Estrogen receptor and Progesterone receptor status in different types of Breast cancers

Shakya G[a], Malla S[a], Sharma M[a] & Panth R[b]

Abstract

Introduction Estrogen Receptor (ER) and Progesterone Receptor (PR) are predictive and prognostic factors in breast cancer. Estrogen Receptor positive(ER+) and Estrogen Receptor negative(ER-) breast cancers behave differently biologically, have different treatment and prognostic implication and thus may also possibly have different risk factor pattern. So, the evaluation of ER and PR status in breast cancer has become essential to decide whether to recommend adjuvant hormonal therapy.

Objective The objective of the present study was to evaluate ER and PR in breast cancers by correlating ER and PR status with different types of breast cancer, age and menopausal status of the patients, MBR histologic grade and TNM stage of the tumor and in addition by finding proportion of ER and PR tumor tissue type.

Methods The present study comprised of 30 breast cancer cases and were subjected to immunohistochemical staining for ER and PR by Labelled StreptAvidin Biotin technique.

Results The result showed that hormonal positivity in breast cancer was 20 percent for ER and 23.3 percent for PR. Invasive Ductal Carcinoma, Not Otherwise Specified, the predominant breast cancer type had hormonal positive rate 19.2 percent for both ER and PR. In age wise distribution, hormonal positivity was higher in postmenopausal period than that in premenopausal group of patients. Analysis of Modified Bloom Richardson(MBR) histologic grade and TNM stage indicated that hormonal positivity declined successively as MBR histologic grade and TNM stage of the tumor increased. The evaluation of proportion of ER and PR tumor tissue type showed that the most common type of breast cancer was ER- PR- (76.7%) followed by ER+ PR+ (20%) and ER- PR+ (3.3%) respectively.

Conclusion The hormone positive breast cancers in the present series was comparatively less as compared to that in western countries but it was comparable with the findings of other Asian countries like India and Thailand.

Key Words Estrogen Receptor, Progesterone Receptor, Breast cancer and Imunohistochemistry

Introduction

Breast cancer comprises of a heterogenous group of diseases. Within the same morphological type of invasive carcinoma, these are biologically diverse diseases with widely different outcomes. Even within the same histological grade there may be marked differences in biological behavior. As these different entities cannot be recognized morphologically, a number of different measurable parameters like ER and PR, HER-2, Cyclin D1 or P27 and P53 are used to indicate the likely behaviour of an individual carcinoma in order to tailor the type of treatment[1]. Out of which ER and PR are routinely assessed in all the patients with invasive breast cancer to decide whether to recommend adjuvant hormonal therapy.[2] Estrogen receptor positive and Estrogen receptor negative breast cancer behave differently biologically, have different treatment and prognostic implications and thus may also possibly have different risk factor patterns.[3] Tamoxifen is a selective estrogen receptor modulator that competes with estrogen for binding to the estrogen receptor. In human, tamoxifen acts as an estrogen antagonist in

Corresponding Author: Dr. Geeta Shakya, **E-mail:** nphl@wlink.com.np, [a]National Public Health Laboratory, Teku, Kathmandu, Nepal, [b]Shree Birendra Army Hospital, Chauni, Kathmandu, Nepal.

breast tissue, inhibiting the growth of estrogen dependent breast tumors.[4] The present study on ER and PR evaluation in breast cancers was carried out by correlating ER and PR status with different types of breast cancer, age and menopausal status of the patients, MBR histologic grade and TNM stage of the tumor and in addition by finding proportion of ER and PR tumor tissue type.

Material and method

Thirty patients diagnosed histologically as Breast Cancer at National Public Health Laboratory (NPHL), Bir Hospital, Shree Birendra Army Hospital and B.P. Koirala Memorial Cancer Hospital (BPKMCH) were included in the study. The study period was between Nov. 2005 to November 2006 .The blocks, histologic slides and histopathological report with Modified Bloom & Richardson Grade and TNM staging of each breast cancer patient were collected at NPHL. Initially, the histologic slides were re-evaluated independently by two pathologists for microscopic type and MBR histologic grade of breast cancer. Subsequently, the blocks were cut and subjected to ER and PR staining by Immunohistochemical method (Labelled streptAvidin Biotin Method). Both positive (endometrial tissue) and negative control (lymph node) slides were run with each batch of the test. The steps of immunohistochemical procedure were followed according to the standard protocol (Histospan B - SAP universal kit with staining protocol).

Screening

All the immunohistochemically stained slides were screened under microscope independently by two pathologists. Staining Pattern is Nuclear for both ER and PR. If cytoplasmic stain is present it is considered as background stain.

Results

Thirty breast cancers slides, immunohistochemically stained for ER and PR were screened. The staining pattern was nuclear. The nuclei which took up brown coloured stain were labelled positive and those which did not take up brown coloured stain but remained purple were labelled negative .The result was read independently by two pathologists and was analysed as: Out of 30 breast cancer cases, 20 percent (6 of 30) were positive for ER and 23.3 percent (7 of 30) were positive for PR.

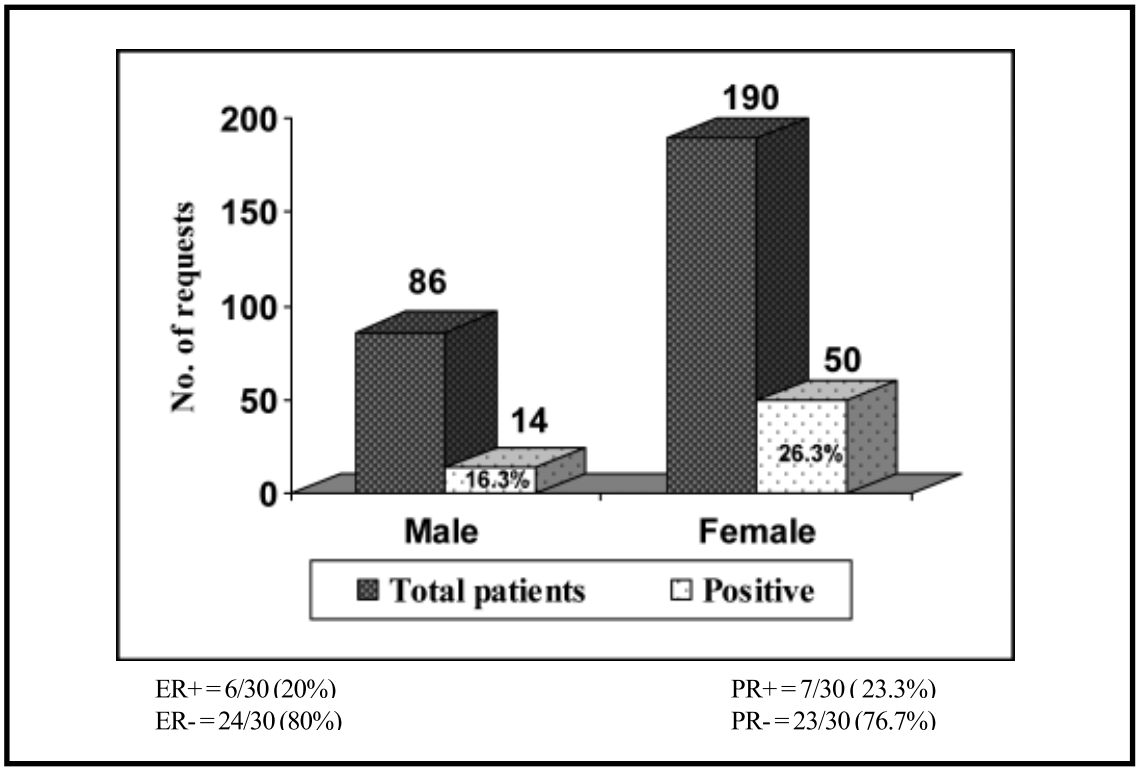

Figure 1: ER/PR status in breast cancers (n=30)

Table 1: ER & PR status in different types of Breast Cancer (n=30)

Types of Breast cancer	Total No. of cases	No. of ER+ cases	No. of ER- cases	No. of PR+ cases	No. of PR- cases
IDC/NOS	26	5	21	5	21
ILC	1	1	-	1	-
Mucinous	1	-	1	-	1
Medullary Cancer	1	-	1	1	-
Metaplastic Carcinosarcoma	1	-	1	-	1
Grand Total	30 (100%)	6 (20%)	24 (80%)	7 (23.3%)	23 (76.7%)

The commonest histological type was Invasive Ductal Carcinoma, Not Otherwise Specified (IDC, NOS) comprising 86.6 percent (26 of 30). In comparison of ER and PR with different types of breast cancers, it was found that 83.3 percent (5 of 6) of ER and 71.4 percent (5 of 7) of PR positive cancers were IDC, NOS. But out of total 26 IDC, NOS cases, only 19.2 percent (5 of 26) were positive for both ER and PR. One case of ILC was also positive for both ER and PR. One case of Medullary carcinoma was negative for ER but positive for PR. There were one case each of Mucinous carcinoma and Metaplastic carcinosarcoma and both were negative for ER and PR.

Table2: ER & PR status in relation to age groups (n=30)

Age groups	Total No. of cases	No. of ER+ cases	No. of ER- cases	No. of PR+ cases	No. of PR- cases
30	1	-	1	-	1
31 - 40	5	-	5	-	5
41 - 50	7	3	4	4	3
51 - 60	12	3	9	3	9
61 -70	3	-	3	-	3
71	2	-	2	-	2
Grand Total	30(100%)	6(20%)	24(80%)	7(23.3)	23(76.7%)

Majority of breast cancers, 40 percent (12 0f 30) presented in age group between 51-60 years. In this age group, both ER and PR positivity were 25 percent. But the hormonal positivity was found to be higher in age group between 41-50 years,42.8 percent (3 of 7) ER positive and 57.2 percent (4 of 7) PR positive. Also there were one case in age group of < 30 years, 5 cases in 31 - 40 years, 3 cases in 61 - 71 years and 2 cases in > 71- years respectively and all of these were negative for ER and PR.

Table 3: ER/PR status in relation to pre and post menopause (n-30)

Menopausal status	Total No. of cases	No. of ER+ cases	No. of ER- cases	No. of PR+ cases	No. of PR- cases
Premenopause	14	2	12	2	12
Postmenopause	16	4	12	5	11
Grand Total	30(100%)	6(20%)	24(80%)	7(23.3%)	23(76.7%)

Out of 30 cases, 53.4 percent (16 of 30) breast cancers were in postmenopausal period. In correlation of ER/ PR with menopausal status it was found that both hormonal positivity in postmenopausal cases, 25 percent (4 of 16) ER positive and 31.2 percent (5 of 16) PR positive were greater than that in premenopausal cases, 14.3 percent (2 of 14) positivity for both ER and PR. In comparision with total 6 positive cases, ER positivity was 66.7 percent (4 of 6) and PR positive cases was 71.4 percent (5 of 7) in postmenopausal period.

Table 4 : ER & PR status in relation to MBR* Histologic Grade (n=30)

MBR* Histologic Grade	Total No. of cases	No. of ER+ cases	No. of ER- cases	No. of PR+ cases	No. of PR- cases
Grade 1	5	2	3	2	3
Grade 2	24	4	20	5	19
Grade 3	1	-	1	-	1
Grand Total	30(100%)	6(20%)	24(80%)	7(23.3%)	2.3(76.7%)

*MBR = Modified Bloom Richardson

As far as ER/PR status with different MBR grades, it was observed that hormonal positivity was maximum in grade I which comprised of 40 percent (2 of 5) for both ER and PR. Hormonal positivity declined as the grade of breast cancer increased. In grade 2 breast cancers, there were 16.6 percent (4 of total 24)ER positive and 20 percent (5 of 24) PR positive. One case of grade 3 tumor was negative for both ER and PR.

Table 5: ER & PR status in relation to TNM stage groups (n=30)

TNM Staging Grade	Total No. of cases	No. of ER+ cases	No. of ER- cases	No. of PR+ cases	No. of PR- cases
Stage I	6	2	4	2	4
Stage II	16	3	13	4	12
Stage III	8	1	7	1	7
Grand Total	30(100%)	6(20%)	24(80%)	7(23.3%)	23(76.6%)

Regarding the hormonal status and TNM stage, the positivity was highest in stage I tumors, 33.3 percent (2 of 6) and the values thereafter successively decreased as the stage of TNM increased. The hormonal positivity in stage II breast cancers were 18.75 percent (3 of 16) for ER and 25 percent (4 of 16) for PR. The stage III tumors showed lowest hormone positivity with 12.5 percent for both ER and PR.

Table 6: Proportion of ER, PR Tumor tissue type (n=30)

Proportion of ER, PR	No. of cases	Percentage
ER+ PR+	6	20.0%
ER- PR+	1	3.3%
ER+ PR-	0	0
ER- PR-	23	76.7%
Grand Total	30	100%

The evaluation of proportion of ER and PR tumor tissue type showed that the most common type of breast cancer was ER- PR- (76.7%) followed by ER+ PR+ (20%) and ER- PR+ (3.3%).

Discussion

The present study consisted of ER positivity 20 percent (6 of 30) and PR positivity 23.3 percent (7 of 30). This value was compared with observations of other authors as ER positive 43.9 percent and PR positive 26.6 percent by Redkar AA *et al.* (1992), ER positive 32.6 percent and PR positive 46.1 percent by Desai SB *et al.* (2000), ER positive 81.2 percent and PR positive 65.3 percent by Zafrani B *et al.* (2000), ER positive 11 percent and PR positive 15 percent by SinghY *et al.* (2002) and ER positive 53.4 percent and PR positive 53.4 percent and PR positive 42.1 percent by Lertsanguansinchai P *et al.* (2002)[5,6,7,8,9].

The hormonal positivity in the present study was higher compared to the hormonal positivity in the study by Y Singh et al. But ER positivity was 4 times less and PR positivity was 3.25 times less than the positive values indicated by B Zafrani et al.[7] The significant variation in hormonal positivity in different studies could be due to variation in ethnicity and variable histologic grade and TNM stage of the disease at the time of diagnosis.

In correlation of ER and PR status with different types of breast cancers, out of total 6 positive cases, 83.3 percent (5 of 6) of ER and PR positives were IDC, NOS. But out of 26 IDC, NOS only 19.2 percent (5 of 26) were positive for both ER and PR. One case of Invasive Lobular Carcinoma found was positive for both ER and PR while a case of medullary carcinoma was negative for ER but positive for PR. One case each of Mucinous and Metaplastic Carcinosarcomas were negative for both ER and PR. Nadi *et al.* found that all pure Tubular, Colloid and Infiltrating Lobular Carcinomas, were ER+. All medullary, Apocrine and Metaplastic Carcinomas were ER-.[10] The study by Robert MM et al. also showed that tumors of special pathological type for example Tubular, Cibriform, Lobular, Medullary and Mucoid were more likely to be ER moderate or rich.[11]19.2 percent of ER and PR positivity in predominant type of breast Cancer, IDC, NOS in the present study was comparatively less than positivity in the literature, 70-80 percent positive for ER and 60-70 percent positive for PR. The reason could be same as mentioned earlier, difference in ethnicity of patients and difference in histologic grade and TNM stage of tumor at the time of diagnosis. But the hormonal positivity in ILC and Medullary Carcinoma was comparable with other studies.[6,10,11] Unexpectedly, ER and PR status in the present study was negative in Mucinous Carcinoma. The reason of hormonal negativity could be due to probably the effect of inappropriate fixation.

In assessment of ER/PR status in relation to different age groups, the hormonal positivity was higher in age group between 41-50 years (42.8% positive for ER and 57.2% positive forPR) compared to 51-60 years group (25% positive for both ER and PR). Hormonal positivity was not recorded before 40 years and after 60 years. But Redkar AA et al. reported that both ER and PR postivity was associated with increasing age.

In this study, 53.4 percent of breast cancers presented in postmenopausal period . In correlation of hormonal positivity with menopausal status also, ER(25%) and PR(31.2%) positivity were greater in postmenopausal than premenopausal period,16.6 percent (2 of 12). Our observations were comparable with results of other authors[10,13,14]. Elvse Lower at al. showed ER positivity in 72 percent of postmenopausal patients and 57 percent in premenopausal patients[12]. According to Redkar AA et al. ER and PR positivity were seen within both pre and postmenopausal subgroups but there was no significant difference between two groups[5].

Redkar AA et al. reported that grade 1 and grade 2 were more often ER positive and PR positive, compared to grade 3 tumors[5]. His report supported our findings as hormonal positivity seen in grade1, grade 2 and grade 3 tumors were 40 percent for both ER and PR, 16.6 percent for ER and 20 percent for PR and negative for both ER and PR respectively. Lertsanguanichai P et al. also mentioned that poorly differentiated grading increase positivity of axillary nodes and higher TNM stage of the breast cancers had more chance of being ER negative and PR negative[9].

In the present study, half of total breast cancers (53.4%) were stage II tumors at the time of diagnosis. In contrast, the study by Y Singh et al. between 1994 to 1999 showed that 51 percent of patient presented with stage II and stage IV breast cancer in Nepalese population The difference in stage of presentation in seven years duration between the present study and the study by Y Singh et al. could be due to the effect of awareness screening compaign in the potential patient population. Robert A et al. emphasized that an important aspect of awareness is dissemination of the knowledge that breast cancer is not rapidly fatal if diagnosed early and many cases is curable. They concluded that the enhanced awareness has considerable potential for improving the stage at presentation and therefore survival[14]. The pattern of declining hormonal positivity with increased TNM stage of disease was comparable with findings of Lertsanguanichai P et al. and Chu KC et al[9,15].

The proportion of ER and PR tumor type has been catagorised as hormone responsive (ER+ PR+ and ER- PR+), hormone non responsive (ER- PR-) and dubious hormone responsive (ER+ PR-).

Table 7: Proportion of ER and PR tumor type according to different authors

Authors	Year of Study	Proportion of ER and PR tumor type (%)			
		ER+ PR+	ER+ PR-	ER- PR+	ER- PR-
Redkar AA *et al.*	1992	23.9	20.0	2.8	53.3
Desai SB *et al.*	2000	25.0	7.4	21.1	46.5
Lertsanguanicha P *et al.*	2002	36.31	15.5	5.79	42.37
Colditz GA *et al.*	2004	61.0	15.0	3.8	19.8
Breast cancer.org	2006	65.0	10.0	0	25.0
Present study	2006-07	20.0	0	3.3	76.7

ER+ PR+ type of breast cancer was the commonest and its occurrence ranged from 61 - 65 percent in most of the literature from western countries[16,17]. Whereas in Asian countries ER- PR- breast cancer was more prevalent as evident from different studies[5,6,7,9]. No significant difference was observed in ER+ PR- breast cancer in western and Asian countries. But ER+ PR- breast cancer was not detected in the present study. It could be probably due to small number of cases. Variation was again found in ER- PR+ breast cancers. In western communities, the incidence of ER- PR+ breast cancer was 0 percent to 3.8 percent but in Asian communities, it ranged from 2.8 percent to 21.1 percent[5,6]. But Navani S and Bhaduri AS indicated that high incidence of ER- PR+ breast cancer reported from India[6] was most likely due to the use of suboptimal manual assays, rather than true genetic differences. ER expression in breast cancer among Indian women may be much higher than previously believed. They commented on above mentioned statement after they used automated immunohistochemistry with Biogenex antibodies. In the process they re-evaluated ER status in 37 Indian patients with Invasive breast carcinoma previously reported as ER- PR+ by a different manual staining protocol in two city hospitals. The automated technique utilized different reagents and staining protocol from those used in manual assays. Of the 37 previously ER- tumors, only 9(24.3%) tumors remained ER-. 28(75.6%) tumors were found to be ER+[18]. Regitnig P *et al.* also commented that automated immunohistochemical technique has advantages over manual technique concerning interlaboratory variability[19].

Conclusion

According to our present study, the hormonal positivity in breast cancers was found to be 20 percent for ER and 23.3 percent for PE. While comparing hormonal positivity with different types of breast cancers, 19.2 percent was positive for both ER and PR in Invasive Ductal Carcinoma, not otherwise specified which was the predominant breast cancer in our series. One case of Invasive Lobular Carcinoma was positive for both ER and PR. While a case of Medullary carcinoma found was negative for ER and positive for PR. Mucinous carcinoma and Metaplastic carcinosarcoma were both negative for ER and PR. In age wise distribution, hormonal positivity was observed in two age groups 41-50 years group, positivity 42.8 percent for ER and 54.2 percent for PR and 51-60 years group, positivity 25 percent for both ER and PR. In correlation with menopausal status, hormonal positivity in postmenopausal period (25% for ER and 31.2% for PR) was greater compared to that of premenopausal period (14.3% for both ER and PR). Analysis of MBR histologic grade and TNM stage group showed that hormonal positivity declined successively as the MBR grade or TNM stage increased. MBR histologic grade I (positivity 40% for both ER and PR) had higher hormonal positivity rate than MBR grade II tumors (positivity 16.6 of for ER and 20% for PR). A case of grade III tumor was negative for both ER and PR. The hormonal positivity in TNM stage I (positivity 33.3% for both ER and PR) was higher than that in stage II (18.75% for ER and 25% for PR) and in stage III (12.5% for both ER and PR). In addition, while assessing the proportion of tumor tissue type, it was found that ER- PR- type of breast cancer was the commonest comprising 76.7 percent of all breast cancers. ER+ PR+ type of breast cancer was 20 percent and ER- PR+ type was 3.3 percent. But no case of ER+ PR- type of breast cancer was found in the present series.

Recommendation

The decision whether to recommend adiuvant hormonal therapy should be based on the presence of hormone receptors, as assessed by immunohistochemical staining of breast cancer tissue. If the available tissue is insufficient to determine hormone receptor status, it should be considered as being positive, particularly in post-menopausal women. Invariably, hormone negative breast cancers overexpress epidermal growth factor receptor, HER-2(erB-2 or neu). These breast cancers behave aggressively but respond well to Herceptin (Trastuzumab). As ER- PR- breast cancers were predominant in the present study, there is possibility that some of these tumors may have overexpressed HER-2 receptors. So, it is worth to evaluate HER -2 receptor along with hormonal receptor in the future.

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