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## Original Article

## Prevalence of molecular subtypes of invasive breast cancer: A retrospective study



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## ABSTRACT

**Background:** Classification of breast cancers into different molecular subtypes using immunohistochemistry as a surrogate tool to DNA microarray technology has been identified. Aim of this study was to find the precise prevalence of molecular subtypes of invasive breast carcinoma using immunohistochemistry and to correlate it with histological and clinical prognostic factors.

**Methods:** A descriptive study design wherein 56 breast carcinoma cases diagnosed between May 2012 and Apr 2014 were reviewed and molecular subtyped using relevant immunohistochemical markers. Age, histological type, tumor size, tumor grade, lymphovascular emboli (LVE), nodal status and basal marker expressions were analyzed for all cases. Correlations between molecular subtypes and clinico-pathological characteristics were evaluated statistically.

**Results:** In our study group, average age of patients was 50.5 years and most of patients were diagnosed in stage II (54%). Luminal A subtype was most prevalent 34%, followed by Basal like/Triple negative subtype 25%. Luminal B and Her2/neu subtypes had same prevalence i.e. 18% each and Breast Tissue like/Unclassified subtype/Penta Negative subtype was 5%. All cases demonstrated positivity for the luminal cytokeratins 8/18. Histological grade and ER negative status showed strong correlations with basal markers.

**Conclusion:** On the basis of hormone receptor, Her2 neu, EGFR and CK 5/6 expressions, breast carcinoma cases were classified into five distinct molecular subtypes which show significant differences in regards to morphological features, prognostic markers and there by predicting possible clinical outcome.

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## Introduction

Breast cancer is the most commonly reported cancer worldwide and second leading cause of mortality.<sup>1</sup> Incidence of breast cancer is progressively increasing over last decades,<sup>2,3</sup> and specially Asian countries have shown marked increase in the incidence.<sup>4</sup> Breast cancer is a malignancy with varied molecular and clinical characteristics. Breast carcinoma has been sub classified in five subtypes based on gene expression profiling using DNA microarray which is a very expensive technique and cannot be used on formalin-fixed, paraffin-embedded samples. Recently studies have established that similar subtypes can be identified using immunohistochemical specific markers as surrogate tool for DNA microarray.<sup>5,6</sup> Breast carcinoma subtypes based on immunohistochemical markers are (a) Luminal A – Estrogen Receptor (ER) and/or Progesterone Receptor (PR) positive and Human Epidermal Growth Factor Receptor 2 (Her2) negative, (b) Luminal B – ER and/or PR positive and Her2 positive, (c) Her2neu subgroup – ER and PR negative and Her2 positive, (d) Basal like – ER, PR and Her2 negative, cytokeratin (CK) 5/6 positive and/or Epidermal Growth Factor Receptor (EGFR) positive, and (e) Unclassified/Penta negative (PN) – ER, PR, Her2neu, CK 5/6 and EGFR all negative<sup>5–7</sup> (Table 1). The molecular subtypes suggest the heterogeneity of breast carcinomas and the possible different cell lineage pathways in breast carcinogenesis. The precise prevalence and clinico-pathological characteristics of these molecular subtypes of invasive breast tumors are not extensively studied in Indian population. The aim of this study was to identify and define the precise prevalence of molecular subtypes of invasive breast carcinoma using immunohistochemistry (IHC) in Indian population and to correlate with the morphological features and prognostic parameters. The morphological features and prognostic parameters i.e. tumor size, tumor type, tumor grade, lymphovascular emboli (LVE) and lymph node status of invasive breast carcinoma of each molecular subtype, were compared.

## Materials and methods

A total of 56 histologically confirmed cases of breast carcinomas diagnosed in the Department of Pathology of a tertiary care institution over a period of two years (May 2012–April 2014) were selected for the present study. Cases with adequate material (in the form of adequate representative viable tumor in the sections or the specimen) were studied. All the cases

were processed for paraffin sections for routine hematoxylin and eosin (H&E) staining and IHC using pre-diluted ready to use antibodies (Table 1).

### Exclusion criteria

Slides showing quantitatively inadequate material were excluded. Cases which had received chemotherapy prior to surgery, cases with previous lumpectomy followed by mastectomy for residual disease were also excluded in our study.

### Light microscopy

H&E stained slides and the paraffin blocks were retrieved from the archives. All the cases were graded and staged according to the 2003 World Health Organization histological classification of tumors of the Breast. The morphological characteristics noted include: tumor size, histological type, tumor grade, mitoses, necrosis, LVE and nodal status.

### Immunohistochemistry

The cases of invasive breast carcinoma were classified into molecular subtypes using immunohistochemical markers: ER, PR, Her-2/neu, CK 5/6 and EGFR (Table 2). Negative controls were obtained by omitting the primary antibodies. As per literature description, interpretation for ER, PR, Her-2/neu (score 2 or more taken positive) was done. For CK immunoreactivity in >10% of tumor cells was taken as positive. Statistical analysis and correlations among categorical variables in the univariate analysis were determined using the Pearson chi-square test. Significance was assumed at p-value less than 0.05.

## Results

### Clinicopathological parameters

Mean age of patients in study population was 50.5 years ranging from 30 to 72 years. 73.2% (41/56) cases presented with non-tender lump breast and rest 26.8% (15/56) presented with other symptoms as positive axillary lymph node, nipple discharge, bone pain etc. The most frequent histological type (89%, 50/56) was infiltrating duct carcinoma, not otherwise specified (IDC, NOS). There were two cases of invasive lobular carcinoma (ILC) and one case each of invasive papillary carcinoma, mucinous carcinoma, medullary carcinoma, and metaplastic carcinoma.

### Tumor size

The average tumor size was 3.4 cm ranging from 1.1 cm to 7.8 cm in their largest dimensions. 14.2% tumors (8/56) were <2 cm (T1), 55.4% tumors (31/56) were in the range of 2–5 cm (T2), and 30.4% tumors (17/56) were greater than 5 cm (T3) in the largest dimensions on presentation. 16/17 tumors (94.1%) in TN group (i.e. Basal like plus PN subtypes) were >2 cm in size followed by Her2/neu+ group with 90% (9/10) cases. LUM

**Table 1 – Pre-diluted ready-to-use antibodies used in the study.**

Antibody	Manufacturer	Clone
CK 8/18	Novocastra	NCL-5D3
CK 5/6	DAKO	D5/16B4
ER	DAKO	1D5
PR	DAKO	PgR636
Her2/neu	DAKO	Polyclonal
EGFR	DAKO	E30

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