# Breast Cancers in Young Women: A Retrospective Study at King Hussein Medical Center

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## ABSTRACT

**Objectives:** To compare the clinicopathological features of breast cancer in two distinct patient populations below and above age of 40 and to investigate whether it is associated with a more aggressive tumor biology and disease progression in young female patients.

**Methods:** A retrospective study conducted at the oncology clinic at King Hussein Medical Center. A total of 90 females with histopathology proven invasive breast cancer aged less than 40 years (group A) were matched with a group of 160 female patients whose age was 40 years or older (group B) during the period of 2007 to 2014. Demographic variables collected included age, mode of presentation, details of radiological imaging. Data reviewed from the histopathology report included tumor histology, site, size, grade, lymphovascular invasion, perineural invasion, number of lymph nodes involved by the tumor, hormonal status of tumors. Recurrence and site of distant metastasis were obtained during regular follow-up.

**Results:** The median age was 35 years (range 24-39 years) in Group A and 55 years (range 40-75 years) in Group B, The median duration of symptoms was longer among patients in group A. Patients in group A had larger tumors, more lymph nodes involved by tumor, higher stage at presentation, more estrogen negative tumor, and more patients developed distant metastasis or local recurrence during follow up.

**Conclusions:** Breast cancer in young patients is associated with more advanced disease, more aggressive histopatholgy and biological characteristics, higher rate of recurrence and distant metastasis.

**Key words:** Breast cancer, Young females, Clinicopathological.

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## Introduction

Breast cancer is the most common cancer among women worldwide, and the leading cause of cancer death in all age groups,[(1)] It is the most common cancer among females (36.8%) and ranked the first in all the years from 1996 -2009 in Jordan,[(2)] it is a disease found mainly in older females , young women make up less than 7.5 per cent of all women diagnosed with the disease each year.[(3)] Although the age definition for young is very variable, The European Society of Breast Cancer Specialists (EUSOMA) working group decided to define "young women" as those under 40 years.[(4)] Breast cancer at young age is associated with a more unfavorable prognosis compared with the disease arising in older

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premenopausal patients.[5] The reasons for worse outcomes in younger women are complex and are likely related to multiple factors, including unfavorable disease biology and delays in diagnosis.[6] Breast cancer in young patients tend to present with a more advanced stage of disease including larger palpable tumors, more lymph node involvement and extensive intraductal component,[7] also they have a greater chance of endocrine unresponsive tumor, and are more likely to present with a higher grade, more extensively proliferating and vessel invading disease.[8] The aim of this study was to determine if breast cancers in young women are associated with a more aggressive tumor biology, disease progression and outcome.

## Methods

In this retrospective, comparative study conducted at the oncology clinic at King Hussein Medical Center of the Royal Medical Services, a total of 90 females with histopathology proven invasive breast cancer aged less than 40 years (group A) were matched with group of 160 female patients which were randomly selected with invasive breast cancer whose age was 40 years and above (group B) and who had surgery at the same time period from 2007 to 2014. Patients diagnosed with Ductal carcinoma insitu or breast sarcoma were not included in this study. Demographic variables collected included age, mode and symptoms at presentation, duration of presenting symptoms, details of radiological imaging results including mammogram, ultrasound of breast and axilla, staging CT, bone and PET scans. Data reviewed from the histopathology report of mastectomy specimen and core biopsy pathology, included tumor histology type, site of the tumor within the breast, size of invasive tumor, histological grade, evidence of lymphovascular invasion, perineural invasion, nipple involvement, skin involvement, the presence of associated ductal carcinoma in situ (DCIS), number of lymph nodes (LN) resected and LN involved by the tumor, nearest resection margin and surgical margin whether was involved by the tumor. Patients whom presented with metastatic disease, core biopsy was done but not mastectomy. All patients were staged according to the American Joint Committee on Cancer (AJCC 2010, seventh edition) TNM Staging System for Breast Cancer. The stage of disease was evaluated before treatment for patients who received neoadjuvant therapy or after pathological diagnosis for patients whom underwent mastectomy or wide local excision at diagnosis. Hormonal status of tumors was recorded to assess estrogen (ER), progesterone (PR) and amplification of HER-2 (HER2 neu expression) of the primary tumors was determined by immune histochemistry. When HER2 expression was equivocal in immune-histochemistry, gene amplification status was determined using FISH (fluorescence in situ hybridization). Surgical treatment, radiation therapy, chemotherapy, and biological treatment and treatment with neo-adjuvant chemotherapy were evaluated. Follow-up information was obtained from patients' medical files at the oncology clinic. Recurrence and site of distant metastasis were obtained during regular follow-up; all the treatments were determined by international therapeutic guidelines. Data were analyzed using means and frequencies. The two groups were compared using Student's t test for means and the chi-squared test for proportions. All statistical calculations were performed using the SPSS (software package for statistical analysis) version 19 for Windows (Chicago, IL). For all analyses, p-values were two-sided and considered to be statistically significant if p-values were $<0.05$. The study was approved by the local ethical committee.

## Results

The median age was 35 years (range 24 -39 years) in Group A and 55 years (range 40-75 years) in Group B. Not one patient in both groups was diagnosed during surveillance mammogram and breast self examination and all patients in both groups were symptomatic at presentation. Most of patients in both groups had presented with breast lump except in 11 patients (2 in group A, 9 in group B) who presented with bone pain due to bone metastasis, three patients presented with nipple discharge (2 in group A and 1 in group B), and one patient in group A had presented with anemic symptoms due to bone marrow infiltration with malignancy. No significant differences between left and right breast tumor in both groups were found. One patient in group A was documented to have

**Table I:** Clinicopathological factors according to age group

| | | Age Group | | |
|---|---|---|---|---|
| | | **Group A** | **Group B** | **P value** |
| Lymphovascular invasion | Absent | 18(30%) | 53(45%) | |
| | present | 41(69%) | 64(55%) | 0.05 |
| | N/A | 31 | 43 | |
| Perineural invasion | absent | 26(50%) | 66(58%) | |
| | present | 26(50%) | 47(42%) | 0.2 |
| | NA | 38 | 47 | |
| Grade | 1 | 2(2%) | 10(8%) | |
| | 2 | 17(24%) | 57(50%) | 0.0001 |
| | 3 | 50(74%) | 46(42%) | |
| | NA | 21 | 47 | |

**Table II:** Ssteroid and her2 receptors in tumors in both groups

| | | Age Group | | |
|---|---|---|---|---|
| | | **Group A** | **Group B** | **P value** |
| ER | Negative | 22(24%) | 17(11%) | 0.01 |
| | Positive | 67(76%) | 137(89%) | |
| | NA | 1 | 6 | |
| PR | Negative | 25(29%) | 30(20%) | 0.07 |
| | Positive | 62(71%) | 113(80%) | |
| | N/A | 3 | 17 | |
| HER | Negative | 44(53%) | 60(75%) | 0.003 |
| | Positive | 39(47%) | 20(25%) | |
| | N/A | 7 | 80 | |
| Triple negative | | 7(8%) | 7(4.7%) | 0.3 |

bilateral breast cancer at presentation. The median duration of symptoms was longer among young patients (8.35 weeks) compared with older patients (7.44 weeks), although this difference was not statistically significant (p = 0.7). Combined Mammogram and ultrasound were high specific for breast cancer in both age groups and most of patients were BI-RADS (breast imaging-reporting and data system) 5. Most of breast masses were in the upper outer quadrant in both groups. Thirteen patients (14%) in Group A and 27 patients (17%) in Group B presented with metastatic breast cancer, but no significant difference was found between two groups (p=0.6). Most common sites of metastasic presentation were different between both groups. In group A sites were lung in six patients, liver in five patients, bone in five patients, bone marrow and lepto-meningeal metastasis in one patient, while in group B most common sites of metastasis were bone in 20 patients then lung and liver of 12 and eight patients respectively. Neo-adjuvant chemotherapy was given more in young age group, 13 patients vs. 11 patients in group B; Patients in group A had larger tumors: mean size of tumor in patients whom underwent mastectomy was 4.42 cm vs. 3.75cm in group B, (p=0.04). All of patients except one in group B had clear margin at histopathology report, the most common histology subtype was invasive ductal cancer (IDC) in 89% of group A and 86% of group B. More invasive lobular histology (ILC) in older age group than young women, (10.6% vs. 2.2%, p =0.004). Tubular, medullary, papillary and cribriform subtypes were documented in one patient in each subtype. Mixed invasive ductal and lobular were documented in two patients in group A and two patients in group B. Multifocal tumors found in five patients in group A and nine patients in group B. Two patients in group A were pregnant and another two patients were lactating at time of diagnosis. The mean nearest resection margin was 12 mm in group A and 15 mm in group B. More histopathological differences between two groups are shown in Table I. Mean number of LNs resected in axillary clearance were same in both groups, (18 lymph nodes) while the mean of LNs involved with metastatic cancer were different between two groups (6 LNs in group A, 4 LNs in group B), an insitu component (DCIS) was present in 90% of the cases in younger

patients and in 75% of the corresponding 0lder patients (p=0.05). Steroid (estrogen and progesterone receptors) and HER2 neu receptors within the tumor are shown in Table II, TNM staging at initial diagnosis presented in Table III.

**Table III:** TNM staging

| | | Age Group | | |
|---|---|---|---|---|
| | | **Group A** | **Group B** | **P value** |
| T | T1 | 9(11.5%) | 27(19.9%) | |
| | T2 | 44(56.4) | 81(59.6%) | |
| | T3 | 18(23.1%) | 22(16.2%) | 0.02 |
| | T4 | 7(9.0%) | 6(4.4%) | |
| N | N0 | 14(18.2%) | 39(28.9%) | |
| | N1 | 28(36.4%) | 46(34.1%) | 0.1 |
| | N2 | 18(23.4%) | 26(19.3%) | |
| | N3 | 17(22.1%) | 24(17.8%) | |
| M | M0 | 77(85.6%) | 133(83.1%) | |
| | M1 | 13(14.4%) | 27(16.9%) | 0.6 |
| Stage | 1 | 5(5.6 %) | 14(8.8%) | |
| | 2 | 34(37.8%) | 61(38.1%) | |
| | 3 | 38(42.2%) | 58(36.3%) | 0.6 |
| | 4 | 13(14.4%) | 27(16.9%) | |

During follow up of patients after diagnosis, among those whom presented with non metastatic breast cancer, 16 patients (20.5%) in the younger group and 13 in the older group (9.7%) developed distant metastasis or local recurrence (p=0.04). Most common sites of metastasis in group A were bone, local recurrence and liver whereas in group B were lung, bone and liver. Brain metastasis was documented among three cases in group A, and one in group B.

At end of our study, 31.1% of all patients in group A had metastatic disease either at presentation or during follow up, in contrast to 24% in group B who had a metastatic disease (p=0.7), the most significant predictive factors for metastasis or local recurrence during follow up were number of LNs involved and lymphovascular invasion (p=0.004 and p=0.05 respectively).

## Discussion

Our study describes the clinical, histopathological characteristics and outcome of invasive breast cancer in young females. The American Medical Association and the American College of Radiology recommend yearly bilateral mammography starting at age 40 and clinical breast examinations once every three years in their 20s and 30s.[9] Unfortunately, most of the our 250 patients were symptomatic at diagnosis, usually with mass, nipple discharge or even symptoms of metastatic disease, as bone ache, similar to Agnese *et al*.[10] who reported that only few young patients with breast cancer were diagnosed by surveillance programs. Another observation in our study is the diagnosis delay in young women which was about 8.35 weeks compared with older patients 7.44 weeks, relatively because breast tissue of younger women is denser and because of low probability of disease at young age.[11,12]

Histopathological analysis showed that the majority of tumors in both groups were invasive ductal carcinomas. Invasive lobular carcinomas mixed invasive ductal and tubular, medullary, papillary and cribriform accounting for the rest. Similarly, Moran *et al*.[13] reported a majority of young patients had invasive ductal histopathology and demonstrated lower frequencies for the other tumor subtypes as well. Invasive lobular type is generally more common in older patients. Current literature supports the hypothesis that breast cancer is generally more aggressive in younger women compared to older women,[14] these studies have identified that tumors in younger patients tend to be larger and are associated with more regional LN involvement, vascular invasion and higher stage of disease.[15] Our data show that the mean size of breast tumor at diagnosis, number of LNs involved by cancer and thus stage of disease in those patients whom underwent surgery were higher in young age groups and were concordant with the literature.[16-18] The median size of the tumors in young women was 4.6 cm, compared with 3.8 cm in the older group. More than 80% of the young patients had LN metastases at diagnosis, N3 disease more in young patients in 22% in contrast to 17% in elderly, also stage 3 more in young in 42% at diagnosis while in 36% in elderly. Livi *et al.* [5] reported that the majority of breast cancer presenting in young women is more likely to show larger tumors. Kroman *et al*.[19] found that younger women are at high risk of having axillary LN disease. Patients with IDC and accompanying DCIS (IDC-DCIS), IDC is assumed to arise from a preexisting DCIS lesion, a recognized precursor for IDC,[20] 90% of the cases in younger patients were associated with

DCIS vs. 75% in older patients, Chagpar *et al.*[21] found that more than one quarter of young patients with invasive carcinoma had concomitant DCIS. In comparison of biomarkers between young and elderly breast cancer patients in our study, we demonstrate that young patients more likely to be aggressive tumor biology, with higher proportion of estrogen receptor negative and HER-2/neu positive tumors, triple negative, and poorly differentiated tumor. The results of our study show that breast carcinomas in women less than 40 years of age exhibit more ER negative tumors in 24% vs. 11% in elderly patents. HER-2 over expression defines an aggressive subtype of breast cancer characterized by rapid cell proliferation, increased angiogenesis, deficient apoptosis, also it is associated with high grade tumors, and lymph node involvement. As well, HER-2 over expression is associated with relative resistance to tamoxifen with reduced sensitivity to chemotherapy. For these reasons tumors with HER2 positive are associated with poor prognosis, higher propenicity of local and distant metastasis and negative survival.[22]

Young women with invasive HER2 positive tumors should be considered for adjuvant chemotherapy and one year of trastuzumab. Breast cancer in our young patients frequently exhibits more HER2 over expression compared with older women, it was expressed in 47% of young patients versus 25% in older patients, this is similar to HER-2 over expression data found by others in women of this age group and older women, McAree *et al.*[12] reported that 52.8% of his young patients were HER-2 positive. In our series of 69 graded tumors in young age group, 50 (74%) patients were grade III, in contrast to 46 (42%) in older patients. Our study shows higher percentage as compared with previous reports of breast cancer grade in women of this age group, Fernandopulle *et al*.[23] reported a 60% grade III tumor in his young patients whilst Sidoni *et al* [24] concluded higher frequency of grade 3 tumors in young compared to elderly patients (38% vs. 17%).

It is well known that patients with triple-negative (ER, PR, HER2 negative) breast cancer have an increased likelihood of distant recurrence and of death compared with women with other types of cancer.[25] Although not reached a significant difference, breast cancer in young female in our study had more triple negative tumors, it was observed in 8% of patients in the young age group in contrast to 4.7% in older patients. In the Carolina Breast Cancer Study,[26] it was seen in 24% of premenopausal women compared with 15% of post-menopausal women. Bacchi *et al.* [27] stated that triple-negative tumors were significantly more frequent in young patients (34.6% vs. 16.2%). Local recurrence or distant metastasis following mastectomy is devastating for the patient. The risk is greatest in the first 2-3 years.[28]

Multiple retrospective series and subset analyses of larger randomized trials have shown that women who develop breast cancer at a young age have an increased risk of recurrence' [29] our results showed that the patient's age at time of diagnosis is an important variable determining the prognosis and outcome of invasive breast cancer. On follow up of these patients there was a higher proportion of local recurrence and distant metastasis in this age group, as 20.5% in young age group compared to 9.7% in the older group developed metastasis or local recurrence after diagnosis.

Another result of this study was more brain metastasis in young age group, brain metastases are unusual metastatic site, with reported rates of 2-13%.[30]

Similar high rates of brain metastases in this age group compared with older ages have been reported in many studies.[31] Approximately 5-10% of breast cancer patients are diagnosed with metastasis at initial presentation,[32] our study showed an overall incidence of metastatic disease at presentation was relatively same between two groups 14.4% vs. 16.9%. The incidence of metastatic disease at presentation was considerably higher than many other studies; Al-Husain *et al*. [33] reported a slightly lower rate of metastatic disease, with 13.2% having metastatic disease at diagnosis.

## Limitations of the Study

Because it is a retrospective study we were not able to measure the mortality rate, also the study involved a short duration of follows up of these patients.

## Conclusion

Breast cancer in young patients is associated with more advanced disease, more aggressive histopathology and biological characteristics, higher rate of recurrence and distant metastasis. Our findings should promote increased awareness and periodic screening of breast cancer in young females by self and health professional clinical breast exam along with mammogram.

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