Molecular Subtypes of Breast Cancer

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Background: Breast cancer is the most common invasive malignancy among women in Bahrain. Hormone receptor status and human epidermal growth factor receptor 2 (HER2) protein overexpression are important parameters in determining the therapeutic options and patient prognosis.

Objective: To evaluate the prevalence of estrogen (ER), progesterone (PR) and HER2 receptor status and as well as the molecular subtypes of breast cancer in Bahrain compared with those reported in other countries.

Design: A Retrospective Study.

Setting: Salmaniya Medical Complex, Bahrain.

Method: Two hundred eighty-six female breast cancer patients were included in the study. Data collected included patient age, tumor type, ER, PR and HER2 receptor status, and molecular subtypes. The data were analyzed using SPSS version 25.

Result: One hundred eighty-eight (65.7%) were ER-positive tumors. One hundred sixty-five (57.8%) PR receptors were positive. Eighty-nine (31.1%) patients had HER2 amplification. One hundred forty-seven (51.4%) cancers were Luminal A and 48 (16.8%) were Luminal B subtype. Forty-one (14.3%) tumors were HER2-type and 50 (17.5%) had triple negative breast cancers among females. Correlation between age and immunohistochemistry (IHC) receptor status was not statistically significant.

Conclusion: The prevalence of molecular subtypes of breast cancer showed some variation among the regional population. Among females in Bahrain, the proportion of HER2-type and triple negative breast cancers is higher than other regional countries.

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Breast cancer is the most common invasive malignancy in females worldwide. In Bahrain, it is the most common cancer among females, with an average age-standardized incidence rate of 52.3 per 100,000 women, which is the highest among all Gulf Cooperation Council states[1,2].

Several clinical and pathological factors, including age, tumor size, lymph node involvement, histological type, and tumor grade could influence the overall prognosis. In addition to these parameters, the hormone receptor status, either estrogen (ER) or progesterone (PR), and human epidermal growth factor receptor (HER2) overexpression have been established as important predictive markers in determining treatment options and patient prognosis[3,4].

Therapeutic strategies in primary breast cancer depend on immunohistochemistry (IHC) staining for ER, PR, and HER2 receptors because it predicts the response to hormonal and targeted therapy[5]. Patients with ER/PR-positive tumors have lower recurrence rates and better survival than those with ER/PR-negative tumors. The addition of tamoxifen to treatment protocols improves prognosis in women with hormone receptor-positive tumors[6]. HER2 overexpression was found to be an independent negative predictive marker of overall survival and relapse time[7]. However, patients with early-stage HER2-positive breast cancer treated with trastuzumab (Herceptin) and chemotherapy have a reduced risk of recurrence compared to patients who received chemotherapy alone, especially in the presence of ER/PR-positivity, such as ER+/PR+/HER2+ (triple positive)[8]. Triple negative (ER/PR-negative and HER2-negative) tumors are more common in younger females and are more aggressive than the other types[9,10].

There are limited studies from regional countries on the prevalence of IHC subtypes of breast cancer and the results vary widely[11-19].

The aim of this study was to evaluate the rate of ER, PR and HER2 receptor expression and molecular subtypes among female patients diagnosed with breast cancer.

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METHOD

Three hundred nine patients were diagnosed with breast cancer between 2009 and 2014. Two hundred ninety-nine were eligible for inclusion in the study; thirteen cases were excluded due to lack of data regarding triple receptor status; therefore, only 286 patients were analyzed for the different molecular subtypes. The exclusion criteria were male patients and the lack of sufficient personal characteristic data. Patients' data included age, tumor type, hormone (ER and PR) receptor status, and HER2 overexpression. ER/PR receptors were considered positive when the receptor concentration was >30/300 (more than 10%). The HER2 expression was considered positive if it stained +3 by IHC or positive by fluorescence in situ hybridization (FISH). These included luminal A (ER and/or PR-positive, HER2-negative), luminal B (ER and/or PR-positive, HER2-positive), HER2-type (ER/PR-negative, HER2-positive) and triple negative (ER/PR/HER2-negative). We divided our cases into two age groups: women ≤53 years ('younger') and women >53 years ('older').

The statistical analysis was performed using the chi-square test and data was analyzed using SPSS; version 25.0.

RESULT

The clinicopathological characteristics of our study population are summarized in table 1. A total of 286 cases of breast cancer were included in the study. The median age was 53 (range 37-66). Two hundred thirty-three (81.5%) patients were non-specific invasive ductal carcinoma (IDC), 19 (6.6%) tumors were invasive lobular carcinoma (ILC) and 34 (11.9%) were other subtypes of IDC or not known. One hundred eighty-eight (65.7%) tumors were ER-positive, 165 (57.6%) were PR-positive and 89 (31.1%) were HER2-positive. One hundred forty-seven (51.4%) cancers were luminal A, 48 (16.8%) cases were luminal B subtype, 41 (14.3%) tumors were HER2-type and 50 (17.5%) patients had triple negative breast cancer, see figure 1.

Table 1: Clinicopathological Characteristics of Patients

Age	
Mean	53.3
Median	53
Range	42-66
Tumor type	
IDC	233 (81.5%)
ILC	19 (6.6%)
Other or unknown	34 (11.9%)
Total	286
ER-receptor status	
Positive	188 (65.7%)
Negative	98 (34.3%)
Total	286
PR-receptor status	
Positive	165 (57.7%)
Negative	121 (42.3%)
Total	286
HER2-receptor status	
Positive	89 (31.1%)
Negative	197 (68.9%)
Total	286
Triple receptor status	
ER+/PR+/HER2-	127 (44.4%)
ER+/PR-/HER2-	15 (5.2%)
ER-/PR+/HER2-	5 (1.74%)
ER+/PR+/HER2+	31 (10.8%)
ER+/PR-/HER2+	15 (5.24%)
ER-/PR+/HER2+	2 (0.69%)
ER-/PR-/HER2+	41 (14.3%)
ER-/PR-/HER2-	50 (17.4%)
Total	286
Molecular subtype	
Luminal A	147 (51.3%)
Luminal B	48 (16.7%)
HER2-type	41 (14.3%)
Triple negative	50 (17.4%)
Total	286

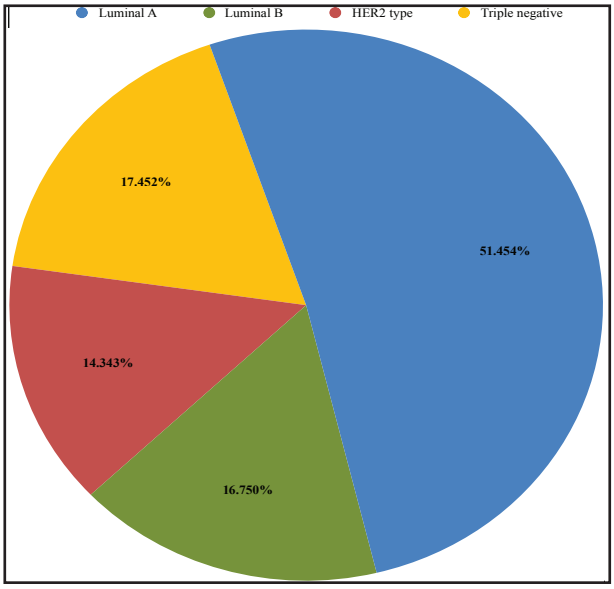

Figure 1: Proportion of Molecular Subtypes of Breast Cancer

DISCUSSION

The study included 286 cases of female breast cancer in Bahrain with a median age of 53 years, which is comparable to that reported in other studies[14,16,18].

The proportion of ER-positive (66.7%), PR-positive (57.7%) and HER2-positive (31.1%) receptor in our study are comparable to other studies in regional countries[10-20]. ER was the most frequent positive receptor in all studies (range 61.2-78.3%), except in Jordan (50.8%), where PR was more common (57.5%)[10-20]. Approximately two-thirds (65.7%) of our cases were ER-positive. Although hormone receptor positivity is associated with better prognosis, the relatively high ER-positive rates do not necessarily mean that there is a correspondingly reduced burden of morbidity and mortality for breast cancer patients. Forty-eight of 188 (25.5%) ER-positive tumors were also HER2-positive. HER2 overexpression was the least common receptor in all studies (range 17.5-46.7%)[10-20].

The most common IHC pattern in our study was ER+/PR+/HER2- in 127 (44.4%) cases and this is also the most common IHC pattern in the literature (range 42.9-65.8%)[11-17]. Our study found two IHC patterns of breast cancer, ER-/PR+/HER2- in five (1.74%) cases and ER-/PR+/HER2+ in two (0.69%) patients, which had not been reported in other regional studies before. The other IHC patterns showed little variation from the other regional studies. The most common IHC subtype is Luminal A[10]. However, the proportion of Luminal A cases (51.3%) in our study is lower than in other studies, range 54.5-65.8%[13-17]. However, in two studies from Bahrain, the prevalence of Luminal A cases was even lower, 24.7% and 42.9%[11,12]. The prevalence of Luminal B breast cancer is variable (range 5.7-32.6%)[10-20].

In a recent study from Bahrain, Luminal B breast cancer is the most common molecular subtype[11]. In the UAE, Egypt and Saudi Arabia, it is the second most common IHC subtype[14,15,19]. In another study from Saudi Arabia and in Bahrain, including our study, it is the third most common subtype[12,13]. It is the least common subtype of breast cancer in the Iraqi population (5.7%)[16]. The rate of HER2-type breast cancer is higher in Bahrain (range 13.4-23.8%) compared to the other countries (range 4.9-14%) although it is the least common subtype in this study (14.3%)[11,12,13-17].

This reflects the prevalence of aggressive tumors among females in Bahrain[12]. The triple negative pattern is higher in Bahrain (range 14.3-18%), including our study (17.4%) compared to other countries (range 8-14.3%), except in one Saudi study, where the prevalence is comparable (17.7%)[12,13].

These differences in the frequency of IHC patterns could be due to different ethnic backgrounds or unexpected heterogeneity of breast cancer that explains the variation in prognosis[13].

The prevalence of Luminal A breast cancer in Bahrain (51.3%) is lower than that in the USA (range 51.4-73%), but the proportion of Luminal B cases in our study (16.7%) is higher (range 10-15.5%)[10,20,21]. The rate of HER2-type disease is significantly higher in our study (14.3%) compared to the USA (range 5-7.2%)[10,20,21]. The proportion of triple-negative cases is also higher in our study (17.4%) than the USA, except in one study, where the prevalence was higher (range 12-20.1%)[10,20,21]. These differences in receptor status suggest that breast cancer in our population is different than in the Western world and that may reflect the relatively aggressive nature of the disease in Bahrain, despite standardization of treatment, stage by stage, compared with the USA.

Many studies have reported that younger age is an independent factor for poor prognosis in breast cancer, highlighting that young women with breast cancer have tumors of higher grade, late stage, larger size and lymph node involvement[9,12]. Recent advances have also shown that breast cancers are more aggressive if they were HER2-positive (Luminal B and HER2-type) or triple negative for ER, PR and HER2[10]. The HER2 receptor was amplified in 33.3% of younger patients compared with 28.1% of older patients. Younger patients with breast cancer are more likely to be HER2-type, as in this study (16.6% versus 11.9%), which is also associated with more aggressive tumor behavior[9]. Contrary to what was previously published regarding the significant proportion of young patients being triple negative, in our study, older patients were more likely to be triple negative (19% versus 15.9%)[9,10,12,22].

Statistical analysis, correlation between age, receptor status and IHC subtype of breast cancer were not significant. Results from our study indicate that patient age is unrelated to the aggressiveness of breast cancer on the basis of ER, PR and HER2 receptor expression alone. As reported in other studies, tumors in younger patients tend to be of a higher histological grade and are more aggressive than breast cancer in older patients; factors are independent of receptor expression[10,23]. In a recent study by Navsaria et al in Bahrain, HER2 overexpression was the least common receptor[24].

This is the largest study of molecular subtypes of breast cancer in Bahrain and our results add to the growing literature that classifies breast cancer into several molecular subtypes. Although our sample size is larger than previously published articles from Bahrain and other regional countries, it remains a retrospective and single-center study. The finding of high prevalence of HER2-type and triple negative breast cancer may help to explain the aggressiveness of breast cancer in Bahrain and implies the need for proper screening and management of such patients through more effective and targeted strategies.

CONCLUSION

The rates of molecular subtypes showed some variation among the regional female population with breast cancer. The expression of ER, PR, and HER2 receptors in female breast cancer in Bahrain is comparable to other regional countries, but there is a high proportion of HER2-type and triple negative breast cancer, reflecting a worse prognosis. However, breast cancer in younger women is not necessarily more aggressive than older women on the basis of molecular subtypes alone, other prognostic factors influencing tumor aggressiveness should be considered. We recommend further comprehensive study of the correlation between receptor status and other important prognostic factors, such as tumor size, lymph node status, tumor type and grade.

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