Original Article

PREVALENCE OF INVASIVE DUCTAL BREAST CARCINOMA SUBTYPES AND ITS ASSOCIATION WITH STAGE, GRADE AND IMMUNE HISTOCHEMISTRY

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ABSTRACT

Introduction: Breast cancer is considered the most important and common cancer worldwide and cause high mortality rate (second cause of death). Breast cancer incidence become high in last decade. Carcinoma of breast classified into five subgroups according to appearance of gene by use DNA microarray. The aim of this study was to recognize and describe the detailed occurrence of molecular subtypes of invasive carcinoma of breast by using immunohistochemistry (IHC) and to associate with the morphological structures and predictive factors. **Method:** A cross sectional study of hundred patients with primary invasive breast ductal carcinoma that were collected from the archive of the teaching laboratories in Baghdad medical city, Baghdad, Iraq. In the period from June 2018 to May 2021. Where the variables taken; age and gender of patients, stage T, N and grade of breast carcinoma. Also PR, ER and HER2neu were taken for each patients. **Results:** mean age (51.51 ± 12) years old, 32% and 30% of patients at age groups 40-49 years old and 50-59 years old respectively, 98% of patients are females and there is 2% males in this study, (50%) of patients at stage T 2, 31% of patients at stage N1, (61%) of patients at grade 2 of cancer development, (65%, 64%, 24%) of patients have ER, PR, HER2neu respectively, 81% of patients diagnosed histopathological as NOS, 6% as metaplastic and 5% as medullary. There is significant association between grading, ER, PR and histopathological diagnosis. **Conclusion:** Most common histopathological type of invasive ductal breast cancer is NOS. Medullary, metaplastic and micro papillary types found at grade 3. Most patients with NOS and papillary histopathological type found at grade 2. All of patients diagnosed as mucinous and papillary carcinoma with positive ER, and all of patients diagnosed as mucinous and papillary with positive PR.

KEYWORDS: Invasive ductal breast carcinoma, subtypes, stage, grade, immune histochemistry.

INTRODUCTION

Breast cancer is considered the most important and common cancer worldwide and cause high mortality rate (second cause of death).[1] Breast cancer incidence become high in last decade.[2] Carcinoma of breast classified into five subgroups according to appearance of gene by use DNA microarray. Currently studies parallel subtypes can recognized using immunohistochemical definite indicators as replacement tool for DNA microarray.[3] Subtypes of breast cancer that identify by immunohistochemically 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".[4,5] The molecular subtypes commend the heterogeneity of breast cancer and the likely unlike cell ancestry paths of breast carcinogenesis. The occurrence and clinico-pathological structures of these subgroups of aggressive breast malignant tumor are not broadly deliberate.[6] Immunohistochemistry (IHC) used to describe intracellular proteins or numerous cell surfaces in all types of tissues. Specific markers used to describe numerous tumor subtypes, confirm tissue of origin, metastatic and afford extra data for prognosis, expecting answer to treatment or assessing remaining cancer post-

treatment. Diagnostic and prognostic markers described although some of them can be included in both.[7] The aim of this study was to identify and define the precise prevalence of molecular subtypes of invasive breast carcinoma using immunohistochemistry (IHC) and to correlate with the morphological features and prognostic parameters. The morphological features and prognostic parameters i.e. tumor size, tumor type, tumor grade, and lymph node status of invasive breast carcinoma of each molecular subtype.

METHOD

A cross sectional study of hundred patients with primary invasive breast ductal carcinoma that were collected from the archive of the teaching laboratories in Baghdad medical city, Baghdad, Iraq. In the period from June 2018 to May 2021. Where the variables taken; age and gender of patients, stage T, N and grade of breast carcinoma. In addition, PR, ER and HER2neu were taken for each patients. Inclusion criteria: both gender, age, histopathological subtypes of invasive ductal breast cancer, histopathological grade, tumor stage, lymph node stage, immune histochemistry (ER,PR,HER2neu). Exclusion criteria: M stage (metastasis) and patients with incompleted reports. Statistical analysis done by SPSS 22, frequency and percentage used for categorical data, mean, median and SD for continuous data. Chi-square used for assessed association between variables. P-value less or equal to 0.05 is consider significant.

RESULTS

Cross sectional study of 100 cases with breast cancer, mean age (51.51 ± 12) years old, 32% and 30% of patients at age groups 40-49 years old and 50-59 years old respectively, 98% of patients are females and there is 2% males in this study, (50%) of patients at stage T 2, 31% of patients at stage N 1, (61%) of patients at grade 2

of cancer development, (65%, 64%, 24%) of patients have ER, PR, HER2neu respectively. As show in table 1 and fig 1.

Table 1: frequency of variables.

Variables		Frequency	Percentage
gender	female	98	98.0
	male	2	2.0
stage T	1	19	19.0
	2	50	50.0
	3	19	19.0
	4	12	12.0
stage N	0	23	23.0
	1	31	31.0
	2	25	25.0
	3	21	21.0
grade	1	6	6.0
	2	61	61.0
	3	33	33.0
ER	negative	35	35.0
	positive	65	65.0
PR	negative	36	36.0
	positive	64	64.0
HER2neu	negative	69	69.0
	positive	24	24.0
	equivocal	7	7.0

In table 2; 51.9% of patients with NOS histopathology in stage T2, 28.4% of patients in stage N1, 69.1% of patients in grade 2, 71.6 and 70.4 have positive (ER, PR) respectively.

Table 2: distribution of variables in patients with NOS histopathology.

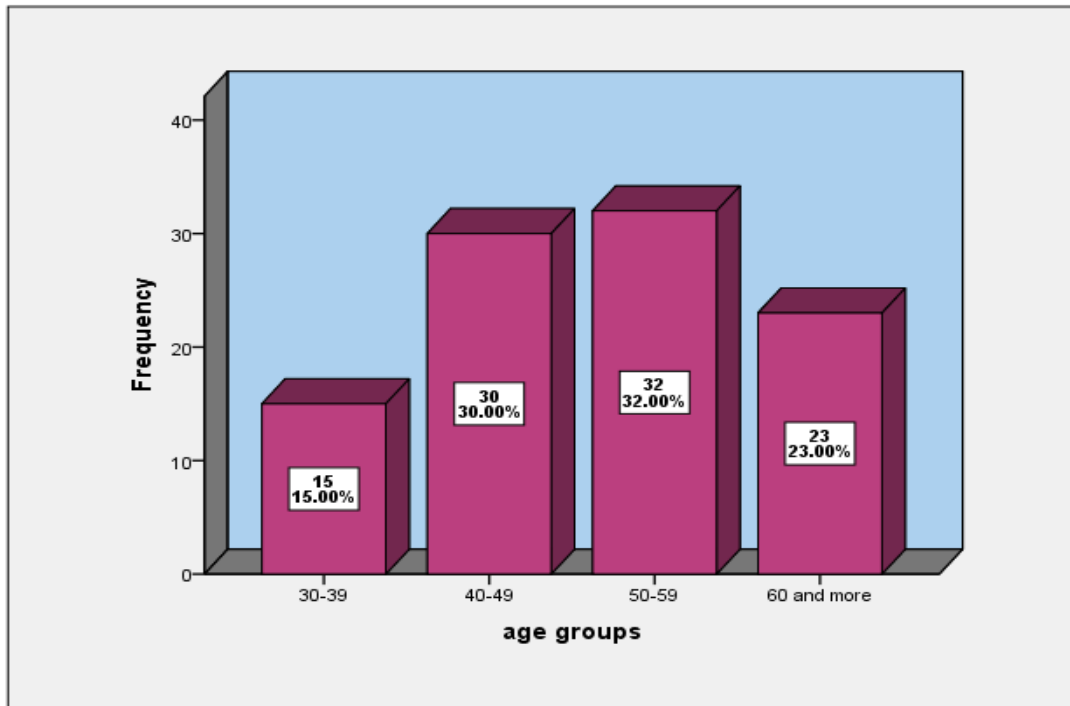| Variables		frequency	percentage
Stage T	1	18	22.2
	2	42	51.9
	3	12	14.8
	4	9	11.1
stage N	0	21	25.9
	1	23	28.4
	2	21	25.9
	3	16	19.8
grade	1	5	6.2
	2	56	69.1
	3	20	24.7
ER	negative	23	28.4
	positive	58	71.6
PR	negative	24	29.6
	positive	57	70.4

Fig 1: distribution of age groups.

According to fig 1: 81% of patients diagnosed histopathological as NOS, 6% as metaplastic and 5% as medullary. And so on.
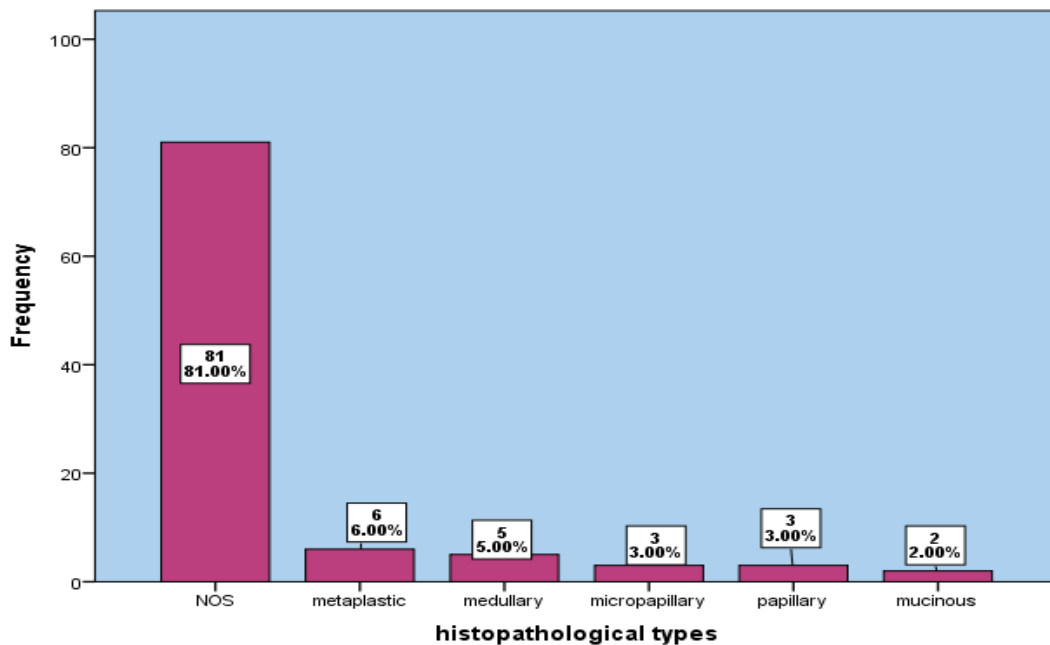

Fig 2: distribution of histopathological types.

There is significant association between grading, IHC [ER, PR] and histopathological diagnosis. (80%, 100%, 66.7%) of medullary, metaplastic and micro papillary respectively diagnosis found at grade 3. (69.1%, 66.7%) of NOS and papillary respectively diagnosis found at grade 2. (100%) of patients diagnosed as mucinous and papillary with positive ER. (100%) of patients diagnosed as mucinous and papillary with positive PR. As show in table 2.

Table 2: association between grading, IHC [ER, PR] and histopathological diagnosis.

variables		medullary	metaplastic	Diagnosis				P-value
				micro papillary	mucinous	NOS	papillary	
grading	**1**	0	0	0	0	5	1	**0.003**
	%	0.0%	0.0%	0.0%	0.0%	6.2%	33.3%	
	2	1	0	1	1	56	2	
	%	20.0%	0.0%	33.3%	50.0%	69.1%	66.7%	
	3	4	6	2	1	20	0	
	%	80.0%	100.0%	66.7%	50.0%	24.7%	0.0%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
ER	negative	5	6	1	0	23	0	**0.0001**
	%	100.0%	100.0%	33.3%	0.0%	28.4%	0.0%	
	positive	0	0	2	2	58	3	
	%	0.0%	0.0%	66.7%	100.0%	71.6%	100.0%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
PR	negative	5	6	1	0	24	0	**0.0001**
	%	100.0%	100.0%	33.3%	0.0%	29.6%	0.0%	
	positive	0	0	2	2	57	3	
	%	0.0%	0.0%	66.7%	100.0%	70.4%	100.0%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	

P-value ≤ 0.05 (significant).

There is no significant association between gender, age groups, stage T, stage LN, HER2neu and histopathological diagnosis.

Table 3: *association between gender, age groups, stage T, stage LN, HER2neu and histopathological diagnosis.*

variables		Medullary	Metaplastic	Diagnosis				P-value
				Micro papillary	Mucinous	Nos	Papillary	
gender	**female**	5	6	3	2	79	3	0.99
	%	100.0%	100.0%	100.0%	100.0%	97.5%	100.0%	
	male	0	0	0	0	2	0	
	%	0.0%	0.0%	0.0%	0.0%	2.5%	0.0%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
age	30-39	1	0	0	0	14	0	0.55
	%	20.0%	0.0%	0.0%	0.0%	17.3%	0.0%	
	40-49	1	2	1	1	25	0	
	%	20.0%	33.3%	33.3%	50.0%	30.9%	0.0%	
	50-59	1	4	2	1	23	1	
	%	20.0%	66.7%	66.7%	50.0%	28.4%	33.3%	
	60 and more	2	0	0	0	19	2	
	%	40.0%	0.0%	0.0%	0.0%	23.5%	66.7%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
stage T	**1**	0	0	0	0	18	1	0.29
	%	0.0%	0.0%	0.0%	0.0%	22.2%	33.3%	
	2	2	2	2	1	42	1	
	%	40.0%	33.3%	66.7%	50.0%	51.9%	33.3%	
	3	3	2	1	0	12	1	
	%	60.0%	33.3%	33.3%	0.0%	14.8%	33.3%	
	4	0	2	0	1	9	0	
	%	0.0%	33.3%	0.0%	50.0%	11.1%	0.0%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	

stage N	**0**	2	0	0	0	21	0	
	%	40.0%	0.0%	0.0%	0.0%	25.9%	0.0%	
	1	1	4	1	0	23	2	
	%	20.0%	66.7%	33.3%	0.0%	28.4%	66.7%	
	2	1	1	0	1	21	1	0.46
	%	20.0%	16.7%	0.0%	50.0%	25.9%	33.3%	
	3	1	1	2	1	16	0	
	%	20.0%	16.7%	66.7%	50.0%	19.8%	0.0%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
HER2neu	negative	4	4	2	2	55	2	
	%	80.0%	66.7%	66.7%	100.0%	67.9%	66.7%	
	positive	0	0	1	0	22	1	
	%	0.0%	0.0%	33.3%	0.0%	27.2%	33.3%	0.27
	equal	1	2	0	0	4	0	
	%	20.0%	33.3%	0.0%	0.0%	4.9%	0.0%	
	total	5	6	3	2	81	3	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	

P-value ≤ 0.05 (significant).

DISCUSSION

Breast cancer is the utmost predominant cancers in females. Numerous factors disturb the prognosis and deterioration of this illness; each kind of breast malignancy displays different performance, and while some kinds of breast malignancy metastasize rapidly, others are sluggish to metastasize.[8,9] In current, study the most of patients with breast cancer, mean age (51.51 ± 12) years old, 32% and 30% of patients at age groups 40-49 years old and 50-59 years old respectively, 98% of patients are females and there is 2% males in this study, (50%) of patients at stage T 2, 31% of patients at stage N 1, (61%) of patients at grade 2 of cancer development, (65%, 64%, 24%) of patients have ER, PR, HER2neu respectively. These results similar to other study also show that there were 45 female and 1 male patients. The utmost public age group was 40–49 years 14 patients, then 50–59 years.[10] So that females in age group (30–59 years) have more risk to developed breast malignancy.[10,11] In other revisions illness obtainable involved 2 (5%) cases of stage I, 16 (35%) stage II, 20 (43%) stage III, and 8 (17%) cases of stage IV illness.[11] So that most patients in stage 3 and 4, this mean that illness features diagnosis mostly in late stage lead to become treatment so hard, and occur in middle age group, in this age group lack of knowledge and poor social and economic details may lead to diagnosis become difficult, community health knowledge requirements to be focused to the social effects that affect breast carcinoma progress.[10,12] Other study demonstration that the patients with HER2+ exhibition deprived survival rates, in addition that the nonappearance of besieged treatments, which is the case in utmost reserve deprived settings.[13] In current study, 81% of patients diagnosed histopathological as NOS, 6% as metaplastic and 5% as medullary. And so on. This is similar to other study done by Moses et al.[13] that show the prevalence of Triple Negative Breast Cancer (TNBC) was 34% (77/226), Luminal A 38% (83/226), HER2 positive was 22% (49/226), and Luminal B was 5% (13/226). High-grade (III) tumors were 68%, stage III and IV constituted 75% of presentations. Histological type was mostly invasive ductal carcinoma (NOS).[13] In current study there is significant association between grading, IHC [ER, PR] and histopathological diagnosis. (80%, 100%, 66.7%) of medullary, metaplastic and micro papillary respectively diagnosis found at grade 3. (69.1%, 66.7%) of NOS and papillary respectively diagnosis found at grade 2. (100%) of patients diagnosed as mucinous and papillary with positive ER. (100%) of patients diagnosed as mucinous and papillary with positive PR. ERs and PRs are both investigative and predictive features and demonstration a dynamic appeal in the treatment of patients with breast cancer.[14] Invasive lobular carcinoma had the maximum incidence of ER appearance. Invasive ductal carcinomas were further frequent, they performed otherwise in terms of their ER position, and those two carcinomas (lobular and ductal) seem to reply improved to hormone treatment. The lowermost incidence of ER and PR appearance connected to the medullary carcinomas, which is reliable with results of other revisions.[15] HER2 receptors are on cell membrane and usually regulator their development, separation, and overhaul. In about 25% of ca. breast, the HER2 gene augmented and the consequence is HER2/neu overexpression that lead to unrestrained growth and separation of breast cells.[16,17] Subsequent to invasive ductal carcinomas, carcinoma in situ had the uppermost incidence of HER2/neu overexpression. In a study showed by Latta et al, more than 50% of noninvasive carcinomas had HER2/neu overexpression, HER2/neu overexpression in this group is related with a advanced occurrence of limited deterioration[18,19]

CONCLUSION

Most common histopathological type of invasive ductal breast cancer is NOS. Medullary, metaplastic and micro papillary types found at grade 3. Most patients with NOS

and papillary histopathological type found at grade 2. All of patients diagnosed as mucinous and papillary with positive ER, and all of patients diagnosed as mucinous and papillary with positive PR.

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