

## RESEARCH ARTICLE

# Change in Trend in Various Clinico-Pathological Factors and Treatment Profile of Breast Cancer Patients: a Tertiary Cancer Centre Experience

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## Abstract

**Background:** Breast cancer is by far the most frequent cancer of women (23% of all cancers), ranking second overall when both sexes are considered together. Since there has been change in clinico-pathological factors and treatment profiles for breast cancer patients over the years, the present study to evaluate the change trends in India. **Materials and Methods:** A detailed analysis was carried out with respect to age, menopausal status, family history, disease stage, surgery performed, histopathology, hormone receptor status, and use of chemotherapy or hormonal therapy. Change in various clinico-pathological factors and treatments of breast cancer cases was recorded and analysed. **Results:** Mean age at presentation was found to be earlier in 2005-2006 compared with 1997-98 (p value: 0.046). More premenopausal women were diagnosed with breast cancer in 2005-2006 when this was compared with initial years of assessment (p value  $\leq 0.001$ ). When change in the receptor status was evaluated, we observed that there was a decrease in cases of ER and PR receptor positivity which was significant (p value: 0.007). Over the period of time, more patients were not offered surgery initially in view of advanced disease when the two time periods were compared (p value:  $\leq 0.001$ ). There was a significant increase in patients who were initially offered neo-adjuvant chemotherapy in view of advanced disease at presentation (p value:  $\leq 0.001$ ). There was increasing number of patients who received palliative treatment for symptoms in 2005-2006 when compared to patients treated in 1997-98 (p value:  $\leq 0.001$ ). **Conclusions:** Changes in mean age at presentation, premenopausal status, and stage at presentation have occurred over the years. More aggressive patterns of disease have become more common with early age at presentation and aggressive biological behaviour with receptor negative tumours.

**Keywords:** Breast cancer - clinico-pathological spectrum - change in trends

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## Introduction

Breast cancer (BC) is the most common cancer among women worldwide (Lotfnezhad et al., 2015). In 2012, there were 1.67 million incident cases from 140 of 184 countries. Around 39% of all cases in 2012 were from Asian countries (Kim et al., 2015).

The majority of global annual new breast cancer cases now occur among poor women who live in low- and middle-income countries (LMICs) (Mathers and Loncar, 2006). Breast cancer (BC) is one of the most common malignancies around the world (Ferlay et al., 2015). In the USA alone, there is an estimate of about a quarter of

million new cases of BC cases during 2014, accounting for 14% of all new cancer cases (Howlander et al., 2013).

Breast cancer in elderly postmenopausal women tend to be less biologically aggressive and to have favorable outcome compared to younger patients. Patients younger than 40 years have higher rates of local recurrence than older patients (Zhou and Recht, 2004; Oran et al., 2014).

Breast cancer is one of the most common cancers in women in both developed and developing countries. It was reported that there were about 1.38 million people diagnosed with breast cancer and ~458,000 deaths result from breast cancer each year (Niu et al., 2013). The incidence of breast cancer in young women has increased

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in Asian population (Keramatinia et al., 2013). Breast cancer affects women about 10 years earlier than their western counterparts and more aggressive disease is for younger age groups (Afsharfard et al., 2013). In Iran, the incidence rate of female breast cancer was 22 per 100,000 populations. The prevalence in this same population was 120 per 100,000 in 2006 (Montazeri 2008; Harirchi et al., 2011).

Breast cancer is an important component of the global cancer problem. It is the most likely reason that a woman will die from cancer (WHO., 2010). Globally, more than one million of breast cancer cases are diagnosed (Jemal et al., 2011). This number is projected to increase to more than two million in 2030 (National Breast Cancer Coalition., 2011). As a consequence of reproductive and nutrition changes, rapid increase of the rates occurs in developing countries (Bray et al., 2004). Despite decrease in mortality rates of breast cancer in developed countries, breast cancer deaths are increasing in the developing countries (Miller, et al. 2010), and it is expected to increase to sixty percent in less than 20 years (Jemal et al., 2011).

The greatest increase in incidence of breast cancer has been in Asian countries (Green and Raina, 2008). The incidence of breast cancer is low in India as compared to developed countries, but the total number of cases and the net mortality is high probably because of the large population, inadequate screening programs, and lack of education (Chauhan et al., 2011). Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India and premenopausal patients constituting about 50% of all patients. Breast cancer incidence peaks among women in forties in Asia and it peaks in sixties in the western world (Agarwal et al., 2007).

Since there is change in clinico-pathological factors and treatment profile of breast cancer patients over years, the present communication is a study to evaluate the change in trends various clinico-pathological factors and treatment profile of breast cancer patients.

## Materials and Methods

The study comprised of 532 biopsy proven patients of carcinoma breast treated between January 1997 to December 2006 in Department of Radiotherapy. A detailed analysis was carried out with respect to age, menopausal status, Family history, disease stage, surgery performed, histopathology, hormone receptor status, and use of chemotherapy or hormonal therapy. All parameters were entered into a computerized database. This data was arranged in table with 2 years time interval. The change in parameters related to demography, investigations and treatment parameters were compared and changes were recorded.

Radiotherapy was performed at cobalt 60 unit. The chest wall or mammary gland was irradiated throughout two tangential opposed fields. The radiotherapy technique included the exposure of axillary and/or supraclavicular and/or internal mammary lymph nodes in patients where it was indicated. The prescribed doses were TD = 50 Gy /25 fractions /5 weeks in all cases.

Statistical analysis: Data was presented in frequency

(%) / mean±sd. To see the change in trend in various clinico-pathological factors over time, Chi Square test with one degree of freedom for linear trend in proportion, and nonparametric test developed by Cuzick (1985) for trend in means were applied. Analysis for linear trend in proportions was done in Epi Info Version 6. Trend in means and other statistical analysis were performed using software Stata 12.1. All the p-values less than 0.05 were taken as significant.

**Table 1. Clinico-pathological and Treatment Parameters of Breast Cancer**

Parameters	No of Breast cancer patients (N=532)
Mean age (years) (range)	47(30-69)
Menstrual status	
Premenopausal	137(25.7)
Postmenopausal	395(74.3)
Family History	
Present	43(8.08)
Absent	489(91.9)
Histologic type	
Ductal	484(90.9)
Lobular	36(6.76)
Medullary	10(1.87)
Papillary	1(0.18)
Tubular	1(0.18)
Surgical treatment	
MRM	243(45.6)
Simple Mastectomy	189(35.5)
BCS	32(6.01)
No surgery	68(12.7)
Chemotherapy	
NACT	122(22.9)
Adjuvant	374(70.3)
No chemotherapy	36(6.76)
Chemotherapy	
CMF	212(39.8)
FAC	266(50)
FEC	28(5.26)
Adjuvant Herceptin	14(2.63)
EBRT	
Radical	454(85.3)
Palliative	78(14.6)
EBRT	
two tangential fields + anterior axillary-supraclavicular field	367(68.9)
two tangential fields+ anterior axillary-supraclavicular field+ internal mammary	87(16.3)
Whole Brain RT	15(2.81)
RT to spine and pelvis	48(9.02)
Total dose	
50Gy/25 F/5Weeks	454(85.3)
30 Gy/10 F/ 2 Weeks	34(6.39)
20 Gy/5 F/1 week	32(6.01)
8 Gy/ 1 F/ 1 Day	38(7.14)
Hormonal treatment	
Tamoxifen	372(69.92)
Anastrozole	27 (5.07)
No hormonal treatment	133(25)
Metastatic disease on presentation	93 (17.4)
Liver	16(2.44)
Lung	27(3.19)
Bone	58(9.02)
Brain	18(2.81)

## Results

Patients of carcinoma breast (532 patients) treated between 1997 to 2006 were included in the study. Clinico-pathological and treatment parameters of breast cancer and contralateral breast cancer patients are shown in Table I.

The mean age of the patients of breast cancer included in this study was 47 years ranging from 30 to 69 years. Among 532 breast cancer patients, 395 patients (74.3%) were postmenopausal and 137 patients (25.7%) were premenopausal. Family history of breast cancer was present in 43 patients (8.08%). Histology of ductal carcinoma was present in 90.9% of the cases (484) followed by lobular (6.76%), medullary (1.87%) and papillary and tubular, each present in 1 case (0.18%). Modified radical mastectomy (MRM), simple mastectomy (SM), breast

conservation surgery (BCS) was performed on 243 patients (45.6%), 189 patients (35.5%) and 32 patients (6.01) respectively, whereas 68 patients (12.7%) did not undergo surgical treatment. Approximately 93% of patients received chemotherapy in Neoadjuvant (22.9%) and adjuvant (70.3%) settings. FAC chemotherapy was given to 50% of the patients followed by CMF (39.8%) and FEC (5.26%). Fourteen patients (2.63%) were given adjuvant herceptin whereas 36 patients (6.76%) did not receive chemotherapy. In RT technique, 367 patients (68.9%) were treated with two tangential fields with axillary and supraclavicular fields. Internal mammary field was added in 87 patients (16.7%) who were having inner quadrant disease. Metastatic disease at presentation was seen in 93 patients (17.450%). Adjuvant tamoxifen was received by 372 patients (69.92%) followed by aromatase

**Table 2. Change in Trend in Various Clinico-pathological Factors Over Time**

Factors	1997-1998 (n=88)	1999-2000 (n=103)	2001-2002 (n=106)	2003-2004 (n=113)	2005-2006 (n=122)	*Chi-square	p-value
Age							
Mean Age±sd	48.6	48.3	47.8	45.2	44.7	-	0.046**
Range							
Menopausal status							
Premenopausal	16 (18)	20 (19)	24(23)	28 (25)	49(40)	14.526	<0.001
Postmenopausal	72 (82)	83 (81)	82(77)	85(75)	73(60)		
Odds ratio	1.0 (ref.)	1.1	1.3	1.5	3		
Stage at presentation							
Stage III	56	62	61	66	57	0.096	0.756
Stage IV	12	16	23	25	37		
Total (III+IV)	68 (77.3)	78 (75.7)	84 (79.2)	91 (80.5)	94 (77.1)		
Stage I	5	4	4	3	8		
Stage II	15	21	18	19	20		
Total (I+II)	20 (22.7)	25(24.3)	22 (20.8)	22 (19.5)	28 (22.9)		
Odds ratio	1.0 (ref.)	0.9	1.1	1.2	1		
Family History							
Present	4 (4.5)	8 (7.8)	8 (7.6)	7 (6.2)	16 (13.1)	3.585	0.058
Absent	84 (95.5)	95 (92.2)	98 (92.4)	106 (93.8)	106 (86.9)		
Odds ratio	1.0 (ref.)	1.8	1.7	1.4	3.2		
Receptor status							
Both negative (ER – PR -)	16 (18.2)	15 (14.6)	18 (17.0)	27 (23.9)	36 (29.5)	7.278	0.007
ER + PR +	30	42	36	30	37		
ER + PR –	25	33	31	26	32		
ER – PR +	17	13	21	20	27		
Either positive (total)	72 (81.8)	88 (85.4)	88 (83.0)	86 (76.1)	86 (70.5)		
Odds ratio	1.0 (ref.)	0.8	0.9	1.4	1.9		
Surgical treatment							
No surgery	2 (2.3)	6 (5.8)	13 (12.3)	15 (13.3)	32 (26.2)	29.867	<0.001
MRM	16	24	47	94	62		
Simple Mastectomy	70	73	46	0	0		
BCS	0	0	0	4	28		
Surgery (M+S+B)	86 (97.7)	97 (94.2)	93 (87.7)	98 (86.7)	90 (73.8)		
Odds ratio	1.0 (ref.)	2.7	6	6.6	15.3		
Chemotherapy							
No chemotherapy	2 (2.3)	1 (1.0)	6 (5.7)	12 (10.6)	15 (12.3)	15.241	<0.001
NACT	8	14	26	33	41		
Adjuvant	78	88	74	68	66		
Chemotherapy (total=N+A)	86 (97.7)	102 (99.0)	100 (94.3)	101 (89.4)	107 (87.7)		
Odds ratio	1.0 (ref.)	0.4	2.6	5.1	6		
EBRT							
Palliative	6 (6.8)	10 (9.7)	15 (14.1)	15 (13.3)	32 (26.2)	15.855	<0.001
Radical	82 (93.2)	93 (90.3)	91 (85.9)	98 (86.7)	90 (73.8)		
Odds ratio	1.0 (ref.)	1.5	2.2	2.1	4.9		

Values are presented in number (%), ref.- reference, \*Chi Square for linear trend, \*\*Based on nonparametric test for trend across ordered groups developed by Cuzick (1985).

inhibitors (Anastrozole/Letrozole) by 27 patients (5.07). Many postmenopausal women were given tamoxifen in view of financial constraints.

In the Table 2, we have tried to observe the change in trends in various clinico-pathological factors and treatment parameters over time. The period from 1997 to 2006 was divided into 2 years interval time and change in trends were noted. There was early presentation in 2005- 2006 when Mean age at presentation was compared with 1997 - 98 and this was significant (p value: 0.046). We observed more of premenopausal women were diagnosed with breast cancer in 2005-2006 when this was compared with initial years of assessment (p value  $\leq 0.001$ ). There was not a significant difference in stage at presentation where we tried to compare early stage (Stage I+II) with advanced stage (stage III+IV). When trend in family history was seen over the years, there was not significant changes. When change in the receptor status was evaluated, we observed that there was a decrease in cases of ER and PR receptor positivity which was significant (p value: 0.007). Over the period of time, more number of patients were not offered surgery initially in view of advanced disease when two time periods were compared (p value:  $\leq 0.001$ ). There was a significant increase in patients who were initially offered neo adjuvant chemotherapy in view of advanced disease at presentation (p value:  $\leq 0.001$ ). There was increasing number of patients who received palliative treatment for symptoms in 2005-2006 when compared to patients treated between year 1997-98 (p value:  $\leq 0.001$ ).

## Discussion

This study was conducted in department of Radiation Oncology with an aim to observe the trend in change in clinico-pathological parameters and treatment parameters over the period of time. Patients who were treated between 1997 to 2006 were taken for analysis and divided into 2 years' time interval and all the changes were recorded.

The average age of the patient at presentation is between 45 and 50 years reported in many published study (Sandhu et al., 2010; Pakseresht et al., 2009) and similar findings was observed in present study. In a study of Breast Cancer Patients at a Tertiary Care Hospital in Marathwada Region of Western India, age group of breast cancer patient was 28 to 85 years with mean age of 52.6 $\pm$  10.5 years (Takalkar et al., 2016). Mean age of the patients was 46.2 years with a range of 28-72 years in a retrospective study on breast cancer patients (Shankar et al., 2015).

There was early presentation in 2005- 2006 when Mean age at presentation was compared with 1997 - 98 and this was significant (p value: 0.046). In comparison to developed countries in Asia and the rest of the world, the incidence of breast cancer is lower; but mortality is significantly higher in developing Asian countries and patients are about 1 decade younger in developing countries than in developed nations (Agarwal et al., 2007).

More than half of the patients (54%) were diagnosed between the age of 40 and 60 years. About 26% were aged younger than 40 years and 20% were aged older than 60 years at presentation was seen in a study done in south India (Surakasula et al., 2014). This shows that now

patients are now presenting at younger age and only 20% patients age at presentation were more than 60 years as shown in this study.

There is no trend data in the incidence of breast cancer in young women in developing countries; however, a study in Goiania, Brazil reported a annual increase of 5.22% in the incidence of breast cancer among age group 30-40 years during the period of 1988-2003 (Freitas et al., 2010). We observed more of premenopausal women were diagnosed with breast cancer in 2005-2006 when this was compared with initial years of assessment (p value  $\leq 0.001$ ).

A younger age at onset among the Asian population has been reported and it has been attributed to a cohort effect that has been decreasing in recent decades (Mousavi-Jarrahi et al., 2013). In a study on breast cancer patients in Pakistan also showed increase number of premenopausal women reporting to hospital for breast cancer treatment. Out Of 105 patients 43 were premenopausal and 62 were postmenopausal. Mean age at diagnosis of patients at premenopausal was 37.4 $\pm$ 7.63 years for diagnosed cases of breast cancer (Memon et al., 2015)

There was not a significant difference in stage at presentation where we tried to compare early stage (Stage I+II) with advanced stage (stage III+IV). A study was Wani observed stage IIB is commonest followed by stage IIIA and stage IIIB (Wani et al., 2012) while Saxena observed that stage IIIB is commonest followed by stage IIIA and stage IIB (Saxena et al., 2005). Majority of breast cancer patients present at relatively late stage in the developing countries probably due to lack of awareness, lack of funding, lack of infrastructure, and low priority in public health schemes (Agarwal et al., 2007).

When trend in family history was seen over the years, there was not significant changes. When change in the receptor status was evaluated, we observed that there was a decrease in cases of ER and PR receptor positivity which was significant (p value: 0.007). Triple negative (ER, PR, and Her2Neu negative) breast cancer is biologically aggressive, resistant to conventional cytotoxic chemotherapy treatment, and associated with reduced survival compared to other subtypes of breast cancer (Kakarala et al., 2010).

Over the period of time, more number of patients were not offered surgery initially in view of advanced disease when two time periods were compared (p value:  $\leq 0.001$ ). This may be attributed to younger age of presentation and its more aggressive nature of disease in young age. This subset of patients were offered Neo Adjuvant Chemotherapy (NACT) and there was a significant increase in patients who were initially offered neo adjuvant chemotherapy in view of advanced disease at presentation (p value:  $\leq 0.001$ ). There was increasing number of patients who received palliative treatment for symptoms in 2005-2006 when compared to patients treated between year 1997-98 (p value:  $\leq 0.001$ ).

Conclusions, Our study has shown that there is increased incidence of breast cancer in young women over the period of time. Change in mean age at presentation, premenopausal status, stage at presentation was seen over the years. More aggressive pattern of disease pattern was

*Change in Clinico-Pathological Factors and Treatment Profile of Breast Cancer Patients: a Tertiary Cancer Centre Experience* seen in view of early age at presentation and aggressive biological behaviour with tumour with receptor negativity. This results guide us to take prompt screening practices starting from younger age and need for personalised treatment in breast cancer.

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