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Original Research Article

Incidence of Expression of ER, PR and Her 2 Neu in Infiltrating Ductal Carcinoma Breast: A Cohort Study

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Abstract

Background: Breast cancer is one of the leading cancer affecting women in India. An early diagnosis has a great significance especially since it carries a high morbidity and mortality rate. It is common among women in both developed and developing countries. *Objectives:* The present study was carried out to determine the histopathological and immunohistochemical pattern of invasive ductal carcinoma breast in a tertiary care institute. *Methodology:* 1418 cases of breast cancer diagnosed as invasive ductal carcinoma (IDC) were studied in the department of pathology of a teaching hospital. Estrogen receptor (ER), Progesterone receptor(PR) and Her-2/Neu expression were assessed using immunohistochemical staining and correlated with other prognostic factors including age, tumour size, grade and histomorphological type. *Study Area:* The study was carried out in the department of histopathology of a tertiary care institute in northern India. *Study Design:* Formalin fixed paraffin embedded paraffin blocks were analysed. The study duration was 9 years (January 2011 – December 2018). *Statistical Analysis:* The results were analyzed using SPSS statistical package version 26.

Keywords: Carcinoma; Breast; Mastectomy; IHC; ER; PR; Her-2/Neu; Prognosis.

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Introduction

Carcinoma breast constitutes an important group of cancers that is heterogenous and also is affected by the result of hormonal markers especially Estrogen receptor (ER) and Progesterone receptors (PR).[1] In India, it has now been ranked as the number one cancer occurring in females with a reported incidence of 25.8 per lac women and mortality rate of 12.7 per lac.[2] Various factors have been implicated that determine the prognosis and risk outcome of the patients.[3] The prognosis of patients

diagnosed with IDC becomes poorer as soon as the tumour increases in its grade. Besides, tumour type such as lobular and medullary subtypes carry a dim prognosis. Other factors indicating a poor prognosis include metastatic deposits in the lymph nodes, ER negativity, PR negativity, Her2/Neu positivity, excess presence of oncogenes and presence of BRCA – 1 oncogene.[4]

The present study was carried out to evaluate correlation between the prognostic factors such as age, side involved, tumour size, morphological grade, involvement of the lymph nodes and presence or absence of lymphovascular invasion (LVI), with the expression of immunohistochemical markers ie ER, PR and Her 2/Neu. These markers were correlated individually as well as in combination.

Materials and Methods

Study area: The present cross-sectional study was carried out on 1418 mastectomy, lumpectomy and core biopsy specimens diagnosed as invasive ductal breast carcinoma received in the department of pathology, of tertiary care teaching institute.

Study Period: The study was conducted for a period of 9 years (January 2011 to 2018). The specimenswere grossed as per the standard protocols, subjected to routine tissue processing followed by Haematoxylin and Eosin (H & E) staining. IHC study was done including ER, PR and Her2/Neu markers in all the cases. Histopathological features were reported before subjecting the sections for IHC analysis.

Inclusion Criteria: 1418 cases having the histo-morphological features ofInfiltrating Ductal Carcinoma (IDC) breast were included in the study.

Exclusion Criteria: All malignant tumors of stromal origin and histological variants other than IDC of breast were excluded from the study. Cases in which all the 3 IHC markers could not be applied were also excluded out from the present study. All patients with incomplete data were also excluded.

Study design: Prior approvalof the institutional ethics committee was taken for the study.

Detailed methodology: Histopathological diagnosis based on the morphological features of the neoplastic cells was made by two independent senior pathologists. In case of a significant difference the cases were re-reviewed and furthermore opinion of a third senior pathologist was taken.

Statistical Analysis: IDC was graded according to the Modified Scarff Bloom Richardson (SBR) scoring system (Nottingham grading System). Lymph node status for metastatic deposits was also assessed in all the cases. IHC panel consisting of estrogen receptor (ER), progesterone receptor (PR) and Her2/Neu was applied on the unstained sections in all the cases using Biocare antibody and results were interpreted. For ER and PR staining Allred scoring system was applied, based on the intensity of staining and proportion of positive tumour cells. Proportion score (PS) was given on the basis of percentage of cells showing nuclear stain (1% with score of 1, 1–10% given score of 2, 11–33% given score of 3, 34–66% given score of 4 and more than 67% given score of 5. Intensity score (IS) was given as 0 with negative staining, 1 with weak staining, 2 with intermediate staining, and 3 with strong staining. By adding the PS and IS, we can calculate the final Allred score (PS + IS = AS).[5] A total score of >2 was considered positive for significant expression of ER and PR. In Allred scoring system, only the invasive tumor cells were assessed as ER/PR staining is present even in normal breast epithelial cells which served as an internal positive control.

Her2/Neu is a cell membrane receptor and depending on the intensity of staining a score of 0-3 was given to the neoplastic cells. For Her-2/ Neustaining, American Society of Clinical Oncology (ASCO) guidelines on the complete membrane staining were taken into consideration. A positive result was given only with immunohistochemical staining intensity of 3+. A negative Her2/Neu result was given when the immunohistochemical staining was 0 or 1+. In between it was considered as equivocal.

Pearson's Chi- square test and student's t-test were applied using SPSS software version 26 for windows (Chicago, Illinois, USA). A p value of <0.05 was considered statistically significant.

Results

The present study included 1418 cases of IDC breast. The agerange of the patients varied from 20 to 84 years. Majority of the cases were in the 41–50 years age group followed by 51–60 years. The lowest number of cases were patient aged more than 80 years of age. Males presenting with breast carcinoma were only 8 (0.6%). The right side breast was affected more than the left side. Majority of the patients 877 (61.8%) had a lump size varying from 2 to 5 cm. Most of the cases 720 (50.8%) belonged to grade II followed by 477 (33.6) cases of grade III and least number of cases 221 (15.6%) belonging to grade I.

Lympho-vascular invasion (LVI) was present in 68.5 (48.3%) of the cases of all the patients lymph nodes were not received in 291 (20.5%) cases. Out of the 1127 (79.5%) cases in which lymph nodes were recovered, 667 (59.2%) showed metastasis with 460 (40.8%) in the node reactive (ie NO) category thus showing lymph node metastasis in majority of the cases.

The patients were divided into four different categories depending on the expression of ER and PR. ER and PR both were negative in 567 (40%) cases and positive in 473 (33.4%) cases. 203 (14.3%) patients displayed ER positivity and PR negativity followed by 175 (12.3%) cases that were ER negative and PR positive. The ER and PR positivity decreased from 42.5% to 28.1% as the grade of the tumour increased and was statistically significant with P value being <0.001. Similarly, even single hormone receptor also decreased with an increase in the tumour grade thus proving that positivity of hormone receptors is inversely proportional to the tumour grade of breast carcinoma.

Her-2/Neu positivity was 14.9% in grade I, 13.1% in grade II and 17.2% in grade III, which showed that the Her-2/Neu expression was directly proportional to the tumour grade. Triple positive cases ie ER, PR and Her-2/Neu positive in the present study were 42 (2.96%) where as 462 (32.6%) cases were triple negative. No definite correlation of markers was seen with (LVI) or with the status of lymphnode positivity.

Table 1 shows the frequency distribution of all 1418 cases of carcinoma breast as per the age distribution, gender, side of breast involved,

Table 1: Frequency Distribution of Cases

Variable		N	%
Age	20–30	61	4.3
	31–40	269	19.0
	41–50	454	32.0
	51–60	337	23.8
	61–70	241	17.0
	71–80	44	3.1
	>80	12	0.8
Gender	Male	8	0.6
	Female	1410	99.4
Side	Left	661	46.6
	Right	757	53.4
Size	<2 cm	419	29.5
	<2-5 cm	877	61.8
	<5 cm	122	8.6
Grade	G I	221	15.6
	G II	720	50.8
	G III	477	33.6
Lymph Node	No LN recovered NX	291	
	NO	460	40.8
	N1	216	19.2
	N2	253	22.4
	N3	198	17.6
LVI	Negative	733	51.7
	Positive	685	48.3
ER	Negative	742	52.3
	Positive	676	47.7
PR	Negative	770	54.3
	Positive	648	45.7
Her2Neu	Negative	1209	85.3
	Positive	209	14.7
ER & PR	ER - PR -	567	40.0
	ER - PR +	175	12.3
	ER + PR-	203	14.3
	ER + PR +	473	33.4
ER, PR & Her2Neu	ER – PR – HER2N-	462	32.6
	ER + PR + HER2N+	42	3.0

size of the lump, histopathological grade, lymph node involvement, status of (LVI), and status of Immunohistochemical marker viz. ER, PR and Her-2/Neu. Table 2 and 3 shows the association of various factors in relation to the IHC markers i.e ER and PR. For ER, significant correlation

Table 2: Association of various factors with ER

Variable		ER Negative		ER Positive		*p* value
		N	%	N	%	
Age	20–30	35	57.4	26	42.6	0.001*
	31–40	162	60.2	107	39.8	
	41–50	243	53.5	211	46.5	
	51–60	169	50.1	168	49.9	
	61–70	111	46.1	130	53.9	
	71–80	21	47.7	23	52.3	
	>80	1	8.3	11	91.7	
Gender	Male	2	25	6	75.0	0.121
	Female	740	52.5	670	47.5	
Side	Left	320	48.4	614	51.6	0.006*
	Right	422	55.7	335	44.3	
Size	<2 cm	216	51.6	203	48.4	0.044*
	2-5 cm	449	51.2	428	48.8	
	>5 cm	77	63.1	45	36.9	
Grade	G I	106	48	115	52.0	0.001*
	G II	354	49.2	366	50.8	
	G III	282	59.1	195	40.9	
Lymph Node	NX	150	51.5	141	48.5	0.221
	NO	258	56.1	202	43.9	
	N1	116	53.7	100	46.3	
	N2	122	48.2	131	51.8	
	N3	96	48.5	102	51.5	
LVI	Negative	400	54.6	333	45.4	0.080
	Positive	342	49.9	343	50.1	

Chi-Square Test: *$p < 0.05$; Significant; **$p < 0.001$; Highly significant

LVI – Lymphovascular invasion

Table 3: Association of various factors with PR

Variable		PR Negative		PR Positive		*p* value
		N	%	N	%	
Age	20–30	34	55.7	27	44.3	0.069
	31–40	144	53.5	125	46.5	
	41–50	266	58.6	188	41.4	
	51–60	176	52.2	161	47.8	
	61–70	124	51.5	117	48.5	
	71–80	24	54.5	20	45.5	
	>80	2	16.7	10	83.3	
Gender	Male	4	50	4	50	0.806
	Female	766	54.3	644	45.7	
Side	Left	344	52.0	317	48	0.110
	Right	426	56.3	331	43.7	
Size	<2 cm	197	47	222	53.0	0.001*
	2.5 cm	500	57	377	43.0	
	>5 cm	73	59.8	49	40.2	
Grade	G I	88	39.8	133	60.2	<0.001**
	G II	406	56.4	314	43.6	
	G III	276	57.9	201	42.1	
Lymph Node	NX	137	47.1	154	52.9	0.013*
	NO	270	58.7	190	41.3	
	N1	128	59.3	88	40.7	
	N2	132	52.2	121	47.8	
	N3	103	52.0	95	48.0	
LVI	Negative	417	56.9	316	43.1	0.043*
	Positive	353	51.5	332	48.5	

Chi-Square Test : *$p < 0.05$; Significant; **$p < 0.001$; Highly significant

LVI – Lymphovascular invasion

existed between the age of the patient, side of breast and histomorphological of tumour grade. For PR significant correlation existed with the size of breast, histopathological grade and, lymph node status. Table 4 shows association of various factors in relation to the IHC marker i.e Her-2/ Neu. Significant correlation existed between the expression of Her 2/Neu and status of positivity.

Table 4: Association of various factors with Her2Neu

Variable		Her2Neu Negative		Her2Neu Positive		*p* value
		N	%	N	%	
Age	20-30	52	85.2	9	14.8	0.639
	31-40	226	84	43	16	
	41-50	386	85	68	15	
	51-60	283	84	54	16	
	61-70	211	87.6	30	12.4	
	71-80	39	88.6	5	11.4	
	>80	12	100	0	0	
Gender	Male	7	87.5	1	12.5	0.858
	Female	1202	85.5	208	14.8	
Side	Left	574	86.8	87	13.2	0.117
	Right	635	83.9	122	16.1	
Size	<2 cm	360	85.9	59	14.1	0.055
	2.5 cm	754	86	123	14.0	
	>5 cm	95	77.9	27	22.1	
Grade	G I	188	85.1	33	14.9	0.141
	G II	626	86.9	94	13.1	
	G III	395	82.8	82	17.2	
Lymph Node	NX	239	82.1	52	17.9	0.007*
	NO	409	88.9	51	11.1	
	N1	189	87.5	27	12.5	
	N2	202	79.8	51	20.2	
	N3	170	85.9	28	14.1	
LVI	Negative	632	86.2	101	13.8	0.291
	Positive	577	84.2	108	15.8	

Chi-Square Test : *$p < 0.05$; Significant; **$p < 0.001$; Highly significant. LVI – Lymphovascular invasion

Table 5: Association of various factors with ER & PR

Variable		ER- PR-		ER- PR+		ER+ PR-		ER+ PR+		*p* value
		N	%	N	%	N	%	N	%	
Age	20–30	25	41.0	10	16.4	9	14.8	17	27.9	0.024*
	31–40	116	43.1	46	17.1	28	10.4	79	29.4	
	41–50	195	43.0	48	10.6	71	15.6	140	30.8	
	51–60	128	38.0	41	12.2	48	14.2	120	35.6	
	61–70	8	36.1	24	10	37	15.4	93	38.6	
	71–80	16	36.4	5	11.4	8	18.2	15	34.1	
	>80	0	0	1	8.3	2	16.7	9	75.0	
Gender	Male	2	25	0	0	2	25	4	50	0.431
	Female	565	40.1	175	124	201	14.3	469	33.3	
Side	Left	242	36.6	78	11.8	102	15.4	239	36.2	0.050
	Right	325	42.9	97	12.8	101	13.3	234	30.9	
Size	<2 cm	150	35.8	66	15.8	47	11.2	156	37.2	0.001*
	2.5 cm	359	40.9	90	10.3	141	16.1	287	32.7	
	>5 cm	58	47.5	19	15.6	15	12.3	30	24.6	
Grade	G I	67	30.3	39	17.6	21	9.5	94	42.5	<0.001**
	G II	285	39.6	69	9.6	121	16.8	245	34.0	
	G III	215	45.1	67	14.0	61	12.8	134	28.1	
Lymph	NX	105	36.1	45	15.5	32	11.0	109	37.5	0.113
Node	NO	202	43.9	56	12.2	68	14.8	134	29.1	
	N1	95	44	21	9.7	33	15.3	67	31.0	
	N2	95	37.5	27	10.7	37	14.6	94	37.2	
	N3	70	35.4	26	13.1	33	16.7	69	34.8	
LVI	Negative	310	42.3	90	12.3	107	14.6	226	30.8	0.171
	Positive	257	37.5	85	102.4	96	14.0	247	36.1	

Chi-Square Test : *$p < 0.05$; Significant; **$p < 0.001$; Highly significant
LVI – Lymphovascular invasion

Table 6: Association of various factors with ER, PR and Her2Neu

Variable		ER- PR- Her2neu-		ER+ PR+ Her2Neu+		*p* value
		N	%	N	%	
Age	20–30	20	90.9	2	9.1	0.954
	31–40	95	91.3	9	8.7	
	41–50	161	92.5	13	7.5	
	51–60	99	92.5	8	7.5	
	61–70	73	89.0	9	11.0	
	71–80	14	93.3	1	6.7	
	>80	–	–	–	–	
Gender	Male	2	66.7	1	33.3	0.116
	Female	460	91.8	41	8.2	
Side	Left	202	91.8	18	8.2	0.914
	Right	260	91.5	24	8.5	
Size	<2 cm	123	90.4	13	9.6	0.438
	2.5 cm	295	92.8	23	7.2	
	>5 cm	44	88.0	6	12	
Grade	G I	51	91.1	5	8.9	0.564
	G II	237	92.9	18	7.1	
	G III	174	90.2	19	9.8	
Lymph Node	NX	86	86.9	13	13.1	0.096
	NO	176	95.1	9	4.9	
	N1	79	94.0	5	6.0	
	N2	60	89.6	7	10.4	
	N3	61	88.4	8	11.6	
LVI	Negative	257	93.5	18	6.5	0.112
	Positive	205	89.5	24	10.5	

Chi-Square Test : *$p < 0.05$; Significant; **$p < 0.001$; Highly significant

LVI – Lymphovascular invasion.

Comparison of combined ER and PR positivity, statistical significance was noted with the age of the patient, size of the lump and grade of tumour as seen in Table 5. When all the 3 parameters ER, PR and Her-2/Neu were analysed in combination none of these were statistically significant (Table 6).

Statistically few of the observations were significant as per the Pearson Chi–square analysis. These included the size of the tumour and Her-2/Neu staining pattern and Nottingham grading vs Her2/Neu status.

Discussion

Carcinoma breast is one of the commonest cancers in women and also globally one of the most importantcause of death in women. It is the most common cancer in Indian females.[1] Majority of the patients belonged to the peri-menopausal and post-menopausal age group. It has been observed that, in Asian patients (IDC) occurs a decade earlier than those from the western countries and also, there is a pattern shift towards the younger age group.[6,7] Factors such as late age of marriage, increasing consumption of fast food and reduction in the breast feeding also play a significant role.[8] In this study, majority of cases had tumor size between 2-5 cms (T2 stage). This is in close concordance with that of other Indian studies conducted by Biswal *et al.*[4], Vedashree *et al.*[6], and Suvarchala *et al.*[9] Study by Siadati *et al.*[10] showed 71% patients of IDC with lump size less than 2 cms. This finding could be explained on the basis of increased awareness regarding breast cancer and more number of breast cancer screening programs in Western Countries as against those in India. In our study right breast was marginally more involved than the left breast, similar to that reported by Geethmala *et al.*[11] This particular parameter is variable in other studies as well, and is not considered clinically significant.

As regards the grading of IDC, in this study, majority of cases belonged to grade II. This observation is in close coherence with many other Indian studies including those by Bisht *et al.*,[12] Vedashree *et al.*,[6] Suvarchala *et al.*[9] and Geethamala

et al,[11] In the study, 59.2% cases had lymph node metastasis and negative in 40.8% of the cases. This is in contrast to the study by Dutta *et al*.[13] where there were almost equal numbers of positive and negative cases of metastasis in the axillary nodes. For the tumour stage, majority of cases in the present study as well as other studies from India predominantly had grade II or III. In contrast in the Western countries maximum cases were of stage 1.[4,14] This finding could be attributed to the efficient screening and awareness programs for breast carcinoma in their country. Triple negative tumors carry a poor prognosis, since they are not amenable to hormone therapy.[15]

In the present era, no biopsy report of IDC can be considered to be complete without the immunohistochemical parameters of analysis ER, PR and Her2 neu. Different methods of analysis are available to study these hormone receptors of which IHC and microarray are important. As compared to microarray, immunohistochemistry provides a relatively easier and less expensive modality that can be done on paraffin embedded tissue. The degree of hormone receptor positivity in the primary tumour predicts the benefit the patient will have after receiving neo-adjuvant therapy[16] Tumors that express both ER and PR have the greatest benefit after endocrine therapy. Normally, Her2/Neu receptors control cell growth and repair of healthy breast cells. It encodes a tyrosine kinase related to epidermal growth factor. Different studies have proved that over expression of HER-2/Neu indicates a reduced response to Tamoxifen and also has a lower life expectancy. Tumors that are negative for ER, PR and HER-2/neu belonged to the higher grade and have been reported in females older than fifty years of age.[8] Over expression of Her- 2/Neu leads the breast cells to grow and divide without any control. These tumors are treated with Transtuzumab (Herceptin), a human monoclonal antibody acting against cells that express Her-2/Neu[1]. Therefore, assessment of Her2/Neu expression in patients with metastatic breast carcinoma is more important clinically.[17,18] Different studies have proved that, Her-2/ Neu positivity is lesser as compared to ER/PR positivity. Higher Her2 immunoreactivity may be inherent in breast carcinomas in Indian women. It can also predict resistance to endocrinal therapy.[13]

ER and PR are endocrine receptors that arepresent on theductal cells and pick up hormone signals resulting in cell growth. The main goal of knowing the receptor status is to provide targeted therapy for giving the correct treatment to the patient. This hormone receptor status is graded using the scoring and grading system as proposed by Allred.[5] They help in determining the prognosis of the tumor as well as in deciding the treatment modality to be used. The role of the pathologist is to accurately assess these biomarkers, while the role of the oncologist is to treat the patient with any of the established therapies, depending on the expression of markers.

Biomarkers can be both prognostic and predictive, or even both. Prognostic markers measure the prognostic outcome of the patient irrespective of other factors. The expression of these biomarkers directly reflects the disease recurrence and/or mortality. On the contrary predictive biomarkers, help in predicting whether a particular patient therapy will be of benefit for theor not. Presence of both ER and PR in a breast cancer is an example of a weak prognostic but strong predictive biomarker. If thetumor expresses ER and/or PR, it can be predicted that the particular patient will definitely be benefited by giving hormonal treatment such as Tamoxifen. Over expression of Her2/Neu is an example of both prognostic as well as predictive biomarker. Her2/Neu expression is known to predict poor prognosis (high recurrence rate and also that the patient will more likely benefit by taking Anthracycline and Taxane-based chemotherapies. Even neo-adjuvants therapies that target Her2/ Neu such as Trastuzumab, will benefit the patient but endocrine-based therapies will not be of use.[2] It is suggested that low expression of PR may be an indicator of activated growth factor signaling in IDC that may represent an aggressive tumor phenotype resistant against hormonal therapy. Nearly one – fourth to one – third of the patients show Her 2/Neu positivity these indicating a poor clinical outcome.[12] HER2 protein and gene overexpression in the present study was associated with features that indicate tumourness aggressive, such as metastasis to the axillary nodes, high tumor grade and, large tumor size HER2 positivity are significant risk factors for rapid tumor recurrence, and conversely, that the luminal A tumour subtype significantly lowers the risk of recurrence of carcinoma breast.

Attimes the results of thereceptor status (ER, PR, and Her2/Neu) may be false negative or false positive. This may be attributed to different classifying system in different centres for positive and negative test results. Errors do occur especially in borderline orreactive cases. In others, tissue from different tumour parts may be Her2/Neupositive or Her2/Neu negative.[1,2] Inspite of the usefulness of this hormone status or the scoring system, it

has its own pitfalls and limitations. Interobserver variations, different interpretation system, quality of reagents, time of tissue fixation, staining, etc., are some of the common errors. There have been varied presentations of hormone markers in the primary and the secondary tumours. Study by Sari *et al.* showed that 8% of the ER positive primary tumours did not express ER in the metastatic deposits, while on the contrary nearly 5% of ER negative tumours showed ER positivity in the secondary deposits.[19] Luminal type B cancer patients have been reported to have a poor prognosis both for recurrence as well as the survival as compared to luminal type A cancers.[20]

Lymph node status is well known to determine the cancer staging and treatment options. It is a vital factor in determining the prognosis of patients with IDC. As the number of metastatic axillary lymph nodes increases the survival rate decreases but the rate of relapse increases. Size of the tumor and HER2 overexpression determine marked risk of early cancer relapse.

Conclusion

After the completion of the present study it was observed that as the size increased the expression of ER, PR decreased significantly Her-2/Neu expression increased. No such significant correlation was established with lympho-vascular invasion or metastasis to the lymph nodes. Tumors with ER and PR positivity possess a better prognosis and respond well to hormonal therapy. Her-2/Neu positive tumors, carry a poor prognosis, but do respond to Transtuzumab therapy. ER negative and triple negative tumors have a bad prognosis and do not respond to endocrinal therapy.

Our results displayed a positive correlation between ER and PR markers whereas there was an inverse correlation with HER-2/Neu. In addition, there was a significant correlation between ER and PR positivity and low grade tumors. The correlation between HER-2/Neu positivity and high grade tumors and metastasis to the lymph nodes was significant. These findings showed the importance of these immunomarkers to be used routinely since they provide valuable prognostic information for best therapeutic decision.

Standardisation of the test procedure and proper interpretation of the test results along with a good coordination between the pathologist and the oncologist is important for optimal results.

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