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Research

Mutational spectrum and profile of breast and ovarian cancer patients in Saudi Arabia's western region: single center experience

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Received: 25 January 2025 / Accepted: 9 May 2025
Published online: 20 May 2025

Abstract

Background The incidence of breast cancer (BC) and ovarian cancer (OC) has increased in Saudi Arabia. The western region of Saudi Arabia presents a unique population with distinct genetic backgrounds, making it vital to investigate the prevalence of BC/OC-associated gene mutations in this area. This study aimed to determine the prevalence and mutational profiles of BC and/or OC predisposing genes in the western region of Saudi Arabia, and to characterize the associated phenotypes in individuals carrying these mutations.

Methods We employed next-generation sequencing (NGS) to identify the mutational spectra of 209 Saudi Arabian patients with BC and/or OC from the Western region.

Results 51/209 (24.4%) patients had a mutation in one of the BC/OC predisposing genes. Overall, 34, 10, and 7 PV/LPV were identified in *BRCA1*, *BRCA2*, and other genes, respectively. Mutations in *BRCA1* were predominant and strongly related to high-grade, triple-negative BC. *BRCA1* NM_007294.4:c.1140dup p.(Lys381Glufs*3), NM_007294.4:c.5095C > T p.(Arg1699Trp), NM_007294.4:c.4986 + 6 T > C (p.?), NM_007294.4:c.5251C > T p.(Arg1751*), and NM_007294.4:c.5067_5074 + 1del p.(Met1689Ilefs*3) were recurrent with NM_007294.4:c.3217_3218del p.(Gly1073*), NM_007294.4:c.5067_5074 + 1del p.(Met1689Ilefs*3), and NM_007294.4:c.5234del p.(Asn1745Thrfs*20) being novel. The combined frequency of recurrent mutations in *BRCA1* was 42%. Concerning *BRCA2*, we identified a recurrent variant NM_000059.4:c.7480C > T p.(Arg2494*) and two novel variants NM_000059.4:c.643del p.(Glu215Lysfs*15) and NM_000059.4: EXon1-8del.

Conclusion In our study, we identified a high prevalence of *BRCA1*/2 variants in the western region of Saudi Arabia, offering novel and important insights specific to this area. We also identified other gene variants, though their impact remains unclear due to the limited sample size. This work represents an important first step in understanding the genetic factors contributing to breast and ovarian cancer in the Western region. It underscores the urgent need for larger studies to comprehensively explore the genetic landscape and better understand how these variants influence cancer risk in this population.

Keywords Breast cancer · Ovarian cancer · Next-generation sequencing · *BRCA1* · *BRCA2* · Germline mutation · Saudi Arabia

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1 Introduction

Breast cancer (BC) is a multifactorial genetic disease caused by the interaction of multiple genes with environmental and lifestyle factors [31, 52]. It is the most frequently diagnosed cancer among women and the primary cause of cancer-related deaths in women globally, following lung cancer [19]. BC incidence rates vary worldwide, most likely due to differences in genetic susceptibility, reproductive patterns, dietary/lifestyle factors, and detection methods [47]. It differs among various ethnic groups and geographical regions [15]. Regions with greater economic development and non-Hispanic Caucasian women have the highest incidence of BC [56]. In the United States, BC affects approximately 425,000 women and kills more than 66,400 women annually, with a higher mortality rate in Black women [27, 28]. In Asia, the incidence of invasive female BC remains considerably lower than in North America and Europe. However, there has been a notable increase in the number of Asian populations, including China, Singapore, South Korea, and Taiwan [51]. This increase has been attributed to the adoption of Western lifestyles. However, Asian women have a unique BC profile that differs from that of Western cultures, including an earlier age of onset and a more significant frequency of aggressive tumors [34]. The incidence of BC among Saudi women has progressively increased over the last decade, making it the most diagnosed cancer in Saudi Arabia [11, 22]. Similar observations were made in other Middle Eastern countries [2, 8, 9, 17, 39]. According to a previous report, there were 3,629 newly diagnosed cases of BC, resulting in 899 fatalities, in Saudi Arabia, with the deaths accounting for approximately 8.5% of all reported deaths [1, 12]. This makes this disease the second-leading cause of death in Saudi Arabia [7, 13, 14, 51].

Hereditary breast and ovarian cancer syndrome (HBOC) is an autosomal dominant disorder. Approximately 20% and 5–10% of all OC and BC cases, respectively, can be explained by a rare pathogenic variant (PV) or likely pathogenic variant (LPV) in one of the cancer predisposition genes, such as *BRCA1* and *BRCA2* [5, 40]. Both genes have the most frequently identified PV/LPV in high-risk individuals, accounting for 80% of inherited OC cases and 30% of all familial BC cases [21, 41]. Furthermore, for BC, the lifetime risk reached 85% and 45% for *BRCA1* and *BRCA2*, respectively, and for OC, 39% and 11%, respectively [32, 33, 42]. Moreover, HBOC patients associated with a *BRCA1*/*BRCA2* mutation have an increased risk of developing other cancer types, such as prostate cancer, pancreatic cancer, and melanoma [16, 37, 53].

The population frequency of *BRCA1*/2 mutation carriers is generally estimated to be around 1 in 400 individuals. However, the incidence of pathogenic variants is notably higher, often several-fold, in populations with founder mutations [36, 50]. The prevalence of germline *BRCA1* and *BRCA2* PV/LPV shows considerable variation across different geographical regions and ethnic groups [36], although some studies suggest that these prevalence rates are relatively consistent [6, 35]. A notable example is the identification of population-specific mutations, such as those found in Ashkenazi Jews [23, 26, 36, 55] and individuals of Spanish ancestry [54]. Furthermore, distinct *BRCA1*/2 PV(s) have been documented across various European populations [25, 29]. In addition to *BRCA1*/2, other genes have been associated with HBOC, including *PALB2*, *TP53*, *CDH1*, *PTEN*, *ATM*, *CHEK2*, *STK11*, and others [24, 44, 45],. However, these genes generally exhibit lower penetrance and frequency compared to *BRCA1*/2. Nevertheless, an individual with a germline PV/LPV in one of these genes has a significantly increased risk of cancer compared to the general population [23, 24]. Genetic studies in hereditary BC in Middle Eastern populations are limited [3, 11, 38]. In Saudi Arabia, the population is homogenous, and consanguineous marriages are common [22]. The prevalence of *BRCA1*/2 PV/LPV in BC patients in the Saudi Arabian population remains poorly understood. The primary aim of this study was to determine the prevalence and impact of *BRCA1* and *BRCA2* PV/LPV in Saudi patients diagnosed with BC and/or OC, using next-generation sequencing (NGS). This approach facilitates cost-effective and efficient genetic testing, enabling simultaneous assessment of multiple candidate genes. Additionally, we aimed to investigate the clinicopathological characteristics of breast cancer associated with these genetic variants, understanding that molecular diagnosis is pivotal in shaping the clinical management of high-risk patients. This approach enables comprehensive family risk assessment, reduces mortality, and supports the implementation of prophylactic measures that can reduce cancer risk by up to 95% in individuals carrying *BRCA1*/2 mutations [38].

2 Methodology

2.1 Ethical consideration and confidentiality

The study protocol was approved by the Institutional Review Board (IRB) of Al-Qura University (UQU) with application number LGCX011122 (issued 09 Jan 2023), and King Abdullah Medical City (KAMC) with IRB reference number 21-782 (issued 08 Oct 2023). All methods were performed according to the guidelines and regulations of UQU and KAMC.

Before participating in the study, all the participants provided written informed consent. This study was conducted in accordance with Good Clinical Practice (GCP) guidance.

2.2 Study population

This retrospective study was conducted in KAMC, Makkah, in the western region of Saudi Arabia. This study adhered to the principles outlined in the Declaration [48]. A cohort of 209 Saudi patients diagnosed with BC or OC at KAMC was enrolled between October 2019 and December 2021. These patients were referred to the Genetic Oncology Clinic (GOC) at KAMC Hospital in Makkah and were included in the study. Detailed information regarding patient demographics, clinical histories, and pathological characteristics was obtained through a comprehensive review of medical records. The variables included in the study were age, family medical history, disease stage, tumor grade, and tumor site. Furthermore, estrogen receptor status, and human epidermal growth factor receptor 2 (HER2)/neu status, particularly in BC cases, were recorded and analyzed. Patients referred to this clinic were at high risk for familial BC or OC according to the criteria outlined by the National Comprehensive Cancer Network (NCCN) guidelines (https://www.nccn.org/professionals/physician_gls/default.aspx).

2.3 DNA extraction and quantification

Peripheral blood samples (2 mL) were collected from patients in EDTA tubes. Genomic DNA was extracted using a QIAamp® DNA Mini Kit according to the manufacturer's instructions (Qiagen GmbH, Hilden, Germany) and then quantified using a Qubit™ dsDNA BR assay kit on a Qubit 2.0 Fluorometer (Thermo Fisher Scientific, Inc., Germany), following the manufacturer's instructions.

2.4 Next-generation sequencing

NGS and variant analysis were performed using the peripheral blood samples. Samples were sent for analysis to Bioscientia International (www.Bioscientia.com, Germany). Based on official genetic reports, Bioscientia used the following method: Genomic DNA was fragmented, and the coding exons of the *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *MRE11*, *NBN*, *PALB2*, *RAD51D*, *STK11*, and *TP53* were sequenced. Genes were enriched using Roche/NimbleGen sequence capture technology and an Illumina system for NGS. Target regions were sequenced with an average coverage of 800-fold. Moreover, a 15-fold coverage was achieved for over 99% of the regions of interest.

Next, NGS analysis was performed using bioinformatics analysis tools and a JSI variant pipeline with a minor allele frequency (MAF) of ≤ 1%. Bioinformatics prediction programs were used to conduct in silico analysis of the identified variants, focusing on their functional relevance, conservation, and potential splice effects. The results obtained from the prediction programs were not considered definitive functional proof. Therefore, our findings can be interpreted within the broader context of clinical observations, family history, and additional laboratory data.

Variants were classified based on the interpretation of sequence variants recommended by the American College of Medical Genetics and Genomics (ACMG). Changes in the pathogenicity classification over time cannot be excluded. Variants classified as benign or likely benign were not previously reported. The putatively pathogenic variations between the wild-type sequence (human reference genome per UCSC Genome Browser: hg19, GRCh37) and the patient's sequence were identified and evaluated based on an in-house established quality scoring system. Variants identified in the main section that did not meet the quality threshold underwent verification through polymerase chain reaction (PCR) amplification, followed by conventional Sanger sequencing. Furthermore, CNV (copy number variant) analysis of NGS data indicating exon(s) deletion or duplication was validated through MLPA (multiplex ligation-dependent probe amplification) utilizing the (MRC-Holland, Amsterdam, the Netherlands).

2.5 Breast cancer subtypes

Immunohistochemical (IHC) staining of formalin-fixed, paraffin-embedded tissue sections was performed to evaluate the expression of progesterone receptor (PR), estrogen receptor (ER), and HER2. The BC subtypes were ER-positive or

PR-positive/HER2-negative (ER + or PR + /HER2 −, luminal A), ER + or PR + /HER2 + (luminal B), ER −/PR −/HER2 + (HER2-enriched), and ER-/PR −/HER2 − (triple-negative, TN).

2.6 Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 25 (IBM Inc., Chicago, USA). Continuous variables were analyzed using means and standard deviations to describe the basic sociodemographic characteristics of the participants and other related factors using counts and percentages.

2.7 Review of existing research on *BRCA1*/2 mutations in Saudi Arabia

To provide context for our study and highlight the significance of *BRCA1*/2 genetic research in Saudi Arabia, we conducted a targeted literature review summarizing previously published studies on *BRCA1* and *BRCA2* germline mutations in the Saudi population. Thus, a structured search was performed in PubMed, and EMBASE databases using the keywords: (*BRCA1*, *BRCA2*, mutation, variant, germline, Saudi Arabia, Hereditary breast cancer, hereditary ovarian cancer and genetic testing). Studies were included if they: Reported germline pathogenic or likely pathogenic *BRCA1*/2 variants in Saudi individuals, used genetic sequencing methods such as NGS, Sanger sequencing, or MLPA, and if they Were published in English and focused on the Saudi population.

3 Results

3.1 General characteristics of the study population

A total of 209 patients (205 women and four men) were assessed according to the NCCN testing criteria. The mean age was 43.54 ± 11.23 years, with an age range of 22−73 years. A total of 171 cases of BC, 36 cases of OC, and 2 cases of both BC and OC were reported (Table 1). Approximately 24.4% (51/209) of the patients had either PV/LPV, 36% (76/209) had a Variant of Uncertain Significance (VUS) and 39% (82/209) had no Class III to Class V variants reported (Table 2).

Among the 51 patients with PV/LPV, 43 had BC (41 females and 2 males), seven had OC, and one had both BC and OC (Table 3). For the BC patients, 28 *BRCA1* and nine *BRCA2* (8 female and 1 male) actionable variants were identified, with a single variant in *PALB2*, three in *ATM*, and two in *CHEK2* (1 female and 1 male) (Table 3). In patients with OC, causative variants were identified in seven of the 36 cases (19.4%): five in *BRCA1*, with one each in *BRCA2* and *BRIP1*, respectively. A *BRCA1* mutation was identified for the female affected by both BC and OC (Table 3).

3.2 Clinicopathological characteristics of mutation-carriers

The age at diagnosis of patients with BC ranged from 22 to 53 years (Table 1). Most patients were < 40 years old (25/43, 58%), with all having ductal carcinoma. Our findings indicated that 83% (24/29) of the individuals carrying *BRCA1* PV/LPV exhibited high-grade BC (grade 3), whereas 78% (7/9) of those with *BRCA2* PV/LPV presented with grade 2 tumors. Triple-negative cases were found in 86% of patients with BC *BRCA1* (25/29) and 44% of patients with *BRCA2* PV/LPV (4/9). When comparing *BRCA1* and *BRCA2* mutation carriers, we found a stronger association between patients with *BRCA1* PV/LPV and young age at diagnosis, high-grade BC, and the triple-negative phenotype. However, the association with low-grade and (ER, PR)-positive tumors was more robust in patients with *BRCA2* PV/LPV (Table 3). This study involved a single patient with BC who had a PV in the *PALB2* gene and was diagnosed at the young age of 29 years. Three cases of BC had an *ATM* PV/LPV, one of which was a triple-negative BC (TNBC). Additionally, two patients harbored *CHEK2* PV (Table 3).

All the OC mutation carriers had high-grade serous adenocarcinomas. The age at the time of diagnosis ranged between 47 and 73 years, and 63% of the patients were diagnosed in the fourth decade (5/8 The majority of mutation carriers (61%) reported a family history of cancer (Table 1). Additionally, two cases of double primary malignancies were observed, exhibiting the *BRCA1* p.Glu1257Glyfs*9 pathogenic variant and a VUS (p.Tyr1716Cys) respectively. We observed one *BRIP1* (PV) in a patient with OC, which was of the high-grade serous type (Table 3).

Table 1 Demographic and general characteristics of the study population and patients with identified PV/LPV

Variable	Study population (n = 209)		Patients with PV/LPV (n = 51)	
	Frequency	Percent (%)	Frequency	Percent (%)
Gender				
F	205	98.09	49	96
M	4	1.91	2	4
Cancer type				
BC	171	82	43	84
BC/OC	2	1	1	2
OC	36	17	7	14
Age (Years)				
BC	Range (22−70)		Range (22–53)	
BC < 40	78	46	25	58
BC > 40	93	54	18	42
OC	Range (32−73)		Range (47−73)	
Family history of cancer				
No	85	41	20	39
Yes	124	59	31	61

F, female, M: Male, BC: Breast cancer, OC: Ovarian cancer

Table 2 Individuals with PVs/LPVs, VUS, and with no identified variant

	Study population N = 209	*BRCA1*	*BRCA2*	*PALB2*	*CHEK2*	*ATM*	*BRIP1*	Other genes of the panel
PVs/LPVs	51 (24.4%)	34	10	1	2	3	1	0
VUS	76 (36%)	6	27	10	3	19	2	8
No variant	82 (39%)							

PV, pathogenic variant, LPV: Likely pathogenic variant, VUS: Variant of unknown significance

3.3 Genetic characterisation of the PV/LPV

We observed 38 distinct pathogenic and likely pathogenic variants in 51 patients. Of these, 61% (23/38) were identified in *BRCA1* and included three novel variants (c.3217_3218del, c.5067_5074 + 1del, and c.5234del). Among the remaining PV/LPV, 21% (8/38) were found in *BRCA2*; 8% (3/38) in *ATM*, 5% (2/38) in *CHEK2*, 3% (1/38) in *PALB2*, and 3% (1/38) in *BRIP1*. In the *BRCA1* gene, we observed all types of variants, including nonsense, insertions/deletions (frameshift), indels, splice sites, and missense (Fig. 1a). Furthermore, we detected five recurrent variants in unrelated families: c.1140dup p.(Lys381Glufs*3), c.5095C > T p.(Arg1699Trp), c.4986 + 6T > C p.(?), c.5251C > T p.(Arg1751*), and c.5067_5074 + 1del p.(Met1689Ilefs*3) (Table 3). The most prevalent variant identified was the frameshift c.1140dup p.(Lys381Glufs*3) in *BRCA1*, identified in 15% (5/34) of *BRCA1* mutation carriers (Tables 3 and 4). All patients had TNBC, while only three had a significant family history of BC. The other frequently recurring variant, c.5095C > T, accounted for 12% (4/34) of the mutation-positive results for *BRCA1*. Three cases (8.8%) were TNBC diagnosed in their 2nd and 3rd decade with no family history of cancer. One of four cases (1/4) had a family history of TNBC and was diagnosed in the second decade, and later with OC at the age of 50 years (Table 3). For *BRCA2*, all mutation types except for missense variants were observed with a single recurrent variant c.7480C > T p.(Arg2494*)identified in three unrelated patients (Fig. 1b, Table 3). No clear genotype–phenotype correlation was observed for both genes.

Moreover, the targeted literature review identified three studies that reported BRCA1/2 germline mutations in the Saudi population. A comprehensive summary of the identified variants from our study, alongside findings from previous studies, is presented in Tables 4 and 5. Fifty-one pathogenic/likely pathogenic *BRCA1* variants have been reported in over 106 patients. Mutations were detected across all gene regions, with notable clustering in exons 10, 11, and 17 (frequencies of 39%, 10%, and 9%, respectively) (Fig. 1a, Tables 3 and 4). For *BRCA2*, approximately 17 mutations were identified, representing 20 patients. The most common recurrent *BRCA1* mutations included c.1140dup p.(Lys381Glufs*3) in 20/106,

Discover Oncology (2025) 16:829 | https://doi.org/10.1007/s12672-025-02640-x

Table 3 Individuals with PVs/LPVs in *BRCA1*, *BRCA2*, and other genes

Patient	Gene	Variant (HGVS nomenclature)	Zygosity	Comment	Age at cancer diagnosis	Tumor type	Histology	Grade/ Stage	Tumour Hormone status		
									ER	PR	Her2
1	*BRCA1*	NM_007294.4:c.40del p.(Val14Serfs*9)	Heterozygous	PV	45	BC	IDC	2	–	–	+
2	*BRCA1*	NM_007294.4:c.68_69del p.(Glu23Valfs*17)	Heterozygous	PV	32	BC	IDC	3	–	–	+
3	*BRCA1*	NM_007294.4:c.135-1del p.(?)	Heterozygous	LPV	49	BC	IDC	3	–	–	–
4	*BRCA1*	NM_007294.4:c.784C > T p.(Gln262*)	Heterozygous	PV	44	BC	IDC	3	–	–	–
5	*BRCA1*	NM_007294.4:c.798_799del p.(Ser267Serfs*19)	Heterozygous	PV	50	BC	IDC	3	–	–	–
6	*BRCA1*	NM_007294.4:c.1140dup p.(Lys381Glufs*3)	Heterozygous	PV	48	BC	IDC	3	–	–	–
7	*BRCA1*	NM_007294.4:c.1140dup p.(Lys381Glufs*3)	Heterozygous	PV	34	BC	IDC	3	–	–	–
8	*BRCA1*	NM_007294.4:c.1140dup p.(Lys381Glufs*3)	Heterozygous	PV	38	BC	IDC	3	–	–	–
9	*BRCA1*	NM_007294.4:c.1140dup p.(Lys381Glufs*3)	Heterozygous	PV	48	BC	IDC	3	–	–	–
10	*BRCA1*	NM_007294.4:c.1140dup p.(Lys381Glufs*3)	Heterozygous	PV	32	BC	IDC	3	–	–	–
11	*BRCA1*	NM_007294.4:c.1961dup p.(Tyr655Valfs*18)	Heterozygous	PV	47	OC	HGSC	HG			
12	*BRCA1*	NM_007294.4:c.2125_2126insA(p. Phe709Tyrfs*3)	Heterozygous	PV	47	OC	HGSC	HG			
13	*BRCA1*	NM_007294.4:c.2952del p.(Ile986Serfs*14)	Heterozygous	PV	48	BC	IDC	3	–	–	–
14	*BRCA1*	NM_007294.4:c.3217_3218del p.(Gly1073*)	Heterozygous	PV\Novel	41	BC	IDC	3	–	–	–
15	*BRCA1*	NM_007294.4:c.3770_3771del p.(Glu1257Glyfs*9)	Heterozygous	PV	44/56	BC/OC	IDC/ HGSC	2/HG	+	+	-
16	*BRCA1*	NM_007294.4:c.4136_4137del p.(Ser1379*)	Heterozygous	PV	22	BC	IDC	2	–	–	–
17	*BRCA1*	NM_007294.4:c.4165_4166del p.(Ser1389*)	Heterozygous	PV	35	BC	IDC	3	–	–	–
18	*BRCA1*	NM_007294.4:c.4524G > A p.(Trp1508*)	Heterozygous	PV		BC	IDC	3	–	–	–
19	*BRCA1*	NM_007294.4:c.4986 + 6T > C p.(?)	Heterozygous	PV	34	BC	IDC	2	–	–	–
20	*BRCA1*	NM_007294.4:c.4986 + 6T > C p.(?)	Heterozygous	PV	48	BC	IDC	2	–	–	–
21	*BRCA1*	NM_007294.4:c.4986 + 6T > C p.(?)	Heterozygous	PV	44	BC	IDC	3	+	+	–
22	*BRCA1*	NM_007294.4:c.5067_5074 + 1del p.(Met1689Ilefs*3)	Heterozygous	LPV\Novel	53	BC	IDC	3	–	–	–
23	*BRCA1*	NM_007294.4:c.5067_5074 + 1del p.(Met1689Ilefs*3	Heterozygous	LPV\Novel	39	BC	IDC	3	–	–	–
24	*BRCA1*	NM_007294.4:c.5074 + 1G > A p.(?)	Heterozygous	PV	26	BC	IDC	3	–	–	–
25	*BRCA1*	NM_007294.4:c.5095C > T p.(Arg1699Trp)	Heterozygous	PV	34	BC	IDC	3	–	–	–
26	*BRCA1*	NM_007294.4:c.5095C > T p.(Arg1699Trp)	Heterozygous	PV	26	BC	IDC	3	–	–	–
27	*BRCA1*	NM_007294.4:c.5095C > T p.(Arg1699Trp)	Heterozygous	PV	50	OC	HGSC	HG			
28	*BRCA1*	NM_007294.4:c.5095C > T p.(Arg1699Trp)	Heterozygous	PV	33	BC	IDC	3	–	–	–
29	*BRCA1*	NM_007294.4:c.5234del p.(Asn1745Thrfs*20)	Heterozygous	LPV\Novel	46/50	BC	IDC	3	–	–	–
30	*BRCA1*	NM_007294.4:c.5251C > T p.(Arg1751*)	Heterozygous	PV	28	BC	IDC	3	–	–	–
31	*BRCA1*	NM_007294.4:c.5251C > T p.(Arg1751*)	Heterozygous	PV	49	OC	HGSC	HG			
32	*BRCA1*	NM_007294.4:c.5332 + 2T > A p.(?)	Heterozygous	PV	51	BC	IDC	3	–	–	–
33	*BRCA1*	NM_007294.4:EXON1-13 del	Heterozygous	PV	35	BC	IDC	3	–	–	–
34	*BRCA1*	NM_007294.4:Exon 5–12 del	Heterozygous	PV	49	OC	HGSC	HG			

Table 3 (continued)

Patient	Gene	Variant (HGVS nomenclature)	Zygosity	Comment	Age at cancer diagnosis	Tumor type	Histology	Grade/ Stage	Tumour Hormone status		
									ER	PR	Her2
35	*BRCA2*	NM_000059.4:c.643del p.(Glu215Lysfs*15)	Heterozygous	LPV\Novel	32	BC	IDC	2	+	+	–
36	*BRCA2*	NM_000059.4:c.8486_8487 + 7delAGGTATGATinsCCTATG p.(?)	Heterozygous	LPV	38	BC	IDC	3	+	+	–
37	*BRCA2*	NM_000059.4:c.4563_4564del p.(Leu1522Glyfs*6)	Heterozygous	PV	73	OC	HGSC	HG			
38	*BRCA2*	NM_000059.4:c.5722_5723del p.(Leu1908Argfs*2)	Heterozygous	PV	39	BC	IDC	2	–	–	–
39	*BRCA2*	NM_000059.4:c.6065C > G p.(Ser2022*)	Heterozygous	PV	38	BC	IDC	2	–	–	–
40	*BRCA2*	NM_000059.4:c.7480C > T p.(Arg2494*)	Heterozygous	PV	42	BC	IDC	2	+	+	–
41	*BRCA2*	NM_000059.4:c.7480C > T p.(Arg2494*)	Heterozygous	PV	49	BC	IDC	2	–	–	–
42	*BRCA2*	NM_000059.4:c.7480C > T p.(Arg2494*)	Heterozygous	PV	42	BC	IDC	2	+	+	–
43	*BRCA2*	NM_000059.4:c.9097dup p.(Thr3033Asnfs*11)	Heterozygous	PV	36	BC	IDC	2	–	–	–
44	*BRCA2*	NM_000059.4: EXon1-8del	Heterozygous	PV\Novel	59	BC	IDC	3	+	+	–
45	*PALB2*	NM_024675.4:c.1056_1057del p.(Lys353Ilefs*7)	Heterozygous	PV	29	BC	IDC	2	+	–	–
46	*ATM*	NM_000051.3:c.8293G > A p.(Gly2765Ser)	Heterozygous	PV	48	BC	IDC	3	+	–	–
47	*ATM*	NM_000051.3:c.5944C > T p.(Gln1982*)	Heterozygous	PV	33	BC	IDC	2	+	+	–
48	*ATM*	NM_000051.3:c.7031G > A p.(Trp2344*)	Heterozygous	LPV	31	BC	IDC	2	–	–	–
49	*CHEK2*	NM_007194.4:c.106C > T p.(Gln36*)	Heterozygous	PV	31	BC	IDC	2	–	–	+
50	*CHEK2*	NM_007194.4:c.636T > G p.(Tyr212*)	Heterozygous	PV	48	BC	IDC	2	+	+	–
51	*BRIP1*	NM_032043.3:c.2392C > T p.(Arg798*)	Heterozygous	PV	63	OC	HGSC	HG			

BC: breast cancer, OC: Ovarian cancer, IDC, infiltrating ductal carcinoma, HGSC: High-grade Serous carcinoma, HG: High-grade, ER: Estrogen receptor, PR: Progesterone receptor, Her2: Human epidermal growth factor receptor 2

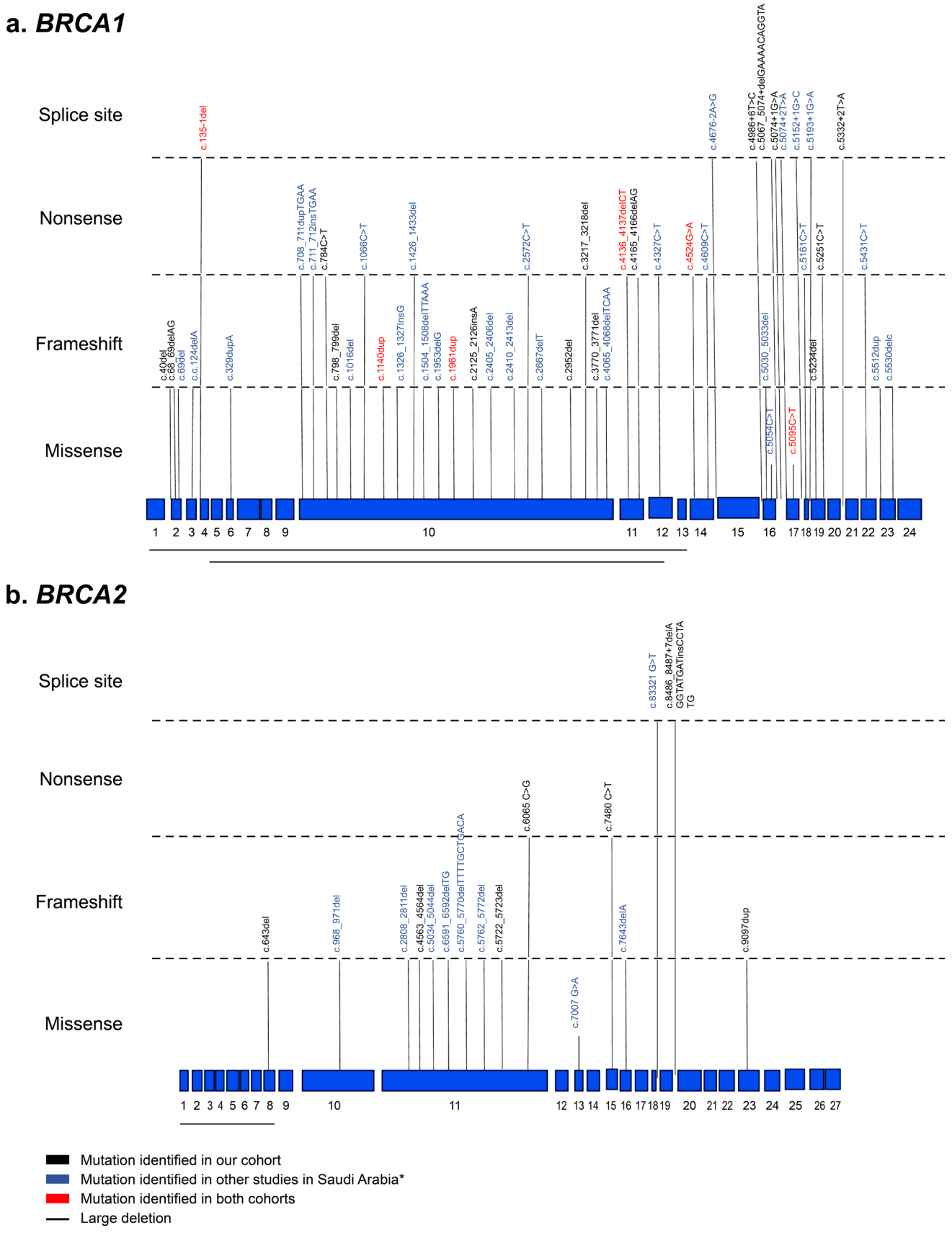

Fig. 1 Distribution of the identified PV/LPV along the (**a**) *BRCA1* and (**b**) *BRCA2* genes in breast and ovarian cancer patients within the Saudi population. *Other studies: Abulkhair O et al. (2018), Alhuqail et al. (2018), and Agha et al. (2022) [47, 49, 50]

Table 4 *BRCA1* gene PV/LPV identified in the Saudi population

No	Variant	Protein change	SNP#	Type of variant	Exon	Comment	No. pt	Current study N = 209	Abulkhair O et al., 2018 [47] N = 310	Alhuqail AJ et al., 2018[49] N = 173	Agha et al., 2022[50] N = 61
1	c.40del	p.(Val14Serfs*9)	rs886040201	Frameshift	2		1	1			
2	c.68_69del	p.(Glu23Valfs*17)	rs80357914	Frameshift	2	Founder mutation in Ashkenazi Jews [55]	1	1			
3	c.69del	p.(Glu23Aspfs*8)		Frameshift	2		1				1
4	c.124del	p.(Ile42Tyrfs*8)	rs80357943	Frameshift	3		1		1		
5	c.135-1del	p.(?)		Splice site	IVS3		2	1			1
6	c.329dup	p.(Glu111Glyfs*3)	rs80357604	Frameshift	6		1			1	
7	c.708_711dup	p.(His238*)		Nonsense	10		1				1
8	c.711_712insTGAA	p.(His238*)		Nonsense	10		1			1	
9	c.784C > T	p.(Gln262*)	rs886037979	Nonsense	10		1	1			
10	c.798_799del	p.(Ser267Lysfs*19)	rs80357724	Frameshift	10		1	1			
11	c.1016del	p.(Lys339Argfs*2)	rs80357569	Frameshift	10		1				1
12	c.1066C > T	p.(Gln356*)	rs80357215	Nonsense	10		1		1		
13	c.1140dup	p.(Lys381Glufs*3)	rs876659327	Frameshift	10		20	5	1	5	9
14	c.1326_1327InsG	p.(Lys443Glufs*3)		Frameshift	10		1		1		
15	c.1426_1433del	p.(His476*)		Nonsense	10		1				1
16	c.1504_1508del	p.(Leu502Alafs*2)	rs80357888	Frameshift	10		1			1	
17	c.1953del	p.(Lys654Serfs*47)	rs886039986	Frameshift	10		1		1		
18	c.1961dup	p.(Tyr655Valfs*18)	rs80357522	Frameshift	10		2	1	1		
19	c.2125_2126insA	p.(Phe709Tyrfs*3)	rs80357871	Frameshift	10		1	1			
20	c.2405_2406del	p.(Val802Glufs*7)	rs80357706	Frameshift	10		1				1
21	c.2410_2413del	p.(Gln804Valfs*10)		Frameshift	10		1				1
22	c.2572C > T	p.(Gln858*)		Nonsense	10	Novel	1				1
23	c.2667del	p.(Ser891Profs*2)		Frameshift	10		1			1	
24	c.2952del	p.(Ile986Serfs*14)	rs80357627	Frameshift	10		1	1			
25	c.3217_3218del	p.(Gly1073*)		Nonsense	10	Novel	1	1			
26	c.3770_3771del	p.(Glu1257Glyfs*9)	rs80357579	Frameshift	10		1	1			
27	c.4065_4068del	p.(Asn1355Lysfs*10)	rs80357508	Frameshift	10		1		1		
28	c.4136_4137del	p.(Ser1379*)	rs397509141	Nonsense	11		10	1	5	4	
29	c.4165_4166del	p.(Ser1389*)	rs80357572	Nonsense	11		1	1			
30	c.4327C > T	p.(Arg1443*)	rs41293455	Nonsense	12		1			1	
31	c.4524G > A	p.(Trp1508*)	rs80356885	Nonsense	14		4	1	3		
32	c.4609C > T	p.(Gln1537*)	rs80357229	Nonsense	14		1		1		
33	c.4676-2A > G	p.(?)	rs80358096	Splice site	IVS14		1		1		

Table 4 (continued)

No	Variant	Protein change	SNP#	Type of variant	Exon	Comment	No. pt	Current study N = 209	Abulkhair O et al., 2018 [47] N = 310	Alhuqail AJ et al., 2018[49] N = 173	Agha et al., 2022[50] N = 61
34	c.4986 + 6T > C	p.(?)	rs80358086	Splice site	IVS15		3	3			
35	c.5030_5033del	p.(Thr1677Ilefs*2)	rs80357580	Frameshift	16		1		1		
36	c.5054C > T	p.(Thr1685Ile)	rs80357043	Missense	16		1			1	
37	c.5067_5074 + 1del	p.(?)		Splice site	IVS16	Novel	2	2			
38	c.5074 + 1G > A	p.(?)	rs80358053	Splice site	IVS16		2	1	1		
39	c.5074 + 2T > A	p.(?)	rs80358089	Splice site	IVS16		1				1
40	c.5095C > T	p.(Arg1699Trp)	rs55770810	Missense	17		10	4		4	2
41	c.5152 + 1G > C	p.(?)	rs80358094	Splice site	IVS17		3		3		
42	c.5161C > T	p.(Gln1721*)	rs878854957	Nonsense	18		1			1	
43	c.5193 + 1G > A	p.(?)		Splice site	IVS18		1			1	
44	c.5234del	p.(Asn1745Thrfs*20)		Frameshift	19	Novel	1	1			
45	c.5251C > T	p.(Arg1751*)	rs80357123	Nonsense	19		4	2	1	1	
46	c.5332 + 2T > A	p.(?)	rs80358182	Splice site	IVS20		1	1			
47	c.5431C > T	p.(Gln1811*)		Nonsense	22	Novel	1			1	
48	c.5512dup	p.(Val1838Glyfs*42)		Frameshift	23	Novel	1		1		
49	c.5530delc	p.(Leu1844Serfs*11)		Frameshift	23	Novel	5			2	3
50	EXON1-13 del						1	1			
51	EXON5-12 del						1	1			
	Total: 51						106	34	24	25	23

Table 5 *BRCA2* gene PV/LPV in the Saudi population

No	Variants	Protein change	SNP#	Type of variant	Exon	Comment	No. pt	This study	Abulkhair O et al., 2018 [47]	Alhuqail AJ et al., 2018[49]	Agha et al., 2022 [50]
1	c.643del	p.(Glu215Lysfs*15)		frameshift	8	Novel	1	1			
2	c.968_971del	p.(Val323Glufs*25)	rs886040847	frameshift	10		1		1		
3	c.2808_2811del	p.(Ala938Profs*21)	rs80359351	frameshift	11		1		1		
4	c.4563_4564del	p.(Leu1522Glyfs*6)	rs483353115	frameshift	11		1	1			
5	c. 34_5044del	p.(Thr1679Serfs*6)		frameshift	11		1		1		
6	c.6591_6592del	p.(Glu2198Asnfs*4)	rs80359605	frameshift	11		1		1		
7	c.5760_5770del	p.(Phe1921Serfs*3)	rs1566233171	frameshift	11		1			1	
8	c.5762_5772del	p.(Phe1921Serfs*3)		frameshift	11	Novel	1				1
9	c.5722_5723del	p.(Leu1908Argfs*2)	rs80359530	frameshift	11		1	1			
10	c.6065C > G	p.(Ser2022*)	rs80358843	nonsense	11		1	1			
11	c.7007G > A	p.(Arg2336His)		missense	13		1			1	
12	c.7480C > T	p.(Arg2494*)	rs80358972	nonsense	15		3	3			
13	c.7643del	p.(His2548Leufs*3)		frameshift	16		1		1		
14	c.8332-1G > T	p.(?)	rs397507979	splice site	IVS18		2		1	1	
15	c.8486_8487 + 7delAGG TATGATinsCCTATG	p.(?)		splice site	IVS19		1	1			
16	c.9097dup	p.(Thr3033Asnfs*11)	rs397507419	frameshift	23		1	1			
17	Exon 1-8del				1-8	Novel	1	1			
	Total:17						20	10	6	3	1

c.4136_4137del p.(Ser1379*) in 10/106, c.5095C > T p.(Arg1699Trp) in 10/106, and p.(Leu1844Serfs*11) in five patients. The combined frequency of recurrent variants in *BRCA1* is 42%, which can be considered high. For *BRCA2*, c.7480C > T p.(Arg2494*) was reported in 3/20 and c.8332-1G > T p.(?) in 2/20 patients (Fig. 1b, Tables 3 and 5).

4 Discussion

Approximately 1:400–1,000 persons are carriers of *BRCA1* or *BRCA2* PV/LPV [33]. However, the frequencies of germline *BRCA1* and *BRCA2* PV/LPV vary across geographical regions and ethnic populations [36]. Patients with *BRCA1*/2 germline PV/LPV have a significantly increased lifetime risk of BC and OC. Moreover, PV/LPV in these and other genes (such as *PALB2*, *TP53*, *ATM*, and *CHEK2*) elevate cancer risk in their carriers. Early recognition of individuals with a PV/LPV in one of the predisposing genes is essential to properly assess cancer risk, initiate appropriate cancer screening for early detection, and improve cancer prevention strategies to avoid potential complications associated with this disease.

Here, we comprehensively analyzed 13 genes in patients diagnosed with BC and/or OC in the western region of Saudi Arabia using NGS. Among the 209 patients, 51 (24.4%) were carriers of a pathogenic germline PV/LPV in one of the BC and/or OC-related genes: 43/171 (25%) in BC, 7/36 (19.4%) in OC, and 1/2 in both BC and OC. This percentage (24.4%) is relatively high compared to other BC studies in Saudi and most other global populations [3, 10]. Contributing factors include the use of potentially different selection criteria for the various Saudi studies performed to date and the homogenous population structure influenced by the common practice of consanguineous marriages compared to the rest of the world. On the other hand, regarding OC, our percentage (19.4%) was in line with previous studies [4, 10, 48].

The clinical characterization of BC with *BRCA1*/2 gene mutations is in line with previous publications for the Saudi and European populations [3, 4, 10, 12, 46, 48, 50], which showed a stronger association between *BRCA1* mutations, younger age at diagnosis, and TNBC compared with *BRCA2* PV/LPV. Moreover, our investigation revealed a predominance of *BRCA1* PV/LPV in 67% (34/51) of the cases, in contrast to the 20% (10/51) attributed to *BRCA2* PV/LPV. This trend corresponds with the results of previous studies conducted in Arab countries [57]. Interestingly, this pattern mirrors observations in Western populations [30, 50] but contrasts sharply with specific Asian populations where *BRCA2* gene PV/LPV is more prevalent [18, 56].

For *BRCA1*, the study identified various prerecorded variants, such as the c.68_69del p.(Glu23Valfs*17) variant, prevalent among both Ashkenazi Jews and individuals of Spanish descent [33, 37–39]. Moreover, c.5095C > T p.(Arg1699Trp), c.1140dup p.(Lys381Glufs*3), and c.4136_4137del p.(Ser1379*) were observed for different ethnic groups, including the Saudi population [3]. The study, however, did reveal novel *BRCA1* variants such as c.3217_3218del p.(Gly1073*), c.5067_5074 + 1del p.(Met1689Ilefs*3), and c.5234del p.(Asn1745Thrfs*20), which are novel and possibly specific to the Saudi population, including c.5030del p.(Thr1677Ilefs*3) previously described by Abulkhair et al. [3]. Additionally, our research revealed the presence of five recurrent variants within *BRCA1*, namely c.1140dup p.(Lys381Glufs*3), c.5095C > T p.(Arg1699Trp), c.4986 + 6 T > C p.(?), c.5067_5074 + 1del p.(Met1689Ilefs*3) and c.5251C > T p.(Arg1751*). Interestingly, the most prevalent mutation was *BRCA1* c.1140dup, previously reported as a potential founder variant in Saudi Arabia [4, 10]. For *BRCA2*, c.7480C > T p.(Arg2494*) was the most frequent mutation not only in our cohort but also in a previous Saudi study [10] and in a Korean study [18]. The current study, however, did detect two novel variants, namely c.643del and a copy number variant that included the deletion of exons 1 to 8.

Cultural factors, including consanguinity and inbreeding, may have contributed to the accumulation of population-specific founder mutations in Saudi Arabia. A comprehensive summary of BRCA1 and BRCA2 variants identified in the Saudi population provides a valuable overview of the mutation spectrum, aiding physicians in clinical decision-making and supporting genetic counseling efforts [4, 10, 48].

These recurrent mutations offer a valuable avenue for targeted *BRCA1*/2 genotyping, which applies to both unselected BC and OC patients and asymptomatic individuals from high-risk families. This approach facilitates efficient and cost-effective population-based screening initiatives similar to those for the Ashkenazi Jewish population. The economic viability of implementing such a testing strategy is subject to variation within healthcare systems. However, a recent study in the United Kingdom underscored its cost-effectiveness, particularly in identifying asymptomatic carriers of PV/LPV, thereby enabling preventive measures before cancer onset [49].

Our data regarding the variants identified in *ATM*, *CHEK2*, *PALB2*, and *BRIP1* remain limited owing to the relatively small number of patients harboring PV/LPV in these genes and the lack of data for the Saudi population. A single recurrent *ATM* c.6115G > A p.(Glu2039Lys) variant has thus far been identified [20, 49], but it was absent in our cohort. Finally, we acknowledge the limitations posed by our small sample size and the exclusive recruitment from a single tertiary referral

center in the Makkah region. This warrants caution when extrapolating our findings to broader patient populations across other cancer centers or regions in Saudi Arabia. Furthermore, the genetic landscape of ethnic mutations in this population has not been studied, Therefore, we emphasize the need for further regional studies to deepen our understanding of the contribution of other non-*BRCA* predisposition genes in this population. Other genes that predispose to BC and OC, were not comprehensively studied, which limits our understanding of the full genetic landscape of hereditary cancer risk in this population. Despite these limitations, this study represents a crucial starting point. Moving forward, we plan to expand this research with a larger sample size and a broader assessment of additional cancer predisposition genes. Future studies will aim to provide a more in-depth genetic characterization of breast and ovarian cancers in the Saudi population, facilitating improved risk assessment and personalized approaches to cancer prevention and treatment.

5 Conclusion

Our study revealed that the prevalence of *BRCA1*/2 variants in the Saudi population appears to be higher than that in the Western population despite a similarity in the pattern. certain mutations were discovered for the first time in this cohort and further research in this area is needed. To establish population-based screening, a genotyping study should be initiated for recurrent mutations identified thus far in *BRCA1*/2. This advancement holds promise for enhancing treatment efficacy through targeted therapies, such as poly (ADP-ribose) polymerase (PARP) inhibitors, in Saudi patients with BC and OC, along with implementing effective preventive measures.

Acknowledgements The authors are grateful to all patients who participated in this study. We also want to thank the Medical Oncology team and the surgical team at King Abdullah Medical City, Makkah, KSA, for their support.

Author contributions Study conception and design: SNE, OE, and ET. Patient recruitment, sampling, and clinical data collection: SNE, MA, OE, and ET. Data analysis and interpretation: SNE, JS, AF, ZA, AM, HHZ and AK. Literature Review: AF, SNE, AM, ZA, HHZ and AK. Writing and editing the manuscript: SNE, OE, AF, HHZ and AK. Overall supervision: SNE. Final approval of the manuscript: All authors.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request. Researchers interested in accessing the data may contact S. Ekram at [snekram@uqu.edu.sa]. Access to the data may require appropriate institutional approvals and compliance with relevant ethical guidelines.

Declarations

Ethics approval and consent to participate The study protocol was approved by the Institutional Review Board (IRB) of St Al-Qura University (UQU) with application number LGCX011122 (issued 09 Jan 2023), and King Abdullah Medical City (KAMC) with IRB reference number 21-782 (issued 08 Oct 2023). This study was performed in accordance with the guidelines of the Declaration of Helsinki. All participants provided signed informed consent prior to inclusion in the study. Written informed consent was obtained from all subjects involved in the study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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