



RESEARCH ARTICLE

STUDY OF PREVALENCE OF PROGNOSTIC AND PREDICTIVE IMMUNOHISTOCHEMICAL MARKERS ER, PR AND Her2/neu AND THEIR CORRELATION WITH AGE IN CASES OF FEMALE CARCINOMA BREAST IN BIHAR (NORTHERN INDIA)

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ABSTRACT

Introduction: Carcinoma breast is one of the commonest cancer in women, both in western world and in developing countries like India. Breast carcinoma is a hormone dependant disease. Immunohistochemical prognostic and predictive markers ER, PR and Her2/neu significantly influences prognosis, survival and selection of therapy in female breast cancer cases.

Aim and objective: The purpose of this study was (i) to evaluate the prevalence of prognostic and predictive markers ER, PR and Her2/ neu by immunohistochemistry in female carcinoma breast cases in Bihar (Northern India), (ii) to compare the pattern of expression of these markers with age of the patients & (iii) to correlate the ER, PR & Her2/neu expressions with each other.

Materials and Methods: This prospective study was carried out in Department of Pathology, Mahavir Cancer Sansthan and Research Centre, Phulwarisharif in between March 2015 to December 2016. 412 female carcinoma breast cases diagnosed by radiology and FNAC and further confirmed by histopathological examination of biopsy were included in this study. Immunohistochemical staining for ER, PR and Her2/neu were done in all 412 cases of female carcinoma breast.

Results: Immunohistochemical markers ER and PR were found positive in 210 (50.97%) and 234(56.49%) cases respectively. Her2/neu was found positive in 148 (35.92%) cases. The Mean± SEM age of the patient in this study was 47.63 ± 0.549 years. Triple negative breast cancer which had poor prognosis was found in only 16 (3.88 %) cases.

Conclusion: In conclusion, the prevalence of ER, PR and Her2/net over expression in our study does not fall within the ranges given in most of the literature. Our results showed higher proportion of ER, PR and Her2/ neu over expression in comparison to most of the studies. Fortunately our results also showed lower proportion of triple-negative breast cancer cases having poor prognosis. The findings suggest that North Indian women in the Bihar have breast carcinoma comparatively at younger age, likely to be more susceptible to conventional hormonal and targeted antibody treatment.

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INTRODUCTION

Breast cancer is the most common cancer in women worldwide. (K. Park, chapter 6, 2017; Lal et al., 2000) Worldwide incidence accounts for 25.2% of all female cancers.(K. Park, chapter 6, 2017) It is most common cancer in women both in developed and developing countries. More than 1.67 million women are diagnosed with breast cancer worldwide including 794000 cases in developed and 883000 cases in developing countries during the year 2012. (K. Park, chapter 6, 2017) Breast cancer is a leading cause of death in

women worldwide with mortality rate of 14.7%.(K. Park, chapter 6, 2017; Sin ghai et al., 2011) About 144937 new cases of breast cancer occurred in India which accounts for 27% of all malignant cases (incidence rate of 25.8 per lac population) and about 70,218 cases of women died of this cancer which accounts for 21.5 % of all malignant cases (mortality rate being 12.7 per lac population) during the year 2012. (K. Park, chapter 6, 2017) In comparison to western countries incidence of breast cancer is low in India, but associated with poor prognosis and high mortality due to late presentation at advanced stage. (Roy and Othieno, 2011) In India, cancer of breast had overtaken cervical cancer (which was the most common cancer in India

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prior to 1990) due to changes in lifestyle and western influences. (Takiar and Srivastav, 2008; Yeole, 2008; Moore et al., 2010; Murthy et al., 2009) In 50% of breast cancer cases, risk factors are not detected. Important risk factors for breast cancers are age, age at menarche or menopause, parity, duration of breastfeeding, changes in breast, genetic, nutritional, environmental, genetic and hormone factors. (Pestic et al., 2007) Invasive breast carcinomas has broad spectrum of molecular, pathological and clinical features with different prognostic and therapeutic implications. (Carey et al., 2006) Breast cancer prognosis depends on various clinicopathological factors including metastatic status of lymph nodes, tumor size, tumor grade, hormone receptor status and HER-2 status. (Mustac et al., 2008) Predictive factor is related to degree to which the patient could respond to specific therapy, while prognostic factor is related to metastatic potential of the tumor. Invasive breast carcinomas are a hormone dependent tumor and one third of patients respond to endocrine therapy. Now a days immunohistochemistry (IHC) is globally accepted method for detection of estrogen (ER) and progesterone (PR) receptors in breast carcinomas. (Harvey, 2012) Both ER and PR show nuclear expression in positive cases. About 80% breast cancer are ER positive ER content is correlated with good prognosis and increased likelihood of response to hormonal therapy. Estrogen and its receptor (ER) play important roles in the genesis and malignant progression of breast cancer. Expression of ER α is closely associated with breast cancer, which regulates the transcription of various genes as a transcription factor, which binds to estrogen response elements (ERE) upstream of the target genes. The combined assessment of ER and PR stratifies breast cancers into four biologically and clinically useful subgroups (ER+/PR+, ER+/PR-, ER-/PR-, and ER-/PR+). Her-2/neu receptor overexpression is found to be an independent poor prognostic factor of tumor (Naeem et al., 2008). Human epidermal receptor-2/neu (Her-2/neu) gene amplification occurs in 20-30% of breast cancers and is associated with poor prognosis, lower response to hormone therapy and chemotherapy. Her-2/neu positive breast cancer predicts response to anti-Her-2/neu antibody. (Huang et al., 2005) Due to established role of trastuzumab in Her2/neu positive carcinoma breast, Her2/neu diagnostics has now become mandatory with immunohistochemistry being the primary test followed by FISH (Fluorescent In Situ Hybridization) in Her2/neu 2+ (equivocal) cases.

The molecular subtypes of breast cancer recognized by their gene signature include: Luminal type A(ER+ and /or PR+ & Her2/neu-) and Luminal type B(ER+ and /or PR+ & Her2/neu+ / Her2/neu-), Her2/neu type(ER-, PR- & Her2/neu +), Basal -like(ER-, PR- & Her2/neu - i.e. Triple negative) and Normal breast -like. Basal like subtype is associated with worst prognosis. Different subtype of breast cancers exhibits specific characteristic and likely to benefitted from different approach of treatment. Immunohistochemistry can be used to assign tumors to various subtypes by study of hormone receptors ER & PR, HER-2/neu and other markers like Ki-67, EGFR, CK5/CK6 etc. (Juan Rosai, 2011) The present study was planned keeping in mind predictive importance of receptor status for the prognosis of breast carcinoma and application of appropriate therapy. The objective of this study was to evaluate the prevalence of prognostic and predictive markers ER, PR and Her2/ neu by immunohistochemistry in female carcinoma breast cases in Bihar (Northern India) and to correlate the pattern of expression of these markers with age.

MATERIALS AND METHODS

This prospective study was carried out in Pathology Department, Mahavir Cancer Sansthan, Phulwarisharif of female patients attending in the Surgery OPD with breast lump, breast ulcer and axillary lymph nodes between March 2015 to December 2016. Complete clinical history taking, clinical examination, radiological examination and immunohistochemical study were performed. 412 carcinoma breast cases diagnosed by radiology (USG, mammography etc.) and FNAC and further confirmed by histopathological examination of biopsy (core needle biopsy, true cut biopsy etc.) were included in this study. Immunohistochemical staining for ER, PR and Her2/neu was done in all 412 cases. This study included biopsy and modified radical mastectomy specimen and excluded cell block sample and neoadjuvant treated cases. Expression of estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu were analyzed in specimens of invasive breast cancer tissue received in the form of core needle biopsy, true cut biopsy and modified radical mastectomy. After formalin fixation, paraffin embedding and staining with hematoxylin and eosin, histopathological features were determined, prior to immunohistochemical examination. Histopathological grade was assessed using Bloom Richardson method, modified by Elston and Ellis. (1991) Tumor tissue was routinely fixed overnight (12 hrs.) in 10% buffered formalin. Representative sections were taken next day, processed and embedded. Four-micrometer thickness sections were, mounted onto poly-L-lysine -coated slides and left to dry overnight at 37°C. They were then deparaffinized, rehydrated and underwent antigen retrieval (citrate buffer, pH 7.1) by microwaving for 20 minutes, Her - 2/neu for 4 minutes. After cooling down to room temperature, the sections were incubated for 20 minutes with 3% hydrogen peroxide to block any endogenous peroxidase activity, washed with TRIS buffer (TBS), and incubated with (power block) for 15 minutes to block any nonspecific staining. They were then washed with TBS, and incubated with primary antibodies (ER clone ID5, PR clone PR88 and Her2 clone EP1045Y, BioGenex) for 1 hour to identify tumor markers by antigen antibody reaction. The sections were then washed with TBS, and incubated with secondary link antibody (super sensitive poly-HRP) for 30 minutes. Then the sections were washed with TBS and incubated for 10 minutes with DAB chromogen. Counter stain with hematoxylin for contrast was done. Both internal and external controls were used for interpretation. Both positive and negative external control slides were used in each staining. Normal breast tissue used as positive internal control for ER and PR. Level of ER is expressed as a product of the percentage of epithelial cells stained and intensity of staining through immunohistochemistry (IHC). According to ASCO (2010), ER or PR was considered positive if finding of more than 1% tumor cell nuclei are immunoreactive. Negative for ER or PR if finding of less than 1% of tumor cell nuclei are immunoreactive (Hammond et al., 2010; David J. Dabbs, 2010). The data were entered and analyzed in Graph Pad Prism Software. The data were analyzed through ANOVA test. Frequencies and percentages of all the variables were computed.

Observation

412 female of invasive carcinoma breast from age 24 to 80 years were included in this study. Youngest patient was 24 years old whereas eldest patient in this study was of 80 years.

Most of the patients are in between age group 31 to 60 i.e. 341 (82.76 %) (Table-1). The Mean \pm SEM age of the patient in this study was 47.63 ± 0.549 years. Immunohistochemical staining for ER, PR and Her2/neu were done in all 412 cases. Out of 412 female breast carcinoma patients immunohistochemical markers ER was found positive in 210 (50.97%) and negative in 204 (49.02%) cases where as PR was positive in 234 (56.49%) and negative in 178(43.20%) cases. Out of 412 cases Her2/neu was found positive (3+) in 148 (35.92%) cases, equivocal (2+) in 226 (54.85%) and negative (0& 1+) in 38 (9.22%) cases (Figure - 1). For the purpose of this study equivocal Her2/neu results were considered negative (Figure - 2). Studies showed that overall ER was positive in 50.97%, PR in 56.79% and Her-2/neu in 35.92% cases (Table - 2). Total cases with both ER+ PR+ are 183(44.4%) and Mean \pm SEM of age of ER+ PR+ cases are 47.67 ± 0.892 years. Unpaired t test was done, p value was 0.970. Total cases of ER+ PR- are 27(6.55%) and Mean \pm SEM of age of ER+ PR- cases are 48.96 ± 1.903 years whereas total cases of ER-PR+ is 51 (12.37%) and Mean \pm SEM of age of ER-PR+ is 49.04 ± 1.517 years. P value was 0.975. Total cases of ER-PR- is 151 (36.65%) and Mean \pm SEM of age of ER-PR- is 46.87 ± 0.841 whereas total number of Her2/neu + cases are 148(35.92%) and Mean \pm SEM of age of Her2/neu expression is 48.05 ± 0.871 . P Value is 0.3282. Total Her2/neu - ve cases in our study is 38 (9.22%) where as we get equivocal result of Her2/neu in 226 (54.85%) cases. Mean \pm SEM of age of Her2/neu negative cases are 48.53 ± 1.797 and Mean \pm SEM of age of Her2/neu equivocal cases are 47.20 ± 0.768 . P value is 0.510 (Table - 3).

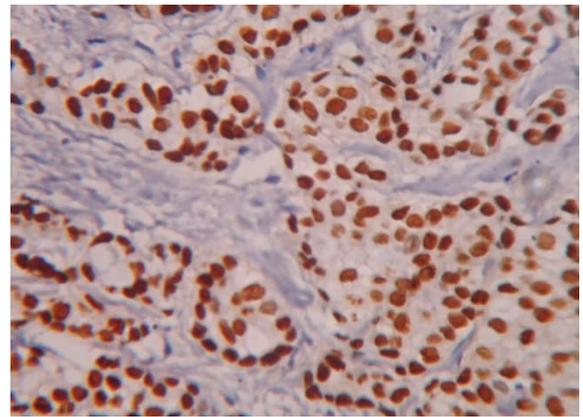


Figure 1. Immunohistochemical Nuclear staining of ER (original magnification x 40)

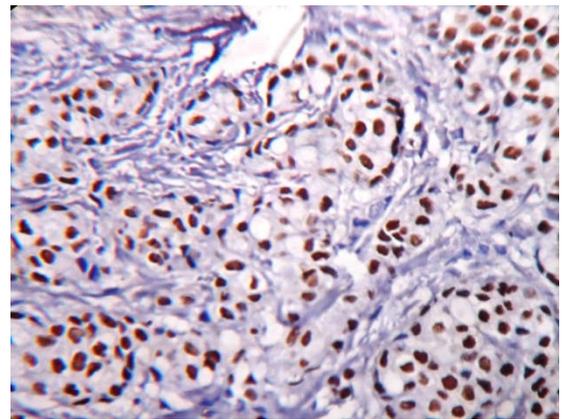


Figure 2. Nuclear staining of PR (original magnification x 40)

Table 1. Frequency & Percentage of age at diagnosis invasive breast carcinoma in study participants

Age group (years)	Frequency	Percentage (%)
21-30	20	4.85
31-40	97	23.54
41-50	153	37.13
51-60	91	22.08
61-70	44	10.67
71-80	7	1.6

P= 0.9702 (Non-significant)

Table 2. Correlation of ER & PR expression

Total cases (412 for ER & PR)	ER+ PR+	ER+ PR-	ER- PR+	ER- PR-
Frequency	183	27	51	151
Percentage (%)	44.4	6.55	12.37	36.65

P= 0.7861 (Non-significant)

Table 3. Correlation of ER, PR & Her2/ neu expression

Total cases (412 for ER & PR & Her2/neu)	ER+ PR+ Her2/neu +	ER- PR+ Her2/neu +	ER+ PR- Her2/neu +	ER+ PR+ Her2/neu -	ER- PR+ Her2/neu -	ER- PR- Her2/neu - (TN)
Frequency	59	14	9	15	3	16
Percentage (%)	14.32	3.39	2.18	3.64	0.72	3.88

P= 0.3282 (Non-significant)

DISCUSSION

In a study conducted in Tata memorial Hospital, Mumbai by Ghosh *et al* in patients age ranging from 20 to 99 years with mean age of presentation 49 years which is slightly higher than our study were Mean \pm SEM age was 47.63 ± 0.549 year. (Ghosh *et al.*, 2011) In a study conducted by Siddique *et al* in

Pakistan in 2000 cases shows almost similar mean age i.e. 48 years in comparison to our study. (Siddique *et al.*, 2000) In our study maximum cases were noted i.e. 37.13 %, 23.54% and 22.08% in the age group of 41- 50 years, 31-40 years and 51-60 years respectively with a mean age of 47.63 ± 0.549 years which was similar to other Indian study conducted by Chakrabarti *et al*, Ghosh *et al.* (2012, 2014) In a study by Babu *et al* most of the patients were over 40 years of age, similar to

our finding majority of breast cancer incidence (71.60%) is observed in > 40 years (Babu *et al.*, 2013). Study carried by Col V Dutta in Army Research Hospital, New Delhi, mentioned majority i.e. 59% of IDC cases were seen among postmenopausal women and the ER/PR status displayed a higher incidence of reactivity with increasing age and receptor negativity was obtained maximum in the menopausal age group.

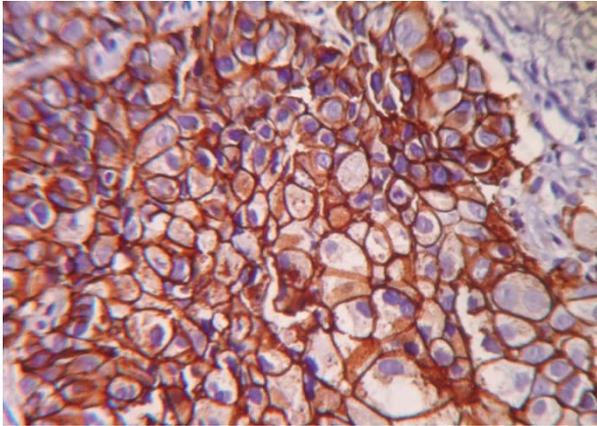


Figure 3. Membrane staining of HER-2/neu (3+) (original magnification x40)

(Dutta *et al.*, 2008) In our study 34.4% cases of infiltrating tumors was recorded in >50 years of age. Our study also show increasing receptor positivity with age which declined after menopausal age. Earlier studies by Azizun-nisa *et al* in 2007 (Azizun-Nisa *et al.*, 2008), Ratnatunga *et al* in 2007 (Ratnatunga *et al.*, 2007), Lal *et al* in 2005 have reported a higher incidence of receptor expressions. Our results are nearly similar to previous studies in India by Ellis *et al* in 2003. (Ellis *et al.*, 2003) In a study of 60 sample by Thiagarajan *et al* in Indian population the mean age of patients 51.17 years with standard deviation 9.859 years which is slightly higher to our study Mean \pm SEM i.e. 47.63 ± 0.549 . (Thiagarajan *et al.*, 2015) ER, PR and Her2/neu positivity were 61.7%, 70% and 56.7% respectively. In comparison to this study ER, PR & Her2/ neu positivity were much lower in our study which was 50.97%, 56.79% and 35.92% respectively. In a study of 126 cases conducted by Rao *et al* mean prevalence of ER, PR and HER-2/neu expression were 36.5%, 31.7% and 2.4%, respectively. (Rao *et al.*, 2013) In comparison to study conducted by Rao *et al* prevalence of ER, PR and Her-2/ neu expression in our study was much high, which was 50.97%, 56.79% and 35.92% respectively. In a study of 43 cases by Nikhra *et al*, mean age of presentation was 49.2 years and percentage of positivity ER, PR and Her2/neu are 39.5%, 41.8% and 32.5% respectively. (Nikhra *et al.*, 2014) In comparison to study conducted by Nikhra *et al* prevalence of ER and PR expression in our study was much high, which was 50.97% and 56.79% respectively and Her-2/neu expression was almost similar i.e. 35.92%.

In our study ER positivity was expressed in 50.97% cases, PR positivity was seen in 56.79% cases and Her2/ neu expression in with mean age of presentation 47.63 ± 0.549 years which differ to study conducted by Ambroise *et al* with mean age of presentation of carcinoma breast was 53.8 ± 11.6 and ER, PR and Her2/neu were 59.2%, 51.1% and 27.1 % respectively. (Ambroise *et al.*, 2011) Mean age of presentation & ER positivity is higher than our study was as PR positivity and

Her2/neu positivity was lower than our study. In a study by Helin *et al* 72 % of invasive ductal carcinoma were ER positive and 55% were PR positive. ER positivity is higher than our study were as PR positivity is almost similar. (Helin *et al.*, 1989) A study by Collins and Schnitt found Her2/neu over expression in 28% of cases which is lower than our study. (Collins and Schnitt, 2005) A recent study of a cohort of women under age 55 revealed that triple negative tumors were the most common breast cancer subtype diagnosed among African-American women accounting for nearly 47%, compared to 22% among whites. (Lund *et al.*, 2009) In our study triple negative tumors consist of 3.39% only, i.e. much lower than these studies. However, in a study from Japan, a higher proportion of post-menopausal women were present in the triple-negative breast cancer group. (Iwase *et al.*, 2010) As prognostic markers like ER, PR and Her2/neu significantly influence prognosis, survival and selection of therapy in breast carcinomas. IHC is now a days, an integral part of breast carcinoma histopathology reporting for prognosis and treatment, in addition to histological diagnosis. Being a cheap and easy method, immunohistochemistry may be suitable for developing countries like India. According to various studies incidence of recurrence is less among those ER, PR and HER2/neu positive cases who have received targeted therapy. Thus study of these important prognostic markers ER, PR and Her2/ neu should be made mandatory in every cases of carcinoma breast, and this facilities should be made available even in underprivileged rural areas. So, that prognosis and survival of all these patients can be properly accessed and positive cases can be provided with targeted therapy.

Conclusion

In conclusion, the prevalence of ER, PR and Her2/neu over expression in our study does not fall within the ranges given in most of the literature. Our results showed higher proportion of ER, PR and Her2/ neu over expression in comparison to most of the studies. Fortunately our results also showed lower proportion of triple-negative breast cancer cases having poor prognosis. The findings suggest that North Indian women in the Bihar have breast carcinoma comparatively at younger age, likely to be more susceptible to conventional hormonal and targeted antibody treatment.

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Abbreviations

ER- Estrogen receptor, PR- Progesterone receptor, Her2/ neu- Human epidermal growth receptor, IHC- Immunohistochemistry, FISH- Fluorescent in situ hybridization, FNAC- Fine needle aspiration cytology, OPD- Out patient door.

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