

Original Research Article

Female breast cancer in different age groups: clinicopathological features and treatment strategies

Ayesha Nuzhat¹, Lamyaa Z. Abu Zaid^{2,3*}

¹Department of Basic Medical Sciences, ²Department of Community Medicine, Faculty of Medicine, King Fahad Medical City, Riyadh, Saudi Arabia; ³Department of Public Health, Community & Occupational Medicine, and Environmental Health, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

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*Correspondence:

Dr. Lamyaa Z. Abu Zaid,

E-mail: labuzaid@kfmc.med.sa

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ABSTRACT

Background: The proportion of breast cancer cases have been alarmingly increasing. In order to investigate the clinical and pathological features of breast cancer arising in all age groups and to provide evidence for therapy based on these features, we intended to conduct this study among three age groups, young (age ≤ 40), middle aged ($>40-50$) and elderly patients (>50).

Methods: This cross-sectional study obtained data from the cancer center registry at King Fahad Medical City and included all women diagnosed as breast cancer between 1st January 2011 till 31st December 2012 and followed until December 2015 (n=155).

Results: 25.2% patients were ≤ 40 years of age, 38.7% were $>40-50$ years and 36.1% were >50 years. The upper outer quadrant of the breast was most frequently area involved in all the three age groups. Majority of the cases were Invasive Ductal Carcinoma (IDC). 51.3% cases were of grade III in patients ≤ 40 years, 43.3% cases in the middle age group ($>40-50$ years) were of grade II and 44.6% patients were of grade III in the elderly group. More T3 tumours were noticed in the younger group and more T2 in the middle age group and greater lymph node involvement N2 in the age group >50 years. The mean survival time for patients' ≤ 40 was 37.6 months, 39.3 months for cases $>40-50$ years and 38.3 for patients >50 years old at the end of three years of follow up. At our cancer centre and among all the groups, majority of patients were treated with a combination of surgery, chemotherapy and radiation

Conclusions: This study identifies clinicopathological features of breast cancer in all age groups in a tertiary care center, Saudi Arabia. Distant metastasis was more prevalent among younger age group and the middle aged women had the best mean survival time after three years.

Keywords: Breast cancer, Age groups, Clinicopathological features, Treatment strategies

INTRODUCTION

Female breast cancer is a major public health problem throughout the world. It is the most common cancer type among women in developed and developing countries. Moreover, it is the principal cause of death from cancer among women globally. Nearly 55% of the worldwide burden is now experienced in developed countries, but

incidence rates are rapidly rising in developing countries as well.¹

According to the annual cancer incidence report published by the Saudi cancer registry, there were 1,853 female breast cancer cases for year 2013. Breast cancer ranked the first among females accounting for 29.1% of all newly diagnosed female cancers (6364) in year 2013.

The ASR was 25.5/ 100,000 for female population. The median age at diagnosis was 50 years.²

The risk of getting breast cancer increases with age. 1.44% and 3.46% of women who are now 40 and 60 years old respectively, will get breast cancer sometime during the next 10 years.³ Most breast cancers develop in older women; from 2002 to 2006, the median age at the time of breast cancer diagnosis was 61 years.⁴ Previous data suggest that about 50% of breast cancers occur in women ≥ 65 years of age and $>30\%$ of breast cancers occur in women >70 years of age.⁵

Histopathological findings of 1869 women with invasive breast cancer who were treated at the Breast Unit, Guy's Hospital, London, in the 10-year period 1983-1992 have been reviewed to find out whether histological features of the tumours were related to the patients' age. The patients were divided into four groups: $< \text{or} = 39$ years, 40-49 years, 50-69 years, and 70 years or more. Results had showed increase in incidence of grade III infiltrating ductal carcinoma in those aged $< \text{or} = 39$ years. Certain tumour types, in particular lobular, were documented more frequently in the oldest age group. Moreover, there was a significant reduction of axillary lymph node metastases, vascular invasion and lymphoplasmacytic stromal reaction with increasing age, all of which were independent of tumour grade. These data suggest that there may be age-related changes in the histology of breast cancer and, in some cases, less aggressive characteristics in the elderly.⁶

Another study had been conducted in France and aimed to clarify the prognostic factor of age, the investigators analyzed 1,266 patients treated for breast cancer at the same institution (mean follow-up: 62 months). Three groups were compared: patients <35 years of age, non-menopausal patients >35 years of age, and post-menopausal patients $<\text{the age of } 70$ years. A higher frequency of undifferentiated tumors, histoprognostic grade-3 cancer, microscopic lymph-node involvement and negative hormonal receptor status was observed in patients under 35 years. Also, clinical tumor size was greater in young patients, suggesting higher stromal activity. Multivariate analysis of overall and metastasis-free survival revealed that age younger than 35 years was an independent risk factor.⁷

Many studies have been investigated potential biological differences that account for the disparate behavior of breast cancers in young women; young women tend to have more triple-negative and fewer luminal A and B breast cancers.⁸⁻¹⁰ As well as tumors that are higher grade, have more extensive intraductal component, more lymphovascular space invasion, and are more likely estrogen receptor -negative.¹¹⁻¹⁴ Although young women do appear to have tumors with more aggressive biological characteristics, these factors alone are insufficient to explain the observed differences in outcome among young and elderly cases.¹⁵⁻¹⁷

A study conducted at the University of Texas MD Anderson Cancer Center from 1973 to 2006 to investigate the locoregional recurrent (LRR) rates among 652 young women (≤ 35 years old) diagnosed with breast cancer. The investigators segregated locoregional treatment into mastectomy with adjuvant radiation (MXRT), mastectomy alone, and breast-conserving therapy (BCT), and they reported that patients treated with mastectomy alone had the highest rates of locoregional failure compared with both MXRT and BCT. In patients with stage II disease, the locoregional treatment approach had a significant impact on LRR (17.7% BCT, 22.8% mastectomy, and 5.7% MXRT; $P=0.02$). These results suggested that patients ≤ 35 years old with stage II disease who choose mastectomy should be counselled that their LRR rate could be significantly improved with postmastectomy radiation. For patients with stage I disease, there were no differences in LRR between those treated with BCT or mastectomy. However, there was a statistically significant benefit in LRR for patients that received systemic chemotherapy. This might conclude that even with small tumors, young women may benefit from systemic therapy and that age should be considered in the discussion of comprehensive treatment.¹⁸

The appropriate treatment for elderly women with breast cancer remains controversial. It is believed that older women have less aggressive biology than middle-aged women, who have less aggressive disease than young women, establishing a continuum of aggressiveness based on age; however, this remains a field of investigation.¹⁹

A study of the Surveillance, Epidemiology, and End Results Registry reported that among patients ≥ 55 years old, there was an association between increasing age and more favorable biological characteristics; older patients had more estrogen receptor-positive tumors and lower proliferative rates.²⁰ Whereas, other researchers suggest that the outcomes for elderly females, when stage is taken into account, are similar to middle-aged females.²¹

Multiple studies all over the world described breast cancer among elderly and young patients only and specially focused on epidemiology and screening. Scarce data is available for middle age group especially in our region. The current study aimed to investigate the clinicopathological features, mean survival time after three years, and the treatment modalities of female breast cancer cases among different age groups.

METHODS

This cross-sectional study used data collected from the cancer center registry at King Fahad Medical city (KFMC) and included all women diagnosed as breast cancer from 1st January 2011 to 31st December 2012 and followed till the end of 2015 in order to calculate the mean survival time after three years for all the age groups. The KFMC cancer center stages cancer records

according to the American joint commission of cancer TNM staging system, as well as the surveillance, epidemiology, and end results (SEER) summary staging system. Clinical information, pathological features, and therapeutic strategies of all the age groups were analyzed by chi-square test.

Time duration of study

6 months after approval of proposal

Sample size

All female breast cancer cases registered at KFMC during the period from first of January 2011 until end of December 2012 and followed for three years (end of 2015).

Sampling technique

Non-probability random sampling technique was adopted.

Data collection tool

Data collection form was designed to collect data from the electronic patients' medical records.

Data analysis procedure

Data analysis was compiled using Statistical Package for Social Sciences (SPSS) software version 20. Frequencies and percentages were taken for categorical variables. Association between different variables was assessed through application of chi-square. P-value less than 0.05 considered as significant.

Ethical consideration

- Ethical approval for conducting this study has been obtained through the Institutional Review Board (IRB) at KFMC (IRB No: 17-067).
- Confidentiality and privacy of the subjects and the research data was maintained appropriately.

RESULTS

Socio-demographic characteristics of study sample (n=155) is depicted in Table 1. In this study, 39 (25.2%) patients were less than or equal to 40 years of age, 60 (38.7%) were more than 40 to 50 years and 56 (36.1%) were more than 50 years of age with the median age at diagnosis being 47 years. Majority of the cases were Saudi nationals and were married.

Table 1: Socio-demographic data of female breast cancer patients (n=155).

Socio-demographic variables	≤40 years N (%)	>40-50 years N (%)	>50 years N (%)
Number of Patients	39 (25.2)	60 (38.7)	56 (36.1)
Marital status			
Single	4 (10.3)	2 (3.3%)	1 (1.8%)
Married	33 (84.6)	55 (91.7%)	39 (69.6%)
Divorced	1 (2.6)	1 (1.7%)	3 (5.4%)
Widowed	0 (0)	0 (0)	8 (14.3%)
unknown	1 (2.6)	2 (3.3%)	5 (8.9%)
Nationality			
Saudi	36 (92.3%)	52 (86.7%)	48 (85.7%)
Non Saudi	3 (7.7%)	8 (13.3%)	8 (14.3%)

Table 2 showed the clinicopathological data of female breast cancer patients by different age. Regarding the tumour location, the upper outer quadrant area of the breast was most frequently involved in all the three age groups, 20 (51.3%) cases in the young group (≤40 years), 25 (41.7%) cases in the middle age group (>40-50 years) and 22 (39.3%) cases aged more than 50 years.

Majority of the subjects were IDC rather than ILC or other types across all age groups and 20 (51.3%) cases were of grade III in patients aged 40 years or less, 26 (43.3%) cases in the age group >40-50 years old were of grade II, and 25 (44.6%) cases were of grade III in patients more than 50 years of age.

In the current study, more T3 tumours were noticed in the younger group ≤40 and more T2 in the middle age group and greater lymph node involvement (N2) in the age group more than 50 years.

For all the groups; the majority of patients were treated with a combination of surgery, chemotherapy, and radiation (Table 3). It was also observed that among the elderly group 10.7% of them opted for a combination of chemotherapy and radiotherapy whereas no cases were treated by this combination among the younger group. The mean survival time for patients ≤40 was 37.6 months, 39.3 months for cases >40-50 years, and 38.3 months for patients more than 50 years old at the end of three years of follow-up (data not shown).

By using the chi square analysis, there were no statistically significant differences between the three age

groups regarding the clinicopathological features or the treatment modalities.

Table 2: Clinicopathological data of female breast cancer patients by different age groups.

Clinic-pathological variables	≤40 years N (%) n=39	>40-50 years N (%) n=60	>50 years N (%) n=56
Tumor location			
Upper outer quadrant	20 (51.3)	25 (41.7)	22 (39.3)
Upper inner quadrant	3 (7.7)	5 (8.3)	5 (8.9)
Lower outer quadrant	3 (7.7)	5 (8.3)	5 (8.9)
Lower inner quadrant	0 (0)	5 (8.3)	6 (10.7)
Overlapping/ multiple	4 (10.3)	7 (11.7)	3 (5.4)
Central	6 (15.4)	4 (6.7)	11 (19.6)
Breast NOS	3 (7.7)	9 (15.0)	4 (7.1)
Tumor grade			
Grade I	2 (5.1)	6 (10)	5 (8.9)
Grade II	16 (41.0)	26 (43.3)	24 (42.9)
Grade III	20 (51.3)	25 (41.7)	25 (44.6)
Grade IV	1 (2.6)	1 (1.7)	0 (0)
Unknown	0 (0)	2 (3.3)	2 (3.6)
Histological type			
Invasive ductal carcinoma (IDC)	36 (92.3)	56 (93.3)	50 (89.3)
Invasive lobular carcinoma (ILC)	1 (2.6)	3 (5.0)	5 (8.9)
Others	2 (5.1)	1 (1.7)	1 (1.8)
Tumor stage			
T0	1 (2.6)	2 (3.3)	2 (3.6)
T1	11 (28.2)	15 (25.0)	18 (32.1)
T2	10 (25.6)	24 (40.0)	14 (25.0)
T3	14 (35.9)	15 (25.0)	14 (25.0)
T4	3 (7.7)	4 (6.7)	8 (14.3)
Lymph node involvement			
N0	22 (56.4)	31 (51.7)	28 (50.0)
N1	14 (35.9)	25 (41.7)	21 (37.5)
N2	3 (7.7)	3 (5.0)	5 (8.9)
N3	0 (0)	1 (1.7)	2 (3.6)
Metastases			
MX	1 (2.6)	0 (0.0)	3 (5.4)
M0	27 (69.2)	53 (88.3)	44 (78.6)
M1	11 (28.2)	7 (11.7)	9 (16.1)

Table 3: Type of treatment for female breast cancer patients by different age groups.

Age Groups (years)	Type of treatment					
	Surgery+ Chemo.+Radio.	Surgery+ Chemo.	Chemo.+ Radio.	Surgery+ Radio.	Chemo.	Unknown
≤40 n= 39	22 (56.4%)	8 (20.5%)	0 (0%)	5 (12.8%)	2 (5.1%)	2 (5.1%)
>40-50 n= 60	37 (61.7%)	8 (13.3%)	1 (1.7%)	6 (10.0%)	5 (8.3%)	3 (5.0%)
>50 n= 56	27 (48.2%)	7 (12.5%)	6 (10.7%)	7 (12.5%)	4 (7.1%)	5 (8.9%)

DISCUSSION

There has been an alarming increase in breast cancer (BC) patients in recent years. Several studies have been reported regarding breast cancer from various countries as well as from Saudi Arabia. BC is the leading cause of

mortality in Saudi Arabia.²² Among Gulf Cooperation Council (GCC) states, an analysis of the number of BC cases per 100000 females revealed 46.4 cases from Bahrain, 44.3 from Kuwait, 35.5 from Qatar, 19.2 from UAE and 12.9 from KSA. Breast cancer has a lower incidence in Saudi Arabia than other Middle East countries.²³

Mean age of BC in western countries has been anticipated to be about 63 years of age. There is also a growing tendency in the 45–49 year-old age group with a declining trend for women older than 49 years.²⁴ Mousavi et al in 2009 conducted a study in Iran and reported 44.2 years of age to be the mean age of diagnosis in their population. Majority of the cases were among 40-50 year-old age group and 32.2% of them were less than 40 years at diagnosis.²⁵

Mehradad et al from Iran in the year 2016 recorded data of 258 patients with breast cancer and reported that the mean age of the patients at diagnosis was 44.2 years (range: 25-71 years).²⁶

In the present study 39 (25.2%) patients were less than or equal to 40 years of age, 60 (38.7%) were more than 40 to 50 years and 56 (36.1%) were more than 50 years of age with the median age at diagnosis being 47 years.

The disease appears among younger females in Saudi Arabia than in USA and European countries. Our data is similar to the annual report of Saudi cancer registry that showed 26.4% of female breast cancer patients developed before 40 years of age.²⁷ compared to only 6.5% in USA female citizens. It implies that mammography should be performed in Arab populations prior to the younger average age at onset.²⁸

Although diagnosis of cancer is stressful at any stage in life, women at an early age encounter many challenges. Especially the patients in the younger age group have aggressive clinicopathologic features, and apart from the disease itself other issues like infertility, pregnancy, bone health, and psychosocial problems are simultaneous and affect their quality of life.

In our study 20 (51.3%) cases were of grade III in patients ≤ 40 years, 26 (43.3.8%) in >40 -50 years old were of grade II and 25 (44.6%) were of grade III in patients more than 50 years of age.

A multicentre nationwide study in China in 2011 found that 15.7% of patients were diagnosed at grade I, 44.9% at grade II, 18.7% at grade III, and 2.4% at grade IV.²⁹ In another study conducted in Egypt on cases diagnosed between 2004 -2008, the majority (88%) of Gharbiah population-based cancer registry (GCR) cases, including those ≤ 40 years of age, were diagnosed with grade II, or moderately differentiated tumors. However, the majority (56%) of younger (≤ 40 years of age) SEER US Surveillance, Epidemiology, and End Result cases were diagnosed with grade III, poorly differentiated tumors.³⁰

In the Iranian study conducted by Mehrdad et al, the authors reported that the most common pathological feature of breast tumor was invasive ductal carcinoma (68.2%) and the rarest were sarcoma (0.4%) and papillary carcinoma (0.4%)²⁶. In our study 36 (92.3%) cases were of invasive ductal carcinoma (IDC) among the younger

age group (≤ 40 years), 56 (93.3%) cases in the middle age group (>40 -50 years) and 50 (89.3%) cases in patients more than 50 years of age. Our data showed that the majority of the cases in all age groups were IDC rather than invasive lobular carcinoma (ILC) or other types.

The worse distribution by extent of disease in younger and older women might be implicated due to diagnostic delays for different reasons and this could have predisposed to the different prognosis observed among age groups.

Literature reports revealed substantial differences in the TNM staging of breast cancer from various countries. Tang et al in 2011 conducted a study in China included 209 patients aged ≤ 35 years and 213 patients aged ≥ 60 but < 70 years, between 2000 -2004 and reported clinicopathological features, molecular subtypes, therapeutic strategies, and their prognosis. Tumor size was of significant difference between the 2 groups ($p = 0.018$), with more T2 and T3 tumors in the young group and greater lymph node involvement in young patients with stage T1 tumors ($p = 0.033$). More patients received chemotherapy in the young group ($p < 0.001$) and preferred breast-conserving surgery ($p = 0.031$).³¹

In the current study more T3 tumours were noticed in the younger group ≤ 40 and more T2 in the middle age group and greater lymph node involvement N2 in the age group more than 50 years.

Kotepui et al from Thailand observed 7,711 breast cancers over a 10 year-period. The vast majority of breast cancer cases (88.8%) were diagnosed by histology as primary lesions in the breast. More than one third (36.4%) of patients with breast cancer had regional lymph node involvement.³²

Barchielli et al conducted a study comprising a large population-based series of 1,182 invasive breast cancers during the period from 1985-1986 in the province of Florence, Italy. The proportion of cases without nodal involvement progressively lowered from 59% in the age group $< \text{or} = 39$ years to 22% in the age group $> \text{or} = 80$ years. The extent of disease was unknown in 14% of cases aged 70-79 years and in 43% of those aged $> \text{or} = 80$ years (other age groups: 3%-5%).³³

For distant metastasis it was quite common in Iranian patients (40, 15.5%) at time of diagnosis.²⁶ In our study distant metastases (M1) was found in 11 (28.2%) cases ≤ 40 , 7 (11.7%) cases >40 -50 years of age and 9 (16.1%) in cases more than 50 years of age.

At KFMC and in all the age groups the majority of patients were treated with a combination of surgery, chemotherapy and radiation. Tang et al reported that more patients received chemotherapy in the young group ($p < 0.001$) and preferred breast-conserving surgery

($p = 0.031$). For many reasons, including body image and quality of life, breast-conserving surgery, whenever possible, is certainly desirable for majority of young women. But when deciding so, risk of local recurrence should be considered although no studies have demonstrated conservative surgery in young women to have a negative impact on survival.³¹

Adjuvant chemo and endocrine therapies in young women raises issues of long term side effects, including the induction of an early menopause, fertility impairment, and adverse effects on bone mineral density and of the development of a second malignancy with radiotherapy.³⁴

The mean survival time of our study subjects at the end of three years was 37.6, 39.3, and 38.3 months for patients aged ≤ 40 , >40 -50, and >50 years respectively. Similar to our results, a French study had been conducted to investigate the influence of age on breast cancer prognosis among premenopausal women and revealed that younger patients had significantly lower survival rates and higher local and distant relapse rates than older patients.³⁵ The 6-year disease-free survival (DFS) was 80% and 66% in the elderly and the young groups in a Chinese study conducted in 2011.²⁹

Specifically, it has been reported in previous studies that women aged less than 40 were 44% and 9% more likely to die of stage I (HR = 1.44; 95% CI, 1.27-1.64) and stage II breast cancer (HR = 1.09; 95% CI, 1.03-1.15), respectively.^{36,37}

Across all histologic subtypes and stages, breast cancer survival rates are comparatively lower for women <40 years of age than for older women.

CONCLUSION

Compared with elderly women, young breast cancer patients and middle aged patients have different clinicopathological features and their response to treatment varies. Patients with different stages of breast cancer have many implications, and henceforth it is required for the clinicians to do proper assessment and concentrate on appropriate treatment strategies for women in different age groups.

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