

RESEARCH ARTICLE

Estrogen Receptor and Progesterone Receptor Status in Breast Cancer in Relation to Age, Histological Grade, Size of Lesion and Lymph Node Involvement

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Abstract

Introduction: Breast cancer is the most common malignancy of women in Kashmir. This study was conducted with the objective of assessing hormone receptor positivity and its correlation with age at diagnosis, tumor size, histological grade and lymph node metastasis. **Materials and Methods:** 132 newly diagnosed cases of invasive breast cancer diagnosed at the Department of Pathology, SKIMS, Srinagar, J&K, were included after excluding biopsies, in-situ lesions and recurrence cases. **Results:** Mean age of the patients was 48.2 years, 59.1% being ≤ 50 years of age. Mean duration of symptoms was 6.32 months. Most lesions (65.1%) were 2-5 cm and 16.7% were ≥ 5.0 cm in greatest dimension. The predominant (80.3%) morphology was IDC-NOS. The majority of the cases presented as grade II (52.1%) lesions and lymph node involvement was present in 65.2%. ER and PR were positive in 66.3% and 63.4% cases, respectively, increasing with rising age. High grade lesions and larger size tumors were more likely to be ER and PR negative. No correlation was found between ER/PR status and lymph node metastasis. **Conclusions:** ER and PR expression in breast cancers in the current study was found to be higher than studies done in India/Asia but lower than studies conducted in the West, even on Indian/Asian immigrants. Markedly lower receptor expression in Indian/Asian studies is likely due to preanalytic variables, thresholds for positivity, and interpretation criteria. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer are strongly advocated for standardization of receptor evaluation and for clinical management of breast cancer patients to provide best therapeutic options.

Keywords: Breast cancer - estrogen receptor - progesterone receptor - preanalytic variables

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Introduction

Globally carcinoma breast is the most common malignancy and the leading cause of cancer death in women, with more than 1,00,000 cases occurring worldwide annually (Parkin et al., 2001). Worldwide, breast cancer comprises 10.4% (World Cancer Report, 2003) of all cancer incidence among women, making it the most common type of non-skin cancer in women and the fifth most common cause of cancer death (World Cancer Report, 2003). In 2004, breast cancer caused 519,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths) (Fact Sheet No. 297: 5). In Kashmir, situation seems worse. It accounted for 15.06% (348 of 2297 cases) of total cancer registrations in females of all ages at Regional Cancer Center of our hospital in last two years.

Breast cancer is a biologically heterogeneous disease

and patients with the same diagnostic and clinical prognostic profiles can have markedly different clinical outcomes. Molecular profiling has provided biological evidence for heterogeneity of breast cancer through the identification of intrinsic subtypes. Analysis of gene expression data suggest that breast cancers can be divided into molecular subtypes which have distinct clinical features, with markedly differing prognosis and clinical outcomes (Perou et al., 2000; Sorlie et al., 2001; 2003; Sotiriou et al., 2003; Nielsen et al., 2004).

A crucial development in the evaluation of breast carcinoma has been the realization that the presence of estrogen and progesterone receptors (ER and PR) in the tumour tissue correlates well with response to hormone therapy and chemotherapy (Hawkins et al., 1980; Barnes et al., 2001). Ovarian steroids are necessary for normal breast development. An imbalance precipitates abnormal processes like epithelial hyperplasia, intraductal and

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invasive carcinoma (Mori et al., 2002). Estrogen is an important mitogen exerting its activity by binding to its receptor (ER) and found in 50-80% of breast cancers (Mori et al., 2002).

Breast cancer survival is linked to early detection, timely appropriate treatment and genetic predisposition. Prognosis is related to a variety of clinical, pathologic and molecular features which include classical prognostic factors viz. histologic type, grade, tumor size and lymphnode metastases. Estrogen and progesterone receptors (ER, PR) and more recently, HER-2/neu have with increasing importance influenced the management of the malignancy (Rampaul et al., 2001; Mori et al., 2002; Gowm et al., 2008).

Materials and Methods

The study was conducted at the Sher-i-Kashmir Institute of Medical Sciences Srinagar, Kashmir, in the department of pathology. Study Period: Two year prospective (January 2010 to January 2012)

Only histopathologically confirmed invasive carcinoma cases were included, In-situ lesions, recurrences, biopsies, sarcomas, benign and secondary lesions were excluded. Modified radical mastectomies, quadrectomy and wide local excision specimens with/without axillary clearance were included. Relevant epidemiological and clinical data was collected from filing section of our department, medical records department and regional cancer centre of our hospital. All the mastectomy specimens received in the department of pathology were fixed by keeping them in 10% formalin overnight. After fixing, macroscopic examination of the specimen was done and findings recorded. Size, quadrant and focality was assessed accurately. Lymph nodes were retrieved meticulously, number noted, and grossly uninvolved nodes were submitted in entirety for processing where as sections of grossly involved nodes were taken. After this, specimens were processed and studied in detail using H and E to get the information about the tumor morphology in detail according to WHO classification and guidelines. Grading of tumors was done according to modified Bloom-Richardson Grading System. Benign tumors were excluded from the study. IHC was performed by using the avidin-biotin complex peroxidase technique with the chromogen diaminobenzidine and antigen retrieval by heating specimen in pressure cooker for 6 minutes. For IHC Formalin fixed and paraffin embedded sections were cut and placed on a glass slides coated with 0.5% poly L-lysine. Endogenous peroxidase activity was blocked

by placing slides in a mixture of methanol and hydrogen peroxide (9:1) for 20 minutes. ER Clone SP1 and PR Clone SP 2, Biocare were used.

ER and PR reactivity of invasive tumors was accessed. Sections from positive breast invasive ductal carcinomas were used as positive controls, negative controls were obtained by omitting the primary antibody. Scoring of ER and PR reactivity was done using Allred scoring system Figure 1A-1D.

Results

A total of 132 cases were included in this study, including 108 Modified Radical Mastectomies, 17 wide Local Excisions and 7 Quadrectomies. Male:Female ratio was 1:43. The mean age was 48.21 years. Youngest patient was 20 years old and oldest was 86 years old. 59.1% cases were ≤50 years. Left breast was involved in 50.8% cases, right in 48.5% cases and 0.7% had bilateral involvement.

Quadrant involvement was Upper Outer-42.9%, Central-19.3%, Upper Inner-9.6%, Lower Outer-7.9%, Lower Inner-3.5%, axilla-0.9% and more than one quadrant was involved in 15.8% cases. Cases with missing information on quadrant were excluded from calculation.

Painless lump (85.3%) was most common presentation. 7.3% presented with nipple discharge, 2.8% presented with painful lump, 1.8% presented with ulceration each. 0.9% presented with metastatic deposits in neck nodes. 0.9% complained of distorted breast shape and 0.9% had congested breast. Mean duration of symptoms was 6.32 months, with 62.7% having <6 months duration, 29.4% having 6-12 months duration and 7.8% having >12 months duration. 9.9% patients had more than one symptom, their longest duration symptom was taken into account. Cases with missing information on presenting symptom and its duration were excluded from calculation.

91% cases were diagnosed on FNAC, 9% cases were diagnosed on biopsy as FNAC was inconclusive. Mammography was done in 31 (23.5%) cases of which 10 (32.3%) were reported as malignant, 1 (3.2%) was suspicious for malignancy and suspicious for benign each. 2 (6.5%) cases were reported as normal. 17 (54.8%) had nonspecific findings. USG Breast was available in 31 (23.5%) cases of which 3 (9.7%) were reported as malignant, 2 (6.5%) as suspicious for malignancy, 1 (3.2%) normal, 11 (35.5%) as hypoechoic, 4 (13.9%) as hyperechoic and 10 (32.3%) had nonspecific findings.

Mean size of lesion was 3.56 cm, ranging from 1 cm to 10 cm. 18.2% lesions were <2 cm, 65.1% were 2-5cm and 16.7% were >5 cm. 81.8% lesions were unifocal where

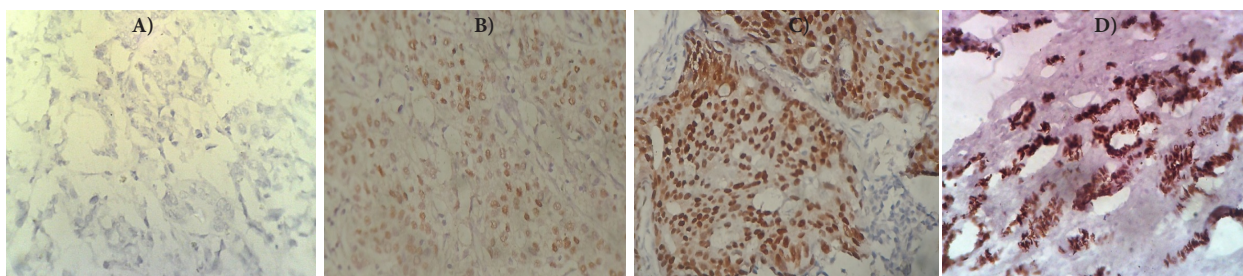


Figure 1. Allred Score. A) 0+0=0/8, B) 5+1=6/8, C) 5+2=7/8 and D) 5+3=8/8.

as 18.2% were multifocal.

Mean number of lymph nodes dissected out was 8.86, highest being 36. Mean number of involved nodes was 3.94. No node was involved in 46 (34.8%) cases, 1-3 nodes in 33 (25.0%) cases, 4-9 nodes in 30 (22.7%) cases and more than 9 nodes in 16 (12.1%) cases. 3 (2.3%) cases had matted nodes with metastasis. 4 (3.0%) cases were WLE without axillary dissection so no nodes could be dissected.

IDC (Infiltrating ductal carcinoma) was the predominant morphological category with IDC NOS (not otherwise specified) 106 (80.30%) cases, IDC Comedo type 5 (3.79%) cases, IDC Cribriform 4 (3.03%) cases, IDC Secretory variant 2 (1.5%) cases and 1 (0.75%) case each of Pappillary, Micropappillary and Solid variants of IDC. There were 4 (3.03%) cases of Lobular Carcinoma, 2 (1.5%) cases each of Metaplastic Carcinoma and Squamous cell carcinoma. Other types included 1 (0.75%) case each of Biphenotypic (mixed Ductal and Lobular) Carcinoma, Colloid Carcinoma, Mucinous Carcinoma and Malignant Clear cell Hidradenoma. Modified Bloom-Richardson Grading was applicable to 119 cases of which 9 (7.6%) cases were grade I, 62 (52.1%) cases were grade II and 48 (40.3%) cases were grade III.

Nipple areola was involved by tumor in 12 (10.7%) cases of 112 cases, 1 (0.9%) case showed features of Pagets disease of nipple. 8 (6.1%) cases had deep resection involvement by tumor. Overlying skin involvement was seen in 3 cases and underlying muscle involvement in 2 cases.

Information on Receptor status was available in 101 cases. 67 (66.3%) cases were ER positive, 64 (63.4%) cases were PR positive. 61 (60.4%) cases were both ER and PR positive, 31 (30.7%) cases were both ER and PR negative, 6 (5.9%) cases were ER positive and PR negative and 3 (2.9%) cases were ER negative and PR positive. Correlation of ER and PR status with age, size of tumor, Modified SBR grade and lymph node involvement is given below (Table 1).

Table 1. ER/PR Status

	No. of case	ER+/PR+	ER+/PR-	ER-/PR+	ER-/PR-
Age at diagnosis (year)					
<40	30	16 (53.3%)	2 (6.7%)	0 (0%)	12 (40.0%)
40-49	17	17 (60.7%)	2 (7.1%)	1 (3.6%)	8 (28.6%)
≥50	43	28 (65.0%)	2 (4.7%)	2 (4.7%)	11 (25.6%)
Size of Tumor (mm)					
1-19	20	13 (65.0%)	2 (10.0%)	0 (%)	5 (25.0%)
20-50	62	39 (62.9%)	3 (4.8%)	2 (3.2%)	18 (29.0%)
>50	19	9 (47.4%)	1 (5.3%)	1 (5.3%)	8 (42.1%)
Grade of Tumor (grade)					
I	7	5 (71.4%)	1 (14.3%)	0 (0%)	1 (14.3%)
II	45	29 (64.4%)	2 (4.4%)	1 (2.2%)	13 (28.9%)
III	40	21 (52.5%)	2 (5.0%)	1 (2.5%)	16 (40.0%)
NA	9	6 (66.7%)	1 (11.1%)	1 (11.1%)	1 (11.1%)
Number of lymph nodes Involved					
0	34	16 (47.0%)	2 (5.9%)	2 (5.9%)	14 (41.2%)
1-3	23	18 (78.3%)	0 (0%)	1 (4.3%)	4 (17.4%)
4-9	23	11 (47.7%)	1 (4.3%)	0 (0%)	11 (47.4%)
>9	15	11 (73.3%)	2 (13.3%)	0 (0%)	2 (13.3%)

Discussion

Worldwide, the incidence of breast cancer varies from 3.9/100,000 in Mozambique to as high as 101.1/100,000 in the U.S (Bolufer et al., 1994; La Vecchia et al., 1994; Rosen et al., 2000; Marugame et al., 2006). Geographic variation in breast cancer incidence can be attributed to racial and genetic differences, cultural differences, as well as environmental exposures that vary throughout the world (Morabia et al., 2000; Rosen et al., 2000). Breast cancer is the most frequently diagnosed cancer in females in developed countries, affecting 1 in 8 women the United States (Jemal et al., 2009). Developing countries are not lagging behind. Breast cancer incidence is increasing in developing countries especially so in urban areas (Deapen et al., 2002; Raina et al., 2005; Murthy et al., 2007)

Cancer incidence studies in Asian Indians and Pakistanis in India and Pakistan as well as emigrants to various countries including Canada, United States, Singapore, UK have documented a rise in breast cancer in premenopausal Indian and Pakistani women (younger than 40) compared to local Caucasian women (Raju et al., 1989; Kamath et al., 1999; Hebert et al., 2006; Gajalakshmi et al., 2007; Ghumare et al., 2007; Murthy et al., 2007; Rao et al., 2008; Rastogi et al., 2008; Goggins et al., 2009; Jack et al., 2009). Lifestyle changes and improvement in diagnosis seem to be the causes for this increase. In contrast overall incidence of breast cancer is declining in the United States in the last decade (Morabia et al., 2002; Couris et al., 2009).

In our study breast cancer was fourth commonest cancer overall in our population, as per register maintained by RCC (Regional Cancer Center) of our institute, lagging behind cancer of esophagus, lung and stomach. However in women breast cancer was the commonest cancer followed by cancer esophagus.

We received about 200 breast specimens in our department during this period and after excluding biopsies, recurrences, sarcomas, secondary and benign lesions, a total of 132 cases were included in this study. MRM (Modified Radical Mastectomies) was the most frequent surgical option in our sample. Out of 132 cases 108 (81.8%) cases had undergone MRM and 24 (18.2%) cases had breast conservation procedure. Other studies from India (Kuraparthi et al., 2007) had lesser percentage of breast conservation procedures. Males accounted for 2.3% of total cases.

The mean age at presentation was 48.21 years and 59.1% cases were ≤50 years. Younger age at presentation as compared to western population (Anjali et al., 2009) was seen in our series which was in concordance with studies done in India and other countries (Peter et al., ???). Infact more percent of breast cancer patients are ≤50 years in Indians in India than in Asian Indian/Pakistani immigrants to USA (Blesch et al., 1999; Wu et al., 2006; Rastogi et al., 2008; Kakarala et al., 2010).

Left breast was involved more commonly than right, and Upper Outer Quadrant was most common in concordance with Naeem et al. (2008). As far as clinical presentation is concerned, Painless lump (85.3%) was predominant presenting symptom followed by nipple

discharge (7.3%). Mean duration of symptoms was 6.32 months. About 37.2% cases had symptom duration of six months or more, so substantial number of cases sought medical attention quite late.

91% cases were diagnosed on FNAC, where as 9% cases required biopsy as FNAC was inconclusive. Mammography and USG breast were done in 31 (23.5%) cases only. 10 (32.3%) were reported as malignant on mammography while as only 3 (9.7%) cases were reported as malignant on USG. Thus mammography was more sensitive than USG but overall both were very less sensitive than FNAC

Mean size of lesion was 3.56 cm and 22 (16.7%) cases had lesion >5 cm at presentation as compared to study by Adedayo A. et al in which only 4.7% cases presented with lesions >5 cm (Adedayo et al., 2009). This again stresses late presentation in our set-up which is mainly due to ignorance.

IDC (Infiltrating ductal carcinoma) was the predominant morphological category with IDC NOS (not otherwise specified) 106 (80.30%) cases. 9 (7.6%) cases were grade I, 62 (52.1%) cases were grade II and 48 (40.3%) cases were grade III while as 13 cases were not graded.

Despite significant progress made to diagnose and treat breast cancer, it still remains the second largest killer in women, just after lung cancer (Irvin et al., 2008). Besides age, stage, tumor grade, lymphnode involvement etc Estrogen receptor is a well established predictive and prognostic factor in breast cancer. Recently, a refined assessment of hormone receptors in breast carcinoma has become necessary to select therapeutic agents according to the recommendations and guidelines for postoperative adjuvant systemic therapy of early breast cancer proposed by the International Consensus Panel during the St Gallen Conference in 2005 (Goldhirsch et al., 2005). The guidelines proposed 3 disease responsiveness categories: endocrine responsive, endocrine response uncertain, and endocrine nonresponsive. As to the method for the detection and quantification of estrogen receptor (ER) and progesterone receptor (PR), immunohistochemical methods have been preferred because of their relative simplicity, low cost, speed of performance, application to small samples, precise identification of reactive elements, simple methods of fixation and storage, ability to be applied to archival material (Fisher et al., 2005), and better ability to predict response to adjuvant endocrine therapy owing to validation studies for ER (Harvey et al., 1999) and PR (Mohsin et al., 2004).

Positive ER/PR status has been associated with decreased breast cancer mortality independently of various demographic factors and clinical tumor characteristics (Dunnwald et al., 2007, Suvarchala et al., 2011) as well as lower local recurrence following breast conservation surgery (Nguyen et al., 2008). The predictive value of PR positivity in the absence of ER is controversial, with some reports suggesting that positive PR, even in the absence of ER, identifies a patient group more responsive to hormonal therapy (Lancet, 1998), but this finding is not universal (Bardou et al., 2003).

In our study Information on Receptor status was

available in 101 cases of which 67 (66.3%) cases were ER positive, 64 (63.4%) cases were PR positive. 61 (60.4%) cases were both ER and PR positive, 31 (30.7%) cases were both ER and PR negative, 6 (5.9%) cases were ER positive and PR negative and 3 (2.9%) cases were ER negative and PR positive. So our patients show much better receptor positivity as compared with studies done in rest of Asia (Desai et al., 2000; Fatima et al., 2005; Kuraparthi et al., 2007; Mudduwa et al., 2009; Shet et al., 2009), where positivity for ER and PR ranges from as little as 28% to maximum of <60%. This difference may be due to genetic differences, however other factors like threshold for positivity, are responsible for atleast some of the difference.

However studies in west (Dunnwald et al., 2007; Veronica et al., 2009, Kakarala et al., 2010) show ER positivity of more than 75% and PR positivity of more than 65% in caucasians and ER, PR positivity of 70% and 60% respectively in Indian/Pakistani immigrant population to US. The sheer sample size of these studies (155175 and 360933 respectively) lends credence to their results which cannot be ignored. Results cannot be expected to vary so much between Asians in Asia and Asians in US as genetically they will be similar. What are reasons for this disparity?

Preanalytic variables, thresholds for positivity, and interpretation criteria seem to be the reasons of which first two are more important. Preanalytic variables which can lead to incorrect results include use of fixatives other than 10% neutral buffered formalin NBF (unless that fixative has been validated by the laboratory before offering the assay), biopsies fixed for intervals shorter than 6 hours or longer than 72 hours, samples where fixation is delayed for more than 1 hour, samples with prior decalcification using strong acids, and samples with inappropriate staining of internal assay controls (including intrinsic normal epithelial elements) or extrinsic assay controls (Elizabeth et al., 2010). ER seems to be more vulnerable to preanalytic variables as earlier studies showed higher number of ER-/PR+ cases most of which subsequently turned out to be ER+/PR+ when repeated with a different set of antibodies using automated IHC (Navani et al., 2005). Higher threshold for positivity (5% by Shet et al) as compared to 1% recommended by American Society of Clinical Oncology/College of American Pathologists (Elizabeth et al., 2010) is another major reason for the disparity.

We compared receptor positivity with age at diagnosis and found that younger patients were less likely to be ER+/PR+ as compared to older patients. Similarly when receptor positivity was compared with tumor grade and size of lesion we found that patients with lower tumor grade and smaller sized lesions were more likely to be ER+/PR+ as compared to patients with high grade tumors and larger. These results were in concordance with study by Dunnwald LK. et al with sample size of 155, 175 and most other studies. However there was no correlation between receptor positivity and lymph nodes showing metastatic deposits in our study. This may be due to smaller sample size in our study.

In conclusion, ER and PR expression in breast

cancers in the current study was found to be higher than studies done in India/Asia but lower than studies done in west even on Indian/Asian immigrants to US and other western countries. Although receptor expression is lower in Indians/Asians compared to Caucasians but markedly lower receptor expression in Indian/Asian studies is more likely due to preanalytic variables, thresholds for positivity, and interpretation criteria. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer are strongly advocated for standardization of receptor evaluation and for clinical management of breast cancer patients to provide best therapeutic options.

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