Research Article

Patterns and Prevalence of Germline BRCA1 and BRCA2 Mutations among High-Risk Breast Cancer Patients in Jordan: A Study of 500 Patients

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Purpose. Knowledge of BRCA1 and BRCA2 mutations has a significant clinical impact on the management and prevention of breast cancer. In this study, we evaluate the pattern and prevalence of germline mutations in BRCA1 and BRCA2 among high-risk Jordanian breast cancer patients selected as per international guidelines.

Methods. BRCA1 and BRCA2 testing were performed at a reference genetic lab. Mutations were classified as pathogenic/likely pathogenic and variant of uncertain significance (VUS). Results. A total of 517 patients, median age: 39 (range: 19–78) years, were enrolled. Among the whole group, 72 (13.9%) patients had pathogenic or likely pathogenic BRCA1 (n = 24, 4.6%) or BRCA2 (n = 48, 9.3%) mutations, while 53 (10.3%) others had VUS. Among 333 younger (≤40 years) patients, mutations were observed in 44 (13.2%). Positive mutations were found in 40 (16.5%) patients with one or more closer relatives with breast cancer and in 20 (35.1%) of the 57 patients with triple-negative disease. Multivariate analysis showed that a triple-negative status, history of two or more close relatives with breast cancer, and history of one or more close relatives with invasive ovarian cancer were associated with significant high odds ratios (OR) of carrying a pathogenic variant, with an OR (95% CI) of 5.08 (2.66–9.67), 3.24 (1.78–5.89), and 2.97 (1.04–8.52), respectively.

Conclusions. BRCA1 and BRCA2 mutations are not uncommon among Jordanian patients. Young age has the weakest association with positive mutations, while patients with triple-negative disease, especially those with an additional positive family history, have the highest mutation rate.

1. Introduction

Accounting for almost 20% of all cancer cases, breast cancer continues to be the most common cancer and the leading cause of cancer-related deaths among Jordanian women. A total of 1145 cases were reported by the Jordan Cancer Registry in its latest annual report [1]; more than 60% of them are treated at our center. Almost 50% of breast cancer patients are diagnosed at the age of 50 or younger. Regionally, more than a third of patients present with locally-advanced or metastatic disease [2, 3].

Published data had shown that 5–10% of breast cancer is hereditary and mostly related to BRCA1 or BRCA2 gene mutations [4, 5]. Efforts to identify such mutations are extremely important given the high penetrance rates among its carriers [6]. In a meta-analysis of published studies, the estimated mean cumulative risk for breast and ovarian cancers by 70 years of age for BRCA1 mutation carriers were 57% and 40%, respectively, while carriers of BRCA2 mutation had a risk of 49% and 18%, respectively [7]. Risk-reduction interventions, such as bilateral mastectomies and oophorectomies, are highly recommended in such patients. More recently, data had shown that specific breast cancer treatment may be informed by the BRCA1 or BRCA2 mutation status. In patients with advanced breast cancer associated with BRCA1 or BRCA2 mutations, olaparib and talazoparib are now approved for treatment [8–11].
Data related to hereditary breast cancer among the Arab countries in general, and Jordan in particular, are scarce, and ranges of positive rates are very wide [12–18]. Knowledge about the pattern and prevalence of ancestry-specific prevalence of BRCA1 and BRCA2 mutations can help policy makers tailor counselling, prevention, and treatment strategies that can better help our particular patients. We recently reported our experience with 100 high-risk patients (median age: 40, range: 22–75 years) treated and followed at our institution. In total, 20 (20.0%) patients had deleterious (pathogenic) and 7 (7.0%) others had suspected deleterious (likely pathogenic) mutations in BRCA1 or BRCA2 genes. Highest mutation rates were observed among patients with triple-negative disease (negative for estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor (HER2) receptors), especially among those with a positive family history of breast and/or ovarian cancer, patients with bilateral or second primary breast cancer, and those with a family history of male breast cancer [19].

The aim of our study is to evaluate, in a larger group of patients, the contribution of germline mutations in BRCA1 and BRCA2 to breast cancer among Jordanian patients with selected high-risk profile as per the National Comprehensive Cancer Network (NCCN) guidelines [20].

2. Methods

Jordanian breast cancer patients with selected high-risk profile, as per the NCCN guidelines [20], were invited for BRCA1 and BRCA2 testing. This includes patients of 40 years of age or younger at the time of breast cancer diagnosis, patients with at least two breast cancer primaries (i.e., bilateral tumors or 2 or more clearly separate ipsilateral tumors, occurring synchronously or asynchronously), the first at the age of 50 years or younger, patients diagnosed at the age of 50 years or younger with one or more close relatives with breast cancer at any age, diagnosed at any age with 2 or more close relatives with breast cancer at any age, diagnosed at any age with one or more close relatives with invasive ovarian cancer diagnosed at any age, diagnosed at any age with a close male relative with breast cancer at any age, and patients with triple-negative disease who are 60 years of age or younger [20]. All patients had their diagnosis, treatment, and follow-up at our center.

Eligible patients were identified by their primary oncologists during their routine clinic visit or during the weekly breast multidisciplinary team (MDT) discussion. Patients who consented to BRCA1 and BRCA2 testing were then referred to our genetic counseling clinic where a lengthy interview and discussion by a trained genetic counselor were carried out. Clinical and psychosocial consequences of positive test results were discussed at length with the patients, and when requested by the patient, such meeting and discussion were also carried out with the spouse and/or family members.

The study was discussed and approved by our Institutional Review Board (IRB), and all patients signed informed consent. BRCA1 and BRCA2 testing were performed at no cost to participants as per part of the routine clinical practice. Ten milliliters of peripheral blood samples were obtained for DNA extraction. BRCA1 and BRCA2 sequencing were performed at Leeds Cancer Center, Leeds, United Kingdom. Based on a standardized variant assessment tool used by reference genetics labs, BRCA1 and BRCA2 mutations were classified as pathogenic/likely pathogenic (positive) and variant of uncertain significance (VUS). Clinical and pathological data were obtained from patients’ medical records, and a detailed 3-generation family history was also obtained by a genetic counselor or one of the investigators.

Analysis was performed using an Agilent SureSelect custom design reagent to screen for germline pathogenic variants. Genomic DNA regions including coding exons and intron/exon boundaries are targeted by hybridization capture and sequenced on the Illumina platform with a sensitivity of at least 95%. The target region of selected transcripts is covered to a minimum read depth of 30x. Analysis for large deletion and duplication is preformed using comparative depth of coverage of NGS data and/or MLPA analysis using P087, P045, and P260.

2.1. Statistical Analysis. Patient characteristics were tabulated and described by ranges, medians, or percentages (%). First-degree close relatives diagnosed with breast cancer and tested later to the index case in the family were excluded from analyses. The $\chi^2$ test or Fisher exact test were used to compare the proportion of positive BRCA1 and BRCA2 pathogenic/likely pathogenic mutations according to the age ($\leq$40 versus $>40$), triple-negative status, first- and/or second-degree family history of breast and/or ovarian cancer, bilateral or second primary breast cancer, number of indications for genetic testing, and family history of male breast cancer. Multivariate analysis using a logistic regression model adjusting for the age, triple-negative status, and bilateral or second primary breast cancer was performed. Odds ratios and their related 95% confidence intervals (CI) were calculated. A $P$ value $\leq$ 0.05 was considered significant. Version 9.4 of SAS software (SAS Institute Inc., Cary, NC) was utilized.

3. Results

Between November 2016 and January 2019, a total of 517 consecutive eligible patients were recruited. The median age of participants was 39 (range: 19–78) years. At the time of diagnosis, 333 (64.4%) patients were 40 years of age or younger. Majority ($n = 420, 81.2\%$) of the patients had hormone receptor (ER and/or PR) positive disease. Human epidermal growth factor receptor (HER2) was positive in 133 (25.7%) by immunohistochemistry (IHC) and/or Fluorescent In Situ Hybridization (FISH), and 57 (11.0%) had triple-negative disease, Table 1.

Among the whole group, 72 (13.9%) patients had pathogenic/likely pathogenic BRCA1 or BRCA2 mutations; 48 (66.7%) of them were in BRCA2, while 24 (33.3%) in BRCA1 and an additional 53 (10.3%) patients had VUS. A total of 242 (46.8%) had their genetic testing because they were 50 years of age or younger with one or more close
showed that such mutations are not uncommon among Jordan and one of the biggest from the region. Our data showed that mutations are not uncommon among Jordanian patients selected and tested as per the NCCN guidelines. Contrary to what is usually seen in western societies, our data indicate that mutation rates are not higher among the younger patients (13.2%) compared to the whole group (13.9%), obviously all with at least one risk factor. The fact that breast cancer is diagnosed at a younger age in our region can be a factor. We are in the process of combining the cohort of younger patients included in this study and our previous one [19] to study the contribution of age, in the absence of other risk factors, to the risk of carrying BRCA1 or BRCA2 mutation.

We also noted relatively high rates of VUS in this group of patients. This could likely be related to racial issues as western reference laboratories might not have enough exposure to the specific mutations encountered in our population. Mutation testing in our previously published study [19] was conducted at a different reference laboratory and had a similar high VUS rate, making the racial hypothesis an interesting one to follow.

Patients with triple-negative disease had the highest mutation rate and, as expected, mostly (80%) in BRCA1. Given this high positive pathogenic mutation rate, additional risk factors did not add to the already high mutation rate. The only exception is probably the presence of a family history of breast cancer in at least two family members. However, studies including a larger number of such patients are needed to address this issue. In addition to patients with triple-negative disease, patients with at least two breast primaries had higher mutation rate (21.7%).

Our positive mutation rates are significantly higher than what our colleagues had recently reported among 281 Lebanese patients [21]. Though it was stated that patients were tested as per NCCN guidelines for mutation screening, the prevalence of mutated BRCA1 or BRCA2 genes was only 6.0% and 1.4%, respectively. In an earlier study, reported by the same group, on 250 Lebanese patients tested between 2009 and 2012 who were considered to be at high risk of carrying BRCA1 or BRCA2 mutations because of presentation at a young age and/or a positive family history of breast or ovarian cancer, 14 (5.6%) carried a deleterious mutation (7 BRCA1, 7 BRCA2) and 31 (12.4%) carried VUS. In the same study, only one (1.4%) of the 74 patients aged \( \leq 40 \) years without a family history had pathogenic mutation, while 8 (10.8%) of the 74 patients aged \( \leq 40 \) years with a positive family history had a deleterious mutation [22]. On the other hand, a recent systematic review and meta-analysis of 14 studies from the region attempted to better describe the prevalence of BRCA1 and BRCA2 mutations in Arab countries. The study has several methodology problems, yet they reported a high rate of 20% [23].

We have no explanation on the significant differences between our rates and what had been reported among the Lebanese. There should be no significant ethnic differences that may account for such variation. In our database, 63 non-Jordanian patients from Syria, Iraq, Libya, and Palestine and not included in our analysis were tested for BRCA1 and BRCA2 mutation following the same indications and methodology of testing, and 8 (12.7%) had positive mutations. Different inclusion criteria for testing or different

| Table 1: Patient characteristics (\( n = 517 \)). |
|-------------------------------|---------------|
| Characteristics               | Number (%)    |
|Age at diagnosis (years)       | Median 39, Range 19–78 |
|Hormonal status                |               |
|ER-positive                    | 392 (75.8)    |
|PR-positive                    | 375 (72.5)    |
|ER- or PR-positive             | 420 (81.2)    |
|ER- and PR-negative            | 97 (18.8)     |
|HER2 status                    |               |
|HER2-positive                  | 133 (25.7)    |
|HER2-negative                  | 318 (61.5)    |
|Unknown                        | 66 (12.7)     |
|Triple-negative                |               |
|Positive family history of breast cancer | 57 (11.0)  |

ER: estrogen receptors; PR: progesterone receptors; HER2: human epidermal growth factor receptor.

relatives with breast cancer at any age; 40 (16.5%) of them were positive for BRCA1 or BRCA2. Among the 333 patients who were 40 years of age or younger, the pathogenic/likely pathogenic mutations were observed in 44 (13.2%) patients, Table 2.

Twenty (35.1%) of the 57 patients with triple-negative disease had pathogenic/likely pathogenic mutations; 16 (80.0%) of them were in BRCA1, and only 4 (20.0%) were in BRCA2. An additional 7 (12.3%) others had VUS. Among 37 patients with triple-negative disease who were 40 years of age or younger, 12 (32.4%) were positive; all except 2 were in BRCA1. Among the patients with triple-negative disease who have a family history of breast cancer diagnosed at an age \( < 50 \) \( (n = 12) \), 5 (41.7%) were BRCA1- or BRCA2-positive. Another 5 (55.6%) of those with two family members with breast cancer at any age \( (n = 9) \) were positive for pathogenic mutation too. Figure 1 illustrates the mutation rates among patients tested for different indications, while Figure 2 details mutation rates among subgroups of patients with triple-negative disease.

We also reviewed the mutation rates based on the number of indications a patient may have had for testing. Among 205 (39.7%) patients who had only one indication as per the NCCN guidelines, only 12 (5.9%) had pathogenic or likely pathogenic mutation compared to 25 (15.1%) among 166 (32.1%) patients with two indications and 35 (24.0%) among 146 (28.2%) patients with three or more indications. No founder mutation was identified, and the type and frequency of specific mutations are illustrated in Table 3.

Multivariate analysis using a logistic regression model was performed. The triple-negative status, history of two or more close relatives with breast cancer, and history of one or more close relatives with invasive ovarian cancer were significant with an OR of carrying a pathogenic variant (95% CI) of 5.08 (2.66–9.67), 3.24 (1.78–5.89), and 2.97 (1.04–8.52), respectively (Table 4).

4. Discussion

This is the biggest BRCA1 and BRCA2 mutation study from Jordan and one of the biggest from the region. Our data showed that such mutations are not uncommon among

Table: Characteristics Number (%)

| Characteristics               | Number (%)    |
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|HER2 status                    |               |
|HER2-positive                  | 133 (25.7)    |
|HER2-negative                  | 318 (61.5)    |
|Unknown                        | 66 (12.7)     |
|Triple-negative                |               |
|Positive family history of breast cancer | 57 (11.0)  |

ER: estrogen receptors; PR: progesterone receptors; HER2: human epidermal growth factor receptor.
testing methodologies may have contributed to this variation in mutation rates.

In our previous study, we addressed the challenges in conducting such studies in a culturally sensitive society with limited resources. Many ethical and cultural difficulties were encountered and continued to be encountered during the course of our study. Ensuring confidentiality and privacy are still major issues in a closely related, relatively small community. However, very few patients (4 patients) expressed their concerns about labeling and stigmatization and, thus, refused the testing when approached by their physicians. Additionally, none of the patients tested positive had issues with sharing and addressing such results with their at-risk family members. Local or regional data on clinical and psychosocial consequences related to positive mutations are lacking. We are in the process of collecting such data as part of a larger genetic testing and genetic counselling project.

Potential employment and social discrimination addressed in our previous report had not surfaced out as major issues in expanding our program. However, insurance issues continued to be a problem. Though governmental cancer care insurance covers for BRCA1 and BRCA2 testing, it does not cover the major part of the reconstruction surgery.

Now that we confirm that BRCA1 and BRCA2 mutations are not uncommon, such testing, counseling, and linking it to risk-reduction surgery should be incorporated into the routine clinical practice nationwide. At our institution, genetic testing has become routinely offered for at-risk patients as per the published NCCN guidelines.

Table 2: Rates of positive BRCA1 and BRCA2 mutation across different indications.

| Variable                                                | Total     | Positive mutations | P value* |
|---------------------------------------------------------|-----------|--------------------|----------|
| Age at diagnosis (years)                                |           |                    |          |
| ≤ 40                                                    | 333       | 15 (4.5%)          | 0.530    |
| > 40                                                    | 184       | 9 (4.9%)           |          |
| Age ≤ 50 years with one or more close relatives with breast cancer at any age |           |                    |          |
| Yes                                                     | 242       | 8 (3.3%)           | 0.1      |
| No                                                      | 275       | 16 (5.8%)          |          |
| Age ≤ 60 with triple-negative disease                    |           |                    | <0.001   |
| Yes                                                     | 57        | 16 (28.1%)         |          |
| No                                                      | 460       | 8 (1.7%)           |          |
| Any age with at least 2 breast cancer primaries          |           |                    | 0.98     |
| Yes                                                     | 57        | 4 (7.0%)           |          |
| No                                                      | 460       | 20 (4.3%)          |          |
| Any age with 2 or more close relatives with breast cancer |           |                    | <0.001   |
| Yes                                                     | 115       | 7 (6.1%)           |          |
| No                                                      | 402       | 17 (4.2%)          |          |
| Any age with one or more close relatives with invasive ovarian cancer diagnosed at any age |           |                    | 0.023    |
| Yes                                                     | 19        | 2 (10.5%)          |          |
| No                                                      | 498       | 22 (4.4%)          |          |
| All patients                                            | 517       | 24 (4.6%)          |          |

*P value comparing risk factor categories.

Figure 1: BRCA1 and BRCA2 mutation rates by indication.
**Figure 2:** *BRCA1* and *BRCA2* mutations among patients with triple-negatives.

| Gene | Exon/intron | Nucleotide change | Amino acid change | Variant type | dbsNP rs | Clinical significance | Database report | Frequency (n) |
|------|-------------|-------------------|-------------------|--------------|----------|----------------------|-----------------|---------------|
| *BRCA1* | Exon 2 | c.66dup | p.Glu23Arg | Duplication/fs | rs80357783 | Pathogenic | Yes | 5 |
| *BRCA1* | Exon 12 | c.4117G>T | p.Glu1373Ter | Nonsense | rs80357259 | Pathogenic | Yes | 3 |
| *BRCA1* | Exon 17 | c.5074 + 3A>G | Splice acceptor | Intervening sequence | rs80358181 | Likely pathogenic | Yes | 3 |
| *BRCA1* | Exon 11 | c.4065_4068del | p.Asn1355Lys | Deletion/fs | rs80357508 | Pathogenic | Yes | 2 |
| *BRCA1* | Exon 18 | c.5123C>A | p.Ala1708Glu | Missense | rs28897696 | Pathogenic | Yes | 2 |
| *BRCA1* | Exon 3 | c.121C>T | p.His41Tyr | Missense | rs1060502353 | Likely pathogenic | Yes | 2 |
| *BRCA2* | Exon 11 | c.2254_2257del | p.Asp752Phefs | Deletion/fs | rs80359326 | Pathogenic | Yes | 8 |
| *BRCA2* | Exon 11/11 | c.2254_2257del & c.5351dup | p.Asp752Phefs and p.Asn1784Lysfs | Deletion/fs-Duplication/fs | rs80359326 & rs80359508 | Pathogenic | Yes | 6 |
| *BRCA2* | Exons 5-11 | Partial duplication (exons 5-11) | Absent or disrupted protein product | Large duplication | — | Pathogenic | Yes | 5 |
| *BRCA2* | Exon 10 | c.1233dup | p.Pro412Thr | Duplication/fs | rs80359270 | Pathogenic | Yes | 3 |
| *BRCA2* | Exon 11 | c.6685G>T | p.Glu2229Ter | Nonsense | rs730881548 | Pathogenic | Yes | 3 |
| *BRCA2* | Exon 11 | c.6486_6489del | p.Lys2162Asn | Deletion/fs-Intervening sequence | rs80359598 | Pathogenic | Yes | 2 |
| *BRCA2* | Intron 24 | c.9257-1G>A | Splice acceptor | — | rs81002889 | Likely pathogenic | Yes | 2 |

**Table 4:** Logistic regression.

| Variable | Odds ratio | 95% CI | P value |
|----------|------------|--------|---------|
| Age at diagnosis <40 | 1.27 | 0.71–2.28 | 0.40 |
| Bilateral or second primary breast cancer | 5.08 | 2.66–9.67 | <0.0001 |
| History of two or more close relatives with invasive ovarian cancer | 3.24 | 1.29–8.58 | 0.043 |

CI: confidence interval.
Additionally, a clinical cancer genetics program was established and operating smoothly with no major issues. Compliance on testing high-risk patients was recently added to our “Key Performance Indicators (KPI),” data on which are collected and reported by our quality office. We are also currently expanding our genetic testing and counseling program to include mutations in genes other than BRCA1 and BRCA2 for high-risk patients who were tested negative. The current study has avoided many of the limitations we had in the previous study. The sample size is not an issue here, though larger studies are needed to study the contribution of each risk factor in its own or in combination to a positive mutation rate.

5. Conclusions

Our recent findings support the conclusion that BRCA1 and BRCA2 mutations are prevalent enough to be incorporated into clinical practice guidelines nationwide and to provide affected women with free access to risk reduction and reconstructive surgeries.

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| CI           | Confidence intervals |
| ER           | Estrogen receptors |
| PR           | Progesterone receptors |
| FISH         | Fluorescent in situ hybridization |
| HER2         | Human epidermal growth factor receptor |
| IHC          | Immunohistochemistry |
| IRB          | Institutional review board |
| MDT          | Multidisciplinary team |
| NCCN         | National comprehensive cancer network |
| VUS          | Variant of uncertain significance |

Data Availability

Data will not be available online as it might contain sensitive information regarding the mutation status.

Ethical Approval

The study was approved by our Institutional Review Board (IRB).

Consent

All patients signed informed consent. Data submitted are entirely unidentifiable, and there are no details of individuals reported within the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

The first author HA conceived the research idea, planned it, supervised data collection, and took the lead in writing the manuscript. The second author LA consulted with patients and supervised informed consent, sample collection, and genetic counselling. The third author DJ participated in analyzing the data and editing the manuscript. All authors have read and approved the manuscript.

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