Annals of Diagnostic Pathology 50 (2021) 151659

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Cytological-Pathologic Correlation

Correlation of expression of hormone and HER2 receptors with various clinico-pathological prognostic parameters and with each other in malignant breast lesion

Swati Sucharita Mohanty

Cytogenetics Laboratory, P.G. Department of Zoology, Utkal University, Bhubaneswar 751004, Odisha, India

ARTICLE INFO

Keywords:
Breast cancer
Estrogen receptors
Progesterone receptors
Human epidermal growth factor receptor-2
Correlation of expression

ABSTRACT

Background: Estrogen receptors (ER), progesterone receptors (PR) and the human epidermal growth factor receptor-2 (HER2) are basic breast cancer molecular markers that are also best recognized prognostic factors and predictors of type of targeted therapy to be given. The objectives are to study the correlation of expression of hormone and HER2receptors with various clinico-pathological prognostic parameters like patient's age at diagnosis, menopausal status, tumor size, histological grade and lymph node status of tumor and with each other in malignant breast lesion.

Methods: For this study histopathology (HP) and immunohistochemistry (IHC) slides of excised specimens of 330 female patients with a palpable breast lump deposited to the pathology department of a hospital as a part of routine diagnostic procedure, were evaluated under the guidance of trained doctors who have minimum 5 years of experience in oncopathology. The author has no direct involvement with patients, informed consent was not necessary and data were collected after getting permission from concerned authority.

Results: This study finds significant relationship between hormone receptors and all clinico-pathological prognostic parameters taken for comparison except age at diagnosis. HER2 status has significant relationship with all clinico-pathological prognostic parameters; hormone and HER2 status suggests an inverse relationship.

Conclusions: Mien of hormone receptors expression in breast cancer is related with better prognostic factors such as older age, postmenopausal status, smaller tumor size, low histological grade and negative lymph node status, however the opposite is correct for HER2. Hormone receptors and HER2 have an inversely proportionate relationship with each other.

1. Introduction

Breast carcinoma is the second-highest prevailing cancer globally after lung with 2.09 million cases in 2018, it is also the second highest cancer prevailing in 2018 with 2,088,849 new cases. In India, there were recorded 162,468 new cases and 87,090 deaths due breast cancer during 2018. It is also the leading carcinoma in Indian metropolitan women, and the second commonage in the Indian bucolic women [1]. India is a country with broad economic, religious, cultural, ethnic divergence and discrepancy in the medical services. The medical assistance proficiency is multifarious, with myriad districts where the beneficial multi-disciplinary medical services, fast screening and cognizance haven't accomplished [2,3]. Most of the patients in India are diagnosed at locally advanced and metastatic stages due to late screening, illiteracy, lack of cognizance and monetary restraint [2], as vital multi-disciplinary medical services are accessible only at a couple of selected regional hospitals [4].

Immunohistochemistry (IHC) has an expanding role in the screening and handling of breast diseases. Antibodies availability, enhanced antigen retrieval knacks and an advanced perception of science have all assisted in greater effectiveness of IHC for diagnostic breast pathology [5]. This study includes hormone receptor such as estrogen receptors (ER) & progesterone receptors (PR) and the human epidermal growth factor receptor-2 (HER2) which are basic biomarkers for breast cancer that are used routinely. Bloom in 1950 noted a poorer prognosis among patients under the age of 50 years in comparison to older age group, whereas Alderson et al. [6] found age at diagnosis to be insignificant. Anders et al. [7] and Cao et al. [8] found similar result as that of Bloom [9]. Clinical staging is the most crucial prognostic determinant having impact on management and survival. The overall five year survival rates

E-mail address: swatimohany16@gmail.com.

https://doi.org/10.1016/j.anndiagpath.2020.151659

Available online 5 November 2020

are 92%, 87%, 75%, 46% and 13% for stage 0, I, II, III and IV respectively [10].

Size of the tumor is one of the major influential independent predictors of tumor outcome in breast cancer [11]. Size of the tumor correlates with the mien and amount of axillary lymph nodes involved. Also cancer recurrence rates increasing with larger tumor size [12]. In patients without nodal involvement, tumor's size is an independent prognostic factor of recurrence. There is overall 5 years survival rate of 99% patients with tumors that were smaller than 1 cm in diameter, whereas it is 86% when tumors were 3–5 cm in diameter [13]. As envisaged, the overall survival decreases with increase in tumor size for a particular nodal group. Also with an increase in the count of metastatic lymph nodes the overall survival rate decreases for a given tumor size [14]. If the size of the primary tumor increases then the risk of axillary lymph node metastases also increases, but both are independent prognostic factors. Lamentably, breast self-examination can't discern breast cancer in time [10,15], which means by the time breast cancers become palpable (2–3 cm), tumors proficient of metastasizing have already done so. Cancers detected by mammographically are smaller and less probably to have metastasized [10].

Histological grade is a significant factor of prognosis that also allows risk stratification for a given stage of tumor [10]. Grade increases with tumor size regardless of age [16]. Grade III tumors have a proportionate 4.4 times' elevated risk of recurrence. This prognostic factor has a noteworthy importance in negative lymph nodes (LNs) and small tumors [13]. Tumor necrosis is associated with high histological grade, lymph node infiltration and decreased survival rate [17].

Adair et al. [18] reported that survival is best with ductal carcinoma in situ (74%) and least with infiltrating lobular carcinoma (34%) and infiltrative duct carcinoma (28%). Morphologic variants of infiltrative duct carcinoma with favourable prognosis are tubular, cribriform, papillary and mucinous. The presence or absence of axillary nodal involvement is a crucial prognostic indicator for early-stage breast cancer. Moreover, there is a positive association between the number of axillary nodes involved and the risk of distant recurrence [12]. Patients with nodal involvement have been documented to have a 4–8 times higher death rate in contrast to patients without nodal involvement [13]. The five year survival for patients without nodal involvement is 82.8% compared with 73% for 1–3 positive nodes, 45.7% for 4–12 positive nodes, and 28.4% for ≥13 positive nodes [12].

HER2over-expression is related to poor survival rate, but its key role is as a predictor of response to antibodies that target this transmembrane protein [10]. Eighty percent of ERPR positive carcinomas respond to hormonal therapy, while about 40% of those with either ER or PR alone respond. ER-positive carcinomas have high possibility to respond to hormone therapy than chemotherapy. Concomitantly, carcinomas that don't express either ER or PR have less than 10% chances of responding to hormonal therapy but have high possibility to respond to chemotherapy [10]. This investigation focuses on basic prognostic biomarkers markers of breast cancer such as estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor-2 (HER2) which are used routinely in identification and grading breast tumors. The objectives are to study the correlation of expression of hormone and HER2receptors with various clinicopathological prognostic parameters like patient's age at diagnosis, menopausal status, tumor size, histological grade and lymph node status of tumor and with each other in malignant breast lesion.

2. Materials and methods

This investigation was carried out after being permitted from the Head, Department of Pathology of Sriram Chandra Bhanja Medical College and Hospital (SCBMCH), Manglabag, Cuttack-753,007, Odisha. The investigation was conducted on histopathology (HP) and immunohistochemistry (IHC) of excised specimens of 330 females with breast carcinoma. The slides were evaluated under the guidance of trained doctors who have minimum 5 years of experience in oncopathology. The author has no direct involvement with patients, informed consent was not necessary and data were collected after getting permission from concerned authority. All excised specimens deposited at the pathology department were subjected to histopathology and immunohistochemistry analysis as a part of routine diagnostic procedure. All histologically proved malignant cases of invasive carcinoma of females, irrespective of age, have been included and taken into account for investigation and analysis. Clinical and investigation findings along with diagnosis were noted down. After diagnosis, the reports and the slides were returned to the respective patients.

Histopathological examination was conducted by using conventional haematoxylin and eosin stain (H and E). Immunohistochemical investigation was evaluated by using Novocastra's ready to use mouse monoclonal antibody and Novolink polymer detection system. Both evaluations were undertaken on formalin fixed paraffin embedded tissue sections. Cancers were graded according to Elston and Ellis' [19] modification of Bloom and Richardson's [20] original classification from 1957. A simple method known as 'Quick score' system described by Leake et al. [21] is used for scoring hormone receptors and American Society of Clinical Oncology - College of American Pathologists [22] guideline recommendations is used for scoring HER2. The hormone receptors and HER2receptors expression were assessed and correlated with prognostic parameters like patient's age at diagnosis, menopausal

Table 1
Distribution of cases (n = 330).

Sl no	According to	Number of cases	Percentage (%)
A	Histological type		
1	Invasive ductal carcinoma	289	87.58
2	Invasive lobular carcinoma	41	12.42
B	Age group in years		
1	<41	73	22.12
2	41–50	182	55.15
3	>50	75	22.73
C	Menopausal status		
1	Premenopausal	111	33.64
2	Postmenopausal	219	66.36
D	Tumor size		
1	T1	47	14.24
2	T2	175	53.03
3	T3	74	22.42
4	T4	34	10.30
E	Histological grade		
1	G I	52	15.76
2	G II	192	58.18
3	G III	86	26.06
F	Lymph node status		
1	N0	61	18.48
2	N1	164	49.70
3	N2	75	22.73
4	N3	30	9.09
G	ER and PR status		
1	ER+vePR+ve	201	60.91
2	ER+vePR−ve	57	17.27
3	ER−vePR+ve	29	8.79
4	ER−vePR−ve	43	13.03
H	ER status		
1	ER+ve	258	78.18
2	ER−ve	72	21.82
I	PR status		
1	PR+ve	230	69.70
2	PR−ve	100	30.30
J	HER2status		
1	HER2+ve	123	37.27
2	HER2–ve	207	62.73
Total		330	100

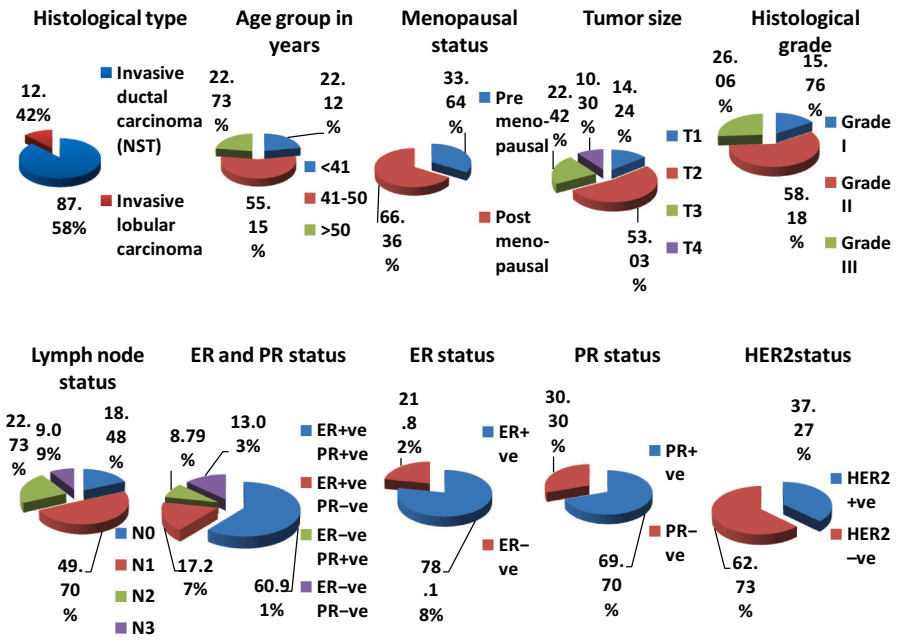

Fig. 1. Distribution of cases ($n = 330$).

status, tumor size, histological grade and lymph node status of tumor. The hormone and HER2receptors expression were also correlated with each other.

Differences in tissue processing and technical procedure may produce variable results. Hence, controls slides were used provided by Biogenex manufacturers. The controls includes: A. Positive tissue control: It is used to show appropriately drafted tissues and staining, B. Negative tissue control: Negative control was used after the positive tissue control to confirm the specificity of the labeling of the target antigen by primary antibody.

The data were arranged in contingency table and were analysed by the Chi-square test (X2) to find the correlation between these prognostic parameters, ERPR and HER2 expression [23-25]. The result was considered statistically significant if p value was less than 0.05. The commercially available statistical software (PAST version 3.04 for Windows; Øyvind Hammer, Natural History Museum, University of Oslo) was used for data analysis. The slides were observed using a research binocular microscope of Motic model.

3. Results

Out of the 330 cases included in this study, invasive ductal carcinoma (IDC) was the most common histological types of breast cancer, accounting for about 289(87.58%) cases. Besides IDC there is also

Table 2
Correlation of various prognostic parameters with ER & PR expression in breast carcinoma (n = 330).

Prognostic parameters	ER/PR status					
	ER+VE PR+VE No. (%)	ER+VE PR−VE No. (%)	ER−VE PR+VE No. (%)	ER−VE PR−VE No. (%)	Total no. (%)	Chi squared p value
A. Age at diagnosis (in years)						
<41	46(22.89%)	10(17.54%)	5(17.24%)	12 (27.91%)	73(22.12%)	0.60717
41–50	110(54.73%)	30(52.63%)	17(58.62%)	25(58.14%)	182(55.15%)	≈0.61
>50	45(22.39%)	17(29.82%)	7(24.14%)	6(13.95%)	75(22.73%)	
B. Menopausal status						
Pre menopausal	69(34.33%)	13(22.81%)	7(24.14%)	22(51.16%)	111(33.64%)	0.017517
Post menopausal	132(65.67%)	44(77.19%)	22(75.86%)	21(48.84%)	219(66.36%)	≈0.02
C. Tumor size						
T1	32(15.92%)	9(15.79%)	6(20.69%)	0	47(14.24%)	0.031005
T2	99(49.25%)	37(64.91%)	17(58.62%)	22(51.16%)	175(53.03%)	≈0.03
T3	47(23.38%)	8(14.04%)	5(17.24%)	14(32.56%)	74(22.42%)	
T4	23(11.44%)	3(5.26%)	1(3.45%)	7(16.28%)	34(10.30%)	
D. Histopathological grade						
G I	35(17.14%)	10(17.54%)	7(24.14%)	0	52(15.76%)	0.025681
G II	121(60.20%)	29(50.88%)	12(41.38%)	30(69.77%)	192(58.18%)	≈0.03
G III	45 (22.39%)	18(31.58%)	10(34.48%)	13(30.23%)	86(26.06%)	
E. Lymph node status						
N0	40(19.90%)	12(21.05%)	9(31.03%)	0	61(18.48%)	0.037748
N1	101(50.25%)	29(50.88%)	13(44.83%)	21(48.84%)	164(49.70%)	≈0.04
N2	44(21.89%)	10(17.54%)	5(17.24%)	16(37.21%)	75(22.73%)	
N3	16(7.96%)	6(10.53%)	2(6.90%)	6(13.95%)	30(9.09%)	
Total no. (%)	201(60.91%)	57(17.27%)	29(8.79%)	43(13.03%)	330	

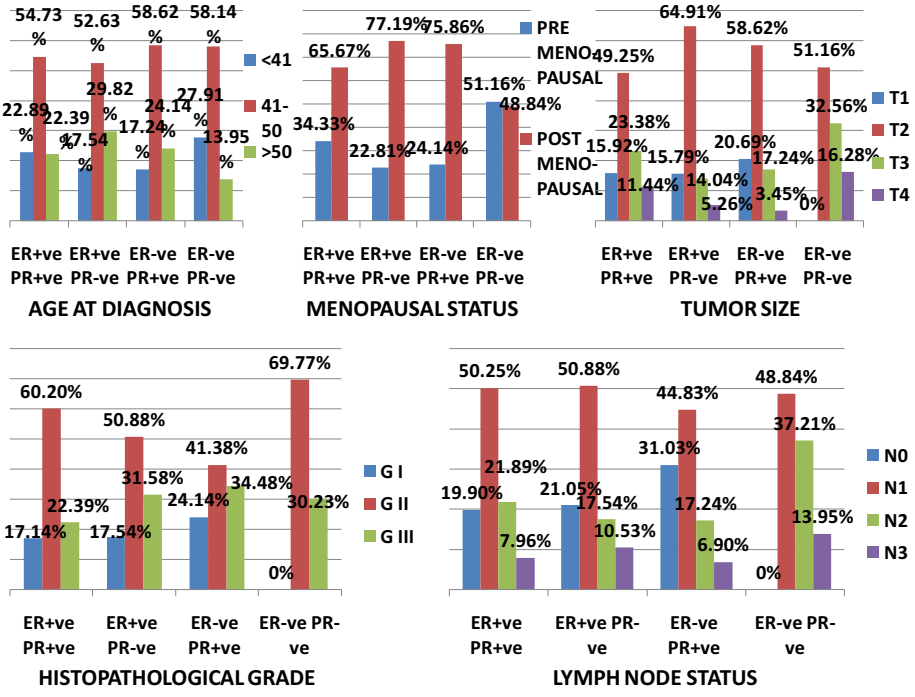

Fig. 2. Correlation of various prognostic parameters with ER & PR expression in breast carcinoma (n = 330).

invasive lobular carcinoma (ILC). The females were divided into three different age groups; <41, 41–50 and > 50 (Table 1). The females' age ranged from 22 to 67 years, with maximum numbers of females in 41–50 years age group (Fig. 1). Mean age at diagnosis was found to be 46.38 years.

ERPR status were divided into four different groups (Table 1); ER positive PR positive (ER+vePR+ve), ER positive PR negative (ER+vePR−ve), ER negative PR positive (ER−vePR+ve) and ER negative PR negative (ER−vePR−ve). The maximum numbers of cases were in ER+vePR+ve group with 201(60.91%) cases (Fig. 1). Regarding only ER status, it was divided into two groups (Table 1) namely ER positive (ER+ve) and ER negative (ER−ve). There were 258(78.18%) in ER+ve group and 72 (21.82%) cases in ER−ve group. PR status was also divided into two groups. There were 230 (69.70%) in PR positive (PR+ve) group and 100(30.30%) cases in PR negative (PR−ve) group. Similarly HER2 was divided into two group (Table 1); where there were 123 (37.27%) in HER2 positive (HER2+ve) and 207 (62.73%) cases in HER2 negative (HER2−ve) group (Fig. 1).

In correlating hormone receptors with age at diagnosis (Table 2) it was found that all four ERPR group types were highest in 41–50 age group (Fig. 2). Further the females were divided into two groups; pre-menopausal group and postmenopausal group (Table 1). Post-menopausal group females were those who had their last menstrual period more than twelve month ago. Maximum numbers of females were in the postmenopausal age group (Fig. 1). When hormone receptors were correlated with menopausal status, all four ERPR group types except ER−vePR−ve were highest in postmenopausal females. Tumor size was divided into four different groups; T1, T2, T3 and T4 stages (Table 1). The maximum numbers of cases (53.03%) were in T2 stage and minimum numbers (10.30%) were in T4 stage (Fig. 1). Correlating hormone receptors with tumor size (Table 2) it was found that all four ERPR group types were highest in T2 tumor size (Fig. 2).

Histological grade was divided into three different groups; grade I (G I), grade II (G II) and grade III (G III) (Table 1). The maximum numbers of cases were in grade II with 192(58.18%) cases (Fig. 1). When hormone receptors were correlated with histological grade (Table 2), all four ERPR group types were highest in grade II (Fig. 2). Lymph node status or nodal involvement was divided into 4 different groups; N0, N1, N2 and N3 stage (Table 1). The maximum numbers of females were in N1 stage with 164(49.70%) cases (Fig. 1). In correlating hormone receptors with lymph node status (Table 2) it was found that all four ERPR groups type were exceeding in N1 stage (Fig. 2).

Correlating HER2with age at diagnosis (Table 3) it was found that HER2+ve and HER2−ve both were highest in 41–50 (Fig. 3). When HER2was correlated with menopausal status, number of both HER2-status were exceeding in postmenopausal females. Correlation of HER2with tumor size (Table 3) showed that both HER2status were highest in T2 stage. Correlation of HER2with histological grade showed that both HER2status were maximum in grade II (Fig. 3).

Correlating HER2with lymph node status (Table 3) it was found that both HER2status were highest in N1 (Fig. 3). When estrogen receptor status was correlated with HER2status it was observed that maximum ER+ve showed HER2 negativity, about 170(82.13%) cases out of 207 (Table 4). Similarly when progesterone receptor status was correlated with HER2 status (Fig. 4) it was observed that 153(73.91%) PR+ve cases out of 207 showed HER2 negativity.

4. Discussion

In this investigation invasive ductal carcinoma (IDC) was the major group (Table 1), counting about 289(87.58%) (Fig. 1) which is comparable to the research of Ayadi et al. [23] and Azizun-Nisa et al. [26] who found the predominant morphology to be IDC accounting about 83.8% and 85.3% respectively. Abdollahi et al. [24] also found similar results where IDC was 90.7%. Kumar and Mukherjee [25] in their study showed that 62% of cases were ER+vePR+ve. This study was consistent with Kumar and Mukherjee, where majority of the cases were ER+vePR+ve (60.91%). In the present study HER2was found to be positive in 37.27%

Table 3
Correlation of various prognostic parameters with HER2expression in breast carcinoma (n = 330).

Prognostic parameters	HER2 status			
	HER2+ve no. (%)	HER2-ve no. (%)	Total no. (%)	Chi squared *p* value
A. Age at diagnosis (in years)				
<41	37(30.08%)	36(17.39%)	73 (22.12%)	0.013816 ≈ 0.01
41–50	65(52.85%)	117 (56.52%)	183 (55.15%)	
>50	21(17.07%)	54(26.09%)	75 (22.73%)	
B. Menopausal status				
Pre menopausal	51(41.46%)	60(28.99%)	111 (33.64%)	0.020351 ≈ 0.02
Post menopausal	72(58.54%)	147 (71.01%)	219 (66.36%)	
C. Tumor size				
T1	9(7.32%)	38(18.36%)	47 (14.24%)	0.044134 ≈ 0.04
T2	69(56.10%)	106 (51.21%)	175 (53.03%)	
T3	32(26.02%)	42(20.29%)	74 (22.42%)	
T4	13(10.57%)	21(10.14%)	34 (10.30%)	
D. Histological grade				
G I	11(8.94%)	41(19.81%)	52 (15.76%)	0.031909 ≈ 0.03
G II	78(63.41%)	114 (55.07%)	192 (58.18%)	
G III	34(27.64%)	52(25.12%)	86 (26.06%)	
E. Lymph node status				
N0	17(13.82%)	44(21.26%)	61 (18.48%)	0.032958 ≈ 0.03
N1	71(57.72%)	93(44.93%)	164 (49.70%)	
N2	29(23.58%)	46(22.22%)	75 (22.73%)	
N3	6(4.88%)	24(11.59%)	30(9.09%)	
Total no. (%)	123(37.27%)	207 (62.73%)	330	

of cases (Table 1) which is comparable to the research of Azizun-Nisa et al. [26] who identified 24.7% of cases as HER2positivite. Ivkovic-Kapicl et al. [27] identified 20% of cases showing HER2 protein over-expression.

In this investigation 41–50 years group was the frequent age group to be affected with 55.15% cases (Table 2). All four type of ERPR status were highest in same 41–50 age group Fig. 2). The information acquired in this investigation was statistically insignificant (p-value>0.05). So our study was consistent with Barnes et al. [28] and ERPR status and age at diagnosis showed no significant relationship. However, it was observed that the number of hormone positive cases increases with advance in age (older age group).The mean age at diagnosis was 46.38 years, contrary to the west where 53–57 years is more susceptible. This is similar to the findings of National Cancer Registry Programme [29], according to which more patients are being diagnosed with breast cancer in their thirties and forties. Ayadi et al. [23] also found that women in his study are relatively younger than those in western countries, with mean age of 51.5 years. Sofi et al. [30] also found the mean age to be 48.2 years. Bloom in 1950 in their study of prognostic markers of breast cancer noted a poorer prognosis among patients under the age of 50 years in comparison to older age group [9], whereas Alderson et al. [6] found age at diagnosis to be insignificant. Anders et al. [7] and Cao et al. [8] found similar result as that of Bloom.

Regarding the menopausal status ER+vePR+ve females were more in postmenopausal group with 65.67% (Table 2). This consistent well with Kumar and Mukherjee [25], who found 68.29% of postmenopausal females were ER+vePR+ve. Similarly Hawkins et al. [31] documented that 61% of postmenopausal patients had ER+vePR+ve tumors (Fig. 2). Premenopausal females were 33.64% of total investigation group which is similar to finding of Kuraparthy et al. [32], who found 27% females in premenopausal group. This correlation between ERPR and menopausal status was concluded to be statistically significant (p-value<0.05).

Regarding size of the tumor at presentation (Table 2); in the study of Azizun-Nisa et al. [26] most of the patients (53%) were at T1 stage but Kamil et al. [33] found the most common stage to be T3 stage. Barnes et al. [28] demonstrated that ER+ve tumors were smaller than ER−ve tumor, while Allegra et al. [34] showed hormone receptors positivity and size of the tumor have no correlation. In this investigation (Fig. 2) most of the tumors in ER+vePR+ve group were at T2 stage with 49.25% cases. Whereas in ER–vePR–ve group 51.16% were at stage T2, while there was none in T1 stage. The above results revealed that ER+vePR+ve tumor were of smaller size. This correlation between hormone receptors and tumor size was found to be statistically significant (p-value<0.05).

Among this study group (Table 2) 60.20% of ER+vePR+ve patients had grade II i.e. moderately differentiated tumor, 17.14% had grade I i.e. well differentiated tumor, while the remaining 22.39% of ER+vePR+ve cases belonged to grade III i.e. poorly differentiated tumor (Fig. 2), this is comparable to research of Azizun-Nisa et al. [28] who showed 55.3% grade II tumors; Kumar and Mukherjee [25], who reported 51% ER+vePR+ve tumors in grade II. In contrast to ER+vePR+ve tumors 30.23% of ER−vePR−ve cases were poorly differentiated (grade III) and 69.77% were moderately differentiated (grade II). None of ER−vePR−ve cases were in well differentiated tumor (grade I). These findings suggest that as the grading of the tumor is increasing, its hormone receptor positivity is decreasing while hormone receptor negativity is increasing. Barnes et al. [28] concluded that as the tumor grade increases ER positivity decreases significantly. The correlation of ERPR and histological grade is statistically significant (p-value <0.05).

In this investigation, (Table 2) most common lymph node stage to be affected in ER+vePR+ve group was N1stage with 50.25% of cases and 19.90% cases were without nodal involvement (N0 stage). While in ER−vePR−ve group 48.84% cases had N1 nodal involvement. This is similar to Kumar and Mukherjee [25], who found 51.61% of cases in ER+vePR+ve group had N1 lymph node status. This differs from results of Azizun-Nisa et al. [26] who found 71.3% patients with nodal metastasis. Allegra et al. [34] conclude that high proportion of node negative cases were in ER+vePR+ve group. Whereas Fatima et al. [35] showed ERPR status and lymph node metastasis had no significant correlation. This study is consistent with Allegra et al. [34] which showed that in contrast to ER−vePR−ve tumors higher percentage of ER+vePR+ve tumors were without node involvement. The correlation of ERPR and lymph node status was statistically significant (p-vaue <0.05) which showed that lymph node involvement is more in hormone receptor negative tumor as compared to hormone receptor positive tumor (Fig. 2).

Over-expression of HER2 (HER2+ve) was highest in 41–50 years of age group with 52.85% (Table 3). Similarly, 56.52% cases in 41–50 age group were HER2–ve (Fig. 3). Kamil et al. [33] reported no relationship between age at diagnosis and HER2status. In contrast to above study Azizun-Nisa et al. [26] concluded that HER2positivity decreased with increase in age which is similar to this investigation (p-value<0.005) i.e.

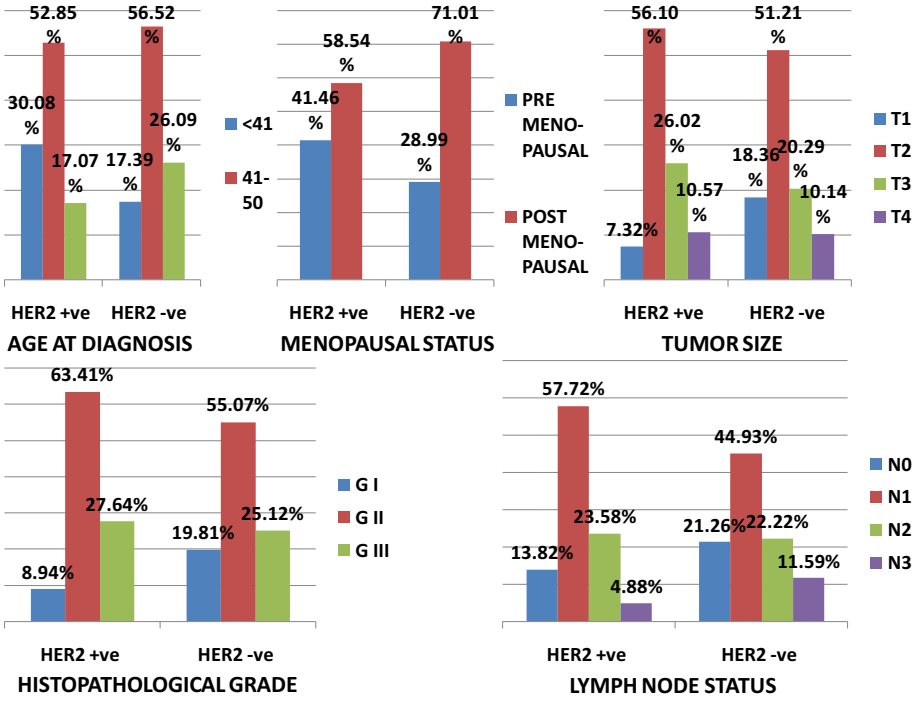

Fig. 3. Correlation of various prognostic parameters with HER2expression in breast carcinoma (n = 330).

Table 4
Correlation of hormone receptor status with HER2status.

Hormone receptor status	HER2 status			
	HER2+ve no. (%)	HER2-ve no. (%)	Total no. (%)	Chi squared *p* value
A. Estrogen receptor status				
ER+ve	88(71.54%)	170 (82.13%)	258 (78.18%)	0.02443 ≈ 0.02
ER-ve	35(28.46%)	37(17.87%)	72 (21.82%)	
B. Progesterone receptor status				
PR+ve	77(62.60%)	153 (73.91%)	230 (69.70%)	0.030621 ≈ 0.03
PR-ve	46(37.40%)	54(26.09%)	100 (30.30%)	
Total no. (%)	123(37.27%)	207 (62.73%)	330	

statistically significant. In the investigation group 58.54% cases of HER2 over-expression were in postmenopausal group (Table 3). HER2–ve was seen maximum in postmenopausal group with 71.01%. This means HER2 over-expression decreases with increase in age. The correlation of HER2 status with menopausal status was found to be statistically significant (p-value<0.05).

This investigation (Table 3) found that in case of HER2negativity, T2cases were 51.21% out of 207. On the other side 56.10% out of 123 were in T2 belongs to HER2+ve. Also HER2negativity cause size of tumor to increase in T3 & T4 stage (Fig. 3), this correlation of HER2-status with tumor size was found to be statistically significant (p-value <0.05). This data is comparable with that of Azizun-Nisa et al. [26] and Ivkovic-Kapicl et al. [27] who found large tumor size and HER2negativity to be strongly connected. Comparing the HER2status with histological grade (Table 3), it was noticed that 55.07% grade II tumors had HER2negative status out of 207. In cases of HER2 positivity 63.41% were in grade II and 27.64% of HER2positivity were associated with higher grade III tumors (p-value<0.05). So, there were more cases in HER2–ve than in HER2+Ve for all the grades and the correlation was statistically significant. This result is similar to Ivkovic-Kapicl et al. [27] and Ludovini et al. [36] who showed all the grade I tumors have HER2negative status. Kamil et al. [33] in his investigation didn't find any association between histological grade and HER2status.

This study observed (Table 3) statistically significance between nodal involvement and HER2status, with 21.26% patients without nodal involvement (N0 stage) had HER2negative status. HER2negativity with nodal involvement was 44.93%, 22.22% and 11.59% for N1, N2 & N3 stage respectively (Fig. 3). Hence the association of lymph node status and HER2 was found to be statistically significant (p-value <0.05). Also Azizun-Nisa et al. [26] and Ludovini et al. [36] showed positive correlated between HER2 and lymph node metastasis. Whereas Ivkovic-Kapicl et al. [27] and Kamil et al. [33] didn't find any association. Correlating HER2 with hormone receptor status (Table 4), it was observed that 82.13% HER2–ve showed ER positivity (p-value <0.05). Similar result (Fig. 4) was found with progesterone receptor i.e. 73.91% HER2–ve showed PR positivity (p-value <0.005). This suggests an inverse relationship between ERPR and HER2. The above results are comparable with that of Ivkovic-Kapicl et al. [27] who showed 82.47% of ER+ve cases and 75.25% of PR+ve cases to be related with HER2–ve status.

5. Conclusion

It is concluded that mien of hormone receptors expression in breast cancer is related with better prognostic factors such as older age, postmenopausal status, smaller tumor size, low histological grade and negative lymph node status, however the opposite is correct for HER2 that is related with inimical prognostic factors like younger age,

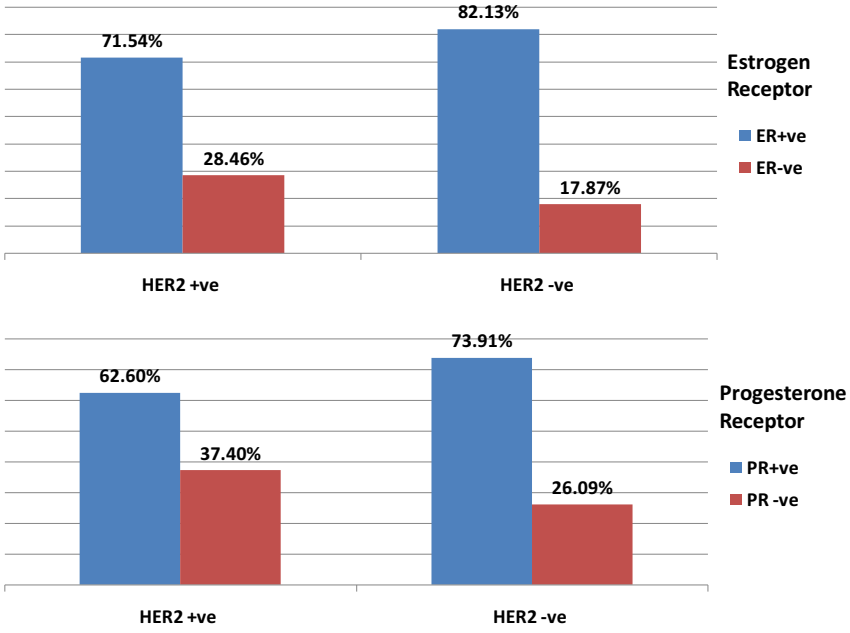

Fig. 4. Correlation of hormone receptor status with Her2 status (n = 330).

premenopausal status, larger tumor size, high histological grade and positive lymph node status. Hormone receptors and HER2 have an inversely proportionate relationship with each other. Further studies can be taken up on newer markers and technologies that are available, which are even quicker by half the time of immunohistochemistry. Such technologies include different immunological assays like ELISA and PCRs. With the above technologies management of breast cancer will be easier, enhanced and quicker for even better prognostic as well as therapeutic implications.

Ethical approval

This article does not contain any studies with human participants performed by the author.

Declaration of competing interest

Swati Sucharita Mohanty has no conflicts that are directly relevant to the content of this study.

Acknowledgements

The author is grateful to head of the Department of Pathology of Sriram Chandra Bhanja Medical College and Hospital, for providing support in the collection of the data and slides. The author acknowledges University Grants Commission - Basic Scientific Research fellowship for providing funding for the study.

References

[1] Mohanty SS, Mohanty PK. Obesity as potential breast cancer risk factor for postmenopausal women. Genes Dis 2019. https://doi.org/10.1016/j.gendis.2019.09.006. In press.
[2] Agarwal G, Pradeep PV, Aggarwal V, et al. Spectrum of breast cancer in Asian women. World J Surg 200; 731(5): 1031–1040.
[3] Chopra R. The Indian scene. J Clin Oncol 2001;19(18):106–11.
[4] Agarwal G, Ramakant P. Breast cancer care in India: the current scenario and the challenges for the future. Breast Care 2008;3(1):21–7.
[5] Yeh IT, Mies C. Application of immunohistochemistry to breast lesions. Arch Pathol Lab Med 2008;132(3):349–58.
[6] Alderson MR, Hamlin I, Staunton MD. The relative significance of prognostic factors in breast carcinoma. Br J Cancer 1971;25(4):646–56.
[7] Anders CK, Johnson R, Litton J, et al. Breast cancer before age 40 years. Semin Oncol 2009;36(3):237–49.
[8] Cao JQ, Olson RA, Tyldesley SK. Comparison of recurrence and survival rates after breast-conserving therapy and mastectomy in young women with breast cancer. Curr Oncol 2013;20(6):593–601.
[9] Bloom HJG. Further studies on prognosis of breast carcinoma. Br J Cancer 1950;4(4):347–67.
[10] Kumar V, Abbas AK, Fausto N, et al. Robbins and Cotran pathologic basis of disease. 8th ed. Philadelphia: Elsevier; 2010 [pp 259-330 and 1065–1095].
[11] Fitzgibbons PL, Page DL, Weaver D, et al. Prognostic factors in breast cancer. College of American pathologists consensus statement 1999. Arch Pathol Lab Med 2000;124(7):966–78.
[12] Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. Oncologist 2004;9(6):606–16.
[13] Stankov A, Bargallo-Rocha JE, Namendys-Silva SA, et al. Prognostic factors and recurrence in breast cancer: experience at the national cancer institute of Mexico. ISRN Oncol 2012;2012:1–7.
[14] Schwartz AM, Henson DE, Chen D, et al. Histologic grade remains a prognostic factor for breast cancer regardless of the number of positive lymph nodes and tumor size : a study of 161 708 cases of breast cancer from the SEER program. Arch Pathol Lab Med 2014;138(8):1048–52.
[15] Hackshaw AK, Paul EA. Breast self-examination and death from breast cancer: a meta-analysis. Br J Cancer 2003;88(7):1047–53.
[16] Henson DE, Chu KC, Levine PH. Histologic grade, stage, and survival in breast carcinoma, comparison of African American and Caucasian women. Cancer 2003;98(5):908–17.
[17] Leek RD, Landers RJ, Harris AL, et al. Necrosis correlates with high vascular density and focal macrophage infiltration in invasive carcinoma of the breast. Br J Cancer 1999;79(5/6):991–5.
[18] Adair F, Berg J, Joubert L, et al. Long-term followup of breast cancer patients: the 30-year report. Cancer 1974;33(4):1145–50.
[19] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathol 1991;19(5):403–10.
[20] Bloom HJG, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957;11(3):359–77.
[21] Leake R, Barnes D, Pinder S, et al. Immunohistochemical detection of steroid receptors in breast cancer: a working protocol. J Clin Pathol 2000;53(8):634–5.
[22] ASCO– College of American Pathologists. HER2 test guideline recommendations. American Society of Clinical Oncology. CAP; 2013. p. 1–5.
[23] Ayadi L, Khabir A, Amouri H, et al. Correlation of HER-2 over-expression with clinico-pathological parameters in Tunisian breast carcinoma. World J Surg Oncol 2008;6:112–9.
[24] Abdollahi A, Sheikhbahaei S, Safinejad S, et al. Correlation of ER, PR, HER- 2 and P53 immunoreactions with clinico-pathological features in breast cancer. Iran J Pathol 2013;8(3):147–52.
[25] Kumar N, Mukherjee S. Correlation of various prognostic factors in breast cancer. IJSRP 2013;3(8):1–4.
[26] Azizun-Nisa Bhurgri. Y, Raza F, et al. comparison of ER, PR & HER-2/neu (C-erb B 2) reactivity pattern with histologic grade, tumor size and lymph node status in breast cancer. Asian Pac J Cancer Prev 2008;9(4):553–6.

[27] Ivkovic-Kapicl T, Knezevic-Usaj S, Djilas-Ivanovic D, et al. Correlation of HER-2/neu protein overexpression with other prognostic and predictive factors in invasive ductal breast cancer. In Vivo 2007;21(4):673–8.
[28] Barnes NL, Boland GP, Davenport A, et al. Relationship between hormone receptor status and tumor size, grade and comedo necrosis in ductal carcinoma in situ. Br J Surg 2005;92(4):429–34.
[29] National cancer registry programme. Consolidated report of hospital based cancoer registries 2012-2014. National Centre for disease informatics and research. ICMR 2016:91–4.
[30] Sofi GN, Sofi JN, Nadeem R, et al. Estrogen receptor and progesterone receptor status in breast cancer in relation to age, histological grade, size of lesion and lymph node involvement. Asian Pac J Cancer Prev 2012;13(10):5047–52.
[31] Hawkins RA, Roberts MM, Forrest AP. Estrogen receptors and breast cancer: current status. Br J Surg 1980;67(3):153–69.
[32] Kuraparthy S, Reddy KM, Yadagiri LA, et al. Epidemiology and patterns of care for invasive breast carcinoma at a community hospital in southern India. World J Surg Oncol 2007;5:56–62.
[33] Kamil M, Yusuf N, Khalid I, et al. Association between HER-2/neu over-expression and clinico-pathologic parameters of breast cancer in northern Malaysia. Ceylon Med J 2010;55(1):9–13.
[34] Allegra JC, Lippman ME, Thompson EB, et al. An association between steroid hormone receptor and response to cytotoxic chemotherapy in patients with metastatic breast cancer. Cancer Res 1978;38:4299–304.
[35] Fatima S, Faridi N, Gill S. Breast cancer: steroid receptors and other prognostic indicators. JCPSP 2005;15(4):230–3.
[36] Ludovini V, Gori S, Colozza M, et al. Evaluation of serum HER2 extracellular domain in early breast cancer patients: correlation with clinicopathological parameters and survival. Ann Oncol 2008;19(5):883.