

Assessing Frequency and Clinical Outcomes of BRCA Mutated Ovarian Cancer in Saudi Women

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Research

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Abstract

Purpose: BRCA gene mutations (BRCAm) had an impact on patients' characteristics and clinical outcomes of ovarian cancer (OC). The frequency and patterns of BRCAm vary among countries and ethnicities. There are limited data from Saudi Arabia (SA); thus, this study aims to determine the frequency, pattern, and impact on patient characteristics and outcomes of BRCAm OC compared to wild-type BRCA (BRCAw) in Saudi women.

Methods: This retrospective study evaluated women diagnosed with non-mucinous OC, fallopian tube, or peritoneal carcinoma who had BRCA status tested in an accredited lab between January 2016 and December 2017. The associations between various parameters and BRCAm were estimated using logistic regression. Statistical analysis performed with SPSS (Version 27).

Result: Sixty-one women with a median age of 52 at diagnosis were analyzed. Germline BRCA mutations were found in 41% of cases (25/61). The most common deleterious germline BRCA1 mutation was c.1140dupG (39%). Most women (72%) had no family history of cancers and 82% had advanced stage. Regardless of BRCA mutations, an optimal overall response rate (ORR) to first-line treatment has been achieved although most cases relapsed (84%) and the majority were platinum-sensitive relapse (85%). Higher ORR to subsequent lines and better survival were obtained in women with BRCA-mutation.

Conclusion: The prevalence of BRCAm of OC was higher in Saudi women compared to regional and most of the international figures. The better clinical outcomes of BRCAm women agreed with the reported evidence. Further studies on BRCA mutations of OC and genetic counseling are highly recommended.

Trial registration number and The addresses of the institution at which the work was performed:

Trial approved by the Institutional Review Board of King Faisal Specialist Hospital and Research Center (RAC # 2171137) and conducted at King Faisal Specialist Hospital and Research Center, PO Box 3354, Riyadh 11211, Saudi Arabia.

Background

In high-income countries, ovarian cancer (OC) is the second most commonly diagnosed gynecological malignancy and the most common cause of death from it [1]. The age-standardized rate (ASR) incidence of OC worldwide is 3.9 per 100,000, and in Arab regions, it ranges between 0.9 and 8 per 100,000 [1, 2]. In Saudi Arabia (SA), OC ranks as the seventh most common cancer among females, with ASR of 3.7 cases per 100,000 and as the fifth leading cause of death, with an ASR of 2.5 deaths per 100,000 [3, 4]. The inherited mutations in OC were found to be the cause for 18% of the OC cases, with the majority being caused by breast cancer associated gene mutations (BRCAm). Furthermore, BRCAm increases the lifetime risk of developing OC from 1.3% in the general population to 44% in BRCA1 and 17% in BRCA2 mutation carriers [5]. A review of 173 women with breast cancer and OC from SA showed that the prevalence of germline BRCAm was 30.7% in OC and 10.2% in breast cancer [6]. In a recent systemic

review from 22 Arab countries, six mutations were shown to be unique to the Saudi population: Four were located in BRCA1 (c.1140dupG, c.5530delC, c.5054C>T, and c.711_712insTGAA), and two were located in BRCA2 (c.2667delT and c.5760_5770del11) [2]. BRCA1 and BRCA2 are tumor suppressor genes that control cell growth and maintain genomic stability [7]. They are responsible for the repair of double-strand DNA breaks (DSBs) through the homologous recombination pathway, and a deficiency in BRCA function leads to genomic instability due to the inability to repair DNA damage through homologous recombination defect (HRD), thereby leading to tumorigenesis [8, 9]. Simultaneously, the mutation weakens tumor cells that can be targeted therapeutically [10], which explains the association between BRCA gene mutations and a better response to DNA-alkylating agents such as platinum in OC [8, 11]. Poly ADP-ribose polymerase enzyme (PARP) is essential for the repair of single-strand breaks of DNA. PARP inhibitors induce the synthetic lethality of cells with HRD, which occurs when there is a simultaneous mutation in two genes leading to cell death; however, no cell death occurs when the mutation is found in only one gene [10]. Many clinical trials have tested the efficacy of PARP inhibitors in the treatment of advanced OC. Early evidence showed improvement in objective response rate (ORR) and progression-free survival (PFS) in heavily treated patients, predominantly in those with either germline or somatic BRCA mutations as HRD occurs in germline BRCA mutations, somatic BRCA mutations, and BRCA promotor hypermethylation cases [12]. Moreover, this benefit has recently been proven to involve all women with advanced high-grade serous OC after response to platinum-based chemotherapy (PBC) regardless of BRCA status [13]. The standard therapy for advanced epithelial OC is PBC following primary debulking surgery (PDS) [14]. Interval debulking surgery (IDS) is a feasible option after neoadjuvant chemotherapy and demonstrated similar survival outcomes as PDS [15]. However, more than 80% of patients experience disease recurrence after completing their treatment, with an unsatisfactory outcome to the second line of management [16].

The primary aim of this study was to measure the frequency and patterns of germline BRCA mutations among OC patients, to compare the clinicopathological characteristics, and to assess the clinical outcomes of BRCA mutant vs BRCA wild-type patients.

Methods

A retrospective study was conducted on all patients diagnosed with primary ovarian, fallopian tube, or peritoneal carcinoma who were tested for BRCA mutations and followed up at the King Abdullah Oncology Centre at the King Faisal Specialist Hospital and Research Center (KFSH&RC) between January 2016 and December 2017. Women with pathological confirmation of serous carcinoma, clear cell carcinoma, and endometrial carcinoma were eligible, whereas those with borderline cancer and mucinous carcinoma were excluded. Germline BRCA mutations were obtained from Myriad Genetic Laboratories Inc., which was certified by the College of American Pathologists and Clinical Laboratory Improvement Amendments as per the National Comprehensive Cancer Network (NCCN) guidelines [17]. This project was conducted in accordance with the ethical principles in Helsinki's Declaration (2000) and was approved by the Institutional Review Board of KFSH&RC (RAC # 2171137). The clinical information collected from the medical records included age, personal and family history of cancer, tumor histology,

grade, Federation of Gynecology and Obstetrics (FIGO) stage, CA125 level, and BRCA status. In addition to lines of chemotherapy, best response, time to progression, platinum sensitivity, and status at last follow-up were evaluated. The tumors were staged according to the 2017 8th Edition of the American Joint Committee on Cancer and the FIGO classification system. The patients were followed up based on KFSH&RC guidelines (every two to three months for the first two years and then every six months). At each visit, clinical assessment and serum CA125 test were performed. The abdominal ultrasound scans were performed every six months, and computed tomography of the chest and abdomen was done every year for five years unless relapse was suspected. Platinum-sensitive relapse was defined as tumor relapse that occurred more than six months after completion of the last cycle of PBC. Tumor response was assessed based on the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1). The clinical outcomes investigated were overall response rate (ORR) to first and subsequent lines, disease-free survival (DFS), and overall survival (OS). The ORR has been defined as the sum of partial and complete responses divided by the total number of patients. DFS was defined as the interval between histologic diagnosis and first progression, death as a result of disease, or last follow-up. OS was defined as the interval between histologic diagnosis and the date of death as a result of disease or last follow-up.

Statistical analysis

Categorical values were described as frequencies compared with Chi-square test or Fisher's exact test, and continuous values were described as the median with interquartile range (IQR) and compared using the Mann-Whitney U test. Associations between various parameters and the BRCA mutations were estimated by logistic regression. The Kaplan–Meier estimator was used to determine DFS, and OS and survival curves were compared using the log-rank test, and a multivariate analysis was conducted using the Cox regression. All variables were tested for the affirmation of the proportionality assumption. Variables that violated the proportionality assumption were entered as time-dependent covariates. BRCA mutations were considered the main effect and were kept in the model at all times. Interactions between BRCA mutations and other significant variables were evaluated, and significant interactions were considered. A p-value of ≤ 0.05 was considered statistically significant. The SPSS for Mac, v27; IBM Corp, Armonk, NY, USA, was performed for statistical analysis.

Results

A total of 61 women were eligible for analysis. The median age at diagnosis was 52 years (IQR: 44–61.5). BRCA mutations were found in 25 women (41%), including 23 with BRCA1 mutations and 2 with BRCA2 mutations. The patient and disease characteristics stratified by BRCA status are shown in Table 1. The main presenting symptom was abdominal distension (35 patients, 57.3%). The logistic regression revealed a significant association between family history of malignancy and BRCA mutations ($p = 0.03$). However, BRCA mutations were not statistically significantly associated with age and stage at diagnosis, patient region, or history of primary cancer.

There were 15 different pathogenic variants identified, including 13 with BRCA1 mutations and 2 with BRCA2 mutations. The three most common deleterious germline BRCA1 mutations were c.1140dupG (9 patients, 39%), c.5530del (3 patients, 13%), and c.5095C>T (2 patients, 8%). The other pathogenic variants were each observed once. Table 2 presents all pathogenic variants of the mutated genes, age, geographical region of the patients, and personal and family histories of cancer. The univariate analysis revealed no association between c.1140dupG, the most common deleterious mutation, and age, stage at diagnosis, relapse rate, platinum sensitivity, or patient region; however, all the OC cases from the western province (3 patients) and 29% (4 patients) from the central region carried the c.1140dupG pathogenic variant of the BRCA1 gene mutation. Of the BRCA wild-type patients, two had a positive family history of cancer, including a mother with a brain tumor and a sister with colon cancer; one patient had a personal history of cervical cancer.

All women in this cohort underwent debulking surgery and received chemotherapy during their treatment; 49% received PDS and then adjuvant chemotherapy, and 51% started with neoadjuvant chemotherapy and IDS with no statistical difference ($p = 0.98$). All women received PBC as the first-line treatment. A total of 87% of both groups received a regimen consisting of IV cisplatin and paclitaxel every three weeks. The patients received a median of three chemotherapy lines; specifically, 21%, 17%, and 62% of patients received one, two, and three or more chemotherapy lines, respectively. The platinum sensitivity dropped with subsequent lines; 14%, 41%, and 73% of women received non-platinum-based therapy as the second-line, third-line, and fourth-line treatments, respectively, and 100% (13 patients) received non-platinum-based therapy as the fifth-line treatment. The ORR to the first line of management was 100%, with a higher complete response (CR) in BRCA mutant women than in wild-type women (92% vs 72.7%, $p = 0.08$). The relapse rate was 84%, and the majority (85%) were platinum-sensitive. Additionally, 84% of BRCA mutant vs. 80% of BRCA wild-type patients experienced platinum-sensitive relapse after first-line therapy ($p = 0.43$). In the subsequent lines of treatment, the ORR also was higher in the BRCA mutant group compared with the BRCA wild-type group: second-line (94.4% vs 64.5%, $p = 0.01$), third-line (84.7% vs 30.6%, $p = 0.002$), and fourth-line (40% vs 22.2%, $p = 0.40$) (Table 3). Thirteen out of 25 women with BRCA mutation received a PARP-inhibitor, namely Olaparib, and over half of the patients received Olaparib after third relapse. (54%, $n = 7$). Olaparib was discontinued due to disease progression in eleven patients and anemia in one patient. Olaparib treatment was still ongoing for one patient. The sample size limited further analysis.

The median follow-up duration was 59 months (IQR: 42–79). The median DFS was longer in the BRCA mutant women 25 (95% CI: 21.7–28.2) vs. 17 (95% CI: 8.7–25) months, $p = 0.02$) (Fig. 1). The Cox regression analysis for DFS adjusted by age and comorbidities was statistically significant for BRCA mutant vs. wild-type patients (hazard ratio (HR) = 0.52, 95% CI: 0.23–0.92, $p = 0.02$). The median DFS of second-line treatment (50 patients) in the BRCA mutant group was 20 months (95% CI: 18.2–21.7) vs. 12 months (95% CI: 7.8–16.1) in the wild-type group ($p = 0.051$) (Fig. 2). The median OS was not reached. However, the five-year OS rate for BRCA mutant patients was 90.9% vs. 66.7% for wild-type patients ($p = 0.19$) (Fig. 3).

Discussion

This is the first study to compare the clinical characteristics and clinical outcomes of BRCAm and BRCAw in Saudi women with OC. The research highlights the higher prevalence, the better clinical outcomes of BRCA mutants, and the importance of early access for BRCA testing and treatment. The frequency of BRCA-associated OC was higher in this current cohort than in a previous study (40% vs. 30%) [6]. It remains unknown whether the high intermarriage between families in SA could explain why Saudi women have a high prevalence of germline BRCA mutations or whether some other factor is involved. The frequency in this cohort is close to the BRCA gene mutations rate found among Ashkenazi Jewish (41%) [18] and Italian women (39.2%–43.5%) [19, 20]. The most common mutations in this study are c.1140dupG, c.5530del, and c.5095C>T, which agrees with recent reports [2, 6]. However, the most common mutations in the Ashkenazi are 185delAG and 5382insC [18] and those in the Italian women are 3875del4 and 1479delAG [19]. The higher percentage of BRCA1 mutations compared with BRCA2 mutations (92% vs 8%) in this study agrees with previous publications although those studies reported higher percentages of BRCA2 mutations [19, 21]. This trend is reversed in some Asian populations, with a higher percentage of BRCA2 mutations compared with BRCA1 mutations [22]. Clearly, the pattern and frequency of BRCA mutations vary significantly in relation to race/ethnicity and geographical location [23].

The median age at diagnosis was lower than that in other regions: 52 vs 63 years; however, there was no statistically significant difference between BRCAm and BRCAw (p -value = 0.13) [24]. There was a greater association of a family history of malignancy and a personal history of cancer with the BRCA mutant patients than in the wild-type patients (p = 0.02 and p = 0.04, respectively), which has been reported earlier [25]. However, most cases of OC did not have a positive family history, as noted in earlier studies [21]. Therefore, the NCCN guidelines recommend susceptibility gene screening regardless of family history for all epithelial OC cases, including fallopian tube cancer or peritoneal cancer diagnosed at any age [17], which has been followed in many institutions [19]. Agreeing with previous studies, abdominal distension the most common presenting symptom in this cohort, and there was no significant difference between BRCAm and BRCAw in terms of FIGO stage at presentation and CA-125 level [21, 26].

The higher ORR to subsequent lines of treatment in the BRCA mutant group agrees with earlier evidence showing that BRCA mutations increase the susceptibility of the cells to be destroyed by chemotherapy [11]. All patients received intravenous doublet PBC in a first-line setting, in agreement with the international standard of care [27, 28]. Intraperitoneal chemotherapy is not approved at KFSHRC as the standard treatment because of its high toxicity profile and worsening quality of life [29].

The higher DFS and OS in BRCA gene mutations have been shown in several previous studies, and this finding corresponds to a better response to chemotherapy owing to the deficiency of mechanisms of DNA repair [30]. This trend was clear in this cohort, which had a prolonged median DFS in the BRCA mutant group (25 vs. 17 months) in the first-line setting, which was statistically significant. Additionally, the median DFS after second-line treatment was eight months longer in the BRCA mutant group (Fig. 2), and

the five-year OS was 90% vs 66% (Fig. 3) in the BRCA mutant group compared to BRCA wild group; however, this difference was not statistically significant, However, longer follow-up is necessary.

We acknowledge that the small sample size likely yielded underpowered comparisons. Moreover, these patients were recruited from a tertiary referral center and therefore may not be representative of patients at primary cancer centers, although they were obtained from the largest referral hospital in the region.

Conclusions

BRCA gene mutations in Saudi women with OC predominantly involve the BRCA1 gene. The founder mutation was c.1140dupG, which was observed in more than one-third of the cases. BRCAm women had a better ORR in subsequent lines of therapy and a longer DFS than the BRCAw-type women.

List Of Abbreviations

ASR	Age-standardized rate
CR	Complete response
DFS	Disease-free survival
DSB	Double-strand breaks
EOC	Epithelial ovarian cancer
HRD	Homologous recombination defect
IDS	Interval debulking surgery
KFSH	King Faisal Specialist Hospital
NCCN	National Comprehensive Cancer Network
OC	Ovarian cancer
ORR	Objective response rate
OS	Overall survival
PARP	Poly ADP-ribose polymerase
PFS	Progression-free survival
SA	Saudi Arabia
FIGO	Federation of Gynecology and Obstetrics

PBC Platinum-based chemotherapy

PDS Primary debulking surgery

Declarations

Ethics approval and consent to participate

This project was conducted in accordance with the ethical principles contained in the Declaration of Helsinki (2000). The Research Advisory Council (RAC) at King Faisal Specialist Hospital & Research Centre, Riyadh, approved the project (RAC # 2171137), and waiver informed consent includes access and use of patient files while maintaining the confidentiality of the data. The identity of the patients remained anonymous since no identifying data or protected health information was recorded.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

HH, HS, NA, and SA shared the idea and wrote the proposal. NA, SA, BS, HA, AS, AO, TM, HO, and HA collected the data. BA and NA formulated the idea, performed the literature review, and wrote the first draft. TE and BA analyzed the data. BA and NA created the tables and figures and edited the manuscript. HH master supervised the patient management and performed the literature review. All authors read and approved the final version of the manuscript.

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Tables

Table 1. Patient, disease, and treatment characteristics stratified by BRCA status (n = 61)

		BRCA mutant <i>n</i> = 25 (41%)	BRCA wild type <i>n</i> = 36 (59%)	
Characteristics		N (Frequency)	N (Frequency)	<i>P</i> -VALUE*
Age at diagnosis				
Median (IQR)		50 (43-56)	55 (46-66)	0.13
Age ≤ 50		14 (56)	15 (41.7)	0.27
Positive personal history of cancer		5 (20)	1 (2.9)	0.04
Positive family history of cancer		7 (28)	2 (5.6)	0.02
Presence of comorbidities*		19 (76)	24 (66.7)	0.43
Histology	High-grade serous	100%	97.1%	0.39
	Endometrioid		2.9%	
High grade		25 (100)	34 (94.4)	0.48
FIGO stage				
	Stage 1	6	3	0.65
	IA	2	0	
	IB	2	1	
	IC	2	2	
	Stage 2	1	4	
	IIA	1	1	
	IIB	0	3	
	Stage 3	15 (58)	21 (55)	
	IIIA	0	2	
	IIIB	1	2	
	IIIC	14	17	
	Stage 4	4	10	
High CA125		20 (80)	26 (72.2)	0.46
Initial management				
	PDS	48%	50%	0.87
	NAC	52%	50%	
No. of lines, median (IQR)		3 (1-5)	3 (2-4.75)	0.79
Lines of treatment				
First line (n = 61)		(n = 25)	(n = 18)	0.26
	PBC	100%	100%	
	Non PBC			
Second line (n = 49)		(n = 18)	(n = 31)	0.79
	PBC	88.9	83.4	
	Non PBC	11.1	16.6	
Third line (n = 39)		(n = 13)	(n = 26)	0.42
	PBC	73.1	64	
	Non PBC	26.9	36	
Fourth line (n = 23)		(n = 10)	(n = 13)	0.38
	PBC	50%	23.1%	
	Non PBC	50%	76.9%	
Fifth line (n = 13)		(n = 7)	(n = 5)	0.68
	PBC	-	-	
	Non PBC	100%	100%	

Categorical values were compared with the Chi-square test or Fisher's exact test, and continuous values were described as the median with interquartile range (IQR) and compared using the Mann-Whitney U test

Comorbidities: hypertension, DM, hypothyroidism, bronchial asthma, dyslipidemia, or osteoarthritis. PBC; platinum-based chemotherapy; non PBC, non-platinum-based chemotherapy (Paclitaxel, Liposomal doxorubicin, Etoposide, Gemcitabine,

Table 2. Patients, age and regions, family history, and deleterious mutations (n = 25)

Age	Region*	Personal History of cancer	Family members/ type of cancer	Gene	Mutation	Protein change
60	South	-	-	BRCA1	c.1140dupG	p.Lys381Glufs*3
38	Central	-	-	BRCA1	c.2410_2413del	p.gln804Valfs*10
56	Southern	-	Sister (breast)	BRCA1	c.1426_1433del	p.His476*
45	Central	Breast Ca	-	BRCA1	c.1140dupG	p.Lys381Glufs*3
49	Central	Breast Ca	-	BRCA1	c.5530del	p.Leu1844Serfs*11
52	Western	Breast Ca	Sister (breast)	BRCA1	c.1140dupG	p.Lys381Glufs*3
52	Central	-	-	BRCA1	c.1140dupG	p.Lys381Glufs*3
41	Central	-	-	BRCA2	c.5762_5772del	p.Phe1921Serfs*3
62	Northern	-	-	BRCA1	c.5074 + 2T>T	
50	Northern	-	-	BRCA1	c.5095C>T	p.Arg1699Trp
48	Western	-	-	BRCA1	c.1140dupG	p.lys381Glufs*3
40	Eastern	-	-	BRCA1	c.1140dupG	p.Lys381Glufs*3
53	Central	-	Sister (breast/ovarian) Father (Colon)	BRCA1	c.135-1del	
45	Central	-	Sister (breast/ovarian) Father (Lung)	BRCA1	c.1140dupG	p.Lys381Glufs*3
43	Central	Breast Ca	Mother and Sister (breast)	BRCA1	c.1140dupG	p.Lys381Glufs*3
48	Central	Pheochromocytoma, Breast Ca	Brother (colon Ca)	BRCA1	c.2405_2406del	p.Val802Glufs*7
43	Central	-	-	BRCA1	c.1016del	p.Lys339Argfs*2
56	Central	-	-	BRCA1	c.69del	p.Glu23Valfs*17
56	Central	-	Sister (breast)	BRCA1	c.5095C>T	p.Arg1699Trp
69	Southern	-	-	BRCA1	c.2572C>T	p.Gln858*
41	Eastern	-	-	BRCA1	c.1140dupG	p.Lys381Glufs*3
67	Central	-	-	BRCA1	c.5530del	p.Leu1844Sarfs*11
35	Southern	-	-	BRCA1	c.708_711dupTGAA	p.His228*
59	Northern	-	-	BRCA1	c.5530del	p.Leu1844Serfs*11
50	Northern	-	-	BRCA2	c.7007G>A	p.Arg2336His

Regions according to the Saudi cancer registry: Central region (Riyadh, Qassim, and Hail), Northern region (Madinah, Tabuk, Jouf, and Northern), Western region (Makkah, Madinah, Jeddah, and Taif), Eastern region (Dammam and Ahsa), and Southern region (Jizan, Naran, Baha, and Asir)

Table 3. Response rate to different lines of chemotherapy based on BRCA status.

Best Response	First line (n = 61)		Second line (n = 49)		Third line (n = 39)		Fourth line (n = 23)	
	BRCAm n = 25	BRCAw n = 36	BRCAm n = 18	BRCAw n = 31	BRCAm n = 13	BRCAw n = 26	BRCAm n = 10	BRCAw n = 13
CR	92%	72.7%	50%	29%	46.2%	7.7%	20%	7.7%
PR	8%	27.3%	44.4%	35.5%	38.5%	19.2%	20%	7.7%
SD	-	-	5.6%	9.7%	-	26.9%	10%	15.4%
PD	-	-	-	25.8	15.4%	34.6%	50%	38.5%
NA	-	3 patients	-	-	-	3 patients	-	4 patients
ORR	100%	100%	94.4%	64.5%	84.7%	30.6%	40%	22.2%
P-Value*			0.01		0.002		0.40	

* Chi-square or Fisher's exact test ; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available; ORR, objective response rate

Figures

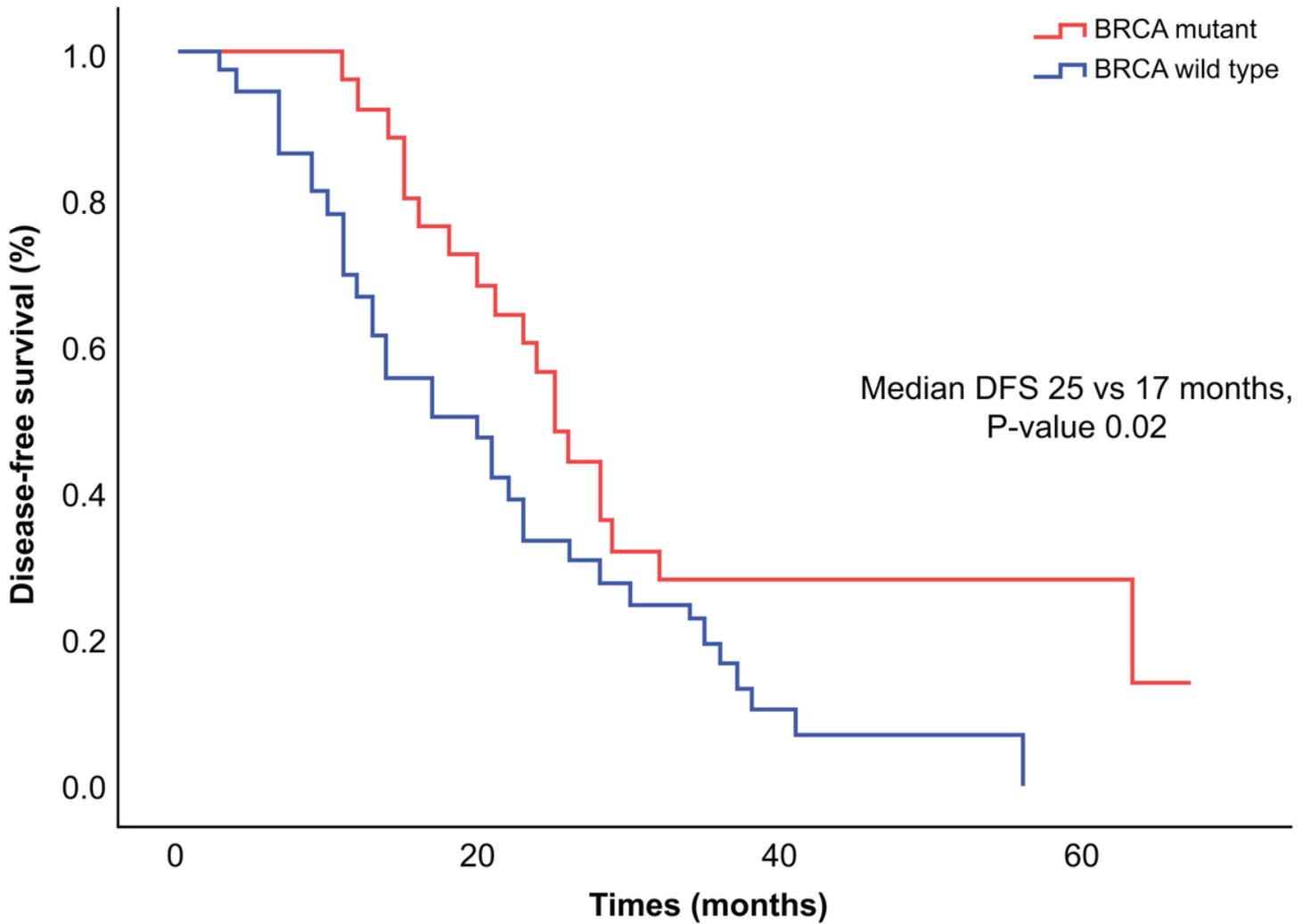


Figure 1

Disease-free survival of ovarian cancer stratified by BRCA status for first-line therapy. The Kaplan–Meier estimator was used to determine DFS among patients with germline BRCA mutation and those without germline BRCA mutation. Two sided P values were calculated with the use of the stratified log rank test and CI denotes confidence interval. The median DFS was longer in the BRCA mutant women 25 (95% CI: 21.7–28.2) vs. 17 (95% CI: 8.7–25) months, ($p = 0.02$).

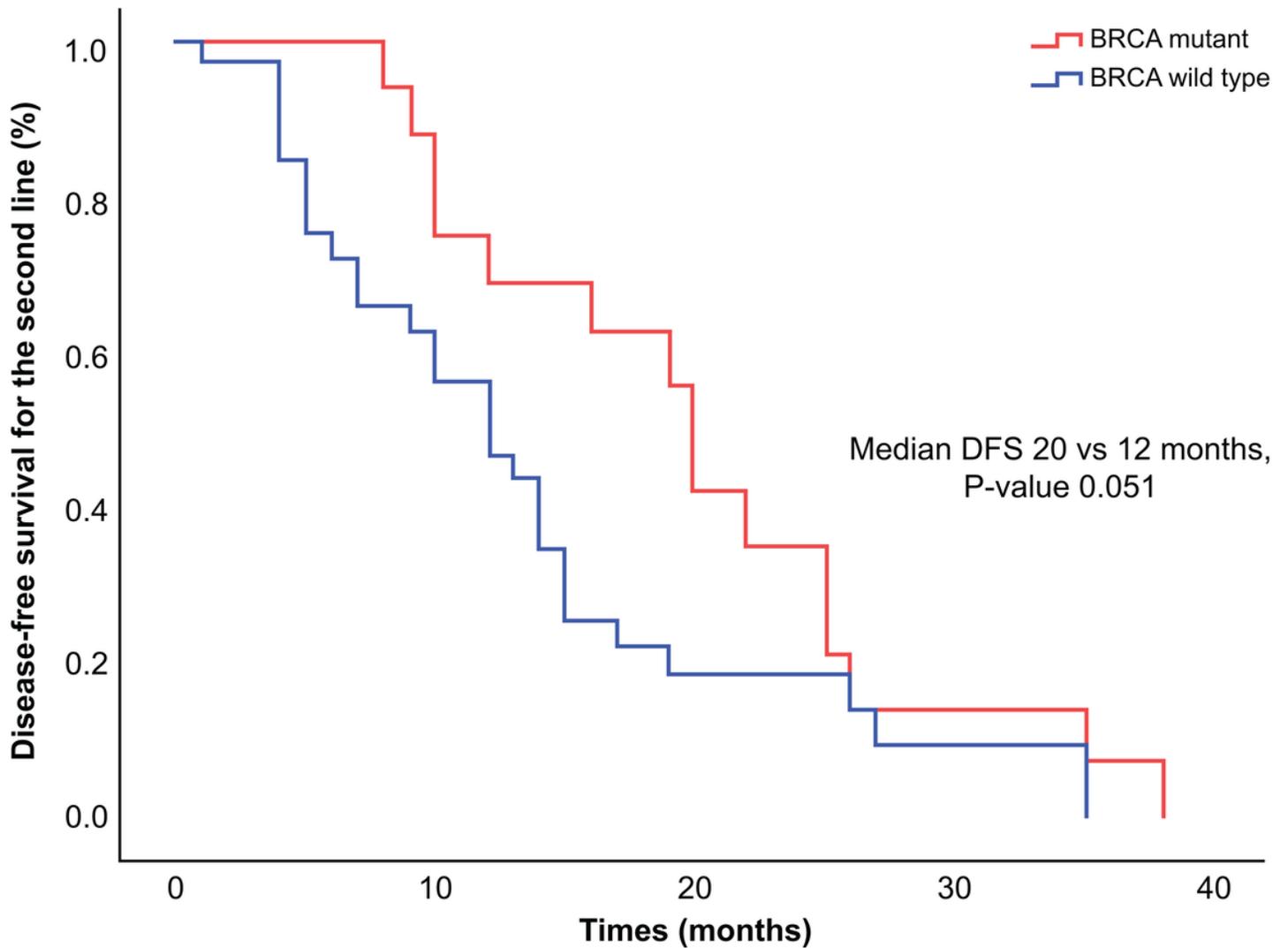


Figure 2

Disease-free survival of ovarian cancer stratified by BRCA status for second-line therapy. The Kaplan–Meier estimator was used to determine DFS for second line therapy among patients with germline BRCA mutation and those without germline BRCA. Two sided P values were calculated with the use of the stratified log rank test and CI denotes confidence interval. The median DFS of second-line treatment (50 patients) in the BRCA mutant group was 20 months (95% CI: 18.2–21.7) vs. 12 months (95% CI: 7.8–16.1) in the wild-type group (p = 0.051)

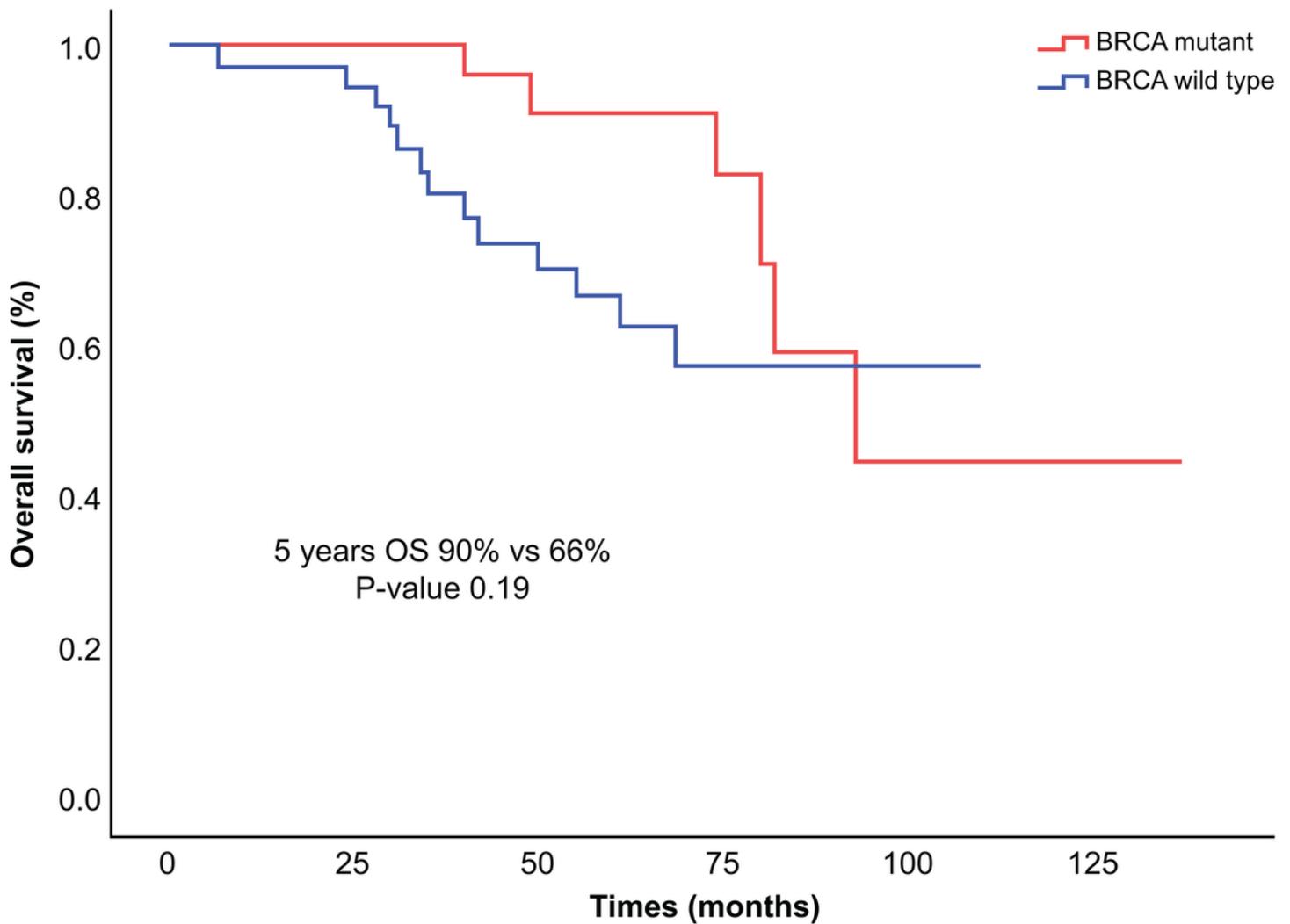


Figure 3

Five-year overall survival of ovarian cancer stratified by BRCA status. The Kaplan–Meier estimator was used to determine OS among patients with germline BRCA mutation and those without germline BRCA mutation. Two sided P values were calculated with the use of the stratified log rank test and CI denotes confidence interval. The median OS was not reached. However, the five-year OS rate for BRCA mutant patients was 90.9% vs. 66.7% for wild-type patients ($p = 0.19$)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FCSTROBEchecklistv4combined.docx](#)