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RESEARCH ARTICLE

Genetic Testing Among Breast Cancer Patients in the Eastern Region of Saudi Arabia: Single-Center Experience

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Abstract

Background Genetic testing for persons with a heightened likelihood of harboring a germline mutation permits early identification and appropriate management. This study aimed to identify the proportion of breast cancer (BC) patients who were offered genetic testing and the prevalence of BRCA mutations among them. Additionally, we assessed the demographic and clinical features of BC patients in the Eastern Region of Saudi Arabia.

Materials and Methods Data from 2535 patients with BC were retrieved from the registry between 2017 and 2021. The data were analyzed and presented using univariate and bivariate statistics. Odds ratios and 95% confidence intervals using logistic regression analysis were computed to identify the predictors of BRCA testing.

Results Patients with BC ranged in age from 18 to 103 years, and the mean age was 49.60 ± 12.14 years. BC was detected in men in 29 (1.1%) cases. Among diagnosed patients with BC, a total of 96 (3.7%) patients underwent testing for BRCA gene mutations. Of them, 36 (37.5%) patients had a BRCA gene mutation. The likelihood of undergoing BRCA testing was higher for those who were diagnosed with the condition before the age of 50, patients who were referred from private institutions, and patients with a history of previously diagnosed cancer. The likelihood of conducting BRCA testing was significantly lower among those with distant metastases.

Conclusion The proportion of BRCA testing among BC patients was found to be relatively low. The development of a cost-effective, locally developed risk assessment tool that incorporates genetic counseling and testing for those with a familial predisposition to BC is imperative.

Keywords BRCA testing · Breast cancer · Hereditary breast cancer · Saudi Arabia

Abbreviations

BC	Breast cancer
KSA	Kingdom of Saudi Arabia
ASIR	Age-standardized incidence rate
HBOCS	Hereditary breast and ovarian cancer syndrome
USPSTF	US. Preventive Services Task Force
NCCN	National Comprehensive Cancer Network

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OCCR	Oncology center registry
KFSH-D	King Fahad Specialist Hospital-Dammam
EMR	Electronic Medical Record
MDS	Minimum data set
ORs	Odds ratios
CIs	Confidence intervals
SD	Standard deviation
COVID-19	Coronavirus disease 2019

1 Introduction

Worldwide, Breast cancer (BC) represents 11.7% of cancer cases and is the fifth leading cause of cancer death [1]. In the Kingdom of Saudi Arabia (KSA), BC is the most commonly diagnosed cancer (17.8%) [2]. It accounts for 30.4% and 0.6% of cancers in Saudi's females and males respectively [2]. The age-standardized incidence rate (ASIR) of BC in KSA has increased over the years; reaching up to 28.8 cases per 100,000 population in 2020 from just over 24.1 cases per 100,000 population in 2015. The Eastern Region of the KSA has the highest ASIR of BC [3]. Moreover, the median age at diagnosis of BC in the KSA is 50 years, compared to 60 years in Western countries [2].

Many risk factors have been documented to increase the risk of BC, including family history or genetic predisposition [4]. Hereditary BC accounted for 5–10% of diagnosed BC cases. BRCA1/2 are high-penetrance BC predisposition gene mutations which are the most reported genetic mutations responsible for hereditary breast and ovarian cancer syndrome (HBOCS). These genes mutations are inherited by an autosomal dominant pattern [4].

Moreover, carriers of BRCA1/2 genetic mutation have 72% and 69% cumulative risk of developing BC by the age of 80, respectively [5]. Furthermore, several studies found that BRCA genetic mutations carriers had higher probability of recurrence and poorer overall and/or breast cancer specific survivals than non-carrier/ non-tested cases [6, 7].

Guidelines for genetic testing were established to identify cases that are more likely to have a genetic predisposition. The National Comprehensive Cancer Network (NCCN) 2020 and US Preventive Services Task Force (USPSTF) guidelines recommend genetic counseling and testing for individuals with personal or family histories of some criteria. These include BC at an age less than 50 years, bilateral breast cancer, breast cancer in a male, both breast and ovarian cancer in the same person, family history of breast or ovarian cancer in a first- or second-degree relative, family member with the BRCA genetic mutation, Ashkenazi Jewish ancestry, multiple cases of breast cancer in the family, and triple-negative BC diagnosed at ≤ 60 years of age [8–10]. In addition, the updated NCCN guideline (version 3, 2024) recommends to test all patient with BC diagnosed at age ≤ 65 years [11].

The application of genetic testing to patients who fulfill the criteria of high risk for hereditary BC helps identifying high-risk individuals before cancer development and refers them for risk assessment and further risk reduction management strategies [12]. However, offering genetic testing for high-risk patients is complicated and challenging since it requires informed consent and has a post-test consequences [13].

The aim of this study was to identify the proportion and characteristics of BC patients who were offered genetic testing for BRCA genetic mutations and the prevalence of BRCA genetic mutations among BC patients in the Eastern Region of Saudi Arabia. Additionally, it assessed the demographic and clinical features of BC patients in the Eastern Region of Saudi Arabia.

2 Methods

2.1 Study Type

This is a retrospective study using secondary data from the oncology center registry (OCCR) at King Fahad Specialist Hospital-Dammam (KFSH-D). The study was registered in Research Registry in September 12, 2023 under the number; researchregistry9511, https://www.researchregistry.com/browse-the-registry#home/. This study is being reported according to the STROCCS statement [14].

2.2 Ethical Approval

An institutional review board approval letter (CLU0002).

2.3 Cancer Registry

The OCCR at KFSH-D was established in 2009 for the systematic identification, collection, storage, quality control, analysis, and reporting of data on cancer cases. The primary data source of the registry is the Electronic Medical Record (EMR) via CNExT software from Solutions of the Public Health Institute. Cancer Registry data are updated and validated through various methods, including reviewing EMR discharge summaries and pathology reports. Moreover, to reduce the possibility of error, misclassification, or bias in cancer registry data, stringent quality control criteria are employed by an independent epidemiologist.

Data collected in the Cancer Registry are based on a predetermined minimum data set (MDS) consistent with international standards for tumor registries. These include age at diagnosis, sex, marital status, nationality, address at

diagnosis, history of previously diagnosed cancer, referral hospital, tumor histological type and clinical stage, tumor laterality (unilateral vs. bilateral), and disease outcome (cured/complication/remission/death).

2.4 Study Subjects

We included all breast cancer patients registered in the Cancer Registry database who had confirmed malignant breast cancer diagnosis by a consulting pathologist from 2017 to 2021 with complete MDS.

2.5 Genetic Analyses Techniques

In this study, significant DNA variations in the BRCA1/BRCA2 genes were tested using targeted next-generation sequencing techniques (NGS). We aimed to assess DNA derived from tissue samples or blood from breast tumor tissue. Laboratory consenting for diagnostic and research purposes, including NGS, took part during clinic visits as per KFSH standard policy.

2.6 Statistical Analysis

Data were analyzed using SPSS Version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Univariate descriptive analysis of BC patients' demographic data was performed using the mean (standard deviation) for continuous variables and proportions for categorical variables. The number and proportion of patients tested for BRCA gene mutations were calculated and compared to the number of BC patients who fit the available criteria for testing, namely, patients diagnosed with BC before the age of 50, patients with bilateral breast cancer, and male BC patients.

Unadjusted bivariate analyses using chi-square/Fisher's exact tests were performed to compare the demographic and clinical criteria of BC patients according to their BRCA testing status. Furthermore, the likelihood of BRCA testing according to the presence of those criteria was assessed through a multiple logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. The model was adjusted for potential confounding variables: age category at diagnosis, referral hospital, history of previously diagnosed cancer, histopathology grading, and clinical stage. Patients' sex and tumor laterality (unilateral vs. bilateral) were not included in the model, as none of the male patients and those with bilateral BC were tested for gene mutations.

Table 1 Characteristics of the breast cancer patients from cancer registry at the KFSH-D, 2017–2021 ($N=2535$)

Characteristic	Total $n=2535$
Age in years (Mean, SD)	49.60 (12.14)
Sex (n, %)	
Male	29 (1.1%)
Female	2506 (98.9%)
Marital status (n, %)	
Single	237 (9.3%)
Married	2085 (82.2%)
Divorced	66 (2.6%)
Widowed	147 (5.8%)
Nationality (n, %)	
Saudi	2303 (90.8%)
Non-Saudi	232 (9.2%)
Address at time of diagnosis (n, %)	
Eastern Region	2419 (95.4%)
Outside-Eastern region	116 (4.6%)
Referred hospital (n, %)	
Ministry of Health	1491 (58.8%)
Other governmental	593 (23.4%)
Private	451 (17.8%)

SD: standard deviation

3 Results

A total of 2591 patients with BC were registered in the cancer registry during the period from 2017 to 2021. Of them, 2535 (97.8%) had sufficient data available and entered the study.

In our Data patients with BC were between the ages of 18 and 103 years old with a mean age of 49.60 (SD = 12.14). The majority were females (98.8%). The mean age of males diagnosed with BC was significantly higher, 60.59 (SD = 12.59), than that of females, 49.47 (SD = 12.08), t (2533) = 4.9, P value < 0.001. The sociodemographic characteristics of the patients with BC are presented in Table 1.

BRCA tests lab results were available only to 96 patients with BC, 37.5% of them were tested positive for BRCA gene mutation. From year 2017 to 2021 the number patients diagnosed with breast cancer had and increasing trend, however, BRCA testing showed a plummet by year 2020 and 2021 (Fig. 1).

Patients younger than 50 years old, had a history of previously diagnosed cancer or referred from a private hospital were more likely to be tested for BRCA gene (Table 2). Patients under 50 were more likely to be tested for BRCA compared to those 50 and older (OR: 4.703, 95% CI: 2.703–8.183, P value = < 0.001). Patients tested for the BRCA gene were also more likely to have a history of previously diagnosed cancer of any type (OR 2.4, 95% CI 1.415–4.017, P value = 0.001), and they were more likely to be referred from a private hospital (OR 1.853, 95% CI 1.172–2.931, P value = 0.008). Only 80 (6%) patients below the age of

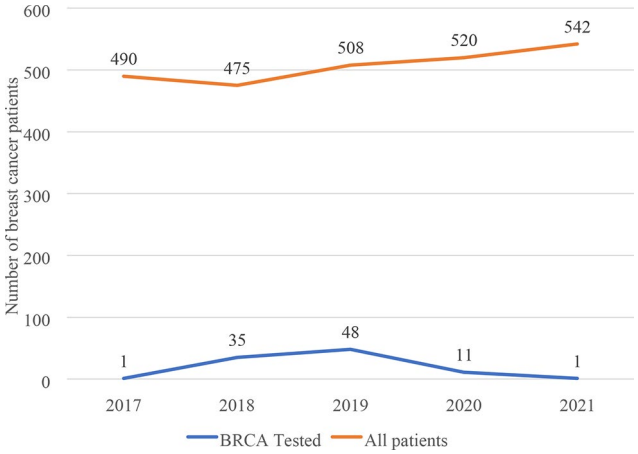

Fig. 1 Distribution of patients with breast cancer and BRCA testing by year

Table 2 Characteristics of patients with breast cancer based on BRCA testing, 2017–2021, ($N=2535$)

Characteristic	BRCA tested $n=96$	BRCA not tested $n=2439$	*P*-value
Age (n, %)			
Less than 50 years	80 (6.0%)	1261 (94.0%)	< 0.001
50 years and above	16 (1.3%)	1178 (98.7%)	
Sex (n, %)			
Male	0 (0.0%)	29 (100.0%)	0.625*
Female	96 (3.8%)	2410 (96.2%)	
Laterality (n, %)			
Unilateral	96 (3.8%)	2435 (96.2%)	1.000*
Bilateral	0 (0.0%)	4 (100.0%)	
Referral Hospital (n, %)			
Ministry of Health	48 (3.2%)	1443 (96.8%)	0.008
Other governmental	13 (2.9%)	438 (97.1%)	
Private	35 (5.9%)	558 (94.1%)	
History of previously diagnosed cancer (n, %)			
No	74 (3.4%)	2089 (96.6%)	0.020
Yes	22 (5.9%)	350 (94.1%)	
Grade/differential (n, %)			
Well-differentiated	9 (3.4%)	254 (96.6%)	0.003
Moderately differentiated	31 (2.6%)	1183 (97.4%)	
Poorly differentiated	56 (5.3%)	1002 (94.7%)	
Stage (n, %)			
In situ	7 (5.1%)	131 (94.9%)	< 0.001
Localized	42 (5.8%)	687 (94.2%)	
Regional	42 (3.6%)	1112 (96.4%)	
Distant	5 (1.0%)	509 (99.0%)	

* Fisher exact test

50 were tested, and neither male patients nor patients with bilateral BC were tested.

Patients with poorly differentiated BC, 56 (5.3%), were more likely to be tested for the BRCA gene than those with well-differentiated BC, 9 (3.4%), and moderately differentiated BC, 31 (2.6%). However, after controlling for confounders, this association was not statistically significant (OR 1.5, 95% CI 0.733–3.233, P value = 0.255). Furthermore, the more advanced the BC stage, the less likely patients were tested for gene mutations (OR 0.169, 95% CI 0.052–0.554, P value = 0.003) (Tables 2 and 3). The logistic regression model was statistically significant, X [2] (9, $N=96$) = 90.806, P value = < 0.001. The model explained 12.8% (Nagelkerke R [2]) of the variance in BRCA testing and correctly classified 96.2% of cases. The model fits the data [$X^2=3.755$, df = 8 and $p=0.879$].

Table 3 Logistic regression analysis for predictors of BRCA testing ($N=2535$), 2017–2021

Characteristic	OR	95% CI		*P*-Value
		Lower	Upper	
Age				
Less than 50 years	4.703	2.703	8.183	< 0.001
50 years and above	Reference			
Referral Hospital				
Ministry of Health	Reference			
Other governmental	0.824	0.436	1.556	0.551
Private	1.853	1.172	2.931	0.008
History of previously diagnosed cancer				
No	Reference			
Yes	2.384	1.415	4.017	0.001
Grade/Differentiation				
Well-differentiated	Reference			
Moderately differentiated	0.724	0.334	1.569	0.413
Poorly differentiated	1.537	0.733	3.223	0.255
Stage				
In situ	Reference			
Localized only	1.202	0.511	2.827	0.673
Regional extension	0.706	0.299	1.667	0.427
Distant metastasis	0.169	0.052	0.554	0.003

OR: odds ratio. CI: confidence interval

The BRCA test results did not differ based on age group; 38.5% of those less than 50 years of age tested positive compared to 31.2% of those 50 years of age or older, X [2] (1,96) = 0.32, P value 0.572. None of the tested patients with well-differentiated BC were BRCA positive, while those with moderately and poorly differentiated BC had similar percentages of positive tests, 13 (41.9%) and 23 (41.9%), respectively, with borderline statistical significance, X [2] (2,96) = 5.965, P value 0.051. Furthermore, patients with different BC stages had almost the same percentages of positive BRCA test X [2] (3,96) = 0.163, P value 0.983. In addition, at the last evaluation after starting management with a median follow-up of 10 months (interquartile range (IQR) 8–15 months), 40% of those who were cancer-free had a positive BRCA test result compared to 29.6% who were still not cancer free, X [2] (1,96) = 0.99, P value 0.319. Moreover, 39% of patients who were still alive at the last evaluation had a positive BRCA test compared to 22.2%

of non-surviving patients (Fisher exact P value 0.476) (Table 4).

4 Discussion

This study examines the probability of BRCA testing within a cohort of individuals diagnosed with breast cancer spanning a wide age range from 18 to 103 years. Statistically significant findings have been found indicating that those below the age of 50, with a prior history of cancer, or referred from private hospitals had a higher likelihood of undergoing BRCA testing. Our observations indicate that a somewhat greater proportion of individuals diagnosed with metastatic breast cancer, specifically above 80%, have a lower likelihood of undergoing BRCA testing.

We found that out of all BC patients registered in the study cohort, 3.7% were considered for BRCA testing. The low testing rate is consistent with previous literature reporting low genetic testing uptake for various hereditary diseases, including BRCA gene testing [15, 16]. Moreover, this study demonstrated that only an overall 1.4% of our BC patients had BRCA gene mutations, unlike the reported estimates in the literature of 5–10% of BC patients who are hereditary [4].

The prevalence of genetic mutations varies in different populations. Tung N et al. (2015) found that the frequency of BRCA mutations was 9.3%[17]. Another study reported that only 8.3% of BRCA gene mutations are present among high-risk patients [18]. A systematic review in Arab countries revealed that the prevalence of BRCA 1/2 mutations among hereditary breast cancer was 17%[19]. Interestingly, BRCA gene mutations were detected in more than one-third of our patients who underwent testing, which might indicate a higher gene mutation in our study population. Similarly, Laitman Y et al. reported that founder mutations in BRCA1 and BRCA2, major risk factors for BC incidence, particularly in geographically or socially isolated cultures with high consanguinity rates, including the Middle East [20].

The limited number of genetic tests may impact the ability to identify individuals with gene changes that have implications for patient care, such as high-risk screening, risk reduction strategies and therapeutic interventions [21]. Furthermore, the presence of genetic mutations has the potential to affect patients' immediate family members, who should be encouraged to undergo additional tests [6]. Moreover, low levels of testing have a negative impact on the economy of the health system [22]. In a study conducted by Sun et al. (2019), it was demonstrated that the implementation of BRCA gene testing in a uniform manner across all patients with breast cancer resulted in high-level cost-effectiveness [23].

Previous research has elucidated the factors contributing to a reduced prevalence of BRCA gene testing, including the absence of test provision by the attending physician, unavailability of the test, or patient reluctance to undergo the testing procedure. The decision to decline a genetic test may be influenced by factors such as the high financial burden associated with the test, concerns over the test's reliability, or apprehensions about the potential violation of confidentiality [24, 25].

According to the USPSTF and NCCN guidelines, genetic testing should be made available to all patients with certain risk factors to assess hereditary risk for BC [6, 7]. Compliance with testing criteria is linked to a high rate of identifying patients with BC carrying a BRCA mutation [26]. In regard to the indication for genetic testing in the current study, although BC patients younger than 50 years of age were more likely to be tested, only 6% of them underwent genetic testing. Furthermore, this study showed that even patients who were highly recommended by the guidelines to perform genetic testing, i.e., Male patients and patients with or bilateral BC were not tested. Unfortunately, we did not have data regarding the family history of hereditary BC [24, 27]. Although our findings suggest that the indication for testing was slightly inconsistent with the USPSTF and NCCN recommendations, the data supplied cannot explain this because various factors can influence genetic testing [27].

In the current study, BRCA carriers were more likely to be younger and have a less differentiated tumor; however,

Table 4 Characteristics of patients with breast cancer based on BRCA testing results ($N=96$), 2017 2021

Characteristic	BRCA positive $n=36$	BRCA negative $n=60$	*P*-value
Age (n, %)			
Less than 50 years	31 (38.8%)	49 (61.2%)	0.572
50 years and above	5 (31.2%)	11 (68.8%)	
Grade/differential (n, %)			
Well-differentiated	0 (0.0%)	9 (100.0%)	0.051
Moderately differentiated	13 (41.9%)	18 (58.1%)	
Poorly differentiated	23 (41.1%)	33 (58.9%)	
Stage (n, %)			
In situ	3 (42.9%)	4 (57.1%)	0.983
Localized	16 (38.1%)	26 (61.9%)	
Regional	15 (35.7%)	27 (64.3%)	
Distant	2 (40.0%)	3 (60.0%)	
Breast cancer status at last appointment (n, %)			
Cancer free	28 (40.6%)	41 (59.4%)	0.319
Not cancer free	8 (29.6%)	19 (70.4%)	
Survival status at last appointment (n, %)			
Alive	34 (39.1%)	53 (60.9%)	0.476*
Dead	2 (22.2%)	7 (77.8%)	

* *Fisher exact test

there was no statistically significant difference between BRCA and noncarriers. This was consistent with other studies in the existing literature [7].

In addition, the current study showed that BRCA gene testing increased during 2018–2019 but then declined in 2020, which could be explained by the effect of the COVID-19 pandemic on health services. This can be attributed to the lockdown and curfew, implemented during the pandemic as well as the inadequate diagnostic facilities and overwhelmed health-care system. In the United States, Chen Z et al. (2018) similarly showed a rising trend in BRCA gene testing during the period from 2003 to 2014 [28]. The COVID-19 pandemic has affected many health services in many countries, including BRCA gene testing [28, 29]. Minucci A. et al. (2021) in Italy also found that BRCA gene testing has been impacted by the complete lockdown caused by the COVID-19 pandemic [30].

4.1 Strengths and Limitations

To the best of our knowledge, this study constitutes an unprecedented effort to evaluate BRCA testing for breast cancer in the Eastern Province. In the context of available knowledge, these findings are unique with a sense of novelty, as no similar study has predicted the possibility of BRCA testing among breast cancer patients in the region.

While the cancer registry is a good source of real-world data, it is important to highlight some of the limitations associated with the registry. The quality and dependability of the data in the EMR and cancer registry are contingent upon the individuals responsible for inputting the data. The potential consequence is that the data quality may exhibit variability, leading to potential errors, misclassifications, or biases. Moreover, since we relied on secondary data, we could not explore the BC family history, although it is an important factor/criterion that may influence testing for BRCA [26, 29]. In addition, it is crucial to note that our study is a retrospective single-centre study with limited sample size. These factors have the potential to impact the effect size in either a positive or negative manner.

5 Conclusion/Recommendations

Hereditary gene testing is low among patients with BC in the Eastern Region of Saudi Arabia. It is strongly advised to enhance the testing procedures for individuals who exhibit a high probability of possessing a BRCA mutation within the healthcare institutes of the Ministry of Health. However, the number of patients recommended to have genetic testing according to international guidelines could be very high in our population, which may inflict a high economic burden. We recommend exploring a locally developed and economically viable risk assessment tool for genetic counseling and testing pertaining to hereditary BC in Saudi Arabia. It is imperative to conduct a further, more extensive investigation to replicate and emphasize our findings on the frequency and predictors of the BRCA gene in the Eastern Region and at the national level.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and Consent to Participate An institutional review board approval letter from KFSH-D was obtained (CLU0002).

Consent for Publication Attached.

Competing Interests The authors declare no competing interests.

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