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CLINICAL OUTCOMES AND PROGNOSTIC FEATURES OF GERMLINE BRCA MUTANT BREAST CANCER PATIENTS: SINGLE-CENTER EXPERIENCE, MADINAH, SAUDI ARABIA

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ABSTRACT – *Objective:* The aim of this study is to evaluate the clinicopathological features and prognostic impact of breast cancer harboring germline *BRCA1/2* mutation.

Materials and Methods: This cross-sectional study was conducted on early and de novo metastatic *BRCA* mutant female breast cancer patients diagnosed at King Salman Medical City, Medina region, Kingdom Saudi Arabia (KSA), since 2022. A germline *BRCA1/2* mutation was confirmed from blood samples by a next-generation sequencing test.

Results: Median age of diagnosis was 35 years old (35-60), and family history of breast cancer was present in 33.3%. Sixty-six percent of patients were in an early stage; however, 34% of patients had de novo metastatic diseases; 22.2% of them had central nervous system (CNS) involvement. On follow-up of early breast cancer patients, 30% developed contralateral breast cancers, 21% developed ipsilateral disease, while 57% developed distant metastasis. Triple-Negative Breast Cancer (TNBC) was found in 45% of these *BRCA1/2* mutant breast cancer patients, which was more prevalent in *BRCA1* carriers accounting for 75% of cases. No differences were found in the toxicity due to breast radiation between *BRCA1* and *BRCA2* patients regarding skin dermatitis, pigmentation, breast or chest wall oedema, and telangiectasia. Most of the de novo metastatic patients were *BRCA2* mutant *vs. BRCA1* (66.5% *vs.* 33.5%). Median progression-free survival (PFS) of all *BRCA*-mutated patients was 13 months. However, *BRCA1* patients showed longer PFS (median; 20 *vs.* 12 months, p=0.4). Median overall survival (OS) of all *BRCA* mutants was 23 months, with better OS in *BRCA1* mutant patients (median OS: 25 *vs.* 19 months, p=0.3).

Conclusions: To our knowledge, this is the first cross sectional study investigating the clinical and prognostic value of germline *BRCA1/2* mutation in breast cancer in our locality. Germline *BRCA1/2* carriers presented with more aggressive disease and poor outcomes. Germline *BRCA2* mutant patients were more often diagnosed at an advanced stage and showed poorer PFS and OS compared to their *BRCA1* mutation carriers counterparts.

KEYWORDS: Breast cancer, Germline, *BRCA1*, *BRCA2*, Clinicopathological features, Saudi Arabia.

INTRODUCTION

Breast cancer is the most common cancer and is considered the leading cause of mortality from cancer in women worldwide[1]. About one in twelve women in the West develops breast cancer at some point in their life[2].

Among the major risk factors associated with breast cancer, the most important is age, followed by a positive family history for breast cancer[3,4]. Approximately 5% to 10% of breast cancer cases are hereditary, and up to 25% of the hereditary breast cancers have been linked to germline mutations of specific genes[5].

Breast cancer was ranked first among Saudi females[6]. There were 2,459 female breast cancer cases. Breast cancer accounted for 17.8% of all cancers reported among Saudi nationals, and 31.4% of all cancers reported among females. The age-standardized rate (ASR) was 28.4/100,000 for the Saudi female population[6]. The five regions with the highest ASR per 100,000 population were the Eastern region at 46.2/100,000, followed by Riyadh with 43.3/100,000, Qassim with 28.1/100,000, Jouf with 25.2/100,000, and the Makkah region with 24.9/100,000. The median age at diagnosis was 51 years (ranging from 20 to 95)[6].

DNA double-strand breaks are a very dangerous form of DNA damage and can be repaired by homologous recombination repair, which includes the breast cancer susceptibility genes *BRCA1* and *BRCA2.* These genes act as a tumor suppressor to promote the homologous recombination repair mechanism, and their inherited mutations result in a homologous recombination repair deficiency, leading to a significant lifetime risk of breast, ovarian, and other cancers[7].

The most studied genes in breast cancers are *BRCA1* and *BRCA2*, whose highly penetrant mutations are associated with the Hereditary Breast/Ovarian Cancer Syndrome, an autosomal-dominant inherited trait predisposing women to both breast and ovarian cancer[8,9]. Women with *BRCA* mutations have a lifetime risk of developing breast cancer and ovarian cancer of 45% to 75% and 18% to 40%, respectively[2,10,11].

Risk for contralateral breast cancer in carriers of a *BRCA2* pathogenic variant is age-dependent and greatest in those diagnosed with breast cancer at an early age (i.e., <40 years)[12,13]. Risk is also greater in *BRCA1* pathogenic variant carriers compared to *BRCA2* pathogenic variant carriers (20-year cumulative risk 30%-40% and 25%, respectively)[12].

The testing for germline mutations in high-penetrance breast cancer predisposition genes has become standard practice for breast cancer patients[14]. *BRCA*-related breast cancer is characterized by a more aggressive phenotype than sporadic breast cancer[15]. Thus, it has been hypothesized that *BRCA*-associated breast cancer has a different prognosis than the sporadic counterpart. The aim of this work was to evaluate the different clinicopathological and prognostic impact of breast cancer ladies harboring germline *BRCA1/2* mutation in our locality in relation to published data worldwide.

It was proven that patients with high-risk, HER2-negative early breast cancer and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants, adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy, were associated with significantly longer survival free of invasive or distant disease than placebo[16]. Also, previous studies showed that in patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer, and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy[17].

MATERIALS AND METHODS

This cross-sectional study was conducted on germline *BRCA* mutant female breast cancer patients diagnosed at the Oncology Center, King Salman Medical City, Medina region, KSA, from January 2022 to December 2024. Early and de novo metastatic patients were included. Initial workup was done for all patients based on National Comprehensive Cancer Network (NCCN) guidelines, including laboratory, radiological, and pathological evaluations. Pregnant, lactating females and prior or concurrent malignancies were excluded.

Germline *BRCA1/2* mutation confirmed from blood samples by next-generation sequencing test (multiplexed amplification-based), which allows detection of *BRCA1* and *BRCA2* variants in germline samples through semiconductor-based DNA sequencing (ThermoFisher, Agilent Technologies, Santa Clara, CA, USA). It detects point mutations and small insertions/deletions in all coding regions (exons) in *BRCA1* and *BRCA2* genes with a limit of detection of more than 5% allele frequency.

The plan of treatment for all early and de novo metastatic patients was discussed in the institutional tumor board, adhering to both NCCN and European Society for Medical Oncology (ESMO) guidelines based on each breast cancer subtype (luminal, HER2-enriched, or TNBC). Early breast cancer patients were under follow-up after finishing primary treatment till the end of the study to assess any local or distant disease recurrence. Patients with de novo metastasis or those who developed metastasis on follow-up were under follow-up to assess treatment response. We tried to assess the clinico-pathological and prognostic behavior of germline *BRCA* mutant breast cancer patients in our locality by comparing these variables between *BRCA1* and *BRCA2* mutant patients.

Statistical Analysis

The statistical analysis was carried out using software Excel 2010 and version 21 of SPSS (Statistical System for Social Science; Armonk, NY, USA). Qualitative data were described in the form of percentages. Quantitative data were described in the form of mean (±) standard deviation (SD). Statistical analysis was performed by comparison between groups using the Chi-squared test. The Kaplan-Meier product-limit estimator was used for calculating survival measures. The log-rank test performed a comparison of the survival; continuous variables were dichotomized at the median cutoff. The *p*-value was calculated for all parameters, with statistical significance defined as $p \leq 0.05$ at the 95% confidence interval.

RESULTS

This study included *BRCA1/2* mutant female breast cancer patients with a median age of 35 years (35-60), mean±SD; 45.6 ± 8.2. None of the patients were diagnosed through the governmental screening program. Family history of breast cancer was present in 33.3% of them. Most of the patients were premenopausal (88.9%). The most common histology was ductal carcinoma, followed by lobular and other subtypes (78%, 12% and 10%, respectively). High-grade (II, III) tumors were presented in 88% while *in situ* components were found in 11% of the studied histology. Radiologically, T3 & T4 tumors presented in 55.5% while high nodal involvement (N2 and N3) was found in 67%. About two-thirds of patients were diagnosed in the early stage (66%); however, 34% of patients had de novo metastatic diseases; 22.2% of them had CNS involvement. After discussion with early breast cancer patients, 62% agreed for prophylactic contralateral mastectomy. TNBC subtype was the most prevalent subtype (45%) in these *BRCA1/2* mutant breast cancer patients, followed by luminal subtype (33%), then Her2-enriched (22%). High Ki67 expression ≥20% was detected in 67%. During follow-up of early breast cancer patients, 30% developed contralateral breast cancers, 21% developed ipsilateral disease, while 57% developed distant metastatic disease, with 21% of them presenting with visceral crisis, as shown in Table 1.

No difference in age of presentation between patients harboring *BRCA1 vs. BRCA2* (median age: 47.5 *vs.* 47 years old, p = 0.3). Baseline CA15.3 and CEA were higher in *BRCA2* mutant patients (Mean±SD; 43.8 ± 30.7 and 6.0 ± 5.3, with non-significant differences, p = 0.09 and 0.7, respectively). In early breast cancer patients, there was no difference regarding time to develop metastasis in both *BRCA1* and *BRCA2* (p= 0.8) (Table 2).

Most patients diagnosed with de novo metastatic disease harbored *BRCA2* mutation *vs. BRCA1* (66.5% *vs* 33.5%), but with no significant difference (p = 0.6). Also, presentation with CNS metastasis at time of diagnosis was equal in both groups (p = 0.7). The triple negative breast cancer subtype was more prevalent in *BRCA1* mutant patients (75% *vs.* 25%) without a significant difference (p = 0.1). We found that Ki 67 (≥20%) expression was reported to be higher in *BRCA1* compared to *BRCA2* (57.1% *vs.* 42.9%, p = 0.2). Large tumor size and high nodal involvement were found to be more common in BRCA2 mutant tumors in comparison to *BRCA1* (T3 and 4 disease; 80% *vs.* 20%, p = 0.1 however, N stage 2&3; 68% *vs.* 32%, p =0.4). During follow-up in early breast cancer patients, 72.5% of *BRCA1* mutant patients developed metastasis *vs.* 27.5% for patients with *BRCA2* mutations (p = 0.2). No differences in the toxicity of

Table 1. Demographic data of studied cases.

Age at Diagnosis (Mean±SD) years Median: 35 years (35-60)		45.6 ± 8.2
CA15.3 at Diagnosis (Mean±SD)		35.2 ± 25.5
CEA at Diagnosis (Mean±SD)		4.8 ± 4.0
Family History of Breast cancer		33.3%
Premenopausal		88.9%
Histological		
Subtype	Ductal	78%
	Lobular	12%
	Others	10%
Tumor		
Grade	Grade I	12%
	Grade II, III	88%
In situ component		11%
BRCA		
Mutation	BRCA1	44.4%
	BRCA2	55.6%
r T3,4		55.5%
r N2,3		67%
Stage at diagnosis	Early disease	66%
	Denovo Metastatic	34%
Early Patients agreed for Bilateral Mastectomy		62%
CNS Metastasis at diagnosis		22.2%
Breast		
Cancer		
Subtype	Luminal Subtype	33%
	Her2 enriched	22%
	TNBC	45%
High Ki67 (≥20%)		67%
Recurrent		
Disease	Ipsilateral	21%
	Contralateral	30%
Developed Metastasis During FU		57%
Metastasis with Visceral Crisis		21%

Table 2. Comparing the clinico-pathological data of BRCA1&2 disease.

	BRCA1	BRCA2	*p*-value
Age at Diagnosis (Mean±SD) years	45.5 ± 6.6	45.8 ± 10.1	0.3
Age Median	47.5	47	
Family History of Breast Cancer	33.3%	66.7%	0.5
Premenopausal	49%	51%	0.4
Denovo Metastatic	33.5%	66.5%	0.6
CNS Metastasis at Presentation	48%	52%	0.7
TNBC	75%	25%	0.1
Luminal	33.3%	66.7%	
Her2 enriched	56.4%	43.6%	
Grade II and III	37.5%	62.5%	0.4
High Ki67 expression (≥20%)	57.1%	42.9%	0.2
T 3,4 disease	20%	80%	0.1
N 2,3 disease	32%	68%	0.4
Developed Metastasis during FU	72.5%	27.5%	0.2
Skin Dermatitis after breast radiation (any grade)	22.5%	20.4%	0.6
Skin Pigmentation after breast radiation (any grade)	68%	64.4%	0.8
Breast Shrinkage after breast radiation	11.4%	13%	0.7
Breast or chest wall oedema after breast radiation	9%	7.5%	0.5
Telangiectasia after breast radiation	7.5%	6.5%	0.9
CA15.3 at Diagnosis (Mean±SD)	24.5 ± 14.4	43.8 ± 30.7	0.09
CEA at Diagnosis (Mean±SD)	3.4 ± 2.2	6.0 ± 5.3	0.7
Time to developed Metastasis in early breast cancer patients (Mean±SD) months	22 ± 7.2	24 ± 6.1	0.8

adjuvant breast radiation were found between *BRCA1* and *BRCA2* mutant patients regarding any grades of skin dermatitis (p = 0.6), any grades of skin pigmentation (p =0.8), breast or chest wall oedema (p = 0.5), or telangiectasia (p = 0.9), as shown in Table 2.

Figure 1 shows the PFS of all *BRCA* mutant patients, with a median PFS of 13 months. However, *BRCA1* patients had a better PFS (median OS: 20 *vs.* 12 months); this difference was not statistically significant (p = 0.4) (Table 3 and Figure 2).

Median OS for all *BRCA* mutants was 23 months (Figure 3). *BRCA1* mutant patients lived longer than *BRCA2* mutant patients (median OS: 25 *vs.* 19 months), but there was no significant difference between the two groups (p = 0.03) (Table 4 and Figure 4).

DISCUSSION

The majority of hereditary ovarian and breast cancers are triggered by mutations in breast cancer types 1 or 2 (*BRCA1* and *BRCA2*), and the pathogenic changes that have been found in these cancers are described by an autosomal dominant pattern of highly penetrant germline inheritance.

BRCA1/2 mutation variants are associated with early-onset primary breast cancer. In a sample of 21,401 families who met German Consortium for Hereditary Breast and Ovarian Cancer testing criteria for *BRCA1/2* mutation variants, it was detected in 13.7% of families with a single case of breast cancer diagnosed at <36 years of age[18]. Ductal carcinoma was the predominant histological pattern in our cohort, consistent with the findings of Abulkhair et al[19].

Family history is a risk factor for breast cancer, and its incidence varies between *BRCA*-related cancer patients[20,21]. O'Shaughnessy et al[22] showed that family history was present in 45.5% of *BRCA* mutation breast cancer patients[20]. Likely, in another report, family history was present in 50% patients[22].

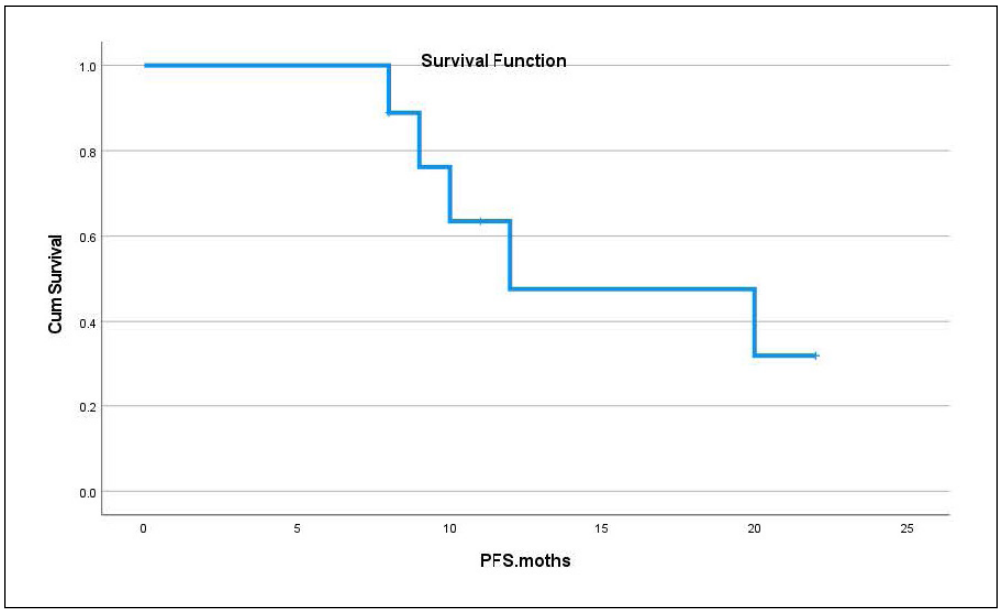

Figure 1. PFS of all BRCA1/2 mutant patients (median PFS 13 months).

Table 3. PFS of BRCA1&2 patients.

	Median PFS (months)	Log rank	*p*
BRCA1	20	0.6	0.4
BRCA2	12		

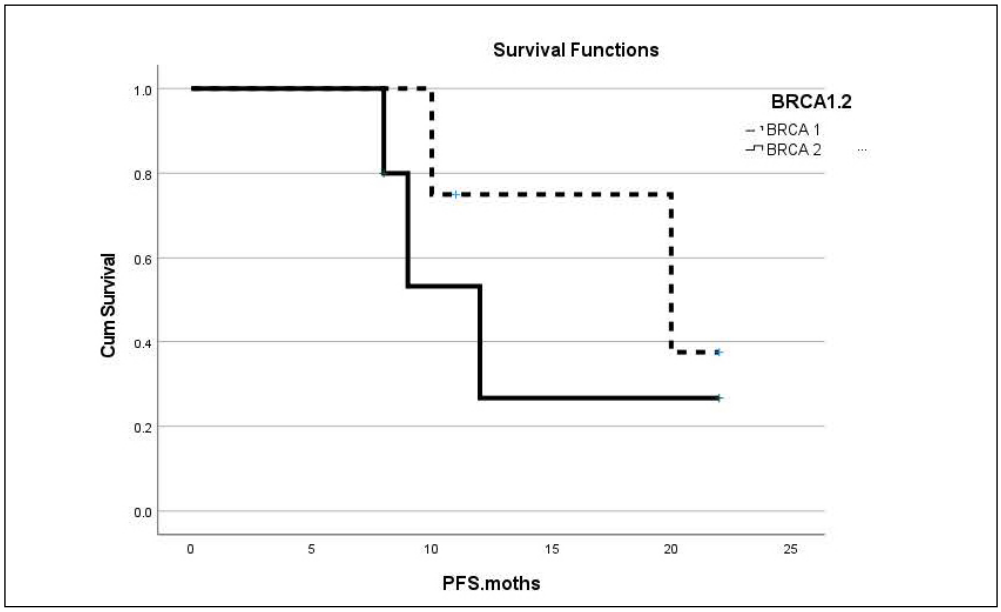

Figure 2. PFS of BRCA1 comparing to BRCA2 mutant tumors.

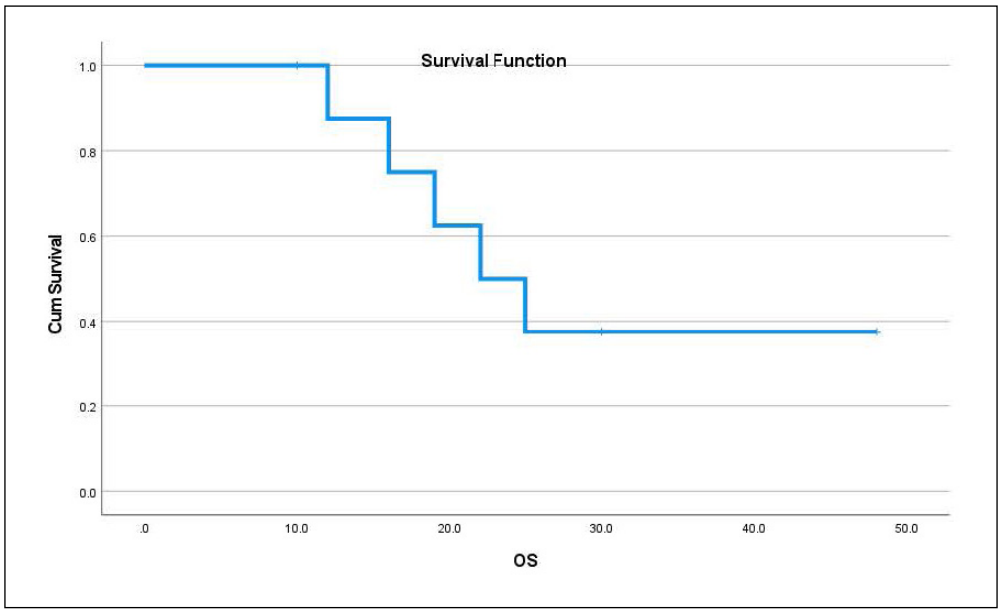

Figure 3. OS of all BRCA1/2 mutant patients (median OS 23 months).

Table 4. OS of BRCA1&2 patients.

	Median OS (months)	Log rank	*p*
BRCA1	25	0.7	0.3
BRCA2	19		

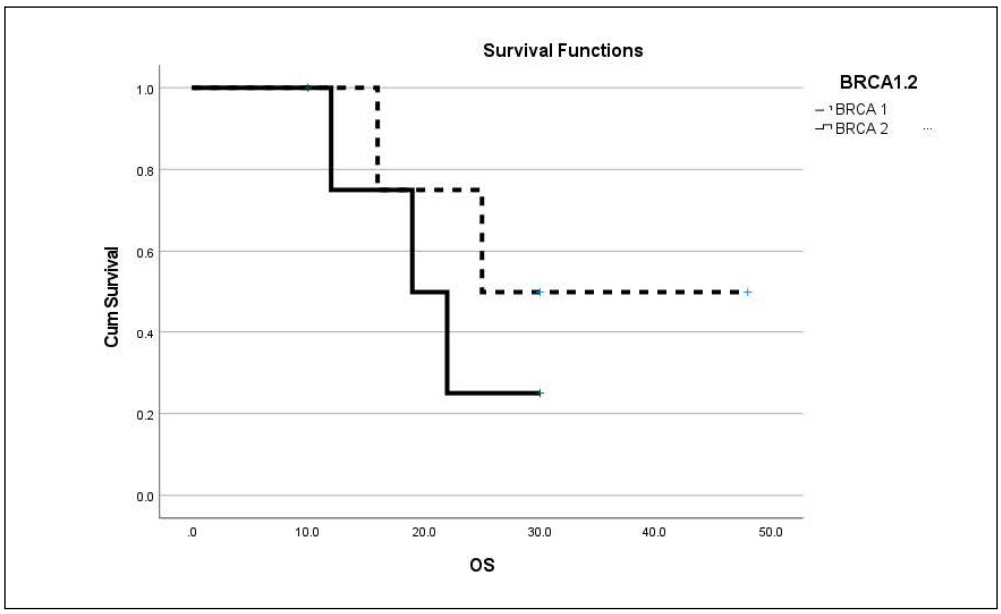

Figure 4. OS of BRCA1 comparing to BRCA2 mutant tumors.

We found that patients with germline *BRCA* mutation presented at a younger age, with one third of them having a positive family history of breast cancer. Chen et al[23] reported that breast cancer was diagnosed at a significantly younger age in germline mutation carriers as compared to non-carriers (median age: 45 *vs.* 50 years, $p = 0.011$. Additionally, we demonstrated that female breast cancer patients ≤45 years old were significantly more numerous in the *BRCA1* variant group, similar to data reported by Osman et al[22].

In our study, we identified that the median age of diagnosis and tumor histopathological findings were similar, compared to the Greek population[24]. Moreover, it was demonstrated that the median age at diagnosis of breast cancer in Mediterranean countries is younger compared with Western European countries[25]. These differences might be attributed to the regional distribution of the population and/or ethnic-specific factors.

Over time, estimates of the probability of ipsilateral recurrence following breast surgery in patients with breast cancer linked to *BRCA* mutations have changed. According to previous research, women with *BRCA* mutation-associated breast cancer do not have a substantially higher risk of ipsilateral breast tumor recurrence following breast surgery and radiation therapy compared to those who were diagnosed with sporadic breast cancer[26-28]. However, many studies have revealed a trend towards a higher risk of ipsilateral recurrence in *BRCA* mutation carriers than sporadic controls[27,29,30].

Although oophorectomy, adjuvant tamoxifen, and adjuvant chemotherapy were shown to lower the chance of ipsilateral recurrence, it is still challenging to determine how much of a risk reduction any of these treatments alone has produced[29,31,32]. Our research reported that 21% of germline *BRCA* mutant early breast cancer patients developed ipsilateral recurrence during follow-up after finishing primary treatment.

According to the majority of research, the incidence of contralateral breast cancer is between 15 and 40 percent[26,27,33,34]. Women with sporadic breast cancer are predicted to have a 3-10% chance of metachronous contralateral breast cancer, compared to the high risk of contralateral breast cancer in those with *BRCA* mutation-associated breast cancer[29,30,34,35].

Individuals with a germline *BRCA1/2* mutation were found to have breast tumors with specific histopathologic characteristics more frequently. For instance, a number of studies have demonstrated that breast cancer linked to *BRCA1* is more likely to be described as ER-/PR-negative and HER2-negative (i.e., "triple negative")[36-38]. In various studies, 4.4% to 16% of patients with triple-negative breast cancer have *BRCA1* mutations[36,39-41]. According to one cohort analysis, carriers of the pathogenic *BRCA2* mutation had an absolute lifetime risk of 40% for hormone receptor-positive (ER+ and/or PR+) breast cancer[36]. Also, according to numerous studies, breast tumors linked to *BRCA1* mutations are more likely to be triple negative, but those linked to *BRCA2* mutations are more likely to be estrogen receptor positive[37,42,43].

In this series, the most prevalent molecular breast cancer subtype with *gBRCA* was TNBC, followed by luminal, then Her2-enriched, which is the same prevalence as a molecular subtype as shown in other studies[23], with more common TNBC in germline mutation, followed by Her2-enriched, then luminal subtypes. Also, we reported that most of BRCA mutation carriers who had TNBC were BRCA1 mutants. This was also consistent with another Saudi cohort that documented that TNBC was more prevalent in BRCA mutant patients[19].

Germline *BRCA2* mutation was slightly more prevalent than the germline *BRCA1* mutation in our locality. Interestingly, we found that other Asian breast cancer patients had more frequent mutations in *BRCA2* than in *BRCA1* mutation[23], which differ from those in Western breast cancer patients[14].

A retrospective single-center study involved an analysis of patients with localized or locally advanced breast cancer who underwent *BRCA* variation testing. Authors found that patients with *BRCA1* variation had more aggressive tumor characteristics, such as higher Ki67 and higher grade[44]. This was similar to our result, but the high-grade tumor was more common in *BRCA2* mutations. Additionally, *BRCA*-associated early-stage hormone receptor-positive breast cancers have a higher Oncotype DX Breast Recurrence Score® compared to those without mutations, indicating a more aggressive disease[45].

It was previously suggested that *BRCA* mutation carriers might be more vulnerable to radiation due to their reduced ability to repair radiation-induced DNA damage[23] . However, Pierce et al[29] identified no increase in acute or chronic morbidity in the skin, subcutaneous tissue, bone, or lung in *BRCA* mutation carriers undergoing radiation therapy. This was consistent with results in our cohort, as we did not report an increased incidence of radiation-induced skin pigmentation, oedema, shrinkage, or telangiectasia as compared to sporadic cases.

BRCA mutation carriers had significantly worse survival when compared with non-carriers. In an analysis of breast cancer patients, the 10-year OS rate was 78.0% for all analyzed groups: 65.9% for *BRCA* mutation carriers and 81.1% for non-carriers. In the univariate analyses, *BRCA* mutation carriers had a significantly higher risk of mortality in comparison to non-carriers [hazard ratio (HR)=1.87]. Increased tumor size (HR=3.64), lymph node metastases (HR=2.45), and higher histological grade (HR=2.84) were significant factors for worse OS. Positive estrogen receptor status was associated with a better OS (HR=0.49)[46].

Different metastatic patterns are linked to different subtypes of breast cancer. Central nervous system (CNS) metastases are often linked to germline *BRCA1/BRCA2* mutant status[47,48]. In this cohort, our results showed that patients harboring a germline *BRCA2* mutation presented more with CNS metastasis than the BRCA1 mutant group. This was similar to previous research done at Dana-Farber Cancer Institute, in which the authors concluded that CNS involvement is frequent in women with germline *BRCA1/BRCA2* mutations who have breast cancer. BRCA2 mutation carriers had a significantly higher frequency of CNS affection [49].

Another report by Ben-Zion Berliner et al[50], found that patients with *BRCA1/2* mutation showed a higher rate of leptomeningeal and temporal lobe involvement, and a shorter survival with CNS disease.

In current research, we reported that the germline *BRCA* mutation is associated with poor prognosis and short PFS and OS. Comparing both mutations, it has been shown that the germline *BRCA2* mutation had poorer survival *vs. BRCA1* regarding PFS and OS. Bayraktar et al[51] found that *BRCA1* carriers diagnosed with breast cancer have worse outcomes compared to non-carriers. Moreover, *BRCA1* mutation carriers had a 30% higher risk of dying than *BRCA1* negative/sporadic cases, which confirmed the results of 3 meta-analysis studies[15,52,53]. Also, van den Broek et al[54] evaluated the association between *BRCA2* and BCSS and concluded that *BRCA2* had worse BCSS compared with the control group (HR 1.57; CI: 1.29-1.86).

Breast cancer-specific survival was significantly worse in *BRCA1* mutation carriers than non-carriers (62% *vs.* 86%, $p < 0.001$), but not in those with *BRCA2* mutations compared to non-carriers (84% *vs.* 86%, $p=0.76$). However, the authors reported that, *BRCA1* mutation status was predictive of worse outcome only in those who did not receive chemotherapy[55]. In another study, no difference in survival rate was seen between *BRCA1* mutation carriers, *BRCA2* mutation carriers, and non-carriers[56]. The interpretation of the above studies is hampered by the lack of data on some other well-recognized prognostic factors, such as tumor grade and hormone receptor status.

According to the idea of a relatively poor prognosis for *BRCA* mutation-associated breast cancer, there is a poorer response rate and a shorter time to progression with palliative therapy in the metastatic context as compared to sporadic breast cancer controls[57].

Additionally, the association between *BRCA* mutational status and survival in patients with breast cancer was evaluated in a systematic review and meta-analysis. The authors reported that, based on follow-up duration, the OS in *BRCA1* and *BRCA2* mutated patients revealed significantly poorer outcomes[58].

CONCLUSIONS

Taking into account the likelihood of distinct prognostic roles for *BRCA1* and *BRCA2* mutations, as well as the fact that breast cancer differs in characteristics among *BRCA1* and *BRCA2* carriers, our study demonstrated that germline *BRCA* mutation female breast cancer patients were more likely to be diagnosed at a younger age, were premenopausal, had a family history of breast cancers, more advanced stage disease with higher grade, high Ki67 expression and short survival. TNBC was more prevalent in *BRCA1* carriers however, germline *BRCA2* mutant patients showed a trend towards poorer PFS and OS when compared with germline *BRCA1* disease. We could suggest the need for future work and research to differentiate pathological, prognostic and survival outcomes in patients with a germline *BRCA1* mutation compared *BRCA2* mutation carriers and to answer whether the prognosis of breast cancer had any difference in between the two groups.

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Authors' Contribution Statement:

Majid Aljahel supervised the work and revised the manuscript; Samir AlFotih and Emad Ibrahim Yagoub Fallatah revised the results and discussion; M. Amine Sekkel, Omar Alharbi, Zayd Jastaniah, Balsam Albondagji, and Khalaf S. Alghamdi contributed to data collection; Ali A. Alshehri contributed to writing the discussion and finalized the corrections from reviewers; Thamer Ahmed and ElBaiomy M.A. contributed to statistical analysis, with ElBaiomy also writing the manuscript; Nasser Mulla and Duaa Alkhayat revised the results and discussion; Hatem Ghazi revised the manuscript; Maamoun M.K. Khoja prepared all materials needed for pathology and genetic analysis; Sherehan A. Abdelsalam was responsible for the revision of all statistical data; Eman Magdy Abokhalaf contributed to data collection and wrote the discussion.

Conflict of Interest:
The authors declare that they have no conflict of interest to disclose.

Ethics Approval:
The study protocol was approved by the King Salman Medical City IRB (H-03-M-11).

Informed Consent:
Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy were respected at all levels of the study. Collected data was not used for any other purpose.

Availability of Data:
Additional data is available from corresponding upon reasonable request.

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