

Is Breast Cancer in Younger Women a More Aggressive Variant ? A Comparative Study

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Introduction: Breast cancer is the commonest malignancy in women in the world. About 5% of all breast cancer patients are 35 years old or younger. Current literature suggests that breast cancer in these younger women may be different in etiology, clinical features and outcome from the disease seen in older women. **Patients and methods:** We included all breast cancer patients who underwent surgical treatment at Surgical Unit IV, Jinnah hospital, Lahore from December, 1998 to December, 2003. All patients who left against medical advice or were lost to follow up before completing treatment at our hospital were excluded. The patients were divided into two groups by age. Those who were 35 years old or younger were placed in group I (88 patients) and those older than 35 years were placed in group II (54 patients), which served as the control group. We compared the clinical presentation, the risk factor profile, and the grade and the stage of the tumor at presentation in younger women and their older controls. **Results:** The mean age in group I was 29.38 years \pm 3.68 years. While the mean age in group II was 44.41 years \pm 7.64 years. The commonest mode of presentation in both groups was a painless lump. (93.2% in group I and 66.67% in group II; p value < 0.001). The distribution of classical risk factors was similar in the two groups. These included family history (12.5% in group I and 11.1% in group II), nulliparity (7.95% in group I and 7.4% in group II), and oral contraceptives use (14.77% in group I and 12.96% in group II). Younger patients presented with a greater number of poorly differentiated (Grade III) tumors compared to the older patients. (73.76% vs. 24.07%; p value < 0.001). They also presented more frequently with hormone insensitive tumors (79.55% in group I vs. 24.52% in group II ; p value < 0.001). Mammography was positive more often in older women compared to the younger ones (97.44% vs. 41.38% ; p value < 0.001). Ultrasound was done in 67.05% of the younger women and 27.78% in the older women. It was suggestive of malignancy in 89.83% of the younger women and 86.67% of the older ones. Modified radical mastectomy was done in 75% of the younger patients (Group I) and 61.11% of the older patients (Group II). Radical mastectomy was done in 19.32% of group I patients and 27.78% of group II patients. Older women underwent breast conservation treatment more often than the younger women (11.11% vs. 5.68%; p value < 0.05) Adjuvant chemotherapy was given more often to younger women (73.86% in group I vs. 9.26% in group II; p value < 0.0001). On the other hand, older patients received hormonal therapy more often than the younger ones (74.07% vs. 20.45%; p value < 0.001). Younger patients also received adjuvant radiotherapy more frequently than their older counterparts (84.32% vs. 49.26; p value < 0.05). **Conclusion:** We conclude that women with breast cancer who are 35 years old or younger have more aggressive tumors than the older patients i.e. they present at a higher stage with poorly differentiated tumors that are frequently hormone insensitive.

Key words: Breast cancer, variant, younger women

Breast Cancer is the commonest malignancy in women. It accounts for 22% of all females cancers in the world ¹. However, only 5% of the cases of breast cancer occur in young women aged 35 years or less ². This percentage is anticipated to be higher in our population since the mean age at presentation of breast cancer patients in Pakistan is lower than Western women, mostly due to the lower life expectancy of our population ³.

It has long been disputed whether breast cancer in this young age group is a different and more aggressive disease than that seen in the older women. A number of reports in literature suggest that the disease is similar in both age groups ^{4,5} while others claim that breast cancer in younger women may differ with respect to etiology, clinical features and outcome ^{6,7}. Hence, there is conflicting evidence in literature regarding the nature of disease with respect to age.

There is, however, considerable evidence in recent literature to suggest that breast cancer in younger women

(5 years or less) is more often poorly differentiated (Grade III) and hormone insensitive compared to that seen in the older women ^{2,8,9,10,11}. Due to a greater frequency of these poor prognostic indices in young breast cancer patients, they have a worse prognosis compared to their older counterparts ^{10,11,12,13,14,15}.

Several questions regarding the nature of the disease in young women need to be answered. First, it remains unknown whether the distribution of classical risk factors of breast cancer is any different in the younger age group. Second, it is unclear if young breast cancer patients present with later stage disease and have more aggressive tumors. Finally, it has to be ascertained whether the younger breast cancer patients receive the same treatment options as their old counterparts. Since there are conflicting reports in literature and most of the evidence is derived from studies conducted in the West, we carried out a comparison of different features of breast cancer in the younger and older age groups.

Patients and methods:

We conducted a cohort over a period of 5 years from Dec.1998 to Dec.2003 at Surgical unit IV, Jinnah Hospital, Lahore. We included all women with breast cancer who underwent surgical treatment at our hospital during this period. Patients who left before undergoing definitive treatment at our hospital were excluded.

The patients were divided into two groups by age. Those who were 35 years old or younger were placed in group I and patients older than 35 years were assigned to group II, which served as the control group. The total sample consisted of 142 patients, 88 in group I and 54 in group II.

All patients with stage I and II breast cancers were potential candidates for breast conservation followed by radiotherapy. However, it was only performed in some of these patients, since the rest either refused breast conservation for fear of radiotherapy or underwent a more extensive surgery due to the surgeon's preference, keeping in view the risk factor status and other patient characteristics. All patients with stage III or IV cancers underwent modified radical or radical mastectomy, depending on the extension of the disease.

All patients (group I and group II) with Stage III and IV cancers received adjuvant radiotherapy. All young breast cancer patients (group I) with lesions ≥ 2.0 cm and/or considerable axillary lymph node involvement and/or systemic metastasis, received adjuvant chemotherapy while older patients with the same disease characteristics were given adjuvant chemotherapy only if their tumors were hormone insensitive and they could not receive hormonal therapy. Tamoxifen was given to all patients (group I and group II) with hormone sensitive tumors. Neoadjuvant therapy was given to those patients with stage III or IV disease, in whom skin closure was anticipated to be difficult due to large tumor size.

A specially designed form was used for data collection. This form took into account the demographic features, mode of presentation, risk factor profile, histological diagnosis, other diagnostic procedures, stage of the disease and the treatment offered. It consisted of 25 variables, most of which were categorical.

The data was analyzed using SPSS version 11.0 software. The significance of differences in categorical variables was evaluated using the chi-square test and the significance of differences in continuous variables was evaluated using the student's t-test. The level of significance was taken as < 0.05 .

Results:

The total sample consisted of 142 patients. There were 88 patients in group I (≤ 35 years old) and 54 in group II (> 35 years old).

Age distribution: The mean age of the patients in group I was 29.38 years \pm 3.68 years and the range was from 18 to 35 years. The mean age of the patients in group II was

44.41 years \pm 7.64 years. The range was from 36 to 66 years.

Mode of presentation: The commonest mode of presentation in both groups was a painless lump. However, patients in group I (younger women) presented with a lump more frequently than patients in group II (93.2% vs. 66.67%, p value < 0.001).

Other modes of presentation included nipple discharge (5.68% in group I, 18.5% in group II) mastalgia (4.55% in group I, 11.11% in group II) and skin changes including erythema and tethering (4.55% in group I, 9.26% in group II). Mean tumor size was larger in group I compared to group II (4.9cm \pm 1.31cm vs. 3.34cm \pm 1.01cm; p value < 0.05)

Risk factor profile: 7.95% of the younger patients were nulliparous compared to 7.4% of the older patients. The difference was not statistically significant. 84% of the younger women and 92.6% of the older women has breast fed for 2 years or more. Again, the difference was not statistically significant. [Table 1]

Family history of breast cancer was positive in first degree relatives in 12.5% of the younger patients and 11.11% of the older ones. The difference was not statistically significant.

Oral contraceptives use in the past ten years was documented in 14.77% of the younger patients and 12.96% of the older patients, the difference being statistically insignificant.

Stage and histology: The commonest stage at presentation was stage III both in group I and II (63% and 22% respectively). 2% of the younger patients presented at stage I, 3% at stage II, 63% at stage II and 20% at stage IV. 8% of the older women presented at stage I, 14% at stage II,

22% at stage III and 10% at stage IV. Hence, most young patients presented at stage III and IV whereas most of the older ones presented at stage II and III. [Figure 1]

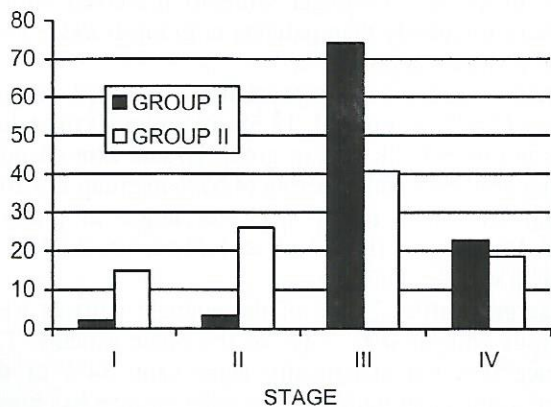
11.36% of the younger patients presented with grade I tumors, 14.77% with grade II and 73.85% with grade III tumors. Among the older patients, 31.48% presented with grade I tumors, 44.44% with grade II and 24.07% with grade III tumors. Hence, young patients had a higher number of poorly differentiated (Grade III) tumors (73.86% vs. 27.07%; p value < 0.001). [Figure 2]

Nodal involvement was seen more frequently in the younger patients (73.86% in group I vs. 40.74% in group II; p value < 0.001). The tumors in younger women were more often hormone insensitive compared to the older women (79.55% in group I vs. 24.52% in group II; p value < 0.001). The commonest histological type was infiltrating ductal carcinoma in both groups (85% in group I and 83% in group II).

Diagnostic modalities: Mammography was done in 32.95% of the younger patients and 72.22% of the older women. 41.38% of the mammograms in young women were suspicious or positive for malignancy compared to

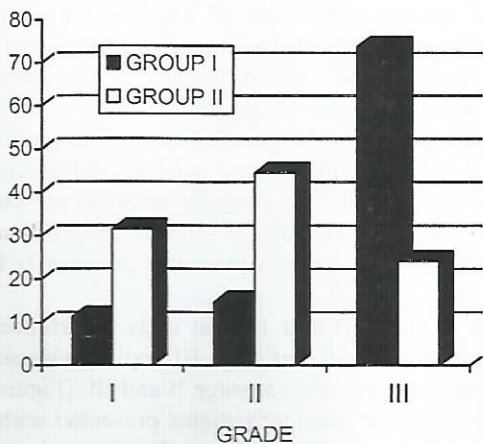
97.44% in older women (p value < 0.001). Hence, the yield of mammography was higher in women older than 35 years.

Fig. 1 TNM stage distribution



Group I: Patients ≤35 years (n = 88)
Group II: Patients > 35 years (n = 54)

Fig. 2 Distribution of tumour grade.



Ultrasonography was done in 67.05% of the younger patients and 27.78% of the older ones. It was suggestive of malignancy in 89.83% of the younger women and 86.67% of the older women.

Treatment: Among the younger patients, 75% underwent modified radical mastectomy, 19.32% had radical mastectomy and 5.68% underwent breast conservation treatment. Among the older women, 61.11% underwent modified radical mastectomy, 27.78% had radical mastectomy and 11.11% had breast conservation treatment. [Table 2]

Adjuvant chemotherapy was given to 73.86% of the younger patients and 9.26% of the older ones (p value < 0.0001). Hormonal therapy was given to 74.07% of the older women and 20.45% of the younger women (p value < 0.001). 84.32% of the younger women and 49.26% of

the older women received adjuvant radiotherapy (p value < 0.05). Neoadjuvant therapy was given to 27.27% of the younger women and 16.67% of the older ones.

Table 1: Comparison of the risk factor profile

Risk factor	Group I percentage of patients	Group II percentage of patients
Family History	12.5	11.11
Nulliparity	7.95	7.4
No breastfeeding	16	7.4
OCP use	14.77	12.96

Group I: Breast cancer patients ≤35 years

Group II: Breast cancer patients > 35 years

Table 2: Comparison of treatment

Treatment	Group I (%age)	Group 2 (%age)
Surgery		
Radical mastectomy	19.32	27.78
Modified radical mastectomy	75	61.11
Breast conservation treatment	5.68	11.11
Adjuvant therapy		
Adjuvant radiotherapy	84.32	49.26
Adjuvant chemotherapy	73.86	9.26
Hormonal therapy	20.45	74.07
Neoadjuvant therapy	27.27	16.67

GROUP 1: Breast cancer patients ≤35 years

GROUP 2: Breast cancer patients > 35 years

Discussion:

Breast cancer in young women aged 35 years or less has given rise to considerable interest because of the possible differences in terms of pathogenesis and prognosis, compared with breast cancer in older women. Published studies on this argument are not easily compared because of contrasting results and differences in the age ranges and the prognostic parameters considered. Moreover, most of the current evidence has been derived from studies conducted in the West. With these considerations in mind, the present study was undertaken to analyze the differences in the clinical presentation and the nature of disease with respect to the age of the patients. The results of our study show that breast carcinomas in the younger women differ in clinical, pathological and biological features from breast carcinomas in older women.

Since women aged 35 years or less rarely have mammography before developing signs of breast disease, they are more likely than older women to present with a palpable mass^{7,14}. Our younger patients presented more frequently with a lump compared to the older controls (93% vs. 66.7%; p value < 0.001). Unfortunately, a consequence of presenting with a palpable mass is that the tumors tend to be larger in size^{6,7}. Our younger patients presented with a mean tumor size of 4.9 cm compared to 3.3 cm in the older women (p value < 0.05).

Various studies have shown that in addition to being larger in size, the breast cancers in young women are more

frequently associated with nodal involvement, compared to older women^{4,7,8}. We found a similar trend in our sample (74% in group I vs. 41% in group II; p value < 0.001).

It has long been argued whether breast cancer in younger women is a more aggressive disease than that seen in older women. However, a large number of studies have recently shown that breast cancer in young women is indeed biologically more aggressive i.e. younger women present with a greater number of poorly differentiated (Grade III) tumors compared to their older counterparts^{2,8,9,10,12}. Tumors in young women are also more frequently hormone insensitive^{9,10,11,12,13}. Our results agree with these earlier observations. Compared to the older controls, our younger patients more often had tumors that were Grade III (74% vs. 24%; p value < 0.0001) and hormone insensitive (79.5% vs. 24.5%; p value < 0.001).

Some authorities have suggested that the aggressive nature of breast cancer in young women may be explained by the observation that these young patients more often have a positive family history of breast cancer in first degree relatives and hence, may have some genetic predisposition^{6,11,13}. It is well established that women who are genetically susceptible develop breast cancer at an early age and their tumors are usually poorly differentiated and hormone insensitive^{1,16}. However, very few of our patients had family history of breast cancer (12.5% in group I and 11.11% in group II). The difference between the two groups was not statistically significant.

The distribution of other risk factors for breast cancer was also similar among the two groups, including nulliparity, lack of breast feeding and oral contraceptive use [Table 1]. Some western studies have shown that younger women with breast cancer are more often nulliparous compared to older breast cancer patients^{7,17}. However, women in our population begin bearing children at a younger age than western women. This may explain the observation that most of our younger patients were parous. The mean number of full term pregnancies, however, was higher in older women (5.5 vs. 3.0; p value < 0.05).

Most of our patients, both in group I and II, presented at Stage III (74% and 41% respectively) [Figure 1]. However, the younger patients presented more frequently at Stage III or IV compared to older women (94% vs. 59%; p value < 0.001). Our results are in accordance with previously recorded data which also suggests that younger patients tend to present at more advanced stages^{9,10,11}. This may be due to a diagnostic delay in the younger patients or because of the more aggressive nature of the disease in this group, or both.

It is believed that there is often a delay in the diagnosis of breast cancer in young women^{2,7,13}. This may be, in part, due to physicians' low index of suspicion in these patients since the incidence of breast cancer in women ≤ 35 years is low. Also, the lack of awareness in our population may lead to a delay in seeking medical

attention. Furthermore, the sensitivity of mammography is lower in younger women^{4,18}. Gillet D et al have reported the false negative rate of mammography to be 50% higher in women under 40 years, than that observed in older patients⁴.

Our results show that only 41% of the mammograms done in the younger women were suspicious or positive for malignancy, compared to 97% of those done in the older women (p value < 0.001). The lower yield of mammography is due to the greater breast glandularity and parenchymal density in younger women¹⁸.

Ultrasonography, on the other hand, had a similar yield in both groups of our patients (89.83% in group I vs. 86.67% in group II). Hence, ultrasonography is a better diagnostic modality than mammography in younger women^{18,19}.

At our institution, older women with breast cancer underwent breast conservation treatment more often than the younger patients (11.11% vs. 5.68%; p value < 0.05). Several other studies have reported a similar trend, mostly due to a higher locoregional recurrence rate following breast conservation treatment in younger women^{7,9}. Also, the majority of our younger patients could not be offered breast conservation treatment since they had advanced cancers.

Adjuvant chemotherapy was given more often to the younger patients, compared to their older counterparts (74% vs. 9%; p value < 0.0001), since a greater number of young patients had nodal involvement and metastatic disease [Table 2]. Young patients tolerate chemotherapy better than the older ones²⁰. However, the adverse effect of chemotherapy on ovarian function and fertility has to be kept in mind when treating young women who want to retain their reproductive potential^{9,20}.

The activity of Tamoxifen, a selective estrogen receptor modulator, against breast cancer, is mainly achieved by blocking the estrogen receptor. It has been shown to reduce the risk of recurrence of breast cancer and to improve survival in patients with hormone sensitive tumors, irrespective of the menopausal status or use of adjuvant chemotherapy²¹. It was used more frequently in older patients (Group II) at our institution, since older patients more often had hormone sensitive tumors than younger ones.

In conclusion, young patients with breast cancer, who are 35 years old or younger, more often present at an advanced stage. This may be in part due to the more aggressive nature of their tumors i.e. they are more often poorly differentiated and hormone insensitive, compared to older patients.

Our study is limited by a relatively small sample size and the lack of long-term follow-up in our patients. Hence, further large scale research is needed to compare clinical features and outcome of breast cancer in the younger and the older patients in our population.

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