Original Article

Breast cancer in young women: The effect of age on tumor biology and prognosis

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ABSTRACT

Background: Breast cancer (BC) is primarily a disease of older or postmenopausal women. Due to the small number of reported patients and difficulty in diagnosing BC in younger women studying this disease in this group has been challenging. Controversy exists regarding the relationship between age and prognosis as young women have generally been found to have a poor prognosis. This study compares breast carcinoma in women above and below 35 years of age highlighting age as an adverse factor in the presentation, recurrence, and prognosis of the disease. **Materials and Methods:** Two hundred and seventy-nine patients, having undergone a BC operation at a tertiary-care center between June 2005 and June 2010 were studied. Prognosis of breast carcinoma in women above and below 35 years was compared based on the stage and grade of the disease at the time of presentation, estrogen receptor/progesterone receptor (ER/PR) and HER2/neu status, recurrent disease on follow-up and mortality. Comparisons between these factors in the two groups were drawn using SPSS version 16.0. **Results:** Forty-seven patients were under 35 years (16.8%), and 232 patients were older than 35 years (83.2%). Women under 35 presented more often with stage 3 or 4 as compared to the other group. Mammogram grades were similar in both age groups. 52.5% of women below 35 years were given neoadjuvant chemotherapy versus 31.5% of women above 35 years. 93% of women in both age groups underwent surgery. There was statistically significant increased ER/PR negativity, HER2/neu positivity among women under 35 years of age as compared to the older group. 12.76% of women below 35 years had locoregional recurrence versus 5.17% of women above 35 years. 17.02% of women below 35 years had metastasis at the time of follow-up versus 6.46% of women above 35 years. Mortality in women under 35 years was 23.4% compared to 16.37% in women above 35 years. **Conclusions:** Young age (<35 years) is strongly associated with several poor prognostic factors. There is a need for aggressive management of BC in these women to reduce the incidence of recurrence, metastasis, and mortality.

Key words: Breast cancer, metastasis, mortality, recurrence

INTRODUCTION

Breast cancer (BC) is one of the most common causes of cancer-related morbidity and mortality worldwide. However, it is primarily a disease of older or postmenopausal women.[1] Women younger than 35 years account for <4% of cases of BC diagnosed each year. Due to the small number of reported patients and difficulty in diagnosing BC in younger women owing to the density of their breast tissue, studying this disease in this group has been challenging.

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Studies have shown BC in younger women to have a poor response to treatment and a bad prognosis.[2-5] This might be either due to a more advanced disease at the time of diagnosis or due to the difference in the tumor biology itself.[1] It has been suggested that BC arising in young women is a unique biological subset characterized by less hormone sensitivity and higher HER2/epidermal growth factor receptor expression.[6]

With the increasing survival from BC, the potential effects of delayed treatment and the impact on quality-of-life have become increasingly important. More than 90% of women whose BC is found in an early stage will survive.[5,6] Further study into this aggressive form of the disease can provide the understanding required for early detection and prompt treatment that can significantly improve women's chances of surviving this disease. The aim of this study was to highlight age as an adverse factor in the presentation, recurrence, and prognosis of BC via comparison of the

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clinical characteristics of the disease in women above and under 35 years of age.

MATERIALS AND METHODS

Study design

This is a retrospective study conducted between June 2005 and June 2008, and as a prospective study between July 2008 and June 2010.

Patients and grouping

Patients that either presented to or referred to the Department of Surgery of a tertiary-care center (University Medical College Hospital) diagnosed with BC stages 1 to 4 with pathologically confirmed evidence were included in the study. The patients were then grouped on the basis of age above and under 35 years both the groups were compared regarding the clinical presentation and the modality of treatment they received. Male BC patients were excluded, along with women who presented with any other carcinoma, carcinoma-*in-situ* or incompletely treated patients. Additional exclusion criteria were any therapy prior to diagnosis (surgery/radiotherapy/chemotherapy), previous history of malignancy and history of any other medical illness, which would otherwise limit the survival of the patient in the absence of malignancy. All patients underwent standard treatment modalities (neoadjuvant or adjuvant chemotherapy, radiotherapy, chemoradiation, and/or surgery: Modified radical mastectomy (MRM)/breast conservation surgery (BCS)/toilet mastectomy depending on the stage of presentation.

Data collection

Following approval of the study protocol by the Institutional Ethical Committee, patients for the study were recruited both retrospectively and prospectively after written informed consent was obtained in the language comprehended by the patient. Patients were selected consecutively after exclusion criteria were applied. Data were collected from patient records, histopathological reports, operation notes, and prospectively by recording clinical details and findings in proformas. All patients were followed-up in order to assess the prognosis. The average follow-up period was 1-year in all the cases. Results were derived based on the performance of the patients after 1-year follow-up period.

Data analysis

Prognosis was assessed based on age, stage of the disease at the time of presentation, estrogen receptor/progesterone receptor (ER/PR) and HER2/neu status, recurrent disease on follow-up and mortality. Other variables that were studied were history of pain, Peau d'orange or nipple discharge, presence or absence of lump, location of the lump, history of breastfeeding, family history of breast or ovarian cancer, menopause, hormonal intake, chest X-ray, ultrasonogram findings, bone scan, mammogram findings, neoadjuvant chemotherapy, surgery and metastasis at follow-up. The data were analyzed using SPSS (version 16.0) and conclusions were drawn based on the percentage. Chi-square test was used to compare the stage, grade, ER/PR, HER2/neu status, and outcomes of the two age groups with the level of significance set at $P < 0.05$.

RESULTS

The study population comprised of 279 women with BC, of which 47 were below 35 years (16.8%) and 232 patients were over 35 years (83.2%). In the under 35 years age group, 57.4% of the women had right-sided disease as compared to 49.5% in the above 35 years age group. 38.29% of women in under 35 years age group presented with a history of pain as against 41.81% of women above 35 years. 17.02% of women below 35 years presented with a history of nipple retraction and discharge versus 15% of women in the other group. Peau d'orange appearance was seen more often in younger women 31.9% versus 6.89% of women above 35 years. 93.10% of women above 35 years had breastfed as compared to 76.59% in the under 35 years group. 10.63% of women below 35 years had family history of breast or ovarian cancer as against 6.89% of women above 35 years. 34.04% of women below 35 years had a history of oral contraceptive intake versus 14.65% of women above 35 years.

Metastasis to distant organs was more in women with age <35. 4.2% of women below 35 years had metastasis to lungs at the time of presentation versus 3.01% of women above 35 years. 4% of women below 35 years had metastasis to the liver at the time of presentation as compared to 9% in women above 35 years. 12% of women in both the age groups showed bone scan positivity at the time of presentation. 93.61% of women below 35 years had infiltrating ductal cancers (IDC) versus 98.7% of women above 35 years. 64% of women below 35 years presented with stage 3 or 4 versus 45% of women above 35 years ($P = 0.03$, significant) [Table 1]. The percentage of women in both the age groups presenting with breast imaging reporting and data system (BIRADS) grade 5 and grade 4 findings in mammogram were similar ($P = 0.983$, not significant) [Table 2].

About 52.5% of women below 35 years were given neoadjuvant chemotherapy versus 31.5% of women

Table 1: Stage of the disease at the time of presentation

	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	Stage 4 (%)
Under 35 years	3 (6.38)	14 (29.78)	25 (53.19)	5 (10.63)
Above 35 years	41 (17.6)	87 (37.5)	74 (31.9)	30 (12.9)

P=0.030

Table 2: Mammogram results according to age group

Mammogram results	Grade 5 (%)	Grade 4 (%)	Not performed (%)
Under 35 years	34 (72.34)	9 (19.15)	4 (8.51)
Above 35 years	170 (73.28)	44 (18.96)	18 (7.76)

P=0.983

above 35 years. 93% of women in both age groups underwent surgery. 29.72% of women below 35 years were ER/PR positive versus 62.55% in above 35 years ($P < 0.001$, significant) [Figure 1]. 40.74% of women below 35 years were HER 2/neu positive versus 19.61% of women above 35 years ($P < 0.001$, significant) [Figure 2]. 12.76% of women below 35 years had locoregional recurrence versus 5.17% of women above 35 years. 82.95% of women below 35 years came for follow-up versus 87.5% of women above 35 years. 17.02% of women below 35 years had metastasis at the time of follow-up versus 6.46% of women above 35 years [Figure 3]. Mortality rate in women under 35 years was 23.4% compared to 16.37% in women above 35 years ($P = 0.004$, all three adverse outcomes measured).

DISCUSSION

Breast cancer is the most common malignancy among women in developed countries, and 12% of the disease occurs in women aged 20–34 years.[7] Though young women constitute a minority of patients, they commonly have distinct concerns and issues as compared to older and postmenopausal women, including queries regarding fertility, contraception, and pregnancy. Young women are more likely to have questions regarding potential side effects of therapy and the risk of relapse or recurrence. The absence of BC screening until the age of 40 or 50 predisposes these younger women to present more often at an advanced stage. The challenges in managing breast malignancy in this age group can at least partially be attributed to this delay in diagnosis.

In our study, women presenting at a younger age group (<35 years) had a significantly worse prognosis when compared to older patients in terms of recurrence, distant metastasis, and mortality. A multitude of reports, including large-scale studies have demonstrated similar worse outcomes in younger women.[2-4,8-14] In 1994, Swanson and Lin found mortality due to BC is greatest in younger women.[15] The younger age group presents more often with a positive family history, the higher BIRADS score on mammography and as locally advanced breast carcinoma. In our study, we found that women under 35 years mostly presented with grade 4 or 5 on mammography and were diagnosed to be in advanced stage 3 or 4 at the time of presentation. Furthermore, young women were found to have an increased rate of local recurrence and distal metastasis at the time

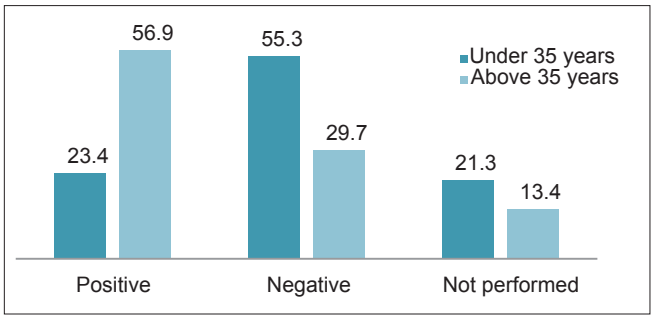

Figure 1: Estrogen receptor/progesterone receptor status of the study population (in %). $P < 0.001$

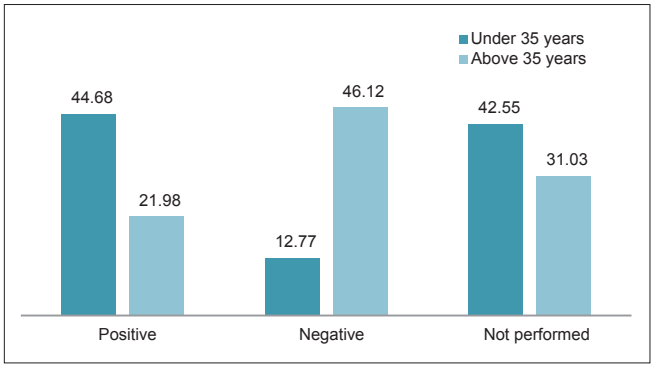

Figure 2: HER 2/neu status of the study population (in %). $P \leq 0.001$

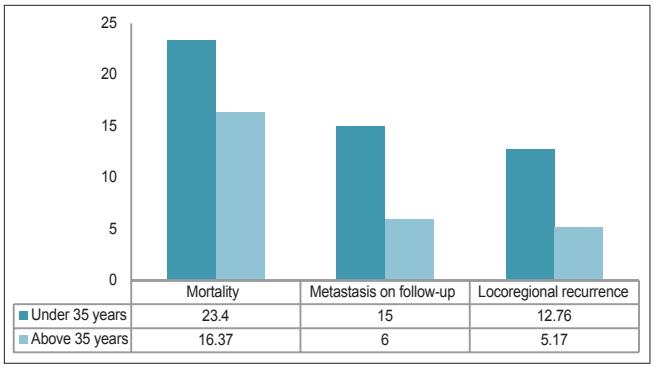

Figure 3: Comparison of outcomes in both age groups (in %). $P = 0.004$

of presentation with a worse prognosis compared to women above 35 years. It has been shown that the risk of recurrence remains high regardless of whether the primary is managed with BCS or MRM.[16-22] Experience at Institute curie showed an association between young age and distant metastasis and also an association between younger women and decreased cancer-specific survival.[23] An update from national surgical adjuvant breast and bowel project protocol B-06 showed that women younger than 40 years perform worse irrespective of the treatment modality.[24] There are equivalent survival rates with BCS and radiotherapy compared with MRM in women with early BC. The role of BCS in women under 35 years of age is controversial owing to their apparent higher risk of local recurrence than older women.[25]

Comparing pathological features and tumor biology, it was found that young patients have a different distribution of pathologic features that have previously been shown to be predictive of treatment failure when compared to their older counterparts.[7] Poor histological grade with necrosis has been shown to have a worse prognosis in younger women. Rosen *et al*.,[26] Fisher *et al*.[27] and Kurtz *et al*.[28] reported an increase in lymphocytic infiltrate and tumor grade in young women with BC. They are more likely to have higher grade, hormone response negative tumors with a high proliferative fraction and lymphovascular invasion.[29]

Majority of BC presenting in young women are invasive and most often are IDC. Younger women are more likely to present with larger tumors and appear to have worse outcomes stage for stage.[3,28] Most of the younger age group women in our study were diagnosed to have invasive ductal carcinoma at the time of diagnosis. Other studies have found that young women are more likely to be diagnosed at an advanced stage and with bilateral disease.[30-33] This leads to the question of whether the poorer prognosis in young women is due to their age alone or due to a different and more aggressive subtype of the tumor in these women, as illustrated by Anders *et al*.[6]

Breast cancer in the young has a greater incidence of being familial, and the identification of BRCA1 and BRCA2 has established the biologic basis of the disease in relation to the young age.[7,34] In our study, women <35 years exhibited a higher familial incidence compared to the older patients. The likelihood of a BRCA mutation is higher in women under the age of 45 with a strong family history of BC and/or ovarian cancer.[35]

The most important prognostic factors include tumor size, nodal status, histological grade, HER2/neu, and hormone receptor status. Younger age group has been shown to be associated with an increased incidence of ER/PR negativity compared to older patients.[2-4] Bal *et al*. have shown that women under 30 years of age with positive receptor status comprise a subgroup of young patients with a better prognosis.[8] Swanson and Lin proposed that when it comes to the management of BC, decisions have to be driven by the tumor biology and performance status rather than the age alone, as it has been suggested that consideration of age does not provide any additional prognostic advantage over other factors.[15]

CONCLUSION

Breast cancer presenting at a young age (<35 years) is strongly associated with increased morbidity, mortality, and metastasis. Hence, a strict surveillance for early detection of BC should be undertaken for a better life for those young women suffering from carcinoma breast.

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