

Differences in clinicopathological features and molecular phenotype of breast carcinoma between patients younger than 40 years and those who are older: A study from Pakistan

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Abstract

Background

The debate whether breast cancer in women under 40 years of age is distinct from breast cancer in women above 40 is still inconclusive with various published studies providing conflicting evidence. The majority of studies however suggest that breast cancer in younger women (< 40) is more aggressive with worse clinicopathological features. However, the issue is by no means settled and a number of studies are still going on. Our objective was to analyze different clinicopathological variables and determine whether statistically significant differences are present between those under 40 and those above 40 years of age. The present paper contributes to this debate by reporting our findings.

Methods

Descriptive cross sectional study of 482 breast cancer cases reported between January and December 31, 2016 which included 380 patients (above 40 years of age) and 102 (under 40 years of age). Variables included grade, stage, axillary lymph node metastases, lymphovascular invasion and molecular groups. p-value less than 0.05 was taken as significant.

Results

Over 21% patients were younger than 40 years. Differences in histologic grade, stages of T1, T2, and T4, Estrogen Receptor (ER) and Progesterone Receptor (PR) status, Her2neu status, triple negativity and molecular groups between patients younger than 40 years and those older than 40 years were statistically insignificant. Differences in stage T3, axillary metastases and lymphovascular invasion were statistically significant.

Conclusion

Statistically significant differences were noted in some clinicopathological variables. Majority of variables indicating more aggressive disease were seen in patients older than 40 years of age. Additional studies with larger number of patients under 40 years of age are required to resolve the issue conclusively so that young women with breast cancer are not treated too aggressively unless there is unequivocal statistical evidence that breast cancer is more aggressive in patients under 40 years of age.

Background

Breast cancer is the most common type of cancer of women in the world. About 5 to 7% cases of breast cancer in the Western countries occur in women under age of 40 years. In Asian women, breast cancer presents relatively earlier compared to the Western countries and the incidence of breast cancer among

young women under 40 years of age is relatively high. Recent studies from Asia have shown that 11% to as high as 28% of all breast cancers are diagnosed in women under 40 years of age and the incidence in young women is increasing in the Asian population [1–10]. Various studies have shown that women who develop breast cancer at a younger age (< 40 years) tend to have more aggressive disease with worse clinicopathological features. Young women with breast cancer have a higher likelihood of biologically aggressive disease and metastatic disease at the time of diagnosis resulting in poorer prognosis and leading in turn to a need for more aggressive treatment. In addition, there is long term toxicity related to treatment as well as psychosocial issues in such patients. Studies have shown that breast cancers in women under 40 years of age are more likely to be of higher grade and stage, and more likely to have axillary lymph node metastases, and lymphovascular invasion. They are more likely to present with more aggressive phenotypes and have poorer survival rates compared to breast cancer in older women. Percentage of young Asian women with risk factors for breast cancer is significant [1–6, 11–13].

The aim of this study was to analyze different clinical, pathological and molecular variables in women with breast cancer in Pakistan and to determine whether statistically significant differences exist in these variables between breast cancer patients under 40 and those above 40 years of age.

Materials And Methods

The Histopathology database of the Section of Histopathology, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital was searched for cases of breast cancer resections reported between January 1, 2018 and December 31, 2018. A total of 482 breast cancer specimens were included in the study. This was a descriptive cross-sectional study through consecutive sampling technique and patients were divided into two groups, those younger than 40 years of age and those older than 40 years of age. Patients were included in both groups until the desired sample size was achieved. The data was double entered by a data entry operator in Epidata (version 3.2) and data entry errors were removed. The clean data was then converted into SPSS (SPSS for windows 15.0; SPSS Inc, Chicago. IL. USA) version 22. Data was analyzed for descriptive and inferential statistics. Frequencies and percentages were calculated for all pathological study variables. Confounding factors were controlled by stratification of age with tumor grade, nodal status, T-stage, Estrogen Receptor (ER) /Progesterone Receptor (PR) and Her2neu, triple negative, lymphovascular invasion and molecular groups to see the impact on age groups classification variables through chi square test. If frequency was found to be less than 5 in 2*2 tables, then Fisher's exact test was applied, p-value less than 0.05 was taken as significant.

Results

A total of 482 mastectomy and breast conservation specimens of breast cancer was reported during the study period (January 1, 2018 to December 31, 2018). Of these, 380 (78.8%) were seen in women older than 40 years of age while 102 (21.2%) were reported in women younger than 40 years of age. Mean tumor size in women above 40 was 5.8 cm (range 0.7 cm to 11.0 cm, median size 5.5 cm) while mean tumor size in women under 40 years of age was 6.2 cm (range 0.5 to 10 cm, median size 5 cm). The

difference between the mean tumor size in women above 40 and those under 40 years of age was not statistically significant. Overall, mean tumor size in all 482 patients was 6.0 cm in maximum dimension (median size 5.5 cm).

Overall, out of 482 patients, 241 (50%) had histological grade II and 235 (48.7%) had grade III tumors. In patients older than 40 years of age (n = 380), 194 (51.1%) had grade II while 182 (47.9%) had grade III tumors. In patients younger than 40 (n = 102), 47 patients (46%) had grade II and 53 (52%) had grade III tumors. Thus younger patients had a greater percentage of high grade disease. The details of tumor grade are shown in Table 1. The differences in histological grade between patients older than 40 versus those younger than 40 years of age were statistically insignificant (grade I, p-value: 0.1538; grade II, p-value: 0.3723; grade III, p-value: 0.4624).

Overall, in all 482 patients, 439 (91.1%) had Invasive Ductal Carcinoma (IDC), Not special type (NST), while 43 (8.9%) had variants including Invasive Lobular Carcinoma. The details of histologic types of breast carcinoma in all patients are shown in Table 2. Out of 380 patients above 40 years of age, 344 (90.5%) had IDC, NST while 36 (9.5%) had other various histological variants. Of the 102 patients under 40 years of age, 95 (93.1%) had IDC, NST while 7 (6.1%) had other various histological variants. The differences in histological tumor type in those above 40 and those under 40 years of age were statistically insignificant. In the 380 women older than 40, axillary lymph node metastases were seen in 200 (52.6%) on histological examination. In the 102 patients younger than 40 years of age, metastatic tumor in the axillary lymph nodes was seen in 40 (39.2%) cases. The differences in positivity and negativity for axillary lymph node metastases between patients older than 40 years of age versus those younger than 40 were statistically significant (p-values: 0.0168 and 0.0164 respectively).

Of the 380 patients older than 40 years of age, 154 (40.5%) had T2 tumors, while 222 (58.4%) had T3 tumors. Of the 102 patients younger than 40 years, 49 (48%) had T2 tumors while 50 (49%) had T3 tumors. The remaining 3 patients had T4 tumors. The details are shown in Table 3. The differences in the T component of the TNM staging system between patients older than 40 versus those younger than 40 years of age were statistically insignificant for T1, T2 and T4 tumors and statistically significant for T3 tumors (p-value: 0.048).

Lymphovascular invasion was seen histologically in 156 out of the 380 (41.5%) patients above 40 and in 28 out of the 102 (27.5%) patients younger than 40 years of age. The difference in the presence of lymphovascular invasion between patients older than 40 versus those younger than 40 years of age was statistically significant (p-value: 0.012).

Of the 380 patients above the age of 40, 270 (71%) had ER and PR positive tumors while 110 (29%) had ER and PR negative tumors. Of the 102 patients under the age of 40 years, 64 (62.7%) had ER and PR positive cancers while 38 (37.3%) had ER and PR negative cancers. The differences in ER and PR positivity and negativity between patients older than 40 years versus those younger than 40 years of age were statistically insignificant (p-values: 0.1048 and 0.1068 respectively).

Of the 380 patients above the age of 40 years, Her2neu was 0 or 1 + in 285 (75%), 2 + in 45 (11.8%) and 3 + in 50 (13.2%) patients. Of the 102 patients younger than 40 years of age, Her2neu score was 0 or 1 + in 72 patients (70.6%), 2 + in 14 (13.7%) and 3 + in 16 (15.7%) patients. The differences in Her2neu scores (0 or 1+; 2+; and 3+) between patients older than 40 years of age versus those younger than 40 were statistically insignificant (p-values: 0.3578, 0.6031 and 0.5139 respectively).

Of the 380 patients above 40 years of age, 72 (18.9%) had triple negative cancers while out of the 102 patients younger than 40 years of age, 23 (22.5%) had triple negative cancers. The differences in triple negative cancers between patients above 40 years of age versus those younger than 40 years of age were statistically insignificant (p-value: 0.417).

Of the 380 patients older than 40 years of age, 137 (36.1%) were Luminal A, 124 (32.6%) were Luminal B and 86 (22.6%) were Basal like. Of the 102 patients younger than 40 years of age, 28 (27.4%), 36 (35.3%) and 27 (26.5%) were Luminal A, Luminal B and Basal like respectively. The details are shown in Table 4. The differences in molecular groups between patients older than 40 versus those 40 years of age were statistically insignificant (p-value: 0.104 for Luminal A, 0.612 for Luminal B, 0.416 for Basal like and 0.608 for Her2neu tumors).

Discussion

In our study, over 21% of all breast cancers occurred in women under 40 years of age. In other studies, percentages of breast cancer under 40 years of age have ranged from 17.2–27.4% [14, 15]. A recent study from the United States argued that although approximately two third of women with breast cancer under 50 years of age are not high risk, women should receive annual mammograms from age 40 years since low risk does not confer protection [16]. A recent study from a single institution in Pakistan which compared its findings with a national US database found that breast cancer in Pakistani patients under 40 years of age was even more aggressive and advanced than breast cancer in a similar age group in the United States [15].

In our study, statistically significant differences (p-value: <0.05) between breast cancer patients under 40 and those above 40 years of age were seen only in the following clinicopathological variables: The patients older than 40 were more likely to have axillary lymph node involvement by metastatic breast carcinoma, pathologic stage T3 cancers, and lymphovascular invasion. Comparison between other variables such as tumor grade, tumor sizes T1, T2 and T4, ER, PR and Her2neu status, triple negativity, histological tumor types and molecular type were not statistically significant between the two cohorts.

Our results are in contrast to the findings in most published studies which show that women under the age of 40 are more likely to develop more aggressive breast cancer with worse clinicopathological features [17]. However, a recent study from China showed that with increased early stage and ER positive breast cancer in young patients and with better systemic treatment strategies, improved survival is being

observed in this age group [18]. A study in 2014 showed that women who developed breast cancer before the age of 40 had a higher risk of developing visceral metastases compared to older women with breast cancer [6]. Three other recent studies also found predominantly unfavorable prognostic factors and more aggressive tumor characteristics in younger women (< 40 years) with breast cancer. Recurrence free survival, metastasis free survival and overall survival were all lower in women under 40 [19, 20, 21].

In contrast, a recent study from Georgia found a relatively low risk of mortality among younger women with breast cancer most likely due to higher proportion of early stage cancer and high level use of chemo and radiotherapy [22].

In our study, 52% patients younger than 40 years of age had grade III cancer. In a study from Singapore which described breast cancer in patients under 40, over 61% had grade III cancers [7].

Unlike our findings, a study from Nepal showed that mean tumor size was significantly larger in young women with breast cancer, axillary lymph node metastases were much more common compared to older women with breast cancer, the proportion of stage III (or IV) disease was higher, the proportion of histological grades II and III was higher, lymphatic and vascular invasion was more common and the proportion of triple negative tumors was higher in breast cancer patients under 40 years of age compared to those over 40. On the other hand, the percentage of ER and PR positive tumors was lower [4]. Another study from Pakistan also demonstrated that younger women (under 40) with breast cancer were more likely to have larger tumors that were high grade, lymph node positive, and ER and PR negative compared to women who were older than 40 years of age [5]. The above findings were supported by a recent study which showed that younger patients with breast cancer were more likely to have larger sized, higher grade and stage tumors with greater frequency of lymph node metastases as well as distant metastases and higher frequency of Her2neu overexpression and less likely to have ER and PR positive tumors compared to older women with breast cancer [12]. Another recent study also showed that young women with breast cancer not only had higher grade cancer and more common lymph node metastases compared to older women but they were more likely to have triple negative and Her2neu positive (Luminal B) tumors [23]. The fact that younger women with breast cancer were more likely to have more aggressive disease (triple negative and Her2neu positive cancers) compared to older women with breast cancer was also reported in a study by Keegan et al [24]. However, a study from Northern Ireland published in 2010 which examined breast cancer in women under 40 years of age found lymphovascular invasion in 50.9% patients and lymph node metastases in 40%. Grade III cancer was found in 40.7%, ER, PR and Her2neu positivity was found in 76.8%, 39.3% and 30.2%, respectively. This study suggested that contrary to findings in other published studies, breast cancer in younger women may be less aggressive and more hormonally responsive. However, the number of patients in this study was very small [25]. Another recent study also demonstrated a high proportion of ER and PR positive cancers in women under 40 years of age. Out of 52 patients under the age of 40 years, 82% and 78% had ER and PR positive cancers, respectively [26]. A study from Pakistan which included a large number of breast cancer patients under 40 years of age (n = 401) as well as those above 40 years of age (n = 405) concluded that although breast cancer in the two groups of patients was biologically distinct with significant differences in grade, tumor stage, receptor

status, there were no significant differences between the two groups with respect to loco regional recurrence free survival, disease free survival and overall survival, and cancers in women under 40 were not associated with poorer outcomes [27]. However, majority of recent as well as older studies suggest that breast cancer in women under 40 years of age is more aggressive with a poorer prognosis than breast cancer in women above the age of 40 years. It is clear that breast cancer in patients younger than 40, although rare, is an important problem [28–31]. Since current survival rates for breast cancer are significant, future fertility is very important for quality of life in young breast cancer survivors. However, chemotherapy given to young patients carries a significant risk of infertility. A recent study demonstrated adverse reproduction health outcomes in young women with breast cancer who were treated with chemotherapy [32].

Our findings show that there are no significant statistical differences in majority of clinicopathological variables between breast cancer patients older and younger than 40 years of age. In contrast to studies which demonstrate that breast cancer in younger women (under 40 years of age) is more aggressive and has a poorer prognosis, our findings show that with respect to the few variables in which there were statistically significant differences between the two groups of patients, more aggressive disease was in fact seen in patients above 40 years of age. Our results are different but there are other studies, discussed above, which support our findings [25, 26]. Additional studies in our setting with larger number of breast cancer patients under 40 years of age may be helpful in confirming or negating our findings. There is however no doubt that breast cancer in patients younger than 40 years of age is becoming a major problem in our country and needs to be clearly recognized and extensively studied for the optimum management of these patients.

Conclusion

Statistically significant differences were noted in some clinicopathological variables. Majority of variables indicating more aggressive disease were seen in patients older than 40 years of age. This is in contrast to findings in a majority of studies which indicate that younger women tend to have more aggressive disease compared to those above 40 years, and are treated more aggressively. However, aggressive treatment in younger women is associated with long term toxicity and psychosocial issues. The findings in our study underline the need for larger studies to resolve this issue permanently and conclusively so that younger women are not treated too aggressively unless statistical evidence is compelling and unequivocal.

Abbreviations

ER; Estrogen Receptor, PR; Progesterone Receptor, IDC; Invasive Ductal Carcinoma, NST; No Special Type.

Declarations

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Availability of data and materials: Data and materials of this work are available from the corresponding author on reasonable request.

Authors' contributions: RI, FR and ZA performed the histological and immunohistochemical evaluation, literature review and drafted the manuscript; AS helped to collect data; JA-B participated with the corresponding, reviewing, editing the drafted manuscript as per journal policy, and submission of the article. All authors participated in the design of the study. All authors read and approved the final manuscript.

Competing interest: It is declared that all authors have no conflict of interest.

Consent for publication: Not applicable.

Ethics approval and consent to participate: As this study was a retrospective study, no patients were identified and no follow up information was taken, ethical exemption was obtained from the institution's Ethical Review Committee.

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Tables

Table 1: Histological tumor grade in our patients (n=482)

| No. | Tumor Grade | All patients (n=482) | Patients >40 years of age (n=380) | Patients <40 years of age (n=102) |
|-----|-------------|----------------------|-----------------------------------|-----------------------------------|
| 1 | I | 6 (1.3%) | 4 (1%) | 2 (2%) |
| 2 | II | 241 (50%) | 194 (51.1%) | 47 (46%) |
| 3 | III | 235 (48.7%) | 182 (47.9%) | 53 (52%) |

Table 2: Histological types of Breast Carcinoma in our patients (n=482)

| No. | Histologic Type | All patients (n=482) | Patients >40 years of age (n=380) | Patients <40 years of age (n=102) |
|-----|--|----------------------|-----------------------------------|-----------------------------------|
| 1 | Invasive ductal carcinoma, NOS (IDC, NOS) | 439 (91%) | 344 (90.5%) | 95 (93.1%) |
| 2 | Invasive lobular carcinoma (ILC) | 17 (3.5%) | 15 (3.9%) | 2 (2%) |
| 3 | Metaplastic carcinoma | 12 (2.5%) | 10 (2.6%) | 2 (2%) |
| 4 | Papillary carcinoma (including Micropapillary Carcinoma) | 11 (2.3%) | 8 (2.1%) | 3 (2.9%) |
| 5 | Mucinous Carcinoma | 2 (0.4%) | 2 (0.5%) | --- |
| 6 | Tubular Carcinoma | 1 (0.2%) | 1 (0.3%) | --- |

Table 3: T components of TNM stage in our patients (n=482)

| No. | T (TNM) stage | All patients (n=482) | Patients >40 years of age (n=380) | Patients <40 years of age (n=102) |
|-----|---------------|----------------------|-----------------------------------|-----------------------------------|
| 1 | I | 3 (0.6%) | 2 (0.5%) | 1 (1%) |
| 2 | II | 203 (42.1%) | 154 (40.5%) | 49 (48%) |
| 3 | III | 272 (56.4%) | 222 (58.4%) | 50 (49%) |
| 4 | IV | 4 (0.8%) | 2 (0.5%) | 2 (2%) |

Table 4: Molecular groups in our patients (n=482)

| No. | Molecular groups | All Patients (n=482) | Patients >40 years of age (n=380) | Patients <40 years of age (n=102) |
|-----|------------------|----------------------|-----------------------------------|-----------------------------------|
| 1 | Luminal A | 165 (34.2%) | 137 (36.1%) | 28 (27.4%) |
| 2 | Luminal B | 160 (33.2%) | 124 (32.6%) | 36 (35.3%) |
| 3 | Basal like | 113 (23.4%) | 86 (22.6%) | 27 (26.5%) |
| 4 | Her2neu | 28 (5.8%) | 21 (5.5%) | 7 (6.9%) |
| 5 | Not known* | 16 (3.3%) | 12 (3.1%) | 4 (3.9%) |

* Could not be classified accurately into any specific molecular group.