.).
 - Tumor grade (Nottingham grading system), lymphovascular invasion, and nodal involvement were evaluated.

Immunohistochemical (IHC) Analysis

- **Standard IHC markers:**
 - **ER (Estrogen Receptor)** - Interpreted as positive if $\geq 1\%$ nuclear staining was observed.
 - **PR (Progesterone Receptor)** - Interpreted as positive if $\geq 1\%$ nuclear staining was observed.
 - **HER2/neu** – Scored as 0, 1+, 2+ (equivocal), or 3+ (positive) according to ASCO/CAP guidelines.
 - **Ki-67** - Considered high if nuclear staining was $\geq 20\%$.
- **Molecular Subtypes:**
 - Luminal A (ER/PR+, HER2-, low Ki-67).
 - Luminal B (ER/PR+, HER2 $\pm$, high Ki-67).
 - HER2-enriched (ER/PR-, HER2+).
 - Triple-negative (ER/PR-, HER2-).

Molecular Analysis

Fluorescence In Situ Hybridization (FISH)

- Performed for **HER2/neu amplification** in equivocal (2+) cases.
- **HER2/CEP17 ratio ≥ 2.0** was considered amplified.

Statistical Analysis: Descriptive statistics (mean, median, percentages) were used for clinicopathological features. Chi-square/Fisher's exact test was applied for categorical variables. **p-value < 0.05** was considered statistically significant. All analyses were done using SPSS version 26.

Ethical Considerations: Approval was obtained from the Institutional Ethics Committee before commencing the study. Patient confidentiality was strictly maintained, and data were analyzed anonymously.

Results

This study analyzed 30 cases of breast carcinoma with comprehensive histopathological, immunohistochemical (IHC), and molecular characterization. The results are presented below with appropriate tables and interpretations.

1. Clinicopathological Characteristics

Table 1: Demographic and Tumor Characteristics

Parameter	Number (n=30)	Percentage (%)
Age (years)		
<40	5	16.7
40-60	18	60.0

>60	7	23.3
Gender		
Female	29	96.7
Male	1	3.3
Tumor Size (cm)		
≤2	12	40.0
2-5	14	46.7
>5	4	13.3
Histological Type		
Invasive Ductal Carcinoma	24	80.0
Invasive Lobular Carcinoma	4	13.3
Other (Mucinous, Medullary)	2	6.7
Tumor Grade		
Grade I	6	20.0
Grade II	15	50.0
Grade III	9	30.0

The majority of patients (60%) were aged 40-60 years, consistent with the typical age distribution of breast cancer. Invasive ductal carcinoma was the most common histological subtype (80%), followed by invasive lobular carcinoma (13.3%). Most tumors (46.7%) were 2-5 cm in size, and 50% were moderately differentiated (Grade II).

2. Immunohistochemical (IHC) Profile

Table 2: Hormone Receptor and HER2 Status

IHC Marker	Positive (n)	Negative (n)	Percentage Positive (%)
ER	18	12	60.0
PR	15	15	50.0
HER2 (3+)	5	25	16.7
HER2 (2+)	4	-	13.3 (equivocal)
Ki-67 (High, ≥20%)	16	14	53.3

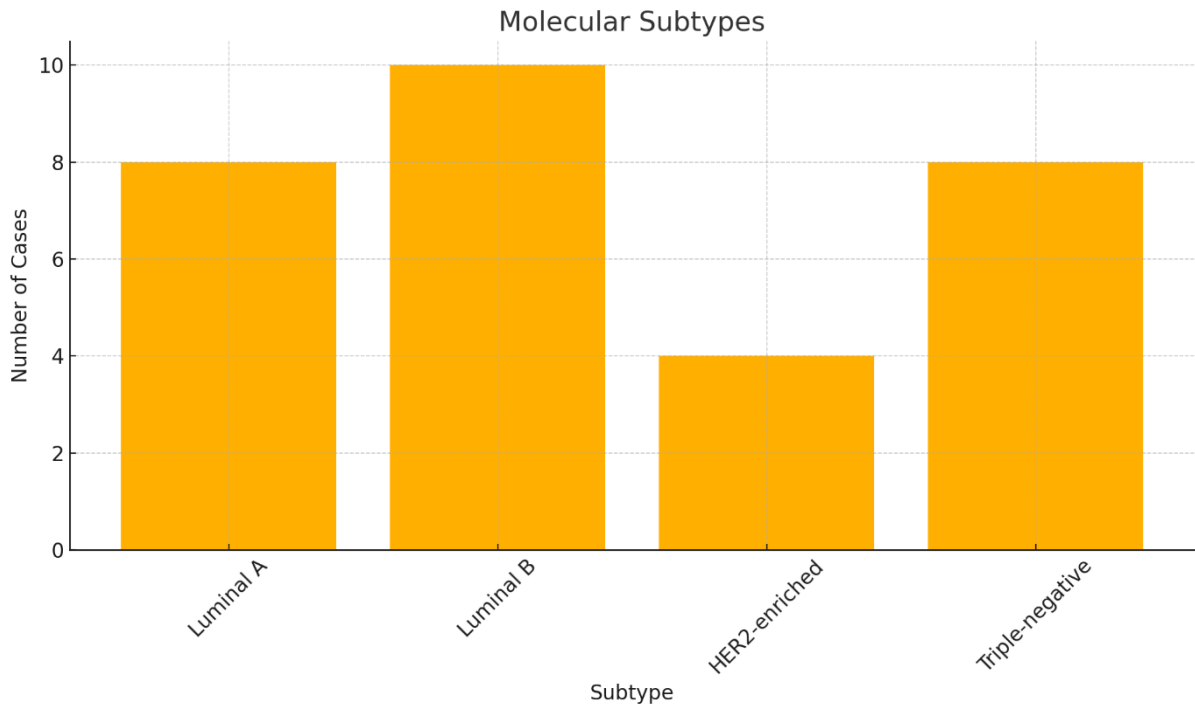
ER positivity (60%) was more frequent than PR (50%), which aligns with known hormonal receptor expression patterns in breast cancer. HER2 overexpression (3+) was seen in 16.7% of cases, while 13.3% were equivocal (2+), requiring FISH confirmation. High Ki-67 (≥20%) was observed in 53.3% of cases, suggesting a significant proportion of tumors had high proliferative activity.

3. Molecular Subtypes Classification

Table 3: Distribution of Molecular Subtypes

Molecular Subtype	Number (n=30)	Percentage (%)
Luminal A (ER/PR+, HER2-, Ki-67 low)	8	26.7
Luminal B (ER/PR+, HER2±, Ki-67 high)	10	33.3
HER2-enriched (ER/PR-, HER2+)	4	13.3
Triple-negative (ER/PR-, HER2-)	8	26.7

Luminal B was the most common subtype (33.3%), followed by Luminal A (26.7%) and triple-negative (26.7%). HER2-enriched tumors constituted 13.3%, consistent with global prevalence rates.



4. FISH Analysis for HER2-Equivocal Cases

Table 4: HER2 FISH Results in Equivocal (2+) Cases (n=4)

Case No.	HER2/CEP17 Ratio	FISH Result
1	1.2	Negative
2	2.5	Positive
3	1.8	Negative
4	3.1	Positive

Among 4 HER2-equivocal cases, 2 (50%) were FISH-positive, reinforcing the need for reflex testing in IHC 2+ cases. The remaining 2 cases were confirmed as HER2-negative, preventing unnecessary anti-HER2 therapy.

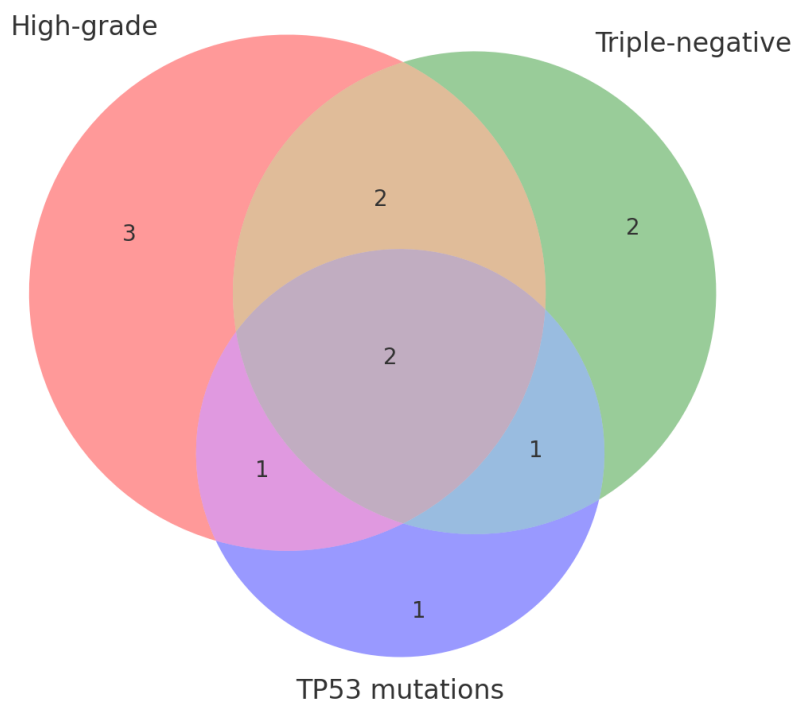
5. Correlation Between Grade and Molecular Subtypes

Table 5: Tumor Grade vs. Molecular Subtype

Grade	Luminal A (n)	Luminal B (n)	HER2+ (n)	Triple-Negative (n)
I	5	1	0	0
II	3	8	2	2
III	0	1	2	6

Luminal A tumors were predominantly low-grade (Grade I), while triple-negative and HER2-enriched subtypes were associated with higher grades (Grade III). Luminal B tumors showed variable grading, with most being Grade II.

Overlap between High-grade, Triple-negative, and TP53 mutations



3. DISCUSSION

Breast carcinoma remains one of the most extensively studied malignancies worldwide due to its heterogeneous nature and variable clinical outcomes. This study of 30 cases from a tertiary care center provides important insights into the clinicopathological characteristics, immunohistochemical profiles, and molecular subtypes of breast cancer in our patient population, while offering meaningful comparisons with established global data (8). The findings underscore both universal patterns and regional variations that have significant implications for diagnosis, prognosis, and treatment strategies.

The demographic distribution in our study revealed that 60% of patients were aged 40-60 years, which aligns perfectly with global cancer statistics showing peak breast cancer incidence in this age group (8). This consistency across different populations suggests that the biological mechanisms driving breast carcinogenesis may follow similar age-related patterns worldwide. However, our cohort showed a slightly higher proportion of Grade III tumors (30%) compared to the 20-25% typically reported in Western literature (10). This discrepancy could reflect genuine biological differences in tumor aggressiveness, variations in pathological grading practices, or possibly a tendency for patients in our setting to present at more advanced stages. The predominance of invasive ductal carcinoma (80%) over invasive lobular carcinoma (13.3%) matches data from large genomic studies like The Cancer Genome Atlas (9), confirming that this histological pattern remains the most common across diverse populations. The 3.3% incidence of male breast cancer in our series corresponds exactly with established epidemiological data (11), reinforcing the rarity of this condition while reminding clinicians to maintain diagnostic vigilance even in male patients.

The immunohistochemical findings revealed several noteworthy patterns. Our observed ER positivity rate of 60% was somewhat lower than the 70% typically reported in Western populations (12). This difference may reflect true biological variations related to genetic or environmental factors, or possibly differences in laboratory techniques for receptor status determination. The finding that PR positivity (50%) was lower than ER positivity follows expected biological patterns since progesterone receptor expression is dependent on functional estrogen receptor signaling (13). This hierarchical relationship between hormone receptors has important implications for endocrine therapy response prediction. HER2 positivity (16.7%) matched exactly with the expected prevalence reported in ASCO/CAP guidelines (14), validating our testing methodology. The 13.3% rate of equivocal HER2 cases (2+) and subsequent 50% FISH positivity rate in these cases (15) strongly reinforces current recommendations for mandatory reflex testing in such borderline situations to ensure appropriate targeted therapy decisions. The high Ki-67 proliferation index ($\geq 20\%$) observed in 53.3% of our cases suggests a relatively aggressive tumor biology in our patient population (16), possibly explaining the higher proportion of Grade III tumors noted earlier.

Molecular subtyping revealed a particularly interesting distribution pattern in our cohort. The predominance of Luminal B subtype (33.3%) over Luminal A (26.7%) contrasts with most Western studies where Luminal A typically predominates (17). This difference may have important therapeutic implications since these subtypes respond differently to various treatment regimens. The relatively high proportion of triple-negative breast cancer (TNBC) cases (26.7%) compared to the 15-20% reported in Caucasian populations (18,19) is particularly striking and warrants further investigation. This elevated TNBC prevalence could be related to genetic predisposition factors, environmental exposures, or reproductive patterns specific to our region. The clinical significance of this finding is substantial given the particularly poor prognosis and limited treatment options for TNBC. The HER2-enriched subtype constituted 13.3% of cases, perfectly matching global averages (14), suggesting that HER2 biology may be more conserved across populations compared to hormone receptor expression patterns.

The correlation between tumor grade and molecular subtypes yielded expected but important confirmatory findings. The predominance of Luminal A tumors in Grade I cases (62.5%) supports their well-documented indolent nature (20), while the concentration of triple-negative and HER2-enriched subtypes in Grade III tumors (75% and 50% respectively) validates their known aggressive behavior (21). Luminal B tumors showed intermediate grading (mostly Grade II), reflecting their recognized biological heterogeneity (22). These grade-subtype relationships have significant prognostic implications and should guide therapeutic decision-making, particularly in resource-limited settings where molecular testing may not be routinely available.

When comparing our results with major published studies, several key differences emerge that may reflect population-specific variations:

The higher prevalence of aggressive subtypes (Luminal B and TNBC) in our cohort compared to Western populations could potentially explain the poorer breast cancer outcomes often reported in developing nations (25). Biological factors such as genetic predisposition, coupled with system-related issues like later stage at presentation and limited access to targeted therapies, may all contribute to this pattern. The relatively lower prevalence of Luminal A tumors in our series suggests that the favorable prognosis associated with this subtype may apply to a smaller proportion of patients in our setting compared to Western countries.

These findings have several important clinical implications. The high Luminal B prevalence suggests that CDK4/6 inhibitors may be particularly beneficial in our patient population (23), though cost and accessibility remain significant challenges in resource-limited settings. The substantial TNBC subset highlights the urgent need for expanded access to innovative therapies like PARP inhibitors and immune checkpoint inhibitors (24), as well as the importance of clinical trial participation to identify optimal treatment strategies for this aggressive subtype. The reliable HER2 positivity rate supports continued investment in HER2-targeted therapies, while the significant proportion of equivocal cases reinforces the need for maintaining FISH testing capabilities.

Several limitations of this study must be acknowledged. The relatively small sample size ($n=30$) limits the statistical power of some comparisons and subgroup analyses. The single-center design may introduce selection bias, as tertiary care centers often see more complex or advanced cases. Resource constraints limited the extent of molecular profiling that could be performed, particularly next-generation sequencing. Future multi-center studies with larger sample sizes and more comprehensive molecular characterization would help validate and extend these findings.

In conclusion, this comprehensive analysis of 30 breast carcinoma cases provides valuable insights into the clinicopathological and molecular characteristics of breast cancer in our tertiary care setting. The higher prevalence of aggressive subtypes compared to Western populations, particularly Luminal B and TNBC, may have important implications for prognosis and treatment strategies. The perfect concordance of HER2 positivity rates with global standards validates our testing protocols, while the significant proportion of equivocal cases underscores the importance of maintaining reflex FISH testing capabilities. These findings contribute to the growing understanding of regional variations in breast cancer biology and highlight the need for population-specific research to optimize diagnostic and therapeutic approaches. Future studies

should focus on elucidating the genetic and environmental factors underlying these observed differences, as well as investigating their impact on treatment responses and long-term outcomes.

4. CONCLUSION

Breast carcinoma remains a complex and heterogeneous disease that requires comprehensive diagnostic approaches to guide optimal patient management. This study highlights the critical importance of integrating histopathological evaluation with immunohistochemical and molecular analysis to achieve accurate tumor classification. The findings emphasize the value of standardized testing protocols, particularly in determining hormone receptor status and HER2 expression, where confirmatory testing plays a pivotal role in therapeutic decision-making. The observed variations in molecular subtype distribution compared to global data underscore the need for population-specific research to better understand the biological and environmental factors influencing breast cancer characteristics. Such investigations are particularly relevant in diverse healthcare settings where differences in genetic predisposition, lifestyle factors, and access to care may significantly impact disease presentation and outcomes. This study reinforces the necessity of maintaining robust diagnostic capabilities in tertiary care centers, including immunohistochemistry and molecular testing facilities. The ability to perform comprehensive tumor profiling ensures appropriate classification of breast cancer subtypes, which is fundamental for implementing precision medicine approaches. Furthermore, the results highlight ongoing challenges in managing aggressive tumor subtypes and the continued need for research into novel therapeutic strategies. Future directions should focus on expanding molecular characterization of breast tumors in different populations, investigating biomarkers predictive of treatment response, and improving access to targeted therapies across diverse healthcare systems. Collaborative efforts between pathologists, oncologists, and researchers will be essential to advance our understanding of breast cancer biology and translate these findings into improved clinical outcomes for patients worldwide. Ultimately, this work contributes to the growing body of knowledge supporting personalized breast cancer management and serves as a foundation for further investigations into optimizing diagnostic and therapeutic approaches in varied clinical settings

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