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Analysis of Clinico-Pathological Characteristics of Indian Breast Cancers Shows Conservation of Specific Features in the Hormone Receptor Sub-Types

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Abstract

Background: Clinical epidemiology studies of breast cancer in India have reported younger age at detection, presentation at a later stage with a greater proportion of Triple Negative Breast Cancer (TNBC). The aim of this study was to examine the standard clinic-pathological variables in the hormone-receptor based sub-types for patterns indicative of intrinsic differences from that reported in Western, Caucasian women.

Methods: Clinico-pathological variables from 645 patients who were diagnosed with breast cancer during 2012 at the regional cancer were retrospectively analyzed for clinical and immunohistochemistry details.

Results: The median age at first diagnosis is 48 years which is decade earlier than that reported in Western case-series, 65% were lymph-node positive, and 33% of all cases were Triple negative Breast Cancers. Sub-type specific examination of tumor size and lymph-node (LN) status showed the HER2 positive tumors to have the highest proportion of tumors that were pT4 and 75% were LN positive. Conversely, despite 92% of TNBCs being grade 3, 40% of them were LN negative.

Conclusion: We confirm the three cardinal clinical epidemiological features reported by other Indian centres. The clinical behavior of the HER2 positive and TNBC sub-types are no different from that reported in Western case-series suggesting that these aspects are innate and conserved.

Keywords: South-India; Breast cancer sub-types; TNBC; Clinico-pathological presentation

Abbreviations

AA: African American; ASCO: American Society of Clinical Oncology; BSA: Bovine Serum Albumin; CAP: College of American Pathologists; ER: Estrogen Receptor; HR: Hormone Receptor; IHC: Immunohistochemistry; KMIO: Kidwai Memorial Institute of Oncology; LN: Lymph Node; NHW: Non-Hispanic White; PR: Progesterone Receptor; RCC: Regional Cancer Center; SEER: Surveillance, Epidemiology, End Results; TMH: Tata Memorial Hospital; TNBC: Triple Negative Breast Cancer; TNM: Tumor Node Metastasis

Introduction

The first clear demonstration of the molecular diversity in breast cancers was reported by Perou et al. [1]. Subsequent studies on breast cancer specimens from women across diverse geographies and demographics world-wide have confirmed the universality of these molecular classes and their relationship to the well-established immunohistochemistry (IHC) based clinical hormone receptor sub-types [2-5].

Over the years reports from Indian centres, that are too numerous to cite have spoken of the varying proportion of these sub-types at their centres [6-12]. Only three incontestable facts emerge from the detailed examination of these reports. 1) The point at which patients seek medical attention in India is most often at the later stages of the disease. 2) The median age of the patients at first diagnosis of breast cancer in most hospital series is a decade lesser than that reported in Western series. 3) The proportion of Estrogen Receptor (ER) negative and TNBCs (Triple Negative Breast Cancer) is almost twice as much as that reported in Caucasian women.

Much of the variability in clinic-pathological characteristics between reports from Indian centres is most likely due to the unavoidable sampling bias that is present in any hospital based case-series. In addition, technical factors involved in IHC based hormone receptor detection and changing cut-offs over the years have contributed their bit to the varying proportions of ER positive tumors reported in these series [6,8,9,13].

In this study, we have examined the clinic-pathological variables of breast cancers diagnosed at the Kidwai Memorial Institute of Oncology

(KMIO), a regional cancer centre at Bangalore in South India during a single calendar year, 2012. Our main motivation to examine the patterns of clinic-pathological presentation in the sub-types was to see if the preponderance of the hormone receptor negative sub-types in Indian women were accompanied by any deviations from the characteristics of the corresponding sub-types reported in Western Caucasian women.

Our study confirms the three cardinal features of the clinical epidemiology of breast cancer in India that has been noted in multiple studies, namely, 1) Presentation for medical care at a late stage; 2) Lower median age at first diagnosis and 3) Higher proportion of HR negative and TNBC tumor sub-types. Additional in-depth examination of clinical and pathological characteristics of the individual sub-types confirms that while the proportions are different each of the sub-types has the same inherent properties reported universally.

Materials and Methods

This is a retrospective study of breast cancer sub-types in patients who were diagnosed with breast cancer at KMIO during the calendar year 2012. A total of 645 cases were analyzed. The pathology details were retrieved from the archives of the department of pathology and medical records at the hospital. Cases of primary breast cancer diagnosed at the department of Pathology at KMIO were included in the study. Tumors that lacked information of patient age and hormone receptor status were excluded from the analysis. The features assessed were age at first presentation, size of the tumor, histologic subtype, tumor grade, lymph node status with hormone receptor status that is, Estrogen receptor, Progesterone receptor (PR) along with growth factor receptor-HER2 as detected by immunohistochemistry (IHC).

All specimens were fixed in 10% neutral phosphate-buffered formalin according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines [14]. The Estrogen and Progesterone Receptors (ER/PR) and the HER2 expression were carried out by IHC. Briefly 5µ thick sections were cut on silane coated slides deparaffinised in xylene and rehydrated graded alcohol. Antigen retrieval was done under pressure in citrate buffer (pH-6) after blocking with 1% bovine serum albumin (BSA). Primary antibodies were applied for the specified period as suggested by the manufacturer in moist chamber. The clones used were mouse monoclonals, ER -1D5 (dil 1:60), PR – PR88 (dil 1:60) and HER2 – CB11 (dil 1:30) from BioGenex. After incubation with secondary antibody (Biogenex) and washed, sections were counterstained with haematoxylin and dehydrated before mounting with DPX mountant. The scoring for ER and PR was done using the Allred scoring system [15,16]. For every batch of staining, the external and internal controls were satisfactory. ER/PR was considered negative for cases which scored '0' with complete absence of staining. The HER2 expression was scored in accordance with the guidelines given by CAP/ASCO [17].

Statistical Analysis

Demographic and clinical details were tabulated for the complete series and the subtypes defined by receptor status. Tumors were divided into four mutually exclusive groups based on the presence or absence of the three receptors, ER, PR and HER2. Statistical differences in the distribution of parameters between the subgroups were tested by Chi-square test or Mann-Whitney U test.

Results

We analyzed data from a total of 645 patients where complete information on hormone receptor and HER2 status was available along with the reported age of the patients.

		All	HR+/ HER2-n (%)	HR-/ HER2-n (%)	HR-/ HER2+n (%)	HR+/ HER2+n (%)
		602	275 (46)	196 (33)	81 (13)	50 (8)
Age	Mean	49	51.4	46.6	49.6	46
	Median	48	50	46	48	45
	<=50 yrs	358 (59)	146 (53)	137 (70)	44 (54)	31 (62)
	>50 yrs	244 (41)	129 (47)	59 (30)	37 (46)	19 (38)
T size	pT1	47 (17)	22 (17)	16 (19)	3 (8)	6 (24)
	pT2	137 (50)	64 (49)	44 (54)	16 (41)	13 (52)
	pT3	22 (8)	11 (9)	7 (9)	3 (8)	1 (4)
	pT4	70 (25)	33 (25)	15 (18)	17 (43)	5 (20)
	*NA	326	145	114	42	25
T size	Mean	3.5	3.5	3.6	3.9	3.3
	Median	3	3	3.5	3.5	3.3
Histology	IDC	507 (99)	218 (97)	168 (99)	72 (100)	49 (100)
	ILC	5 (1)	4 (2)	1 (1)	0	0
	Mixed	2	2 (1)	0	0	0
	NA	88	51	27	9	1
Grade	1	8 (2)	7 (4)	0	0	1 (3)
	2	81 (18)	57 (30)	13 (8)	4 (6)	7 (17)
	3	358 (80)	124 (66)	140 (92)	62 (94)	32 (80)
	NA	155	87	43	15	10
LN*-status	Negative	113 (35)	55 (38)	39 (39)	11 (26)	8 (28)
	Positive	206 (65)	91 (62)	62 (61)	32 (74)	21 (72)
	NA	283	129	95	38	21
pN	pN0	113 (35)	55 (37)	39 (39)	11 (25)	8 (28)
	pN1	91 (29)	39 (27)	32 (32)	11 (25)	9 (31)
	pN2	70 (22)	38 (26)	16 (16)	8 (18)	8 (28)
	pN3	45 (14)	14 (10)	13 (13)	14 (32)	4 (13)
	NA	283	129	96	37	21

*NA – Not available, LN-Lymph Node

Table 1: Shows the clinic-pathological features of the cases segregated into the 4 receptor based sub-types.

Tumors were grouped into four major subclasses, based on the receptor status as follows: Hormone receptor (HR) positive HER2

negative (HR+/HER-), HR negative and HER2 positive (HR-/HER2+), HR positive and HER2 positive (HR+/HER2+), and the TNBCs (HR-/HER2-). 43 of the 645 patients had an initial HER2 status assessed as equivocal, but were not tested further to unambiguously assess the status of HER2. Hence only 602 patients were fitted into the 4 sub-classes. Table 1 shows the clinic-pathological features of the cases segregated into the 4 receptor based sub-types.

The mean and median age of the patients at diagnosis was significantly lower (48 years) when compared to Western case-series as reported previously [12,18]. Half of the tumors were between 2-5cm (pT2) in size and a quarter of them involved either the overlying skin or underlying muscle (pT4), and thus were locally advanced. Invasive ductal carcinoma was the predominant histological sub-type in this series at >97%, confirming the rarity of the lobular sub-type that has been noted in other Indian series in the past [10,13]. A majority of the tumors (80%) were grade 3.

Compared to the women who had HR+/HER2- tumors, women with TNBCs had a median age at diagnosis that was 4 years lesser, (Mann-Whitney U, $p<0.0001$), and a full 70% were under 50 years at the time of diagnosis. They also had a much higher proportion of grade 3 tumors, 92% vs. 66%, (Mann-Whitney U, $p<0.0001$).

The proportions of the Hormone Receptor Sub-classes are Similar to Other Large Series from India

Of all 645 samples 340 were ER positive (53%) and 262 were PR positive (41%) and 252 (39%) were dual hormone receptor positive (ER+/PR+).

Figure 1 shows the proportional distribution of the 4 subtypes amongst the 602 tumors, 46% of the cases were HR+/HER2-, 33% were TNBCs, and the overall proportion of HER2 positive was 22%. The proportions of TNBCs as well as HER2 positive tumors in the Kidwai case-series is marginally higher than that reported in similar case series, where the relative proportions of TNBCs and HER2 positive were 29.8% and 16.7% respectively [9].

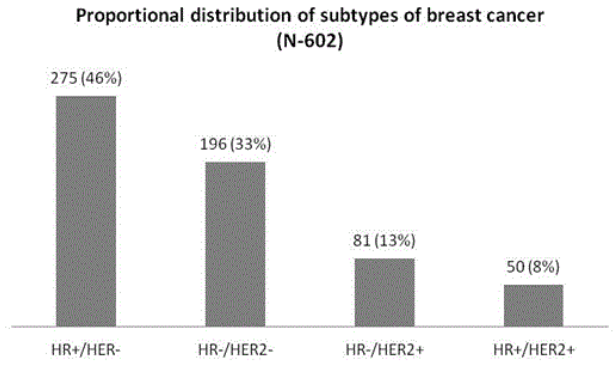

Figure 1: Distribution of breast cancer sub-typed based on a combination of hormone receptors and HER2. TNBCs (HR-/HER2-) are a third of all tumors and HR+/HER2- are about half.

Multiple hospital-based case-series from our country have reported an earlier median age at first diagnosis of breast cancer [9,12,19,20]. However the mixture of varying proportions of both post-menopausal ER positive tumors and TNBCs obscures the age distributions of the specific sub-types. We plotted bar-graphs of the age distribution in these two categories binned into 5 year intervals as seen in Figure 2. The HR+/HER-.subtype had notable numbers starting from the 35-39 year group, a peak occurrence at 45-49 years, and significant numbers of cases persisted up to the 65-69 years age-group. TNBCs had an earlier start with more than 10% of all such tumors in the 30-34 age groups, a peak occurrence in the 45-49 year age-group, and in contrast to the HR+/HER- class they show a rapid decline thereafter with no age bin past 54 years that contributed 10% of all cases. This pattern of the disease indicates the peaking of TNBCs in the pre-menopausal group and a rapid tapering of the disease in the post-menopausal group.

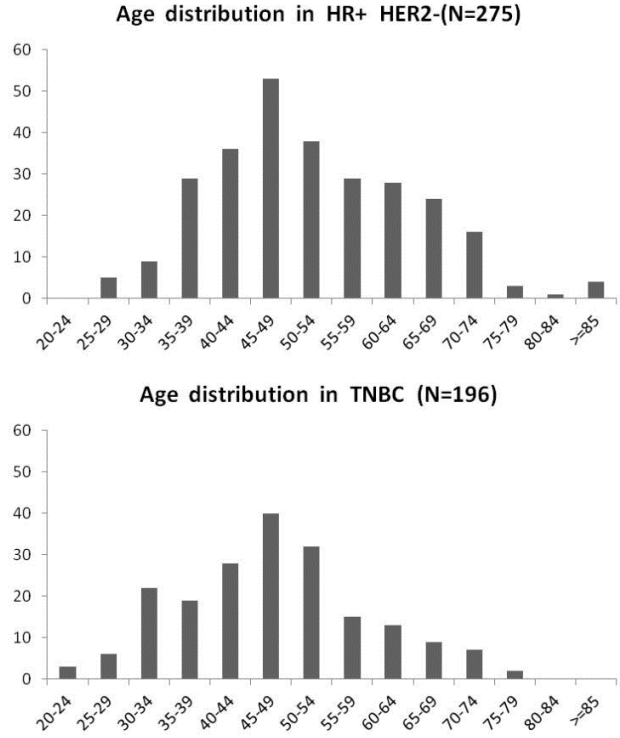

Figure 2: Comparison of the age-distribution in TNBCs and HR+/HER2-ve. Both sub-types have a peak in the 45-49 age bands; however TNBCs are present at significant numbers earlier in the 30-34 age band and show a drastic drop after 54 years, while significant numbers of HR+ tumors are seen till 74 years.

Tumor Size and Nodal Involvement in the Subtypes of Breast Cancer

Breast cancer subtypes are known to have distinct biological behaviours with clearly demonstrable differences in rates of growth and modes of spread [21,22]. In Western case-series HER2 driven tumors as a group usually have the highest rates of proliferation [23], and Basal-like tumors that are mostly TNBCs, have a tendency to spread early by the hematogenous route without invading the regional nodes [24]. To see whether these patterns were recapitulated in our case series we tabulated the distribution of tumor sub-types into pathological T size groups. 276 tumors were available with documented T size as seen in Figure 3. As indicated earlier, majority of

the tumors ranged from 2-5 cm (pT2), in all the four subgroups. There was no difference in the T size distribution between the HR+/HER2- and the TNBCs. However, HR-/HER2+ had a significantly higher mean tumor size (3.9 cm vs. 3.5 cm) and the highest proportion of pT4 tumors (44%) of all classes indicating the most aggressive behaviour. This feature has been noted in population-level data such as the SEER [25].

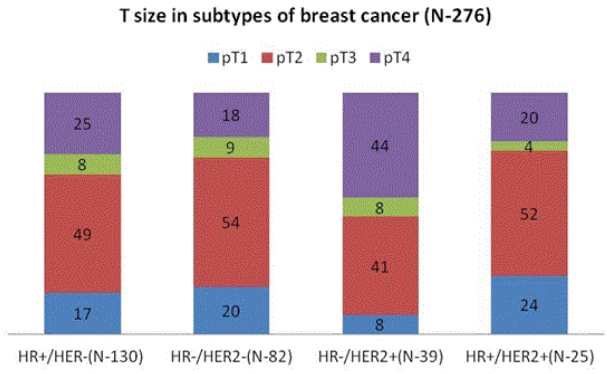

Figure 3: Shows the size of tumors in the sub-types. The HR-/HER2+ subtype has the most aggressive tumors with almost half of them being T4.

We next estimated the pattern of nodal involvement in the subtypes. Based on the number of lymph nodes containing tumor deposits, the tumors were categorized into classes (N0, N1, N2 and N3) prescribed in the TNM classification scheme. This analysis has been performed on 319 cases with available data.

As seen in the Figure 4, the pattern of LN involvement amongst the 4 sub-types differed with the HR-/HER2+ class showing the highest proportion (50%) of patients with significant (>3) nodal involvement, while TNBCs formed the other end of the spectrum with the smallest proportion (29%) of patients with more than 3 lymph nodes involved, confirming a greater tendency on the part of these tumors to spread hematogenously early in the course of the disease.

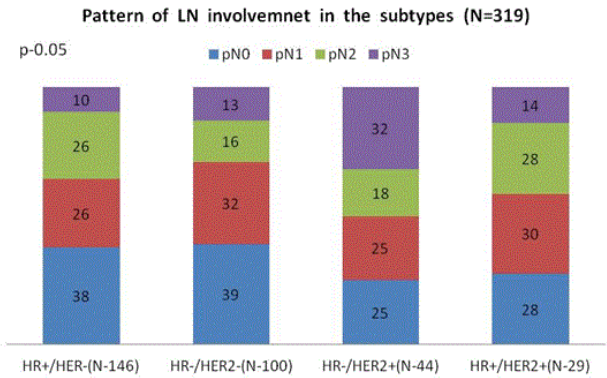

Figure 4: Pattern of lymph node involvement in the sub-types. Half of all HER2+/HR- subtype have more than 3 nodes affected while only 29% of TNBCs have more than 3 nodes.

Discussion

The primary motivation for this compilation of data was to look past the undisputed difference in the proportions of the sub-types in India to see if the clinic-pathological behavior of the individual sub-types were in any way different from the behavior of the same sub-type noted in the case of Western Caucasian women.

At levels of 47% ER negative and 33% TNBC, the proportions from this series in a Regional Cancer Centre of south-India are on par with the numbers noted at the TMH (Tata Memorial Hospital, Mumbai [9] which has the largest patient load of any centre in India. Like in their study, our analysis too was restricted to one calendar year to avoid the alterations induced in the receptor detection assays and the reporting guidelines. This suggests that the broad clinical epidemiological observations support a pan-India phenomenon, rather than loco-regional patterns, and is mostly due to demographic factors.

The truly interesting comparisons are between Indian data and data from other geographies and ethnicities. Gapstur et al. noted in a large series (n=13239) that 35% of African American (AA) women had Hormone Receptor (HR) negative breast cancer compared to 20% of Non-Hispanic white (NHW) women [26]. However, the highest proportion of TNBCs reported to date is from the comparatively small series from West-Africa (n=507) of Huo et al. who reported an unprecedented proportion of 55% TNBCs [27]. Our series confirms the observation showing a very high proportion of TNBCs (33%).

The younger age at first diagnosis is obviously related to the demographics of the population in India. The median age of women in India at the 2011 census was 25 years compared to 35 years for the population of USA [28].

The proportion of women with tumors measuring less than 2 cm and having no nodal involvement (i.e. early breast cancer) much lesser compared to any other series [29]. Only 17% of women presenting to KMIO had T1 tumors, and approximately a third had node-negative disease. This confirms the continuation of an established pattern of late clinical presentation in all regional cancer centres in this country, despite recent efforts towards improving awareness [19,20]. In contrast, at least half of all subjects in both AAs as well as NWHs have early breast cancer (stage IIIA or earlier) at the time of first diagnosis [25].

There are a strikingly low proportion of low grade tumors reported by both KMIO and TMH, and as a consequence the proportion of high grade tumors in both series is about 80%. The factors responsible for the very high proportion of high grade tumors are unclear, but might be explained partly by the larger proportion of late stage pT3 and pT4 tumors.

Though this analysis was done on all consecutive cases reported by the department of pathology over one year, the tumors that lacked information of tumor size and nodal status could not be included. Despite such limitations, the data in our series matches closely with that reported at TMH and hence minimizes the possibility that it represents a sampling bias. It is obvious that the basis of the phenomenon of greater proportion of HR negative breast cancer and TNBCs in any particular case-series is multifactorial including demographic structure, innate biological factors, parity, socio-economic and cultural determinants. The most frequently reported positive correlations have been noted between ethnicity, particularly African American, higher parity and younger age-structure of the population. It is likely, that with change in the demographics of our population with the ageing of our nation, and decreased parity due to

urbanization-globalization, the proportion of the HR negative and TNBC category is likely to decrease over the coming decades and start resembling the proportions noted in Western case-series. To conclude, our data supports the contention that the behavior of a tumor is determined by its intrinsic molecular make-up, regardless of the proportion of a particular sub-type in a population. Secondly late stage tumors of a particular sub-type have largely the same biological behaviour noted in earlier stages of presentation.

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