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Abstract

Objective: The purpose is to study the prevalence of BRCA1 and BRCA2 mutations in high-risk Bahraini patients diagnosed with breast cancer, its relation to family history, and to determine the clinicopathologic features of breast cancer associated with these genetic mutations, over a period of 7 years.

Background: Breast cancer is the most common type of cancer occurring in women and the second most common type generally. Approximately 12% of women worldwide will develop carcinoma of the breast sometime during their life. Additionally, 72% of women with an inherited BRCA1 mutation and 69% of those with a mutated BRCA2 will develop breast cancer by 80 years of age. The incidence of breast cancer in Bahraini women have increased over the last decade. Still, the data on BRCA1 & BRCA2 mutations in relation to breast cancer patients is limited in the Arab region, not omitting Bahrain as a country with deficient BRCA prevalence data.

Methods: This retrospective study was carried out in Salmaniya Medical Complex, Bahrain, to determine the prevalence of BRCA1 and BRCA2 mutations and to observe the breast cancer’s histopathologic features that are associated with these mutations.

Results: 271 patients underwent the BRCA gene testing between 2013 and 2019. Out of 271 patients, 35 were excluded. Out of the 236 breast cancer patients, 219 (93%) did not have the mutation. The BRCA gene was carried by a total of 17 (7%) patients; 13 (5%) BRCA1 and 4 (2%) BRCA2. Thirteen BRCA carrier patients had invasive ductal carcinoma (IDC) (76%), 2 had ductal carcinoma in situ (DCIS) (12%), while 2 patients’ histopathology was not available. Molecular subtypes showed 4 triple negative basal sub-type (TNBC), 10 positive ER and PR hormonal status, 1 positive HER-2, while 2 patients’ hormonal receptor status was not available. Two BRCA1 carriers had both breast and ovarian cancers. A total of 5 (2%) breast cancer male patients were among the tested population, out of which, 1 (0.4% of the total and 20% of the male patients) was a BRCA2 carrier. Out of the 236 patients, 76 (32%) were younger than 40 years of age at the time of diagnosis. Then again, out of the 17 BRCA carrier patients, 7 (41%) were younger than 40 years.

Conclusion: The prevalence of BRCA mutation in high risk Bahraini breast cancer patients is 7%. Among those patients, BRCA1 mutation is the most prevalent (5%) and invasive ductal carcinoma (IDC) is the most common histopathological subtype. However, there was not enough data to conclude the most prevalent molecular subtype of breast cancer in BRCA carriers due to deficiency of overseas pathology reports for patients operated outside Bahrain. When developing treatment plans for younger patients with breast cancer, inherited syndromes and precisely BRCA mutations need to be considered. Bahrain is implementing genetic testing for breast cancer patients ≤ 50 years of age since 2018, according to NCCN guidelines. We will continue to build our database to better characterize breast cancer subtypes and determine their hereditary pattern for identification of high risk families in Bahrain and for future development of more specific therapeutic approaches.

Key words: Breast cancer, BRCA1, BRCA2, BRCA mutation, Bahrain, Arab region

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Introduction

Breast cancer is the most common type of cancer occurring in women and the second most common type generally. Approximately 12% of women worldwide will develop carcinoma of the breast sometime during their life. On the contrary, 72% of women with an inherited BRCA1 mutation and 69% of those with a mutated BRCA2 will develop breast cancer by 80 years of age. The form of inheritance for breast and ovarian cancer with pathogenic variants in BRCA1 and BRCA2 displays an autosomal-dominant pattern and a markedly elevated risk of developing breast and ovarian cancer, with breast cancer occurring at a particularly early onset. The number of breast cancer patients has been increasing in Bahrain, which may be attributed to the increase in awareness toward breast cancer and the growing national screening program. From the age of 40, Bahraini women are eligible for a screening mammogram, which has led to earlier detection of cancer cases. Early detection is defined by the World Health Organization (WHO) as the recognition of cancer symptoms and signs to enable its diagnosis before advancement of the disease process.

Data is currently scarce on the prevalence of BRCA mutations. A number of studies have shown a varied prevalence among geographical areas and ethnic groups, while others suggest similar mutation prevalence amongst different ethnicities and races. BRCA1 and BRCA2 mutations are being tested in high-risk patients with breast cancer; affected young individuals and patients with positive family history of breast and/or ovarian cancer. The purpose of testing for BRCA1 and BRCA2 mutations in the aforementioned subgroups of patients is to identify families who are at an increased probability of developing hereditary breast and ovarian cancer during their lifetime, in comparison to the general population. Therefore, genetic counseling, alongside risk reduction options are being offered to these patients. Given these concerns, the principal objectives of this study aim to determine the BRCA mutation prevalence in Bahraini women and its relation to family history, as well as to determine the clinicopathologic characteristics of the breast cancer associated with these genetic mutations.

Methods

Study design

This retrospective study recruited breast cancer patients between 2013 and 2019 at Salmaniya Medical Complex (SMC), Bahrain.

Data Collection & Statistical Analysis

The patients Data has been collected from the overseas laboratory at SMC, Bahrain and iSeha system. Microsoft Excel used to create a patient data sheet. SPSS statistics was used for statistical analysis.

Eligibility

All high-risk breast cancer patients who underwent BRCA mutation testing between 2013 and 2019 were included in the study. Patients diagnosed with breast cancer and having at least one of the following high-risk criteria, were qualified for enrollment in the study: a relative with a known mutation in BRCA gene; one or more individuals with breast cancer on the same side of the family; ovarian cancer; male breast cancer; a first- or second-degree relative with breast cancer diagnosed at age <45; triple negative breast cancer; and bilateral breast cancer. The patient’s age group ranges from 22–72 years. Exclusion criteria included ovarian cancer patients, non-Bahraini women with breast cancer, and high-risk individuals with a strong family history of breast cancer who underwent BRCA testing.

Laboratory Testing

Most patients attended the genetic outpatient clinic for the genetic testing, whereas some patients had their blood sent while admitted as inpatients. Blood was withdrawn from all patients and sent overseas for DNA extraction. Genetic testing was carried out by SRL Diagnostics Lab–Mumbai, India.

Results

There was a total of 271 individuals who underwent BRCA testing between 2013 and 2019; 236 of which were diagnosed with breast cancer. Out of 271 patients, 35 patients were excluded from the study; 9 were non-Bahraini, 12 had ovarian cancer, and 14 were labelled as high-risk with a strong family history of breast cancer. Out of the 12 ovarian cancer patients, 3 were BRCA1 and 3 were BRCA2 carriers.

In total, 231 breast cancer patients were women and 5 were men. Patients diagnosed with breast cancer before age 40, comprised 76 (31%) of the total studied population. Of 241 patients, 219 (93%) had no mutation. BRCA1 or BRCA2 mutations were identified in 17 (7%) patients; 13 (5%) BRCA1 and 4 (2%) BRCA2—Figure 1. However, other genetic variants of breast cancer were not studied.
Among the BRCA carriers, the most common histopathological subtype of breast cancer is IDC in 15 patients, followed by DCIS in 2 patients. None of the BRCA positive patients had an invasive lobular carcinoma (ILC) subtype. Hormone positive breast cancers were the highest in number (10), followed by TNBC (4), and lastly HER-2 positive (1)—Table 1. However, 2 of the BRCA carriers were operated abroad due to which, their pathology reports were lacking.

Both breast and ovarian cancers were diagnosed in 2 BRCA2 carriers; both breast cancers were IDC with positive hormone status. Additionally, the ovarian cancer was diagnosed first at a younger age in both patients. Out of the 5 breast cancer male patients, 1 (0.4%) was a BRCA2 carrier. The histopathology of the obtained core biopsy had shown IDC, however his final histopathology report after the mastectomy showed DCIS with no invasive component identified.

Discussion

To our knowledge, the prevalence of BRCA mutations has not been previously studied in Bahrain; the current prospective study is the first to examine BRCA mutations in the country. The goal of this study was to conclude the prevalence of BRCA mutations in high risk Bahraini breast cancer patients and to determine the most common molecular subtype. It concluded that 7% of high-risk breast cancer patients had BRCA mutations, which is lower than frequencies reported from Saudi Arabia (12.9%) and slightly higher than those reported from Lebanon (5.6%). In Qatar, 32 out of 82 breast cancer patients have shown positive BRCA testing, which is significantly higher than the BRCA prevalence in Bahrain. However, similarly their data have shown that IDC is the most common histopathological type in comparison to ours, with no ILC detected in any of the BRCA positive patients. An Omani study limited their BRCA testing to patients aged ≤ 40, bilateral breast cancer, or hormone negative/triple negative cancers, therefore the figures were less in contrast to our study and that made it difficult to conclude a comparative BRCA prevalence among the 2 countries.

Breast cancer is classified as a heterogenous disease, both histopathologically and genetically. BRCA1 and BRCA2 mutations are responsible for the majority of inherited breast cancers. Furthermore, increased risk for breast cancer has been linked to other genes including ATM, CHEK2, PALB2, BRIP1, however, genetic variants other than BRCA1 and BRCA2 were not considered in the current study.

Breast cancer is increasing in young women in Bahrain; 76 (31%) patients out of the total tested high risk breast cancer population were diagnosed before age 40. Out of the 17 BRCA carrier patients, 7 (41%) were younger than 40. Hence, genetic testing in Bahrain is being implemented for women diagnosed with breast cancer below age 50 since 2018, conferring to NCCN guidelines.

Conclusion

In high risk Bahraini breast cancer patients, the prevalence of BRCA1/2 mutation is 7%, falling within the widely varied international prevalence range 1.3–36.9%. The data on BRCA mutation prevalence and its relation to breast cancer in the Arab region is currently scarce, which leads to deficient comparisons amongst the Arab countries. Women of younger age in Bahrain are being diagnosed with breast cancer, and the numbers are increasing. A large percentage of those (41%) were found to be BRCA carriers, therefore the country is heading towards the correct path in aiming to genetically test patients at ≤50 and targeting high-risk families. Finally, our study highlights the limitations of genetic testing locally, where local central laboratories are unavailable for genetic testing, leading to a financial burden on the country and on the genetic field specifically.

Ethical approval

This research has been granted ethical approval from the ethical research committee in Salmaniya Medical Complex, Bahrain.

Funding and Conflict of Interest:

We have no conflicts of interest to disclose.
References


