BREAST CANCER IN YOUNG WOMEN-A COMPLETELY DIFFERENT SPECTRUM WITH GREATER CHALLENGES: A RETROSPECTIVE ANALYSIS AT A TERTIARY CANCER CENTER.

Oncology

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ABSTRACT

Introduction: Breastcancer is a major health burden worldwide. It is most common cancer among women in both high-resource and low-resource settings and is primary cause of cancer death among women globally. There is at least 10-fold variation in breast cancer incidence worldwide. Most rapid rises are seen in developing countries. According to recent GLOBOCANproject(year 2012), recent trend of breast cancer in India are worrisome. This includes-rising numbers of breast cancer cases in India,age shift (more young ladies affected),late presentation (directly decreases long term survival of the patient),lack of awareness and screening,andaggressive cancers in young(generally, the younger the age below menopause, the more aggressive the cancer).

Methods: Retrospectively data wereanalyzed from hospital medical records according to predetermined plan of study.Two groups were made, one of young breast cancer patients with age less than 40 years and the other of older breast cancer patients with age more than 40 years. Variables in relation to risk factors,clinicopathologicfeatures,biomarker expression levels and treatment modes were analyzed between two groups in relation to outcome.

Result: Present study is a retrospective analysis done of 1274 patients of breast cancer treated between January 2006 to December 2008 at Kidwai Memorial Institute of Oncology. Out of which,data of 96 patients were found to be incomplete and hence were excluded from analysis. Out of 1178 studied patients, 344 patients (29.20%) were younger than 40 years. The analysis showed that young patients had a greater median tumor diameter at presentation (3.5 cm),higher lymph node positivity(60.20%),higher LVI (52%),higher perinodal invasion(42%), and higher distant metastasis(10%). Triple negative cancers (TNBC) were higher in young patients(41%). Higher number younger patients underwent breast conservation surgery (BCS) and completed adjuvant chemotherapy and radiotherapy.

Conclusion- Incidence of breast cancer in young women is increasing in India and has been found to be more aggressive than breast cancer presenting in old age group. The aggressive nature is because of late presentation of disease, high grade of disease, high prevalence of poor histopathological factors and high risk biomarker expression levels.

KEYWORDS

breast cancer, young women, therapeutic challenges.

Introduction

Breast cancer is a major health burden worldwide leading to increased number of new cases diagnosed every year. Initially developed countries were having higher incidence of breast cancer but recent data revealed rising incidence in developing countries too, resulting in a comparable incidence now. More than 100,000 cases are diagnosed every year in India and the number is estimated to be doubled by the year 2030. A significant and clinically relevant fact noticed is that the Indian women present at relatively younger age as compared to western women. Early presentation of breast cancer in Indian women directly correlates with increased burden of breast cancer in younger women in India[1,2.]

Carcinoma breast is divided in to four common subtypes based on gene expression studies. Two subtypes are derived from estrogen receptor ER negativetumors (basal like and HER-2 positive) and two are derived fromERpositive tumors (luminal A and B)[3].

Breast cancer in younger women is associated with a different presentation. Breast cancer in younger women usually presents at later tumor stage and with large tumor size. Lymph node involvement is higher than in older population [4,5].

It is relatively more aggressive in nature, histopathologically presenting with higher tumor grade. Based on the literature available carcinoma at younger age is associated with more aggressive biology which leads to poorer outcome possibly because of unavailability of effective screening program and hence late presentation[6,7,8].

Cancer in younger women requires different treatment strategy, fertility preservation remains the important consideration among them. Various aspects should be considered before choosing treatment modality as these patients belongs to reproductive age group and hormonal variations can affect adversely the fertility. Although retrospective studies have been done in India comparing clonicopathoplogical factors in both the groups.Our study compares clinicopathological features along with comparison of variables in relation to risk factors ,biomarker expression levels. This study also highlights various treatment challenges in younger women and comparison of treatment modes were between two groups in relation to outcome.

Methodology

This is a retrospective study done from January 2006 to December 2008 at our institute. Female patients with histologically proven non metastatic breast cancer, presenting before 40 years of age were included in the study. Patients with insufficient data or lost to follow up were excluded from the study. Clinical data of all patients satisfying inclusion criteria was collected from old hospital records. The data were analyzed with respect to demographic characteristics, clinicopathological features, risk factors, biomarker expression, and treatment modalities. As all patients were diagnosed by triple assessment method (clinical examination, radiological examination, histopathological examination), the diagnostic characteristics were analyzed in all patients to correlate grade, stage and severity of the cancer. Presence or absence of known risk factors for breast cancer, family history and genetic predisposition were noted. Reports of histopathological examination was collected to note the information regarding tumor size, tumor type, tumor grade, nodal status, perinodal extension, presence or absence of lymphovascular emboli etc. Status of estrogen receptor, progesterone receptor, HER-2 neu receptor was noted in all patients. Data of treatment details, surgical procedures, radiotherapy, chemotherapy, hormone therapy etc. were collected for those patients who were already diagnosed and taking treatment at the

time of presentation.

Definition of "young" age group-

There is still controversy on how best to define "young" breast cancer patients. Zhou and Recht researched the definition of "young age" by searching MEDLINE and Cancer Lit databases[9]. They found that women "35 to 40 years of age or younger" defined a group of patients in which age was an independent risk factor for higher rates of recurrence of invasive breast cancer. Accordingly, patients that were aged <=40 years are considered "young patients". Therefore, in this study, we divided all patients into either a "young" <=40 years group and an "older" >40 years group.

Follow up details of successive visits were analyzed regarding complications, recurrence, completion of post-operative medical treatment and effects on fertility. Approval from Institute Ethical Committee was taken before conducting the study. Statistical analysis was done by using SPSS 22 software.

Chi-squaretest and Fisher's exact test were used for univariate analysis and binary logistic regression methodwas applied for multivariate analysis. A 'P value' of <0.05 was considered as significant for all analyses.

Result
Records of 1274 patients were analyzed. Out of which data of 96 patients were found to be incomplete and hence were excluded from analysis. Of 1178 patients 344 (29.20%) patients were found to be in younger age group (less than 40 years) while 834 patients were in older age group (more than 40 years). (Figure 1)
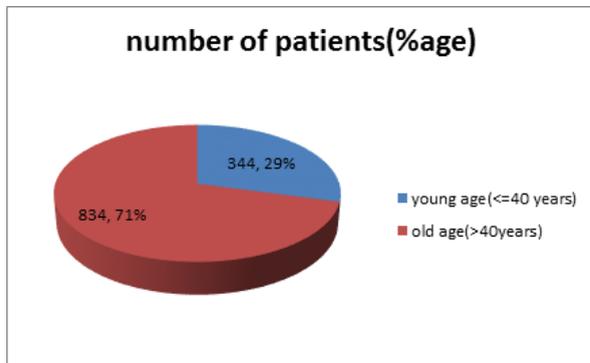

Figure 1.Age distribution

Comparison of risk factors for ca breast between two groups
As we know that life time exposure to estrogen is a risk factor for ca breast, hence we analyzed the risk factors that are related to life time estrogen exposure between the two groups.

We found that earlier age of menarche was significantly associated with ca breast in young women as compared to older patients. Younger patients also showed a significantly lower number of pregnancies and births, and a lower breastfeeding rate than older ca breast patients. Patients Characteristics are summarized in table 1a to 1d.

Table 1a. Patient characteristics

Characteristics	Young age group (≤ 40 years)	Old age group (≥ 40 years)	P – value
	n (%)	n (%)	
Age at Menarche (years)			
<= 10	10 (0.30%)	1 (0.13%)	
11-12	53 (16%)	87 (10.50%)	
13-14	194 (57.23%)	382 (45.80%)	
15-16	72 (21.30%)	255 (30.50%)	< 0.001
17-18	15 (4.60%)	94 (11.20%)	
>=19	2 (0.57%)	15 (1.87%)	
Total	344	834	

Table 1b. Patient characteristics

Number of pregnancy	Young age group (≤ 40 years)	Old age group (≥ 40 years)	P - value
0	70 (20.40%)	175 (21%)	< 0.001
1	86 (25.10%)	178 (21.30%)	
2	82 (23.90%)	172 (20.60%)	
3	49 (14.10%)	135 (16.10%)	
4	28 (7.90%)	90 (10.90%)	
>=5	29 (8.60%)	84 (10.10%)	
Total	344	834	

Table 1c. Patient characteristics

Number of birth	Young age group (≤ 40 years)	Old age group (≥ 40 years)	P - value
0	74 (21.50%)	161 (19.30%)	
1	186 (54.10%)	356 (42.70%)	
2	68 (19.90%)	186 (22.30%)	
3	12 (3.30%)	76 (9.10%)	< 0.001
4	3 (0.90%)	35 (4.10%)	
>=5	1 (0.30%)	20 (2.50%)	
Total	344	834	

Table 1d. Patient characteristics

Breast feeding histoty	Young age group (≤ 40 years)	Old age group (≥ 40 years)	P - value
Yes	232 (67.50%)	592 (71%)	< 0.001
No	27 (7.90%)	19 (2.30%)	
Data missing	85 (24.60%)	223 (26.70%)	
Total	344	834	

Comparison of Histopathological and biomarker level between two groups

Patients in younger age group had a median tumor diameter of 3.5 cm as compared to 2.9 cm in older group patients. Similarly younger patients had a significantly higher number of lymph node metastasis, distant metastasis, lymphovascular invasion, and perineural invasion. With respect to biomarker expression level, younger patients had a significantly higher ER+/PR+ expression level, lesser Her-2 levels, and a higher number of triple- negative breast cancers. (Table 2, Fig 2, Fig 3)

Table 2. Tumor Characteristics

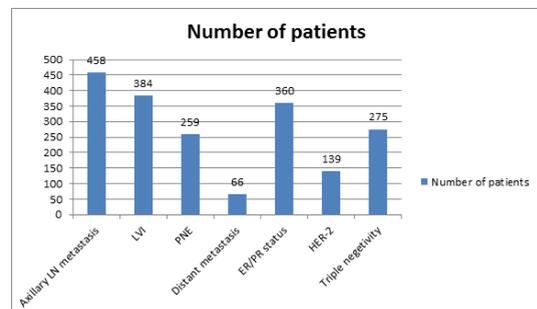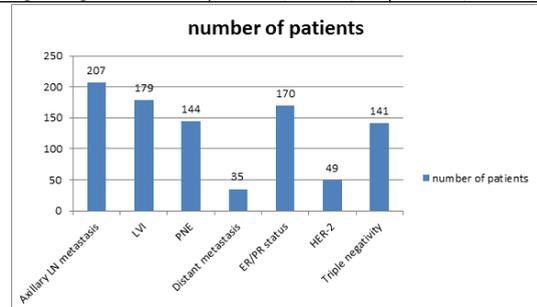| Characteristics	Age <= 40 years N =344	Age > 40 years N= 834
Axillary LN metastasis	207 (60.20%)	458 (55%)
Lymphovascular invasion	179 (52.10%)	384 (46.04%)
Peri-nodal extention	144 (41.9%)	259 (31.05%)
Distant Metastasis	35 (10.17%)	66 (7.90%)
Er+/pr+ Status	170 (49.50%)	360 (43.20%)
HER-2 +ve STATUS	49 (14.50%)	139 (16.70%)
Triple-negative cancer	141 (40.90%)	275 (32.97%)

Figure 3.- Tumor Characterstics in old age group

Comparison of treatment modes between the two groups

Patients in different age groups have different coompliances to different treatment modalities, which affect their choice of treatment.

We found that greater number of younger patients underwent breast conservation surgeries as compared to older patients, higher number of younger patients underwent and completed adjuvant chemotherapy, radiotherapy, and endocrine therapy. As far as treatment with Herceptin (trastuzumab) is concerned, although younger patients received more Herceptin, the utilization rate in both the groups was low. (Table 3, Figure 4, Figure 5)

Table 3. Treatment Modalities

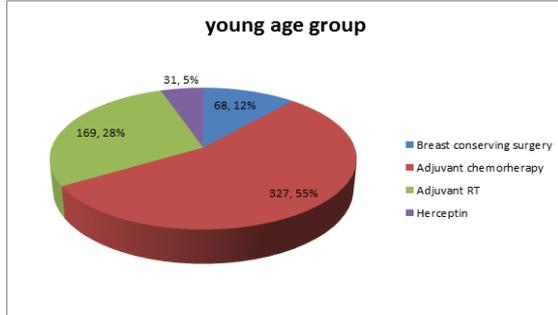| Characteristics	Age <= 40 years	Age > 40 years
	n =344	n= 834
Breast conserving surgery	68 (19.76%)	66 (7.90%)
Adjuvant chemotherapy	327 (95%)	667 (80%)
Adjuvant radiation therapy	169 (49%)	225 (26.90%)
Herceptin (trastuzumab)	31(8.90%)	30 (3.50%)

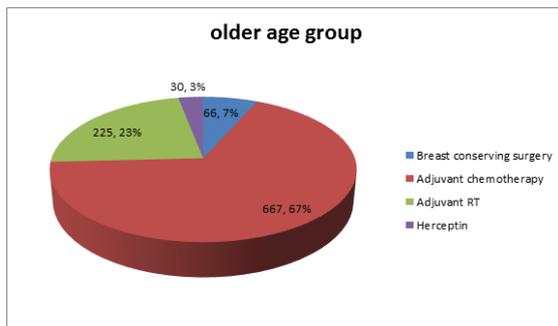**Figure 4. Treatment Modalities in young age group**

Figure 4. Treatment Modalities in old age group

Univariate analysis of factors affecting survival in young age group (<=40 years) patients

Off all factors analyzed, Four factors were found to be associated with decreased survival in younger age group patients. Significantly higher survival was found among patients of early breast cancer(EBC) as compared to locally advanced breast cancer patients, lower grade (grade 1 &2) as compared to higher grade (grade 3), perinodal extension, and lymphovascular invasion. There was a trend towards node positive and triple- negative breast cancer patients having lesser survival than node negative and hormone receptor positive patients, however this did not reach statistical significance. (Table 4, Figure 5a to 5h)

Table 4. Summary of variables and their significance

Variables	Outcome		Total (344)	P – value
	Alive n(%)	Death n(%)		
Clinical stage				
EBC	229 (90.80%)	23 (9.20%)	252	0.026
LABC	65 (70.60%)	27 (29.40%)	92	
Grade of tumor				
I+II	187 (93.50%)	13 (6.50%)	200	0.048
III	115 (79.80%)	29 (20.20%)	144	
Peri-nodal extention				
Yes	111 (77.10%)	33 (22.90%)	144	0.007
No	191 (95.50%)	9 (4.50%)	200	

Lymphovascular invasion				
Yes	139 (77.60%)	40 (22.40%)	179	0.019
No	159 (96.30%)	4 (3.90%)	165	
L.N status				
+Ve	161 (78%)	46 (22%)	207	0.108
-Ve	134 (97.80%)	3 (2.20%)	137	
Tumor size				
<= 2	64 (94.20%)	4 (5.80%)	68	0.684
>2	236 (85.50%)	40 (14.50%)	276	
Estrogen receptor				
+Ve	110 (91.70%)	10 (8.30%)	120	0.315
-Ve	180 (80.30%)	44 (19.70%)	224	
Progesteron receptor				
+Ve	144 (92.30%)	12 (7.70%)	156	0.108
-Ve	150 (79.70%)	38 (21.30%)	188	
HER-2				
+Ve	66 (82.50%)	14 (17.50%)	80	0.999
-Ve	210 (88.90%)	26 (11.10%)	236	
	24 (85.70%)	4 (14.30%)	28	
Triple-negative breast cancer				
Yes	111 (78.80%)	30 (21.20%)	141	
No	189 (93.10%)	14 (6.90%)	203	
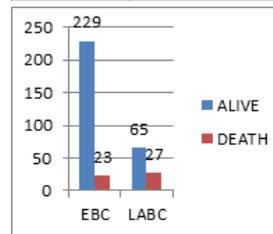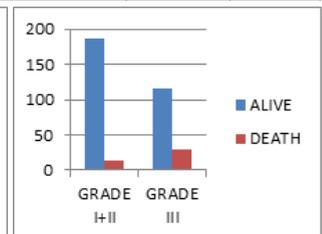
Figure 5a   **Figure 5b**
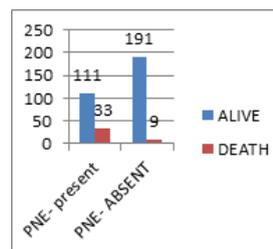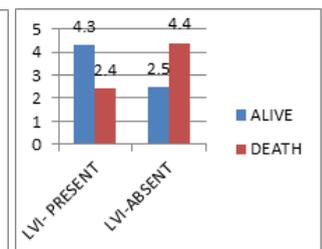
Figure 5c   **Figure 5d**
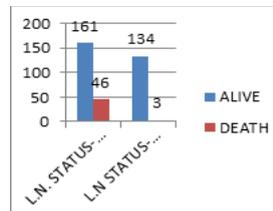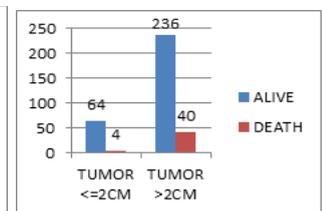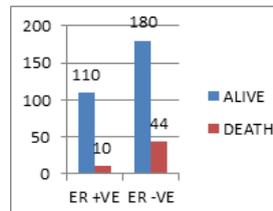

Figure 5e   **Figure 5f**
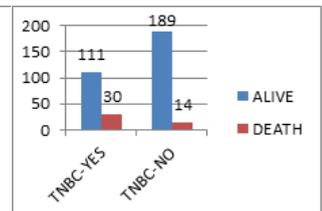

Figure 5g   **Figure 5h**

Discussion

Incidence of carcinoma breast at younger age is increasing in India. Breast cancer in Indian population presents almost one decade earlier than in Western and the incidence was found to be two fold higher in Asian population[10]. Lack of effective screening protocol for this age group may be the possible cause, hence majority of the patients presents with symptomatic palpable lump in later stage of the disease.

A study was conducted by McAree et al. on breast cancer women under 40 years of age. Results of their study showed significantly higher number of patients (98.2%) presenting as a symptomatic lump. While similar study done by Foxcroft et al. showed symptomatic presentation in 93% patients [11,12].

Younger women presents with more aggressive behavior of the tumor than older women. Larger tumor size at presentation, higher tumor grade, higher lymph node involvement, higher incidences of lymphovascular emboli and hormone receptor negativity contributes to the aggressive behavior of the tumor[17].

Fernandopulle SM conducted a pathological study of breast carcinoma in women of less than 35 year age group. Their study showed 40-61% of lymph node positivity[13]. Lymph node involvement is found to be related to patient's survival rate. Previously done studies showed 94.4% survival in node negative patients while 81.6% survival in node positive patients [14]

Hormone receptor status shows different pattern in younger age group. Estrogen receptor has been found to be predominantly negative in younger women. Triple negativity is also more commonly seen in Indian population [15].

Poor prognosis of breast cancer is directly related to Lymphovascular emboli and perinodal extension . Various studies have been done to relate the association of Lymphovascular emboli with prognosis. The incidence of Lymphovascular emboli is reported from 25.3% to 50.9 % in younger patients[13]. Another study done by Deshmukh SP showed statistically significant correlation of Lymphovascular emboli and Perinodal extension [16].

Owing to aggressive tumor behavior, genetic predisposition, larger tumor size and inadequate resection, incidence of local recurrence in carcinoma breast of younger patients is higher as compared to older age group. Various studies have reported local recurrence rate in younger age group as 10-16% [17].

Treatment protocol differs in younger age group as compared to older age group. Studies have reported higher incidences of local recurrence rate than older age group when treated with breast conservation surgery[18]. Study conducted by Voogd and colleagues, comparing mastectomy versus breast conservation surgery with radiotherapy revealed nine times greater risk of recurrence in younger age group than older age group. However younger patients treated with mastectomy did not show higher recurrence rate. Hence adequate radiotherapy, chemotherapy or hormone therapy should be considered to reduce local recurrence[19].

Chemotherapy induced amenorrhea have been found to be associated with better prognosis in younger age group and overall survival was improved in women who had atleast 6 months of chemotherapy induced amenorrhea. Data suggests that therapeutic effect of Chemotherapy is due to ovarian suppression[20]. While in hormone responsive tumors use of LHRH agonist is associated with fewer side effects [21,22].

Aromatase inhibitors can stimulate the recovery of ovarian function in chemotherapy induced amenorrhea. Hence they should be used only with serial checking of estradiol and gonadotropin levels to ensure that ovarian function is not recovering [23].

A prospective study compared chemotherapy induced amenorrhea among CMF regimen and ACT regimen. They found that the rate of chemotherapy induced amenorrhea was similar in both the groups however patients treated with CMF showed reduce chances to resume their menses and Tamoxifen was associated with increased risk early menopause [24].

Conclusion
The incidence of breast cancer in higher in young women in India as compared to western population. We found that ca breast in young patients differs from that in older patients with respect to various clinicopathological features, risk factors and treatment modes. We could also correlate several factors in younger age group patients that are associated with aggressiveness of breast cancer in this age group and results in poor survival.

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