Original Article

TNM staging and classification (familial and nonfamilial) of breast cancer in Jordanian females

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Abstract

PURPOSE: Staging of breast tumor has important implications for treatment and prognosis. This study aims at pinpointing the frequency of each stage among familial and nonfamilial breast cancers. MATERIALS AND METHODS: Ninety-nine Jordanian females diagnosed with familial and nonfamilial breast cancer between 2000 and 2002 were enrolled in this study. All breast cancer cases were staged according to the TNM classification into in situ, early invasive, advanced invasive and metastatic. RESULTS: Forty-three cases were familial breast cancer and 56 were nonfamilial. One female breast cancer was diagnosed with ductal carcinoma in situ (DCIS) cancer. Fifty cases were diagnosed in early stages of invasive breast cancer, of which 31 cases were familial, 29 cases were classified as advanced invasive, where 21 cases were nonfamilial and 19 cases were metastatic stage of breast cancer, with 16 nonfamilial cases. Stage 2b was the most common stage of early invasive cases and represented 48% of the early stage of breast cancer. On the other hand, among cases diagnosed with advanced invasive breast cancer, stage 3a was the most common stage and represented 89.6% of the advanced stage. Interestingly, all cases of stage 3a belonged to TNM stages of T2N2M0 and T3N1M0. The tumor size in all cases of Jordanian females diagnosed with advanced invasive breast cancer exceeded 2 cm in size due to selection bias from symptomatic women in our study. CONCLUSION: The incidence of nonfamilial breast cancer was slightly higher than that of the familial type amongst studied the Jordanian females studied. The early invasive stage of breast cancer was more common in the familial while the advanced invasive and metastatic breast cancer cases were encountered more often in the nonfamilial type. Our study was based on a small sample and symptomatic women. Therefore, more research with larger population samples is needed to confirm this conclusion.

Key words: Breast cancer, BRCA1/2 Jordan, TNM staging

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Introduction

Cancer becomes one of the most common diseases in our lives today, and breast cancer is now the most common female malignancy worldwide, with up to a million cases annually. Breast cancer affects almost every eighth women in the world and its incidence has been rising in both developed and developing countries.¹ Breast cancer could be either familial, due to numerous known and unknown genetic mutations, e.g. BRCA1, BRCA2, P53, or nonfamilial, linked to predisposing factors like obesity, early menarche, delayed or absent childbearing, age, use of hormone replacement therapy and/or unknown causes.²⁻⁴ Tumors of the breast are believed to arise from terminal ductal lobular units and comprise two common morphological types: ductal and lobular neoplasia.⁴ Other types include tubular, medullary, mucinous types and Paget disease. Staging and morphology of breast tumor has important implications for treatment and prognosis.⁵ In the American population, the distribution of cancer stages has changed significantly: in situ and early stage of invasive cancer has increased while diagnosis of metastatic breast cancer has decreased.⁶ This may be due to the implementation of a screening program and advanced screening technology, which allows detection of breast cancer at an early stage. It would be of interest to determine the relation between various morphological types and age of patient as well
as to show the frequency of each stage among different age group and among familial and nonfamilial breast cancer. Very limited studies have correlated pathological staging and the presence of familial and nonfamilial types of breast cancer. Lakhani et al.\(^7\) found that familial breast cancer related to BRCA1/2 has lower frequency of lobular morphology compared to nonfamilial breast cancer, but familial breast cancer unrelated to BRCA1/2 has not shown any significant morphological difference from all breast cancer types combined.

Among Jordanian females, Tarawneh and Nimri (2005)\(^8\) reported that histopathological distribution of Jordanian female breast cancers showed that 80.6% were infiltrating ductal carcinoma, 5.3% were lobular carcinoma, 1.9% were adenocarcinoma and the remaining were other morphology. The previous study was helpful in describing the prognostic stages of breast cancer but did not highlight the incidence of both familial and nonfamilial cases among Jordanian females. The objective of this study was to categorize the breast cancer stages among Jordanian females according to the TNM staging (tumor-node metastasis) and to identify the average age of each pathological stage and, finally, to determine the frequency of familial and nonfamilial breast cancer cases among each stage.

**Materials and Methods**

**Patients**

Ninety-nine Jordanian females diagnosed with breast cancer were enrolled in this study to determine the incidence, the type (familial or nonfamilial) and the stages of breast cancer. Samples were collected over a 2-year period between 2000 and 2002 from females diagnosed with breast cancer attending the Al-Basheer Governmental Hospital for breast cancer diagnosis and treatment. The patient's age ranged from 22 to 73 years, with an average age of 50 years. The age of the familial breast cancer participants ranged between 22 and 73 years and the age of the nonfamilial breast cancer participants ranged between 35 and 69 years. A signed permission was obtained from every female enrolled in this study, and each female was interviewed directly about her family history of breast cancer. For all cases, pathological analysis was recorded over a 2-year period between 2000 and 2002.

**Classification and pathological staging of breast cancer**

Breast cancer cases were classified into familial or nonfamilial types. The criterion used to consider a particular patient with familial breast cancer was based on the fact that at least two of her relatives (first or second-degree relatives) were affected with invasive cancer at any age.\(^9\);\(^10\)

All breast cancer cases were staged at diagnosis from 0 to 4 [Table 1] depending on the combination of TNM (T: tumor size, N: cancerous node, M: metastases) category [Table 2]. This staging was defined by the NCI-NIH (National Cancer Institute–National Institute of Health), USA, and revised by the American Joint Committee on Cancer Staging System for Breast Cancer (AJCC).\(^6\)

**Statistical Analysis**

Statistical analysis was carried out using the statistical package for social sciences (SPSS9.0.0; SPSS Inc., Chicago, IL, US America). Statistical significance was set at \(P < 0.05\).

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**Table 1: Definition of breast cancer stages according to the National Cancer Institute**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 is carcinoma in situ</td>
<td>Tumors that have not grown beyond their site of origin and invaded the neighboring tissue. They include:</td>
</tr>
<tr>
<td></td>
<td>- ductal carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td>- lobular carcinoma in situ</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Tumor size &lt;2 cm, metastases to other organs and tissues not available</td>
</tr>
<tr>
<td>Stage 2a</td>
<td>Tumor &lt;2 cm in cross-section with involvement of the lymph node or tumor from 2 to 5 cm without involvement of the axillary lymph nodes</td>
</tr>
<tr>
<td>Stage 2b</td>
<td>Tumor more than 5 cm in cross-section (the result of axillary lymph node research is negative for cancer cells) or tumor from 2 to 5 cm in diameter with the involvement of axillary lymph nodes</td>
</tr>
<tr>
<td>Stage 3a</td>
<td>Also called local spread of breast cancer: tumor more than 5 cm with spread to axillary lymph nodes or tumor of any size with metastases in axillary lymph nodes, which are knitted to each other or with the surrounding tissues</td>
</tr>
<tr>
<td>Stage 3b</td>
<td>Tumor of any size with metastases into the skin, chest wall or internal lymph nodes of the mammary gland (located below the breast inside of the chest)</td>
</tr>
<tr>
<td>Stage 3c</td>
<td>Tumor of any size with a more widespread metastases and involvement of more lymph nodes</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Defined as the presence of tumors (regardless of the sizes), spread to parts of the body that are located far removed from the chest (bones, lungs, liver, brain or distant lymph nodes)</td>
</tr>
</tbody>
</table>
**Results**

**Breast cancer stages of Jordanian females**

Based on the staging criteria described in Table 1, of the 99 Jordanian females with breast cancer, only one case was diagnosed with *in situ* cancer (DCIS) without any evidence of invasion of her breast tissues [Table 2]. Fifty cases (50.5%) were diagnosed in early stages of invasive cancer (stages 1 and 2). The remaining 48 cases (48.5%) were classified as advanced invasive and metastatic stage of breast cancer in 29 and 19 cases, respectively [Table 2].

According to the detailed TNM staging system, our study shows in Table 2 that stage 2a and 2b were the most common stages among early invasive cases in Jordanian females. The majority of early invasive cases were T2N0M0 and T2N1M0, with the tumor size between 2 and 5 cm. On the other hand, among cases diagnosed with advanced invasive breast cancer, stage 3a was the most common stage, with 26 of 29 cases (about 90%). Interestingly, all cases of stage 3a belonged to either T2N2M0 (48%) or T3N1M0 (42%), and the tumor size in all cases exceeded 2 cm in size, which may be due to the fact that the majority of the women in our study were diagnosed at a clinically palpable stage. Metastatic cancer cases were shown to account for 19% of all observed cases.

**Frequency of familial and nonfamilial breast cancer among Jordanian females**

As shown in Table 3, although the frequency of early invasive cases was higher in familial than in nonfamilial types (62% vs. 38%), the difference was not statistically significant. On the other hand, advanced invasive and metastatic cases were shown to be significantly ($P < 0.05$) higher in the nonfamilial type than in the familial type (72% and 84% vs. 28% and 16%, respectively).

**Distribution of breast cancer stages among different age groups**

Patients’ age ranged from 22 to 73 years. Of the 99 enrolled females enrolled in our study, 19 women were aged below 41 years, 28 were aged between 41 and 50 years, 36 were aged between 51 and 60 years and 16 were aged above 60 years [Table 4]. Detailed determination of frequency of each breast cancer stage among the different age groups revealed that young females aged below 41 years of age were diagnosed with *in situ* in one case (5.2%), early invasive in five cases (26.3%), advanced invasive in six cases (31.6%) and metastatic in seven cases (36.8%) of breast cancer. In female age groups 41–50 and ≥61 years, no significant differences were observed among the frequencies of the different stages of breast cancer, as shown in Table 4. However, in the group aged 51–60 years, significant differences were observed among different stages (63.9%, 27.8% and 8.3% for early invasive, advanced and metastatic cancer, respectively).

**Table 3: Frequency (number and percentage) of familial and nonfamilial breast cancer types among different stages of breast cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of cases</th>
<th>Nonfamilial</th>
<th>Familial</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>In situ</em></td>
<td>1</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Early invasive</td>
<td>50</td>
<td>19 (38)</td>
<td>31 (62)</td>
</tr>
<tr>
<td>Advanced invasive</td>
<td>29</td>
<td>21* (72)</td>
<td>8* (28)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>19</td>
<td>16* (84)</td>
<td>3* (16)</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>56 (56.6)</td>
<td>43 (43.4)</td>
</tr>
</tbody>
</table>

* $P < 0.05$, Figures in parentheses are in percentage
Classification of familial and nonfamilial breast cancer by age in Jordanian females

Regardless of frequency among different breast cancer stages, breast cancer in our study was mostly of the nonfamilial type [Table 3]. In the age group <50 years, familial breast cancer was more frequent than nonfamilial breast cancer. However, in the age group 51–60 years and more than 60 years, nonfamilial breast cancer was more frequent than the familial type, as shown in Figure 1.

Discussion

The most frequent stage of breast cancer observed in this study was the early stage invasive cancer, which accounts for 50.5% of our cases. This may suggest improvement in the health education program from governmental hospitals in Jordan, which allows detecting breast cancer at early stages when the treatment is less aggressive and better supported by the women, and they have a better prognosis. This reflects an increase in community awareness and early detection of breast cancer among Jordanian females. However, advanced stage invasive cancer and metastatic cancer made up about 49.5% of the breast cancer diagnosed cases in our study. Interestingly, the present data showed that stage 2b of early invasive cancer and stage 3a from advanced invasive cancer were the most common stages. This may be an important predictor of disease recurrence and impact on survival because nearly 70–80% of patients with negative node status survive around 10 years, the prognosis worsening with an increase in the number of positive nodes. [10]

Familial breast cancer occurs among patients with a family history of breast cancer, but only 5–10% of the cases are attributed to inheritance [10] of autosomal genes (BRCA1 and BRCA2). The results of this study showed that the incidence of advanced invasive and metastatic breast cancer was higher in the nonfamilial than in the familial type. Previous studies showed that familial breast cancer is relatively more aggressive and has a poor prognosis [11]. The pathology of non-BRCA1/2 cancers was different from the pathology of BRCA1/2 cancers, and even histological phenotypes of BRCA1 mutation cancers can be differentiated from BRCA2 cancers [11,12]. Breast cancer in non-BRCA1/2 families was of lower grade, less mitosis and less lymphocytic infiltrate [12]. BRCA1 mutations are highly proliferative and poorly differentiated [13] and more lymphocytic infiltrate, while cancer associated with BRCA2 exhibited a higher score for tubule formation and lower mitotic count [7]. Therefore, treatment of breast cancer can take a variety of forms, dependent on the histological type, the grade and the stage of the cancer and the family history [14].

The literature on breast cancer in Arabian women is limited. The present study indicated that in women below the age of 41 years, the incidence of metastasis was the highest (36.8%). In females above 41 years of age, the incidence of early invasive cancer was the highest (50%, 63.9%, 50%) and of metastasis was the lowest (17.9%, 8.3%, 25%) among age groups 41–50, 51–60 and 60 years, respectively. In a comparative study by Barak et al. [4] between Arab and American females diagnosed with breast cancer, 54% of Arab females at the time of diagnosis of breast cancer were <50 years old, while 37% of the American women were under 50 years of age. Khatib and Modjtabi [10] reported that breast cancer was the number one cancer among women in the Eastern Mediterranean region. Unlike in the USA, Jordanian breast cancer is more commonly diagnosed in Jordanian women under the age of 50. This is because the population pyramid in Jordan shows that 90% of the females were below 50 years old [15] and not because of an increased risk among younger age groups. Patients younger than 35–45 years

Table 4: Age distribution and frequency (number and percentage) of different stages of breast cancer among the different age groups

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of cases</th>
<th>In situ</th>
<th>Early invasive</th>
<th>Advanced invasive</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;41</td>
<td>19</td>
<td>1 (5.2)</td>
<td>5 (26.3)</td>
<td>6 (31.6)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>41–50</td>
<td>28</td>
<td>0 (0)</td>
<td>14 (50)</td>
<td>9 (32.1)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>51–60</td>
<td>36</td>
<td>0 (0)</td>
<td>23* (63.9)</td>
<td>10* (27.8)</td>
<td>3* (8.3)</td>
</tr>
<tr>
<td>≥61</td>
<td>16</td>
<td>0 (0)</td>
<td>8 (50)</td>
<td>4 (25)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>1</td>
<td>50</td>
<td>29</td>
<td>19</td>
</tr>
</tbody>
</table>

*P < 0.05, Figures in parentheses are in percentage
old at the time of diagnosis of invasive breast cancer have been found to have a worse prognosis than older patients,[16] and have a significantly increased risk of dying from breast cancer.[17,18]

In conclusion, nonfamilial breast cancer frequency was slightly higher than that of familial breast cancer among breast cancer Jordanian females diagnosed with breast cancer in our study. The early invasive stage of breast cancer was observed in the familial type while advanced invasive and metastatic breast cancer cases were recorded in the nonfamilial type. Further research or study is still needed to clarify the actual status of breast cancer and the staging among breast cancer Jordanian females.

References


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