ORIGINAL ARTICLE

A PROSPECTIVESTUDY OF ESTROGEN, PROGESTRONE AND HER2NEU RECEPTOR IN CASES OF BREAST CANCER IN A TERTIARY CARE HOSPITAL OF BHAVNAGAR, GUJARAT, WESTERN INDIA

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ABSTRACT

Introduction: Hormonal receptors in breast have an implication on the outcomes of breast cancer in women. The objectives of the study were to know the incidence and therapeutic importance of ER/PR & HER2NEU receptor status and it's relation to recurrence in breast cancer cases.

Methodology: A prospective study was conducted over a period of two years from 2012-2013 on 30 newly diagnosed cases of breast cancer admitted at a tertiary care centre in Bhavnagar. Patientswere clinically staged and either posted for surgery or for neo-adjuvant chemotherapy. In case they were posted for Modified Radical Mastectomy, the specimen of the breast tissue was sent to histo-pathological examination and immunohistochemistry to determine the ER, PR & HER2NEU receptor status of the breast specimen. On basis of clinical and histo-pathological staging patient received chemotherapy and hormonal therapy. Patients were then monitored for recurrence of breast cancer.

Results: The present study found 53.3% breast cancer patients positive for ER, 36.6% patients positive for PR, 53.3% co-positive for ER/PR and 56.6% patients positive for HER2NEU receptor. Breast cancer patients $\leq$50 years age were 56 times more likely to test positive for ER receptors; 5.7 times more likely to test positive for PR receptors and those >50 years of age were 25.6 times more likely to test positive for HER2NEU receptors. ER/PR negative patients (who are conventionally not treated with Tamoxifen) were 28.6 times more likely to experience recurrence of breast cancer at six months than EP/PR positive patients who are treated with Tamoxifen. HER2NEU receptor positive patients were 5.2 times more likely to experience recurrence of breast cancer than HER2NEU receptor negative patients.

Conclusion: Post-operative recurrence is significantly less in ER/PR positive breast cancer patients who are treated with Tamoxifen hormonal therapy and is significantly high in HER2NEU receptor positive patients.

Key words: Breast cancer, Estrogen receptor, Progesterone receptor, HER2NEU receptor, Tamoxifen

INTRODUCTION

Breast cancer is the most common cause of death in middle-aged women in western countries. In 2004 approximately one and a half million new cases were diagnosed worldwide. Invasive Breast cancer metastasize via local, lymphatics & hematogenous routes.[1] Current thinking places the metastatic event early in the progression of breast cancer, probably before initial clinical evaluation in the majority of patients.[1]Metastatic disease is the principal cause of death from breast cancer.[1]This concept argues for a systemic approach to breast cancer, administered in concert with local treatment, as the local treatment

can deal with near or distant micro-metastasis. Patients who benefit from chemotherapy or hormonal therapy do so because metastasis is prevented, cured, or delayed.[1]The first prospective trials of systemic treatment combined oophorectomy, to deprive patients of estrogens, with radical mastectomy. But now-a-days newer drugs available which replaces the oophorectomy and even may give better results.[1]

Many breast cancers are sensitive to the hormone estrogen. This means that estrogen causes the breast cancer tumor to grow.[2] Such cancers have estrogen receptors on the surface of their cells. They are called estrogen receptor-positive cancer or ER-positive cancer. Some women have what is called HER2-positive breast cancer. HER2 refers to a gene that helps cells grow, divide, and repair themselves. When cells (including cancer cells) have too many copies of this gene, they grow faster. Historically, women with HER2-positive breast cancer have a more aggressive disease and a higher risk that the disease will return (recur) than women who do not have this type. However, this may be changing with specifically targeted treatments against HER2.Over the course of a lifetime, 1 in 8 women will be diagnosed with breast cancer.[3]

The current study was carried out to study incidence and therapeutic importance of ER / PR & HER2 NEU receptor status and it's relation to recurrence in Breast cancer cases.

METHODOLOGY

The study was conducted over a period of two years from 2012-2013 on patients admitted at Sir Takhtsinhji General Hospital, a tertiary care centre in Bhavnagar, Gujarat.In this study, 30 newly diagnosed cases of breast cancer were included with their proper written and informed consent. Once the patient was admitted for complains of breast lump, detailed history and clinical examination was done. Women also underwent detailed investigations like hemoglobin level, complete blood count, random blood sugar, renal function test, liver function test, mammography, ultrasound of both breast and axilla, x-ray chest and fine needle aspiration from breast lump. Based on these investigations, patient was clinically staged and patient was either posted for surgery or for neo-adjuvant chemotherapy. After the operative intervention (Modified Radical Mastectomy), the specimen of the breast tissue was sent to histo-pathological examination and immuno-histochemistry to determine the ER, PR & HER2 NEU receptor status of the breast specimen. On basis of clinical and histo-pathological staging, patient received chemotherapy and hormonal therapy. Then the patients were monitoredfor recurrences. Patients with benign breast disease, recurrence of cancer and metastasis were excluded from the study. Permission from Institutional review board was obtained to conduct the study.

RESULTS

In total 30 newly diagnosed cases of Breast Cancer with a mean age of 51.87 ($\pm$ 12.94) years were included in this study.

As elucidated in table 1, ER positivity was seen in 53.3% patients; PR positivity was seen in 36.6% patients and HER2NEU receptor positivity was seen in 56.6% patients. Also, younger age groups (31-50 years) were more likely to test positive for ER/PR receptors. Out of 16 ER positive patients, 81.3% were in the $\leq$50 years age group and 18.8% were >50 years of age. This difference was statistically significant (chi-square=16.476, $p<0.001$). Breast cancer patients $\leq$50 years age were 56 times more likely to test positive for ER receptors.

The PR receptor positivity also followed the same pattern. Out of 11 PR positive patients, 72.7% belonged to $\leq$50 years age, while 27.3% were above 50 years. This difference was statistically significant (chi-square=4.739, $p=0.029$). Breast cancer patients $\leq$50 years age were 5.7 times more likely to test positive for PR receptors. ER/PR co-positivity was seen in 53.3% of the breast cancer patients. Out of 16 ER/PR co-positive patients, 81.3% patients were $\leq$50 years of age and 18.8% were >50 years of age. This difference was statistically significant (chi-square test=16.476, $p<0.001$).

However, HER2NEU positivity was seen more in older age groups. Out of 17 HER2NUE positive patients, 82.4% belonged to >50 years age group and 17.6% were $\leq$50 years of age. This difference was statistically significant (chi-square=13.274, $p<0.001$). Breast cancer patients >50 years of age were 25.6 times more likely to test positive for HER2NEU receptors.

Table 1: Age distribution of Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2NEU receptor among breast cancer patients (n=30)

Age groups	ER positive (%)	ER negative (%)	Total (%)	p-Value	OR (95% CI)
31-40 years	9 (56.3)	1 (7.1)	10 (33.3)	0.001	
41-50 years	6 (37.5)	1 (7.1)	7 (23.3)		
51-60 years	0	5 (35.7)	5 (16.7)		
61-70 years	0	4 (28.6)	4 (13.3)		
71-80 years	1 (6.3)	3 (21.4)	4 (13.3)		
	ER positive (%)	**ER negative (%)**	**Total (%)**		
≤50 years	13 (81.3)	1 (7.1)	14 (46.7)	<0.001	56.3 (5.1-614.9)
>50 years	3 (18.8)	13 (92.9)	16 (53.3)		
	PR positive (%)	**PR negative (%)**	**Total (%)**		
31-40 years	5 (45.5)	5 (26.3)	10 (33.3)	0.043	
41-50 years	5 (45.5)	2 (10.5)	7 (23.3)		
51-60 years	0	5 (26.3)	5 (16.7)		
61-70 years	0	4 (21.1)	4 (13.3)		
71-80 years	1 (9.1)	3 (15.8)	4 (13.3)		
	PR positive (%)	**PR negative (%)**	**Total (%)**		
≤50 years	8 (72.7)	6 (31.6)	14 (46.7)	0.029	5.7 (1.1-29.8)
>50 years	3 (27.3)	13 (68.4)	16 (53.3)		
	ER/PR co-positive (%)	**ER/PR co-negative (%)**	**Total (%)**		
31-40 years	9 (56.3)	1 (7.1)	10 (33.3)	0.001	
41-50 years	6 (37.5)	1 (7.1)	7 (23.3)		
51-60 years	0	5 (35.7)	5 (16.7)		
61-70 years	0	4 (28.6)	4 (13.3)		
71-80 years	1 (6.3)	3 (21.4)	4 (13.3)		
	ER/PR co-positive (%)	**ER/PR co-negative (%)**	**Total (%)**		
≤50 years	13 (81.3)	1 (7.1)	14 (46.7)	<0.001	56.3 (5.1-614.9)
>50 years	3 (18.8)	13 (92.9)	16 (53.3)		
	HER2NEU positive (%)	**HER2NEU negative (%)**	**Total (%)**		
31-40 years	2 (11.8)	8 (61.5)	10 (33.3)	0.009	
41-50 years	3 (17.6)	4 (30.8)	7 (23.3)		
51-60 years	5 (29.4)	0	5 (16.7)		
61-70 years	4 (23.5)	0	4 (13.3)		
71-80 years	3 (17.6)	1 (7.7)	4 (13.3)		
	HER2NEU positive (%)	**HER2NEU negative (%)**	**Total (%)**		
>50 years	14 (82.4)	2 (15.4)	16 (53.3)	<0.001	25.66 (3.63-181.44)
≤50 years	3 (17.6)	11 (84.6)	14 (46.7)		

Table 2: Mean, standard deviation and unpaired t-test between positive and negative receptors with age

	Age±SD	P value*@
ER positive (n=16)	42.88±9.639	<0.001
ER negative (n=14)	62.14±7.294	
PR positive (n=11)	45.18±10.638	0.029
PR negative (n=19)	55.74±12.801	
HER2NEU positive (n=17)	58.88±10.203	<0.001
HER2NEU negative (n=13)	42.69±10.25	

*Equality of variances assumed as Levene's test p-value>0.05, @Independent sample t test was applied for calculation of p vlue

Table 2 reinstates our finding with the mean age of ER positive patients being significantly lower than the mean age of ER negative patients (mean difference of -19.2 years, p<0.001). The mean age of PR positive patients was significantly lower than the mean age of PR negative patients (mean difference of -10.5 years, p=0.029). Also, the mean age of HER2NEU receptor positive patients was significantly higher than the mean age of HER2NEU receptor negative patients (mean difference of 16.2 years, p<0.001).

Table 3: Association betweenTamoxifentreatment andrecurrence at six months in ER/PR patients (n=30)

Tamoxifen treatment in ER/PR status	Recurrence (n=18)	No recurrence (n=12)	Total (n=30)	p-Value,	OR (95% CI)
ER/PR -ve patients not treated with Tamoxifen	13 (92.9)	1 (7.1)	14 (100)	0.001	28.6
ER/PR +ve patients treated with Tamoxifen	5 (31.3)	11 (68.8)	16 (100)		(2.88-283.07)

Figure in parenthesis indicate percentage

Table 4: Association between HER2NEU receptor status and recurrence at six months (n=30)

HER2NEU receptor	Recurrence (n=18)	No recurrence (n=12)	Total (n=30)	P -value	Odds Ratio (95% CI)
Positive	13 (72.2)	4 (33.3)	17 (56.7)	0.035	5.2 (1.06-25.3)
Negative	5 (27.8)	8 (66.7)	13 (43.3)		

As shown in Table 3,out of 18 patients who experienced recurrence, 92.9% were either ER negative or PR negative, while 31.3% patients who were ER/PR positive and were treated with Tamoxifen did not experience recurrence. This difference was statistically significant (chi-square=11.808, p=0.001). ER/PR negative patients (who are conventionally not treated with Tamoxifen) were 28.6 times more likely to experience recurrence of breast cancer at six months than EP/PR positive patients who are treated with Tamoxifen.

As illustrated in Table 4,out of 18 patients experiencing recurrence of breast cancer, 72.2% tested positive for HER2NEU receptor, while 27.8% tested negative for this receptor. This difference was statistically significant (chi-square=4.434, p=0.035). HER2NEU receptor positive patients were 5.2 times more likely to experience recurrence of breast cancer than HER2NEU receptor negative patients.

DISCUSSION

The present study focused on the prevalence of ER, PR and HER2NEU receptors & their role in treatment and prognosis of breast cancer patients managed at a tertiary care hospital in Bhavnagar, Gujarat.

The present study found 53.3% breast cancer patients positive for ER, 36.6% patients positive for PR, 53.3% breast cancer patients co-positive for ER/PR and 56.6% patients positive for HER2NEU receptor. Ghosh S, et al. (2014) reported similar percentages with ER positivity seen in 56.3% breast cancer patients and PR positivity seen in 53.1% patients.[4]Zubeda S, et al. (2014) reported 32.56% patients positive for ER, 32.23% patients positive for PR and ER/PR co-positivity to be 26.77%only in their study in Southern India.[5]Their research reported HER2NEU receptor positivity of 35.71% and 46% of the breast tumors to be triple negative.[5]A study from Maharashtra reported 44.6% ER positivity, 40.4% PR positivity, 34.2% HER-2 positivity and 34% to be triple negative.[6]

The present study found an inverse relation between ER/PR co-negativity and HER2NEU positivity, which although being an interesting finding was first reported by the researchers in South India.[5]This trend of ER/PR co-negativity and HER2NEU positivity seems to be a common phenomenon in the Asian population, as evidenced in studies conducted in Sri Lanka and Pakistan.[7,8]

The present study found that younger women are more likely to test positive for ER and PR receptors and to test negative for HER2NEU receptors. The present study found that 18.8% of the ER positive breast cancer patients were >50 years of age; 27.3% of the PR positive breast cancer patients were above 50 years of age and 82.4% of the HER2NEU receptor positive patients belonged to >50 years age group. Similar results were reported by Angarita FA, et al. (2015) with women >80 years testing negative for HER2NEU receptors, but their research found hormone receptor positivity in this age group.[9]The study in Southern India found 50% of ER positive patients above 50 years of age; 46.59% PR positive patients above this age and 42.26% HER2NEU receptor positive patients above 50 years of age.[5]This reestablishes the fact that in the Indian context, the receptor positivity is seen more in the elder age group than in the younger age group.

The current research also found lower levels of recurrence in ER/PR positive patients who are treated with Tamoxifen. This was in contradiction to what Bijker N, et al. (2001) found in their study, the dis-

crepancy in the results may be due to the fact that hormonal therapy was not given in their research.[10]However, our finding was supported by a study published in The Lancet (2011) by Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which highlighted that in ER-positive disease, allocation to Tamoxifen halvedthe recurrence rate during years 0–4 and reduced it by athird during years 5–9 (with little further effect afteryear 10), so over all time periods the recurrence ratereduction averaged 39% (RR 0·61) for any recurrence.[11]In ER-poor disease,however, there was no apparent effect on recurrence (RR 0·97) for any recurrence, 95% CI 0·88–1·07.[11] As per our best knowledge, ours' is the first study in India to have given evidence regarding the usefulness of Tamoxifen in reducing recurrence in ER/PR positive breast cancer patients.[11] They further reported in their research that local recurrence,contralateral breast cancer (generally new primary), anddistant recurrence were all substantially reduced byTamoxifen (each $p<0·00001$).[11]The present study also found higher levels of recurrence in HER2NEU receptor positive patients. This finding was supported by the research conducted by Bijker N, et al. (2001).[10]

CONCLUSION

We conclude from our study that ER/PR& HER2NEU receptor status of the breast cancer patients help us planning the regime of the chemotherapy and hormonal therapy. An important conclusion consequent to our study is that post-operative recurrence issignificantly less in ER/PR positive breast cancer patients who are treated with Tamoxifen hormonal therapy and is significantly high in HER2NEU receptorpositive patients.

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