Age-Related Frequency of Triple Negative Breast Cancer in Women

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ABSTRACT

Objective: To determine frequency of triple negative breast cancer (TNBC) in Pakistani women with respect to age.

Study Design: Observational study.

Place and Duration of Study: Armed Forces Institute of Pathology (AFIP), Rawalpindi, from July 2005 to July 2010.

Methodology: Pathological records of all specimens of breast cancer were reviewed and data was obtained for estrogen receptor (ER), progesterone receptor (PR) and HER-2 neu receptor proteins. Specimens having complete record of all three proteins were included for analysis. TNBC was defined as those who were ER, PR and HER-2 neu negative. Overall frequency as well as frequency with respect to age was calculated. Descriptive and categorical variables were analyzed using SPSS version 17.

Results: Eight hundred and fifteen patients out of 4715 (17.28%) were found to be TNBC. Mean age of diagnosis of TNBC was found to be 46.26 ± 12.22 years of age while other breast cancers had a mean age 52.90 ± 9.78 years (p < 0.001). In the TNBC group, 537 patients (65.88%) were aged < 50 years while 278 patients (34.11%) were aged > 50 years while majority of patients with other breast cancers were elderly females (p < 0.001).

Conclusion: TNBC comprised 17.28% of the breast cancers in Pakistani women diagnosed at the studied centre. A higher frequency of TNBC was noted in significantly younger patients.

Key Words: Triple negative breast cancer (TNBC). Estrogen receptor (ER). Progesterone receptor (PR). HER-2 neu.

INTRODUCTION

Breast cancer (BC) is one of the most common cancers among females worldwide. An estimated 1.5 million are affected each year and of these approximately 170,000 are of the triple negative breast cancer (TNBC) phenotype.1 United States has the highest incidence; in 2009, 192,370 American women were diagnosed with breast cancer and an estimated 40,170 died of the disease.2 Pakistan has the highest incidence of the disease in Asia. Approximately 90,000 females are affected each year and almost 40,000 die of the disease every year.3

Therapeutic options for BC vary from primary surgery to neoadjuvant/adjuvant chemotherapy, hormonal therapy or targeted radiotherapy as dictated by subtypes distinguished by expression of ER, PR and HER-2 neu proteins. TNBC describes subtype of breast cancer that fails to express ER, PR and overexpress HER-2 neu protein on immunohistochemical (IHC) analysis.4 It is a distinct clinical entity affecting young premenopausal women with frequency varying between 10 - 17%.5 More than 90% of TNBC fall within category of basal-like breast cancer so called due to its molecular mimicry with basal epithelial cells in other parts of the body. Prevalence of TNBC is highest in premenopausal African-American females (39% vs. 15% in non African-American females) suggesting significant disparities in its incidence among different racial groups.6

It is an important area of research both for researchers and clinicians because it is a poor prognostic factor for disease-free and overall survival (OS), no effective targeted therapy is available and clustering of TNBC in young premenopausal women. To-date, little work is done in Pakistan to establish demographic features and frequency of this important clinical entity.

The objective of this study was to find out the frequency of TNBC in cases of breast and its association with age in Pakistani women.

METHODOLOGY

Pathological records of all women with invasive breast cancer diagnosed at AFIP, Rawalpindi, from July 2005 to July 2010, were studied. Pathological records were reviewed for ER, PR, HER-2 neu status and age in years, at diagnosis. TNBC was defined as those patients who were ER, PR, and HER-2 neu protein negative. Other breast cancers were defined as those that were positive for any of these tumor markers.

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Analysis was carried out on formalin fixed and paraffin embedded (FFPE) tissue specimens. ER/PR status was determined using ER antibodies (ID5 IgG1 recombinant ER protein from mouse pretreated with AR Citra plus) and PR antibodies (IA6 IgG1 synthetic peptide of PR from mouse pretreated with AR Citra) from Biogenex Laboratories, USA. All red scoring guidelines were followed to define ER/PR positivity. Score of proportion as well as score of intensity was combined to determine status. A score of 0 - 2 was considered negative while that of 3 - 8 was taken positive (sensitivity and specificity of all red score 99.4% and 99.5% respectively). HER-2 neu over expression was determined using ACE chromogen CB11 IgG1 synthetic peptide from mouse (Biogenex Laboratories, USA). HER-2 neu over expression was assessed as 3+ (positive), 2+ (borderline) and 0–1+ (negative) following Royal College of Pathologist guidelines. All the data reviewed was entered into Statistical Package for Social Sciences (SPSS) software version 17 for windows (SPSS Inc., Chicago, IL, USA) and analyzed through its statistical package. Mean ± SD was used for quantitative data like age while frequency and percentage was calculated for qualitative data like TNBC. Chi-square and t-test were applied for categorical and numerical variables respectively. P-value of less than < 0.05 was taken as significant.

**RESULTS**

Pathological records of 5540 FFPE specimens were reviewed with regard to ER, PR, Her-2 neu status and age at diagnosis. Complete ER, PR and HER-2 neu status record was present in 4715 specimens (85.10%) and were included in the study for analysis. Eight hundred and fifteen out of 4715 patients (17.28%) were found negative for ER, PR and HER-2 neu proteins (TNBC). The mean age of diagnosis of TNBC was 46.26 ± 12.22 years while other breast cancers had mean age of 52.90 ± 9.78 years at diagnosis (p < 0.001). Majority of TNBC patients were found to be less than 50 years of age. Five hundred and thirty seven (66.88%) patients with TNBC were < 50 years while only 278 (34.11%) patients were older than 50 years of age. Other breast cancers were more common in elderly females (n=2509 (64.33%)). The difference of occurrence of TNBC with respect to age is statistically significant (p < 0.001) when compared to other breast cancers group as shown in Table I.

**DISCUSSION**

Breast cancer is a strikingly heterogeneous disease with variable clinical, pathological and molecular features. It was characterized by size only for many years with significant management limitations. Later on, histological classification system was introduced which divided BC into 18 different subtypes and invasive ductal carcinoma not otherwise specified (IDC NOS) was found to be most common variety. However, this histomorphological division also failed to form homogeneous groups for treatment categorization. This heterogeneous nature of the disease has significant implications both for physicians and their patients increasingly as treatments are now targeted towards molecular markers. So gene expression profiling came into existence and five distinct gene expression profile based subtypes have been identified by cDNA microarray analysis associated with distinct treatment strategies and prognosis. Three of these are derived from ER-tumors (basal like, HER-2 neu positive and normal like) and two from ER+ subtypes (luminal a and b). Still, there are certain BC subtypes that neither express steroid receptors nor over express HER-2 neu proteins the so called TNBC. This variety accounts for 10-17% of all breast cancers.

Current study focuses on frequency of TNBC in Pakistani women with context of age at presentation. Pathological record of 4715 samples was studied. TNBC was found in 815 patients. Frequency revealed is significantly closer to upper margin of the range quoted worldwide. Majority of the patients had age < 50 years at presentation. Mean age of diagnosis of TNBC is 46.26 ± 12.22 years which is significantly younger than that quoted worldwide. A study conducted at Women College Hospital and University, Toronto, Canada, revealed frequency of 11.2% with mean age of presentation as 53 years. More than 90% of TNBC fall within basal like subtype (BBC) so called for its gene expression type that mimics basal epithelial cells in other parts of the body and characteristics morphology that includes high proliferation rate, central necrosis and pushing border. Basal like breast cancers are over represented in African-American women, and in BRCA-I mutation carriers. After adjustment for age and stage at diagnosis, African-American women are almost 3-fold more likely than white women to have TNBC. It should be emphasized that not all TNBC are BBC and vice versa although there is a considerable overlap between them with 25% discordance rate. Although TNBC are defined by IHC analysis, currently there is no established criteria to diagnose BBC. However, immunohistological markers characterizing BBC are ck5, ck6, ck14, ck18, p63, p-cadherin, vimentin, EGF, HER-1, c-kit and IGFR 13,14. TNBC constitutes a clinically challenging type as it occurs more frequently in younger women < 50

<table>
<thead>
<tr>
<th>Variable</th>
<th>TNBC (n = 815) Frequency (percentage)</th>
<th>Other breast cancers (n = 3900) Frequency (percentage)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50</td>
<td>537 (65.88%)</td>
<td>1391 (35.66%)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Age &gt; 50</td>
<td>278 (34.11%)</td>
<td>2509 (64.33%)</td>
<td>&lt; 0.001</td>
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years,10,16 African-American women,4,5,12,16,17 oral contraceptive use > one year,18 BRCA-1 mutation carriers12,13 and women in low socioeconomic group.18 TNBC are histologically aggressive with poor prognosis,19 high mitotic grades, of large tumor size, more aggressive expression profile with low bcl-2 but high p53 and ki 67 expression20 leading to poorer OS, breast cancer specific survival (BCSS) and relapse free survival (RFS).21

In general, adjuvant therapeutic options for TNBC include cytotoxic agents and targeted therapies. Notably TNBC can have higher pathological complete response (pCR) to chemotherapy especially taxanes and anthracyclines but early relapse is more likely.5,14,22 Targeted therapies currently being developed or under evaluation include inhibition of poly adp-ribose polymerase-1 (PARP-1),23 epidermal growth factor receptor (EGFR) also known as HER-124 and vascular endothelial growth factor (VEGF).25 None of these have yet reached approval level by US FDA.22 Not only therapeutic options are limited for TNBC but also there are no current guidelines that specifically adhere to the management of this grave variety culminating towards a clinical dilemma both for patients as well as clinicians. TNBC is a heterogeneous disease with high recurrence and poor survival rate which poses important clinical challenge. Few studies to-date have focused on etiologic risk factors and currently little data is available in Pakistan on its true incidence and etiology. It is hoped that these results would be extended further. There is no clear proven effective single agent that targets a driving vulnerability in TNBC. This also provides a wide array for researchers and novel therapeutic options are needed to counter this aggressive tumor affecting women in their peak life.

CONCLUSION

In the studied group of Pakistani women, there was a considerably high frequency of TNBC in premenopausal women. Prognosis-related implications need to be further explored.

REFERENCES


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