Histopathological spectrum of breast diseases in a multi-ethnic population of Karachi, Pakistan

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Objective: To generate national level statistics to calculate the disease burden and to implement awareness and screening programs for breast cancer.

Methodology: All breast biopsies received at the Dow Diagnostic Research and Reference laboratory (DDRRL) during 2008-2012 were included in the analyze the spectrum with implementation of latest intrinsic molecular sub-typing.

Results: Out of 2740 cases, 1493 (54.50%) were diagnosed as benign and 1247 (45.40%) as malignant lesions. Most frequent lesion in male was gynecomastia. However, in females, most common benign lesion was fibroadenoma with a frequency of 745 (27.91%), while invasive ductal carcinoma II was the most common malignant lesions observed in 584 (21.88%) cases. Mean age of patients with benign lesion was 30 years

and malignant lesion was 45 years. Selected cases (n=460) were stained for ER, PgR and Her-2 expression. Of these, ER expression was found in 208 (44.30%) biopsies, PgR was found to be positive in 183 (38.90%) and Her-2 was positive in 44 (47.20%) biopsies. Intrinsic molecular sub-typing showed that 36% tumors were basal like, 28% were Lumial A, 18% were Luminal B Her-2 positive, 2% were Luminal B Her-2 negative and 16% were Her-2 positive.

Conclusion: Our study delineates interesting facts including increased magnitude of breast cancer prevalence in our setup (2008-2012). We represent four years data to demonstrate breast diseases specturm in the largest diagnostic and refernece laboratory of Sindh. (Rawal Med J 201;40: 52-58).

Key Words: Breast diseases, breast cancer, fibroadenoma, gynecomastia.

INTRODUCTION

In general benign breast lesions are more common than malignant lesions, however, data regarding benign breast diseases is limited.[1] According to the World health Organization (WHO) the According to the WHO, breast cancer causing 460,000 deaths in 2008 and ranked 5th leading cause of death worldwide, after lung, stomach, liver and colon cancer and mortality rate of breast cancer will continue to rise to 13.1 million by 2030.[2] In United States alone, breast cancer ranked 2nd leading cause of death and emerging the most prevalent malignancy in China, Japan, Taiwan, Singapore and India.[1,3] In Pakistan, the first cancer registry in Karachi compiled 3 years data (1994-1997) and reported that breast cancer is the most common malignancy in females with prevalence of 33.1% and age specific incidence rate (ASR) is 51.7.[4] A report from Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC)

cancer registry 1994-2011 had 53,382 neoplasms of which, 10,771 were breast cancer and was leading cause of death.[5]

Benign Breast Diseases (BBD), which include inflammatory, epithelial and stromal proliferations are more prevalent than malignant lesions.[6] Most common risk factors for breast cancer are delaying child bearing, low parity, decreases breast feeding, increase body mass index, high fat consumption, westernization of diet.[7,8] Morphologically breast cancer is divided into various subtypes according to WHO breast cancer classification system.[9] It is strongly linked with, and classified according to, tumor cell receptor status. The receptors estrogen and progesterone are prognostically as well as therapeutically very important as they determine likelihood of therapeutic benefits using endocrine mode of therapeutics.[10] HER-2 expression and concordance rate has been reported with positive HER-2 performed by IHC and fluorescence in-situ

hybridization (FISH) in breast carcinoma.[11] It is one of the important receptor and its staining correlates with worst tumor prognosis.[11]

More recently, the 12th St Gallen International Breast Conference (2011) led to a consensus for the latest intrinsic molecular sub-typing that classify breast tumors into Lumina A; B, Erb-B2/epidermal growth factor (Her-2/neu) overexpression and Triple negative (ductal) tumors. This mode of classification is helpful in predicting the best possible outcome but also very fruitful in selecting the appropriate therapy.[12] In this molecular era, despite increasing awareness of early screening, prevalence of breast cancer remains high in Asian countries because of pathological characteristics, biological behavior, incidence and survival rate of the population is still under reported, so there is a dire need to establish a accumulative epidemiological data report which represents the patterns of benign and malignant lesions at national and International level in addition to gain insight and understanding the pathological basis of breast diseases and to re-evaluate health planning and screening program for appropriate age in our genetically distinct population including various neglected underdeveloped areas.

METHODOLOGY

The study was conducted during 2008-2012 at the department of Histopathology, Dow Diagnostic Research and Reference Laboratory (DDRRL), Dow University of Health Sciences, Karachi, Pakistan. Parameters like name, age, gender, socio economic status, specimen laterality and clinical history were noted. Histopathological diagnosis, type of tumor and tumor grade were recorded. Selected cases were used for ancillary measures which included ER, PgR and HER-2 using Immunohistochemistry. Allred score and College of American Pathologistlogist (CAP) guidelines were followed for quantification of ER, PgR and HER-2 respectively.[9]

RESULTS

Out of 2740 breast biopsies, 1493 (54.50%) were diagnosed as benign and 1247 (45.40%) as

malignant lesions. 71 (2.59%) biopsies were from male patients while the rest, 2669 (97.4%), were from females. In males, gynecomastia was the most frequent lesion with a frequency of 46 (64.78%). However, and alarmingly, out of 71 male biopsies, 11 (15%) cases of male patients were diagnosed as malignant. In females, the most common benign lesion was fibroadenoma with a frequency of 745 (27.91%), while invasive ductal carcinoma II (IDC-II) was the most common malignant lesion with a frequency of 584 (21.88%) (Table 1).

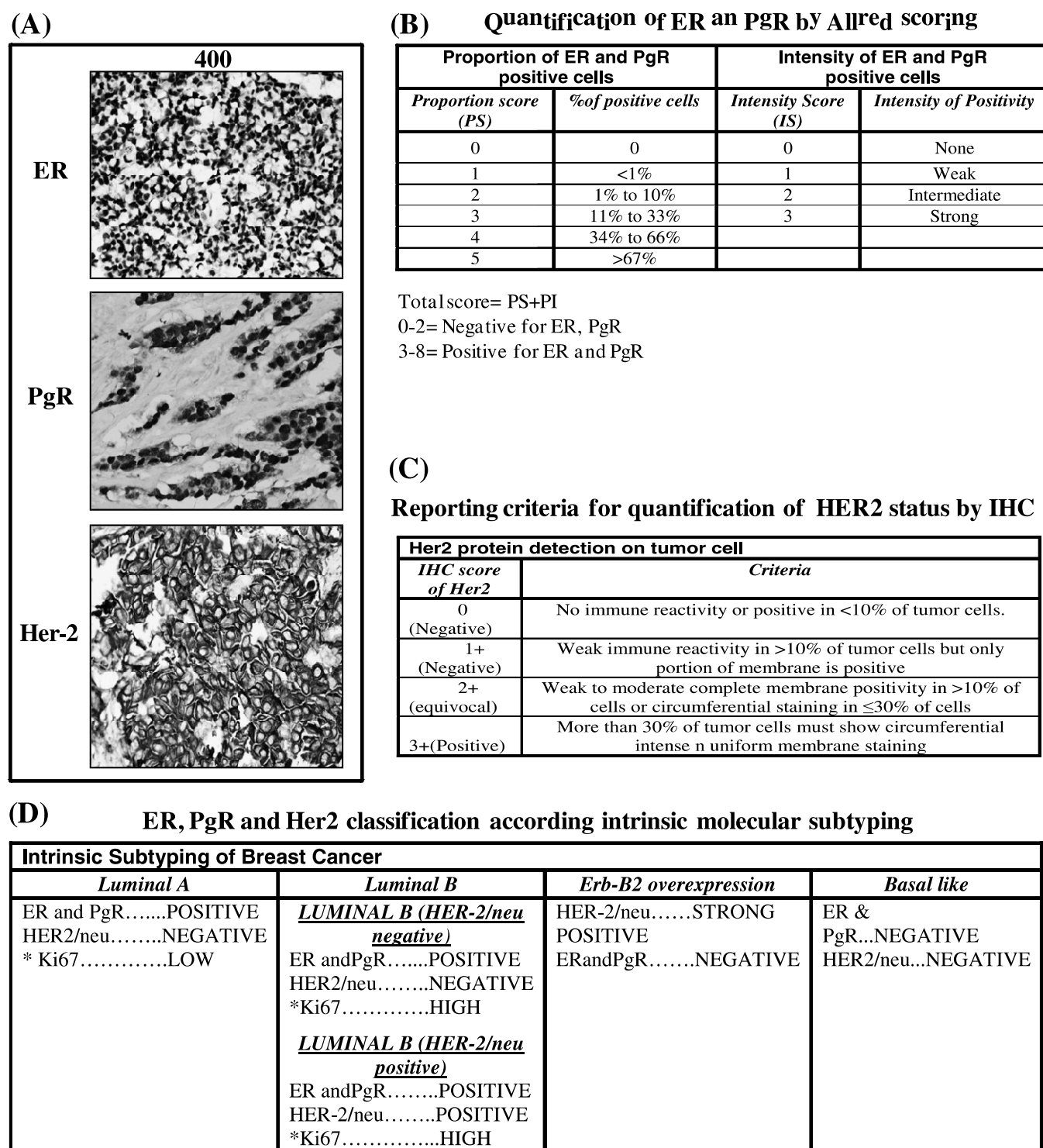**Figure 1. Age distribution of breast tumors.**
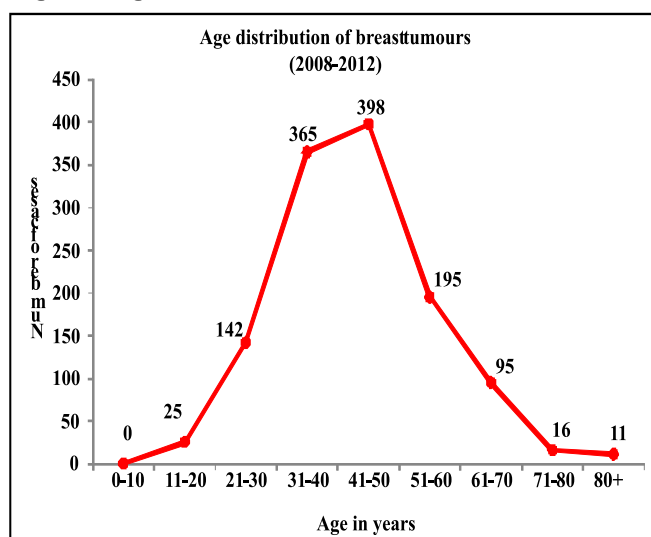
Mean age for breast lesion was found to be 30-50 years (Figure 1). The youngest age recorded for invasive ductal carcinoma was 14 years. Of the 2669 female biopsies, 460 were stained for ER, PgR and Her-2 expression (Figure 2 A-C), in order to classify the tumors according to the latest intrinsic molecular sub-typing (Figure 2 D). Of these, ER expression was found in 208 (44.30%) biopsies, PgR was found to be positive in 183 (38.90%) and Her-2 was positive in 44 (47.20%) biopsies. Most of the cases which were positive for ER, PgR and Her-2 lie in 40-50 year of age group, as demonstrated in (Figure 3A). Intrinsic molecular profiling of breast cancer showed that 36% of the tumors were basal like, 28% were Luminal A, 18% were Luminal B Her-2 positive, 2% were Luminal B Her-2 negative and 16% were Her-2 positive tumors (Figure 3B).

Table 1. Frequencies of breast diseases.

Type of Lesion	Number	Percentage
Inflammatory conditions		
Acute mastitis and abscess	204	7.64%
Chronic mastitis	34	1.27%
Duct ectasia	25	0.93%
Granulomatous mastitis	4	0.14%
Galactocoele	1	0.037%
Xanthogranulomatous inflammation	1	0.037%
Proliferative non-neoplastic conditions		
Fibrocystic changes	257	9.62%
Sclerosis adenosis	2	0.07%
Benign tumors		
Fibroadenoma	745	27.91%
Benign phylloides tumor	60	2.24%
Intraductal papilloma	11	0.41%
Lipoma	6	0.22%
Hemangioma	1	0.03%
Malignant tumors		
Dysplastic or malignant cells*		
Carcinoma	76	2.84%
Few atypical cells	32	1.98%
Ca *in-situ*		
DCIS	9	0.33%
Papillar DCIS	3	0.11%
Lobular carcinoma in situ	1	0.03%
Invasive Breast Cancer		
IDC II	584	21.88%
IDC	268	10.04%
IDC III	166	6.21%
IDC I	61	2.28%
Lobular carcinoma	7	0.26%
Papillary carcinoma	5	0.18%
IDC with squamous differentiation	2	0.072%
Metaplastic carcinoma	1	0.03%
Phylloides		
Borderline phylloides tumor	2	
Malignant phylloides	7	0.07%
Other malignant lesion		0.26%
Metastatic carcinoma	5	0.18%
MPNST	3	0.11%
Sarcoma	2	0.07%
Neuroendocrine carcinoma	2	0.07%
B-cell lymphoma	2	0.07%
Paget's disease	1	0.03%
Spindle cell lesion	1	0.03%
Lymphoproliferative disorder	1	0.03%
Small round blue cell tumor	1	0.03%
Others		
Benign breast tissue	42	1.57%
Acessory breast	10	0.37%
Epidermal inclusion cyst	8	0.29%
Nodular hiradenoma	2	0.07%
Fistulous tract	1	0.03%

Figure 2. ER, PgR and Her-2 staining of breast cancer tissues and molecular intrinsic sub-typing.

(A)

(B) Quantification of ER an PgR by Allred scoring

Proportion of ER and PgR positive cells		Intensity of ER and PgR positive cells	
Proportion score (PS)	*%of positive cells*	*Intensity Score (IS)*	*Intensity of Positivity*
0	0	0	None
1	<1%	1	Weak
2	1% to 10%	2	Intermediate
3	11% to 33%	3	Strong
4	34% to 66%		
5	>67%		

Total score= PS+PI
0-2= Negative for ER, PgR
3-8= Positive for ER and PgR

(C)

Reporting criteria for quantification of HER2 status by IHC

Her2 protein detection on tumor cell	
IHC score of Her2	*Criteria*
0 (Negative)	No immune reactivity or positive in <10% of tumor cells.
1+ (Negative)	Weak immune reactivity in >10% of tumor cells but only portion of membrane is positive
2+ (equivocal)	Weak to moderate complete membrane positivity in >10% of cells or circumferential staining in ≤30% of cells
3+(Positive)	More than 30% of tumor cells must show circumferential intense n uniform membrane staining

(D) **ER, PgR and Her2 classification according intrinsic molecular subtyping**

Intrinsic Subtyping of Breast Cancer			
Luminal A	*Luminal B*	*Erb-B2 overexpression*	*Basal like*
ER and PgR.......POSITIVE HER2/neu........NEGATIVE * Ki67.............LOW	*LUMINAL B (HER-2/neu negative)* ER andPgR.......POSITIVE HER2/neu........NEGATIVE *Ki67.............HIGH *LUMINAL B (HER-2/neu positive)* ER andPgR........POSITIVE HER-2/neu........POSITIVE *Ki67..............HIGH	HER-2/neu......STRONG POSITIVE ERandPgR.......NEGATIVE	ER & PgR...NEGATIVE HER2/neu...NEGATIVE

Formalin fixed tissue sections from breast cancer tissues were stained with α-ER, α-PgR and α-Her-2 antibodies. (A) Representative microphotographs of original magnification x400 are shown. (B-C) Quantification criteria for ER, PgR and Her-2 staining are shown. (D) Criteria for classifying breast cancers according to molecular intrinsic sub-typing. ER=estrogen receptor; PgR=progesterone receptor.

Figure 3. (A) Age distribution with receptor status of patient (2008-2012). (B) Intrinsic molecular sub-typing of selected cases.

(A)

(B)
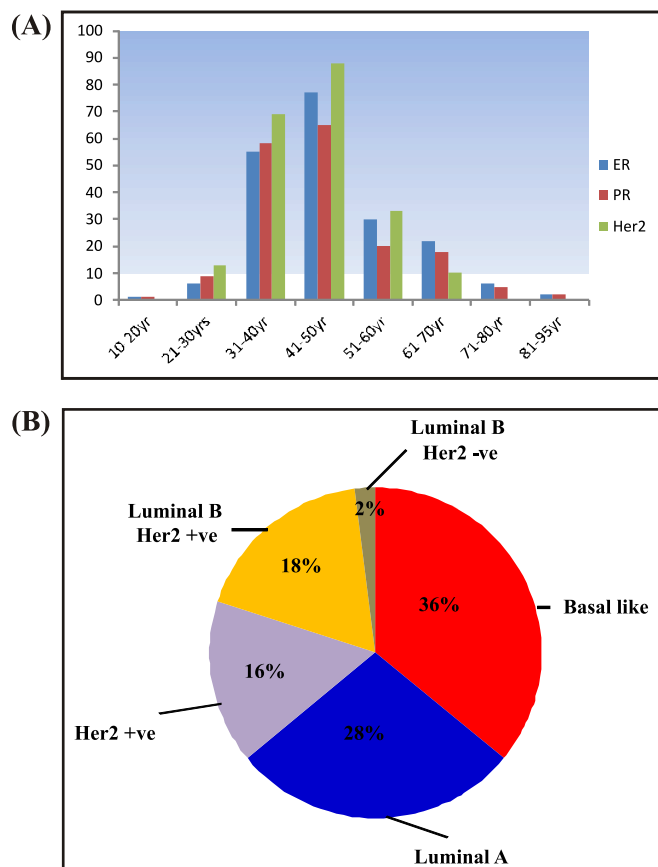
DISCUSSION

Data regarding spectrum of breast diseases is scanty in Pakistan. Few independent centers, which are active in reporting, are working on this aspect, however most of them targeting breast malignancies only in female patients. This leaves behind other breast diseases and benign disorders. Recent studies concluded that more than half of the patient visited breast clinics suffer from benign diseases.[14-16] Male to female ratio of biopsy received in our set up were found out to be 1:36. In males, gynecomastia is the most commonly reported lesion in Asian countries.[14,15,17-19] In this study, gynecomastia was most common lesion in males. However, and strikingly, a small percentage of male biopsies were diagnosed as breast cancer in the present study.

Literature suggests that there are variations in incidence of breast cancer at particular age for example in UK and USA peak age for breast cancer

diagnosis was in between 60-70 years.[1,2] In Asian countries such as China, Japan, India and Taiwan mean age reported was 45-50 years.[1,18-20] In our population, it is found to be 45 years. This incongruence in age may be due to several factors such as differences in delay menarche, multiparty, breast feeding habits, lifestyle, genetic makeup, environmental factor ethical/racial and sciocoeconomic fators. Moreover, the awareness and availability of health care resources are very important untouched aspects. Noticeably, and alarmingly, the youngest age of breast cancer in our study was found out to be 14 years. It is quite alarming as incidence of breast cancer in Asian countries was usually reported in age group of 30-40 year.[1-3]

In our study, Invasive ductal carcinoma II (IDC-II) was found to be the most common type. However, in European countries Grade I is more common.[1] It is most probably because of awareness, strict screening protocols and advance diagnostic facilities all leading to early grade diagnosis. However, data from India, China, Taiwan, Japan and different centers in Pakistan including Karachi cancer registry, Agha Khan University Hospital (AKU), SKMCH & RC also showed IDC-II as the most common cancer in female.[1,4,5,18,19,21,22] In Pakistan, deficiency in cancer registries at national level, lack of awareness, limited access to the facilities and insufficient breast clinic services attributes to the delaying in diagnosis and increase mortality rate. Probably for these reasons, Pakistan exhibits the highest breast cancer mortality rate in Asia.[23]

Receptor status (ER, PgR and Her-2 status) is an important investigation in determining the prognosis of the patients.[11,24,25] Receptor status by immunohistochemistry (IHC) is routinely done and studies showed equal concordance result of receptor status by IHC and microarray studies.[26] Recently, St. Gallen International on the primary therapy of early breast cancer suggested new molecular sub-typing based on receptor status.[12] In the UK, according to the molecular subtyping most of the cases were reported as luminal A as compared to the Triple negative cases.[27] In our population increasing number of triple negative cases lead a clue that what

influences drives emerging triple negative cases. Although if receptor status is mentioned along with grade, as mention in latest intrinsic molecular sub-typing (Luminal system), better sub classification is generated, which can help clinicians for better therapeutics.[18] To the best of our knowledge, molecular intrinsic sub-typing has not been previously reported from any laboratory in Pakistan. It is therefore important to classify tumors according to the intrinsic molecular sub-typing (Luminal system) not only to re-shape the existing classification modalities but also to predict/alter therapeutic and prognostic indices.

CONCLUSION

With an alarming increase in mortality and morbidity of breast cancer, we need to address changing trends for risk factor and monitored and revised screening guidelines. Cancer registries need to be established and local as well as national level to streamline the epidemiological data, to incorporate the latest protocol and classification in histopathological reporting as well as to improvise the existing awareness and screening programs.

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