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The Association Between Clinicopathological Features and Molecular Markers in Bahraini Women With Breast Cancer

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Abstract

Introduction: Breast cancer (BC) is a heterogeneous disease and a major public health burden in Bahrain. Based on hormone receptor status (ER, PR, and HER2), BC can be divided into four molecular subtypes: Luminal A, Luminal B, HER2+, and Triple negative, each of which display distinct clinical behaviour.

Patients and Methods: This retrospective study included 216 patients diagnosed with BC between November 2017 and May 2019 at the Bahrain oncology centre. The clinicopathological characteristics (age, size of tumour, grade, lymph node involvement, metastasis) were examined, in addition to immunohistochemical markers (ER, PR, and HER2), and BRCA 1 and 2 status (when indicated). SPSS was used to evaluate the correlation between the molecular subtypes and different clinicopathological features.

Results: BC in Bahraini women was relatively of large size (68.5% larger than 20mm), with frequent metastasis to the lymph nodes (57.4%). The mean age at diagnosis was 51.8 years \pm 11.5, with invasive ductal carcinoma (IDC) being the most common histological type (90.3%).

The most common molecular subtype was Luminal A (60.2%), followed respectively by luminal B (19%), triple negative (13.4%) and HER-2 (7.4%).

Discussion: Significant differences were found between the subtypes regarding grade ($p \leq 0.001$) and BRCA mutation status (0.001). Triple negative subtype was associated with highly-aggressive behaviour compared to the other subtypes. It presented at younger age, with high grade, large tumor size, and predominance to distant metastasis. It was also linked with positive BRCA mutations.

Conclusion: A significant proportion of Bahraini females with BC present with aggressive features (i.e. younger age, poorly differentiated tumors, and lymph node involvement). Expectedly this was associated with underlying aggressive molecular subtypes (namely TNBC). The aggressive properties of such molecular subtype mandate further molecular testing to identify more accurate prognostic and predictive targets for effective treatment and risk reduction strategies.

Keywords: Breast Cancer, Molecular subtypes, Bahrain, Triple negative breast cancer, BRCA mutation.

Introduction

Breast cancer (BC) is the most common malignancy in females worldwide, affecting 2.1 million women annually, and is the leading cause of cancer-related mortality among women⁽¹⁾. BC represents a considerable burden in Bahrain by constituting 21.4% of all cancer cases. As stated by GLOBOCAN 2018⁽²⁾, the age-standardized incidence rate and mortality rate in the Bahraini population are 44.1 and 14.9 per 100,000 respectively, compared to 46.3 and 13 per 100,000 worldwide. BC

exhibits vast heterogeneity in terms of its biological and histopathological characteristics; which translates into different clinical behaviours. This elicits different

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treatment responses and prognostic values, which raises the need for customized therapeutic plans⁽³⁾. Previous histological classification which did not cover this diversity are therefore of a limited use, and new classifications are emerging⁽⁴⁾. Advances in gene expression profiling (GEP) using DNA microarrays has improved our understanding of BC by dividing it into several molecular subtypes based on the expression of specific genes⁽⁵⁾. Nowadays, immunohistochemical staining of the tumor tissue sample is used as an alternative for genetic testing which is not feasible and extremely expensive⁽⁶⁾. Based on the expression of ER, PR and HER2, tumors could be classified into 4 molecular subtypes⁽⁵⁾: Luminal A, Luminal B, HER2, and Triple negative; each of which display distinct clinical behaviour providing a new tool for personalized medicine⁽⁷⁾. Moreover, BRCA1 and BRCA2 genes play an integral role in DNA double-strand break /repair mechanism, contributing to the maintenance of DNA stability. Therefore, mutations in BRCA1 and BRCA2 genes predispose to breast cancer and are considered the most common germ-line mutation in familial cases of breast cancer⁽⁸⁾. Current evidence suggests that it is likely that tumors arising in BRCA mutation carriers have the same gene expression profile to certain molecular subtypes of breast cancer namely Triple-negative subtype. Triple-negative breast cancer (TNBC) is the most aggressive clinically and holds a poor prognosis⁽⁹⁾. Due to the absence of well-defined molecular targets (i.e. ER, PR and Her2 receptors), treatments such as hormonal therapy and anti-HER2 monoclonal antibodies are ineffective. New treatment options other than neoadjuvant chemotherapy are therefore needed. Accordingly, identification of the prevalence of such relevant subtypes can further be used to develop effective targeted treatments. The aim of this study is to determine the clinicopathological characteristics of BC in the Bahraini population and to correlate them with each molecular subtype. We also aim to explore the relationship between BRCA mutation and relevant subtypes.

Patients and Methods

Study design

This retrospective study was conducted at the Bahrain Oncology Centre in King Hamad University Hospital (KHUH). It incorporated all cases registered at the centre from November 2017 to May 2019. Patients were excluded according to the following criteria: non-Bahraini patients, in situ lesions, and patients with insufficient information. A total of 216 patients were enrolled in this study and a serial number was assigned to each one by a gatekeeper to ensure confidentiality. Ethical approval for this study was obtained from the Research and Ethics Committee

of both KHUH and Royal College of Surgeons in Ireland (RCSI).

Data collection

The parameters of the study were retrieved from patients' electronic medical records and pathological reports. Extracted information were documented in a form using Microsoft Excel 2018, which included: age at diagnosis, histopathological type, tumor size, lymph node status, distant metastasis, Scarff-Bloom-Richardson (SBR) grade, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER-2) status, and BRCA1/2 status. Patients were staged according to the AJCC TNM staging system⁽¹⁰⁾. To ensure quality and minimize human error, all values were checked by two reviewers.

Immunohistochemical analysis and molecular subtyping

IHC staining was performed using Autostainer Link 48 system from DAKO to determine the status of ER, PR and HER-2. Allred, a semi-quantitative scoring system, was used to interpret the status of ER and PR by combining the proportion of stained tumor cells and the intensity of the nuclear staining in one score. ER/PR expression was considered positive if the Allred score was between 3-8 and negative if it was less than 3. Her-2/neu was scored from 0 to 3+ according to the American Society of Clinical Oncology/ College of American Pathologists guideline in 2013⁽¹¹⁾. Tumor specimens were considered HER-2 negative if they were 0 or 1 and positive if they were 3. A two score was considered equivocal and was further evaluated by fluorescence in situ hybridization. Based on the IHC findings for ER, PR and HER-2 markers, four main molecular subtypes of BC were defined:

- Luminal A: (ER and/or PR positive, HER2 negative)
- Luminal B: (ER and/or PR positive, HER2 positive)
- Triple negative: (ER, PR and HER2 negative)
- HER-2 (ER and PR negative, HER2 positive).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software (version 25.0). Statistical significance between BC molecular subtypes and clinicopathologic characteristics were examined using Chi-square test for the categorical variables and one-way ANOVA for continuous variables (age in years and tumor size in millimeters). When expected cell counts were less than 5, Fisher's exact probability test was used. The results were considered statistically significant when the p-value is less than 0.05.

Results

Characteristics of patients

The detailed clinicopathological data for the 216 patients enrolled in this study are shown in Table 1. The mean age at diagnosis was 51.8 years \pm 11.5, and the median was 52 years (range from 27 to 86 years). Of these patients 19.9% were 40 years or less. The most common histological type was invasive ductal carcinoma (IDC) of no special type accounting for 90.3% of all cases, followed by invasive lobular carcinoma (ILC). Whereas other types of tumors including papillary adenocarcinoma, sarcoma spindle cells, metaplastic and mucinous carcinoma accounted for 2.3%. The bulk of the tumors according to SBR grading system were of grade II accounting for 57.9% followed respectively by the grade III (29.6%), and grade I (12.5%). About one third (31.5%) of patients have tumor sizes of less than 20 mm while two thirds had tumor sizes greater than 20 mm (T2 and T3). More than half of the patients (57.4%) had lymph node involvement and only 11.6% presented with distant metastasis. Based on the IHC results 78.2% of women with BC were positive for ER, 69% were positive for PR and 26.4% were positive for HER-2. As a result, luminal A was the most prevalent subtype with a proportion of 60.2% followed respectively by luminal B (19%), triple negative (13.4%) and HER-2 (7.4%) (**Figure 1**). Of the 216 patients enrolled in this study, only 60 patients (27.8%) were tested for BRCA mutations. Of those, 18.3% were BRCA positive (100% BRCA1 – 0% BRCA2). Surprisingly 12.2% of the patients, who were labeled as negative for BRCA mutations, were found to have other variants of undetermined significance (VUS). Among those genes, were BRCA1 and 2 variants, which were different than the classical pathological mutations associated with hereditary breast and ovarian cancer syndrome.

Association between molecular subtypes and clinicopathologic features

In addition to studying the clinicopathological characteristics of the tumors in the population as a whole, each of the four molecular subtypes had been correlated with age at diagnosis, tumor size, grade, lymph node status, and metastasis (Table 2). The molecular subtypes differed significantly by histological grade ($p \leq 0.001$) and BRCA status (0.001). In relation to age at diagnosis, triple negative subtypes were noticed to present at a younger age (mean=47.9 years) compared to the remaining subtypes. With regards to tumor size, the majority of triple negative tumors (75.9%) presented with a size larger than 20 mm, which is larger than what was documented in the other subtypes. As for the grade, Luminal A and Luminal B subtypes had the highest proportion of well-differentiated tumors (17.7% and 9.8% respectively). Interestingly, none

Characteristics	Variable	Count (%)
Age	Mean \pm SD	51.75 \pm 11.52
	Median	52
Tumour size	Mean (mm) \pm SD	32.19 \pm 21.50
	T1 (\leq 20mm)	68 (31.5)
	T2 (<20 – \geq 50mm)	113 (52.3)
Grade	I	27 (12.5)
	II	125 (57.9)
	III	64 (29.6)
Lymph node	Negative	92 (42.6)
	Positive	124 (57.4)
Metastasis	No	191 (88.4)
	Yes	25 (11.6)
Histological type	IDC	195 (90.3)
	ILC	16 (7.4)
	Other	5 (2.3)
ER	Negative	47 (21.8)
	Positive	168 (78.2)
PR	Negative	67 (31)
	Positive	149 (69)
HER2	Negative	159 (73.6)
	Positive	57 (26.4)
Molecular subtype	Luminal A	130 (60.2)
	Luminal B	41 (19)
	HER2+	16 (7.4)
	Triple negative	29 (13.4)

Table 1. Characteristics of Breast Cancer patients in Bahrain

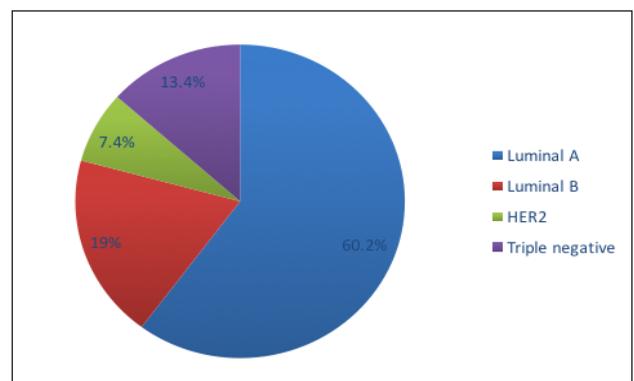


Figure 1. Distribution of molecular subtypes in Bahraini population

of the tumors with triple negative and HER2 subtypes were well-differentiated (**Figure 2**). Meanwhile, Triple negative was found to have the highest percentage of poorly differentiated grade III tumors (72.4%). Although triple negative tumors had the least percentage of positive lymph nodes (41.4%) compared to the other subtypes, it had the highest proportion of distant metastasis (13.8%). The highest percentage of BRCA mutations were observed in Triple negative patients (35.3%) (Figure 3).

Discussion

Molecular subtypes classification is becoming an important guidance tool in understanding the heterogeneity of BC. This study was conducted with

the aim to get more insight into this classification and investigate their correlation with the clinicopathological features in our population. The age at diagnosis illustrates a key prognostic factor for BC as tumors in younger woman seem to represent a special entity that tend to behave more aggressively⁽¹²⁾. In our study, the mean age at diagnosis was 52, which is higher than what was reported in Morocco⁽³⁾, KSA (13), Iraq⁽¹⁴⁾, Turkey⁽¹⁵⁾, and Carolina breast cancer studies⁽¹⁶⁾. Conversely, china⁽¹⁷⁾ and south Korea⁽¹⁸⁾ reported higher mean age. Higher ages at diagnosis in our population can be explained by the population age structure, social, economic, genetic, and environmental differences, in addition to the screening programmes targeting older population⁽¹⁹⁾. In our study,

Clinic-pathological parameter		Luminal A no (%)	Luminal B no (%)	HER2+ no (%)	Triple negative no (%)	P-value
Mean age ± SD		52.93 ± 11.54	50.64 ± 11.07	52.06 ± 9.86	47.86 ± 12.40	0.168
Mean size ± SD		32.27 ± 21.25	29.78 ± 19.30	34.59 ± 27.72	33.92 ± 22.51	0.841
Size	T1	39 (30)	15 (36.6)	7 (43.8)	7 (24.1)	0.079
	T2	71 (54.6)	22 (53.7)	3 (18.8)	17 (58.6)	
	T3	20 (15.4)	4 (9.8)	6 (37.5)	5 (17.2)	
Grade	I	23 (17.7)	4 (9.8)	0 (0)	0 (0)	≤0.001
	II	79 (60.8)	30 (73.2)	8 (50)	8 (27.6)	
	III	28 (21.5)	7 (17.1)	8 (50)	21 (72.4)	
Lymph node	Negative	51 (39.2)	18 (43.9)	6 (37.5)	17 (58.6)	0.057
	Positive	79 (60.8)	23 (56.1)	10 (62.5)	12 (41.4)	
	No	115 (88.5)	37 (90.2)	14 (87.5)	25 (86.2)	
Metastasis	yes	15 (11.5)	4 (9.8)	2 (12.5)	4 (13.8)	0.953
	Negative	30 (23.1)	5 (12.2)	3 (18.8)	11 (37.9)	
BRCA	Positive	3 (2.3)	2 (4.9)	0 (0)	6 (20.7)	0.001
	Not done	97 (74.6)	34 (82.9)	13 (81.3)	12 (41.4)	

Table 2. Correlation between clinicopathological parameters and molecular subtypes

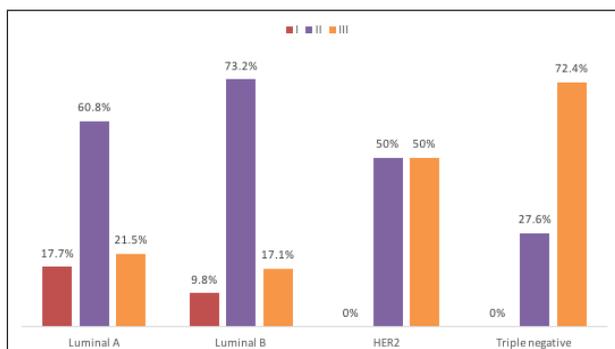


Figure 2. Relationship between Tumor grade and molecular subtypes

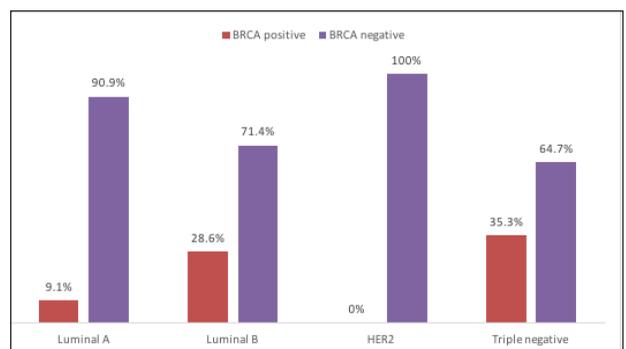


Figure 3. Relationship between BRCA status and molecular subtypes

19.9% of patients were diagnosed before age 40. Young age at the time of diagnosis confers a poorer prognosis, as tumors tend to display more aggressive behaviour, with a high rate of recurrence, and are generally less responsive to treatment⁽²⁰⁾. The most common histological type in our study was Invasive ductal carcinoma (IDC), which is in accordance with the literature data^(3, 14, 15). Invasive lobular carcinoma was the second most common at 8.1% which is slightly higher compared to what has been reported in Ivory⁽⁹⁾, Morocco⁽³⁾, Iraq⁽¹⁴⁾ and China⁽¹⁷⁾. Notably, while the mean tumor size in our patients was 32.19 mm, in western countries⁽²²⁾, the mean size was considerably lower at 18 mm, signifying early detection and diagnosis. Moreover, tumors with higher grade (II and III), constituted a significant proportion (87.5%) much higher than what was reported in other countries^(9, 15, 16, 23). In agreement with a previous study conducted in Bahrain⁽²⁴⁾, more than half of our patients had positive lymph node involvement at the time of diagnosis. In comparison, more developed countries including USA and Poland⁽¹⁶⁾, reported a lower percentage of lymph node metastasis. This high number of large-sized tumors with high-grade and positive lymph nodes at the time of diagnosis could be attributed to the accumulation of undetermined genetic lesions in the population caused by increased environmental insults and consanguineous marriages, as well as the lack of public health awareness, and ineffective screening programmes.

Assessment of hormone receptor (HR) status using IHC assays is essential in selecting management plans and predicting prognosis. ER and PR positive tumors correlate with favourable prognostic features and usually undergo hormonal therapy with Tamoxifen, aromatase inhibitors, or other modulators⁽³⁾. In this study, the expression of ER and PR receptors was higher than findings reported in USA⁽¹⁶⁾, Turkey⁽¹⁵⁾ and China⁽²³⁾. However, high ER and PR positivity do not necessarily correlate to reduced morbidity and mortality of BC patients. Consistent with prior reports from USA⁽²²⁾, Europe, Asia^(13, 17, 18), and Africa⁽³⁾, Luminal A was the most common subtype in this study, followed by luminal B, triple negative, and HER2 subtypes, respectively. Triple negative subtype represents 13.4% of our population, which is similar to those reported in neighbouring countries^(14, 25). However, variable difference does exist between different populations^(15, 16, 26). This could be linked to genetic and ethnic differences, demographic age distribution, environmental factors and methodology discrepancies.

Analysis of data from the Bahraini population showed differences in tumor characteristics by molecular subtypes (Table 2), supporting the notion that molecular subtyping might be of value for understanding tumor behaviour and predicting response to treatment. As reported in other studies^(3, 9), triple negative subtype was associated with

clinic-pathological characteristics indicative of highly-aggressive behaviour and poor prognosis compared to the other subtypes. Less than 30% of women with metastatic TNBC survive 5 years, and almost all die of their disease despite adjuvant chemotherapy, which is the mainstay of treatment. TNBC is associated with young age at diagnosis⁽⁴⁷⁾, high grade (72% grade III), large size (75.8% >20mm) and predominance to distant metastasis (13.8). This pattern is attributed to the high rate of p-53 mutation, in addition to downregulated retinoblastoma gene⁽²⁶⁾. Triple negative BC has been associated with a lower incidence of lymphatic dissemination compared to other subtypes⁽²⁷⁾, which is explained by some researchers⁽²⁸⁾ by the preference of distant metastasis in this subtype to spread through the haematogenous rather than lymphatic rout.

A significant correlation has been observed between BRCA status and molecular subtypes ($p=0.001$). Since BRCA testing is indicated for young women with BC and or with strong family history of ovarian and breast cancer, BRCA mutation was tested in 17 patients from a total of 29 patients who presented with TNBC. Surprisingly 35.3% of those tested showed positive BRCA which is significantly higher than other subtypes. This percentage of BRCA positivity could be even higher since 41.4% of TNBC patients were not tested. This confirms the well-established correlations between BRCA mutation and TNBC⁽²⁸⁾. However, 64.7% of TNBC were BRCA negative, 27.3% of those were found to have other variants, which raises the need for a more comprehensive genetic panel-based testing. More recently, it has been established that there are other genetic factors and molecular drivers that play role in the pathogenicity of TNBC other than BRCA. Recently Brian Lehmann and his colleagues⁽²⁹⁾ classified TNBC into 7 distinct subtypes based on gene expression profiling (GEP): two basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), a luminal androgen receptor (LAR) subtype, and an unstable (UNS) subtype. Using these molecular subtypes in identifying innovative personalised treatment strategies such as immunomodulators appears to have both predictive and prognostic values⁽²⁹⁾. For example, the use of poly-ADP ribose polymerase (PARP) inhibitors has been found to be especially beneficial with BL1 and 2 subtypes which are known to have high frequency of BRCA 1 and 2 mutations⁽³⁰⁾. In addition, LAR cell lines were uniquely sensitive to Bicalutamide (an AR antagonist)⁽³⁰⁾.

Conclusion

In conclusion, this study highlights that a significant proportion of Bahraini females with BC present with aggressive features (i.e. younger age, poorly differentiated

tumors, and lymph node involvement). Expectedly this was associated with underlying aggressive molecular subtypes (namely TNBC) which constitutes a significant percentage of BC. The aggressive properties of such molecular subtype mandate further molecular testing to identify more accurate prognostic and predictive targets for effective treatment and risk reduction strategies. We recommend that all patients with TNBC should be offered extensive genetic testing to identify those genes associated with hereditary breast and ovarian cancer syndrome, including not only BRCA genes. In addition, further molecular subtyping of TNBC should be performed for optimal patient management.

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