RESEARCH ARTICLE

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The Impact of *BRCA1* Expression on Survival Status in Ovarian Serous Carcinoma of Egyptian Patients

Nancy H. Amin[1]*, Bassant A. Ahmed[1], Amany A. Abou-Bakr[1], Saad Sayed Eissa[1], Hanan R Nassar[2], Mai Gad[1], Mohab Eissa[1]

Abstract

Objectives: The present study aimed to investigate the impact of *BRCA1* protein expression on the patients' outcome of ovarian serous carcinoma, and its correlation with different clinicopathologic features. **Methods:** Immunohistochemistry with *BRCA1* was done for 80 cases of ovarian serous carcinoma that had a positive family history. Correlation with clinico-pathologic variables and patients' outcomes was investigated. **Results:** *BRCA1* expression was detected in 61.2% of the studied cases. A significant relation with patients' age, tumor grade and tumor stage was found (P<0.05). Also, there was a significant decrease in disease free survival (DFS) & overall survival (OS) in the positive *BRCA1* group. Metastasis, recurrence, residual disease, and mortality rate showed significantly higher figures in patient with *BRCA1* expression (P<0.05). **Conclusion:** Positive *BRCA1* expression had proven to be associated with advanced stage & grade of tumors, as well as worsened prognostic survival parameters (metastasis, recurrence, residual disease, and mortality) in patients with ovarian serous carcinoma.

Keywords: *BRCA1*- genomic instability- ovarian serous carcinoma

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Introduction

The carcinoma of ovaries is ranked as the 7th most common cause of mortality among other malignancies and is 6th most commonly occurring carcinoma among other cancers (Kerio et al., 2022). Ovarian cancer has one of the highest death-to-incidence ratios and is considered the deadliest of gynecologic malignancies (Bradbury et al., 2021).

In the Middle East Cancer Consortium (MECC) nations, epithelial ovarian carcinoma is the leading cause of mortality for females with pelvic malignancies (Charitini and Komodiki, 2015). Two-thirds of ovarian cancer mortality is attributed to high-grade serous carcinoma. The Federation of Gynecology and Obstetrics (FIGO)'s highest age at diagnosis and surgery and the presence of co-morbidity are among the most important predictors of high mortality in ovarian cancer (Ørskov et al., 2016). In 2018, 184,799 deaths occurred due to ovarian cancer, accounting for 4.4% of the entire cancer-related mortality among women. Based on Globocan 2018, the age-standardized rates (ASR) of ovarian cancer mortality were 3.9 (Bray et al., 2018). In Egypt, ovarian cancer is the second female cancer. According to the most recent Egyptian National Cancer Institute (NCI) cancer registry, primary malignant ovarian tumors represent 1.82% of all primary malignant neoplasms, 32.58% of female genital tract malignancies, and 42.76% of all ovarian lesions. Malignant ovarian surface epithelial tumors account for 49.16% of all ovarian cancers, while serous carcinoma accounts for 46.38% (Mokhtar et al., 2016).

In contrast to other malignancies such as colorectal and cervical cancers, there is a plethora of substantial evidence concerning biomarkers for ovarian cancer risk detection (Hunn and Rodriguez, 2012). Due to the late presentation of most ovarian cancer cases, the lack of evidence on the early molecular or tissue biomarker changes associated with these tumors, and the relative inaccessibility of the ovary, it is challenging to identify women at elevated risk for the illness. Thus, risk identification is essentially based on the different epidemiologic factors as patients' age, family history and harboring genetic mutations (Momenimovahed et al., 2019). Carcinogenesis is a multistep process, and tumors commonly contain numerous mutations that regulate genome integrity, cell division, and cell death. The processes of DNA damage signaling, and DNA repair tightly regulate the integrity of the cellular genome. (Gorodetska et al., 2019).

Approximately, 10–15% of epithelial ovarian cancer (EOC) patients carry germline mutation in *BRCA1* or *BRCA2*. The prevalence of BRCA mutation varies among different EOC subtypes. It is highest in high grade serous subtype which was reported up to 20–25% (Manchana et al., 2019).

*[1]Department of Pathology, National Cancer Institute, Cairo University, Egypt. [2]Department of Medical Oncology, National Cancer Institute, Cairo University, Egypt. *For Correspondence: nancy.amin@nci.cu.edu.eg*

BRCA1 and *BRCA2* are tumor-suppressor genes encoding proteins that are essential for the repair of DNA double-strand breaks by homologous recombination (HR). Functional BRCA proteins are involved in the maintenance of genome stability. Cells that lack either *BRCA1* or *BRCA2* repair these lesions by alternative, more error-prone mechanisms (Stoppa-Lyonnet, 2016).

BRCA1 (17q21, chromosome 17: base pairs 43,044,294 to 43,125,482) is a 24-exon protein containing 1,863 amino acids. It comprises of several domains that are necessary for its many tasks (Pulukuri, et al., 2022). Exons 11 through 13 encode the primary portion of *BRCA1*, and mutations in these areas are often identified in breast cancer patients (Gorodetska et al., 2019).

The majority of *BRCA1* gene mutations are frame shift insertions/deletions, non-synonymous truncations, and splicing site disruptions that result in missense mutations or production of non-functional proteins. In general, mutations in the *BRCA1* gene increase the risk of developing several forms of cancer, including breast and ovarian cancer in females, male breast cancer, and prostate cancer. In addition, *BRCA1* mutation carriers may be at increased risk for developing other forms of cancer, such as colon, rectal, pancreatic, and stomach cancer (Sharma et al., 2018).

Although the risk of ovarian cancer in carriers of *BRCA1* and *BRCA2* mutations is less than 3% by the age of 40, this risk increases to 10% by the age of 50. The 10-year risk of developing ovarian cancer in individuals with breast cancer is 12.7% and 6.8% in the carriers of *BRCA1* and *BRCA2* mutation (Andrews and Mutch, 2017). Cumulative risk of ovarian cancer up to the age of 80 is 49% in *BRCA1* mutation carriers and 21% in *BRCA2* mutation carriers (Kotsopoulos et al., 2018).

Materials and Methods

This retrospective study was carried out on eighty cases of Egyptian women patients diagnosed as ovarian serous carcinoma. All patients have a positive family history of breast/ovarian cancer. To avoid false results as a consequence of using biopsy material, we used the whole tumor tissue sections of ovariectomy/Panhysterectomy. Cases were retrieved from the Pathology Department, National Cancer Institute (NCI), Cairo University, throughout the period from January 2014 to December 2018. Follow up time was up to seven years. Most of the included patients (95%) received neoadjuvant/adjuvant chemotherapy.

Microscopic review of the cases for confirming the diagnosis and tumor grading were assessed according to World Health Organization (WHO) Classification of Female Genital Tumors, Fifth Edition, 2020 (Cheung et al., 2020).

Pathologic stage was determined by examining the excised specimens, according to tumor-node-metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC), 8th edition (Cheung et al., 2020).

Immunohistochemistry (IHC)

Sections of 4 µm were cut from the paraffin-embedded tissues and placed onto positive charged slides. Standard immunostaining was done using BenchMark ULTRA (Ventana) autostainer according to the manufacturer's instruction. Primary monoclonal antibodies (ready-to-use) were used as follows: Rabbit monoclonal antibodies against *BRCA1* (287.17), Cat No (SC- 135732). All immunostaining slides had positive control sections for quality control prepared from human breast carcinoma tissue.

BRCA1 protein immunohistochemical analysis

The whole slide was examined by using the high-power field (x400) and the regions of greatest immunostaining were selected for evaluation. The cases were considered as positive (aberrant) for *BRCA1* expression when neoplastic cells revealed nuclear/cytoplasmic staining scored more than 10%, regardless of the intensity (Sirisabya et al, 2007; Lesnock et al, 2013; Shawky et al, 2014).

Statistical Methods

Data were analyzed using MedCalc ver. 20 (MedCalc, Ostend, Belgium). Numerical data was described as median or range or mean and standard deviation as appropriate, while qualitative data were described as number and percentage. Chi-square (Fisher's exact) test was used to examine the relation between qualitative variables as appropriate.

Survival analysis was done using Kaplan-Meier method. Comparison between two survival curves was done using log rank test. Multivariate analysis was done by regression model to test for independent prognostic effect with calculating hazard ratio and its 95% confidence interval. Bonferonni corrections of p-value were done to avoid hyperinflation of type 1 error which arises from multiple testing. A p-value less than or equal to 0.05 was considered statistically significant. All tests were two tailed. The ROC Curve (receiver operating characteristic) was used to evaluate the sensitivity and specificity for quantitative diagnostic measures.

Results

Clinicopathological findings

Detailed clinical and pathologic features are shown in Table 1. Follow up time was up to 84 months. For the whole group, the mean disease-free survival (DFS) time was 14.7 months (range; 1 – 60) and the mean overall survival (OS) time was 23.5 months (range; 1 – 84), with (45%) of patients had metastasis, (32.5%) had recurrence, (43.7%) had residual disease, and (36.2%) died.

Expression of BRCA1 protein and its correlation with clinicopathologic characteristics

The 80 patients were classified according to *BRCA1* expression into 2 independent groups: negative *BRCA1* group (31 patients; 38.8%) and positive *BRCA1* group (49 patients; 61.2%). Representative examples of OC cases with expression of *BRCA1* are shown in Figures 1and 2.

Comparative studies as regards basic clinical data using Mann-Whitney's U and Chi square tests are shown in table 2. There is a highly significant increase in age,

Table 1. Clinicopathologic Characteristics of the Studied Cases (no. =80).

Variables		Frequency (%) / Mean ± SD
Age (years)		56 ± 9.9
Laterality	Bilateral	55 (68.7%)
	Lt	14 (17.5%)
	Rt	11 (13.8%)
Presenting symptoms	Abdominal distension	1 (1.3%)
	Abdominal pain	14 (17.5%)
	Bleeding	5 (6.2%)
	Pelvi-abdominal mass	60 (75%)
CA125	High	78 (97.5%)
Stage	1A	5 (6.2%)
	1B	3 (3.7%)
	1C	8 (10%)
	2A	5 (6.2%)
	2B	1 (1.3%)
	3A	15 (18.8%)
	3B	15 (18.8%)
	3C	25 (31.2%)
	4A	2 (2.5%)
	4B	1 (1.3%)
Grade of tumor	Low grade serous carcinoma	30 (37.5%)
	High grade serous carcinoma	50 (62.5%)
Regional LNs	positive	24 (30%)
	negative	56 (70%)
Operation done	Extended radical hysterectomy	1 (1.3%)
	Ovarian cystectomy	10 (12.6%)
	Pan-Hysterectomy	69 (86.2%)
Chemotherapy	None	4 (5%)
	Taxol/carbo	76 (95%)
Type of chemotherapy	None	4 (5%)
	Adjuvant	45 (56.2%)
	Neoadjuvant	26 (32.5%)
	Neoadjuvant/Adjuvant	5 (6.2%)

in positive *BRCA1* group; compared to negative *BRCA1* group ($p < 0.0001$) while a non-significant difference as regards all the remaining basic clinical data (history of breast cancer, laterality, presenting symptoms and CA125 level) ($p > 0.05$) was found. A significant correlation was detected with higher stage and grade of tumor, in positive *BRCA1* group; compared to negative *BRCA1* group ($p < 0.05$) but there was a non-significant correlation with LN status ($p > 0.05$).

Association of BRCA1 with OS and DFS

A significant decrease in DFS, and OS was noted, in positive *BRCA1* group; compared to negative *BRCA1* group ($p < 0.01$). Also, a significant increase in metastasis, recurrence, residual disease and mortality rate, in positive *BRCA1* group compared to negative *BRCA1* group ($p < 0.05$) was found (Table 3, Figure 4). Table 4 shows that the mean survival time was markedly decreased in *BRCA1* positive group compared to *BRCA1*

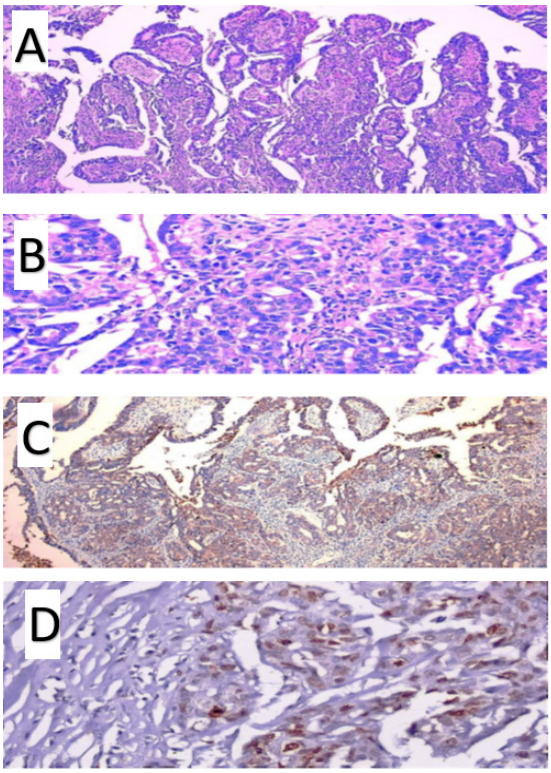

Figure 1. A & B Hematoxylin and Eosin Images of a Case of Low-Grade Serous Carcinoma (x100 & x400 respectively). C & D Immunostained images for BRCA1 showing cytoplasmic & nuclear reaction (x100 & x400, respectively)

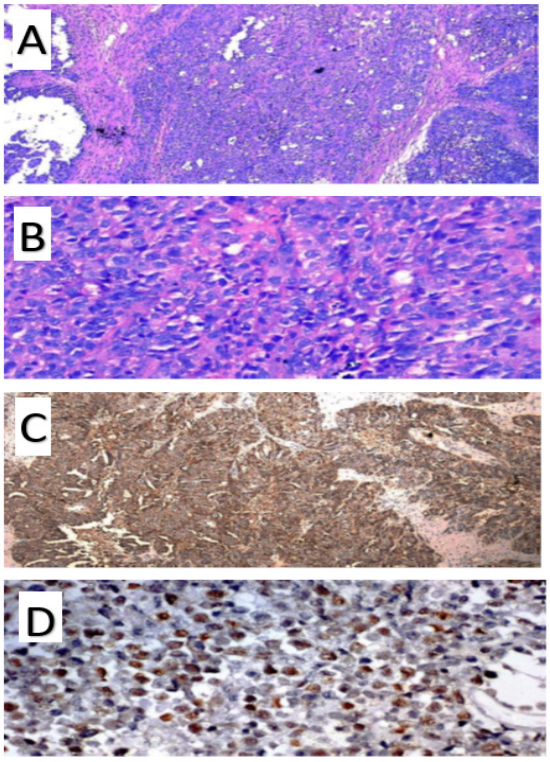

Figure 2. A & B Hematoxylin and Eosin images of a case of high-grade serous carcinoma (x100 & x400 respectively). C & D Immunostained images for BRCA1 showing strong nuclear and cytoplasmic reaction (x100 & x400, respectively)

Table 2. The Relation between *BRCA 1* and Clinico-Pathological Variables

Variable		Negative BRCA1 group (31)	Positive BRCA1 group (49)	Mann-Whitney's U test
		Median (IQR)	Median (IQR)	P value
Age (years)		47 (45 – 50)	61 (57 – 66)	< 0.0001
Laterality	Bilateral	21 (67.7%)	34 (69.4%)	0.873
	Lt	5 (16.1%)	9 (18.4%)	
	Rt	5 (16.1%)	6 (12.2%)	
Presenting symptoms	Abdominal distension	0 (0%)	1 (2%)	0.472
	Abdominal pain	4 (12.9%)	10 (20.4%)	
	Bleeding	1 (3.2%)	4 (8.2%)	
	Pelviabdominal mass	26 (83.9%)	34 (69.4%)	
CA125	High	31 (100%)	47 (95.9%)	0.257
Total LNs		0 (0 – 1)	0 (0 – 4)	0.8216
Stage	1A	4 (12.9%)	1 (2%)	0.046
	1B	0 (0%)	3 (6.1%)	
	1C	3 (9.7%)	5 (10.2%)	
	2A	0 (0%)	5 (10.2%)	
	2B	0 (0%)	1 (2%)	
	3A	3 (9.7%)	12 (24.5%)	
	3B	6 (19.4%)	9 (18.4%)	
	3C	13 (41.9%)	12 (24.5%)	
	4A	2 (6.5%)	0 (0%)	
	4B	0 (0%)	1 (2%)	
Grade of tumor	Low grade serous carcinoma	16 (51.6%)	14 (28.6%)	0.039
	High grade serous carcinoma	15 (48.4%)	35 (71.4%)	
Positive LNs		9 (29%)	15 (30.6%)	0.881
Operation done	Extended radical hysterectomy	0 (0%)	1 (2%)	0.507
	Ovarian cystectomy	3 (9.7%)	6 (12.2%)	
	Pan-Hysterectomy	27 (87.1%)	42 (85.7%)	
	Segmental resection	1 (3.2%)	0 (0%)	
Chemotherapy	None	2 (6.5%)	2 (4.1%)	0.637
	Taxol/carbo	29 (93.5%)	47 (95.9%)	
Type of chemotherapy	None	2 (6.5%)	2 (4.1%)	0.221
	Adjuvant	13 (41.9%)	32 (65.3%)	
	Neoadjuvant	13 (41.9%)	13 (26.5%)	
	Neoadjuvant/Adjuvant	3 (9.7%)	2 (4.1%)	

negative group.

Multiple regression analysis showed that the decrease in tumor stage had an independent effect on increasing DFS; with significant statistical difference (p = 0.015) as well as the chemotherapy treatment had an independent effect on increasing OS; with significant statistical difference (p = 0.0014).

Discussion

This study explores the prevalence of *BRCA 1* mutation in a cohort of ovarian serous carcinoma from Egyptian patients that had a family history of breast/ovarian cancer, and correlating the *BRCA1* status with the clinical outcome, and comparing the findings with the incidence of expression in other parts of the world.

Different studies have reported different results about the status of *BRCA1* expression in epithelial ovarian cancer (EOC). In our study, about two thirds of the patients (49/80; 60.2%) had positive *BRCA1* expression. In concordance with our results, Singer et al., (2019) investigated the prevalence of germline BRCA mutations in a population-based cohort of Austrian women diagnosed with ovarian cancer and its association with family history of cancer. They prospectively collected family pedigrees of 443 Austrian ovarian cancer patients who had been tested for the presence of a germline *BRCA1* or 2 mutations and correlated the familial breast and ovarian

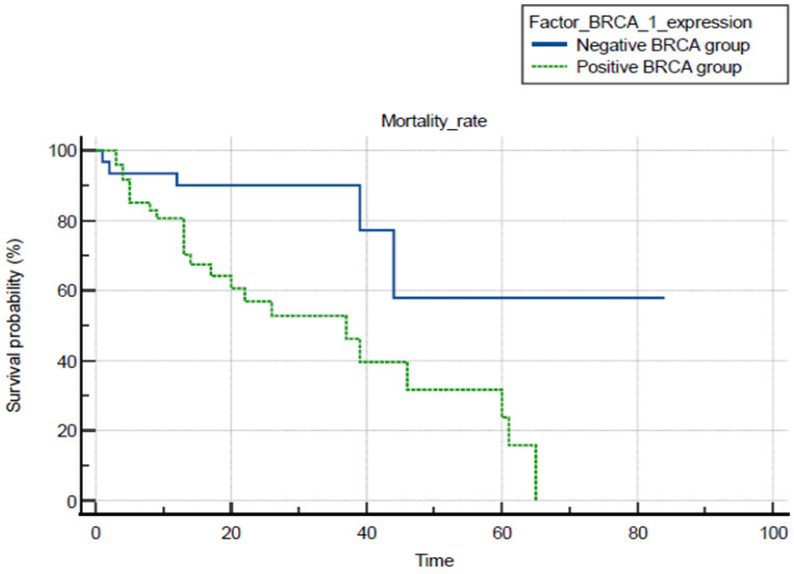

Figure 3. Kaplan-Meier Survival Curve of the Two Groups as Regards Mortality Rate

Table 3. The Relation between *BRCA1* and Patients' Outcome as well as Survival Parameters

Variable		Negative BRCA1 group	Positive BRCA1 group	Mann-Whitney's U test
		31	49	
		Median (IQR)	Median (IQR)	P value
DFS		16.5 (11 – 24)	10 (5.2 – 14.7)	0.005
OS		26 (18.5 – 37.7)	14 (8.7 – 27.7)	0.009
Variable		Negative BRCA group	Positive BRCA group	Chi square test
		-31	-49	P value
Metastasis	+ve	5 (16.1%)	31 (63.3%)	< 0.0001
Recurrence	+ve	1 (3.2%)	25 (51%)	< 0.0001
Residual disease	+ve	6 (19.4%)	29 (59.2%)	0.0005
Mortality rate	+ve	5 (16.1%)	24 (49%)	0.003

cancer burden with the prevalence of BRCA mutations and disease onset. The probability of carrying a gBRCA mutation in patients without family history of cancer is 14% (95% CI 9%-22%), as opposed to 45% (95% CI 31%-59%) of patients with at least one family member with ovarian cancer, and 47% (95% CI 40%-54%) if other relatives have developed breast cancer. If both breast and ovarian cancer are diagnosed in the family, the probability of carrying a germline *BRCA1BRCA1* or 2 mutations is 60% (95% CI 50%-68%). They concluded that the rate of germline *BRCA1* or 2 mutations in ovarian cancer patients without a family history or breast or ovarian cancer is low. However, in women with additional family members affected, the prevalence is considerably higher than previously reported (singer et al., 2019).

Table 4. The Relation between *BRCA 1* and Mean Survival Time

Factor	Mean	SE	95% CI for the mean
Group *BRCA1* negative	62.6	8.6	45.7 to 79.5
Group *BRCA1* positive	34.4	4.1	26.2 to 42.6
Overall	43.9	4.3	
Log-rank test	P = 0.004		

Also, another study by Harter et al., 2017 reported a rate of 21% (109/523) in patients with first diagnosis or relapsed disease, and 43% in patients have a positive family history. While the prevalence of *BRCA1*/2 germline mutation in a selected cohort of high-risk Middle Eastern population (early onset and history of familial ovarian cancer) revealed that *BRCA1*/2 contribute to 20.5% (24/117) in EOC using targeted capture sequencing analysis (Siraj et al., 2017). Upon expanding this cohort to include unselected series of additional 290 Saudi patients with invasive epithelial cancer they estimated the prevalence of *BRCA1*/2 germline mutation among unselected EOC to be 12.3% (50/407). Eighty-seven percent of these *BRCA1*/*BRCA2* germline mutations are found in women diagnosed with serous tumor (Siraj et al., 2019).

In a study done by Hjortkjær et al., (2019) on Danish population-based epithelial ovarian carcinoma cohort, 70% of patients with epithelial ovarian carcinoma carried a germline mutation in *BRCA1*/*BRCA2* genes. A population-based study of 209 women with invasive OC treated in the Tampa Bay area found that 32 patients (15.3%) had

mutations in *BRCA1* or 2 (Pat et al., 2005).

A large Kin-cohort study conducted in Ontario in 977 patients with invasive OC observed a similarly high total mutation frequency for *BRCA1* and 2, which was 13.2% (Risch et al., 2006). In contrast, a population-based Danish study of 445 confirmed OC cases in which both DNA sequencing and MLPA analysis were conducted to analyze both *BRCA1* and 2 genes for coding sequence mutations and large genomic rearrangements detected deleterious mutation in only 5.8% OC cases (Soegaard et al., 2008).

The difference in mutation prevalence that observed in previous studies may be due to different selection criteria used in each study. The prevalence of mutations is also thought to be highly dependent on ethnicity and familial burden. Comparative study between the *BRCA1* positive and *BRCA1* negative groups in our population revealed highly significant increase in age ($p < 0.0001$) as well as tumor stage and tumor grade ($p < 0.05$) in *BRCA1* positive group compared to *BRCA1* negative group. Which was similar to the findings of Manchana et al., 2020. Kalachand et al., (2020) revealed that, *BRCA1*/2 mutations were found to be significantly associated with stage III/IV disease (P=0.03). While in a study by Shawky et al., (2014) revealed that no significant association between *BRCA1* expression and tumor grade or stage in OC patients.

Hodgson and Turashvili, (2020) concluded that, for tubo-ovarian cancer, an approach driven by histological tumor features has been adopted in a number of institutions given the strong association between high-grade serous morphology and *BRCA1* mutations. It is generally recommended that every tubo-ovarian/primary high-grade serous carcinoma be tested for at least somatic *BRCA1*/2 gene mutations.

The present study revealed a non-significant difference as regards treatment data ($p > 0.05$), same as reported by Manchana et al., (2020). Regarding outcome and survival, our study revealed the cases with positive *BRCA1* expression are significantly associated with worse OS and DFS in OC patients (34%, 95% CI 26.2% to 42.6%, P=0.004), independent of all studied prognostic factors.

The same results were reported by Evans et al., (2009) large study that done on a cohort of 3532 women at increased risk of ovarian cancer was screened at five European centers between 1991 and 2007. Five year and 10-year survival in *BRCA1*/2 mutation carriers was 58.6% (95% CI 50.9% to 66.3%) and 36% (95% CI 27% to 45%), which was significantly worse than for non-BRCA carriers (91.8%, 95% CI 84% to 99.6%, both 5- and 10-year survival p=0.015). In contrast, Kalachand et al., 2020 revealed that patients with *BRCA1*/2-mutated tumors showed a trend toward improved DFS as compared to those with *BRCA1*/2-intact tumors (median survival: 17 vs. 6 months [HR, 0.48;95% CI, 0.22–1.06; P=0.07] and 20 vs. 11 months [HR, 0.53;95% CI, 0.26–1.09; P=0.08], respectively). Overall survival is significantly improved in patients with *BRCA1*/2-mutated tumors (median survival of 39 months) as compared to that in patients with *BRCA1*/2-intact disease (median survival of 26 months) (HR, 0.44; 95% CI, 0.19–0.99; P=0.045).

The study done by Hjortkjær et al., (2019) showed the BRCAness phenotype was associated with improved overall survival in the high-grade serous carcinoma subgroup with a median overall survival of 4.4 years (95% CI 3.0 to 5.3) versus 2.2 years (95% CI 1.9 to 2.4) in BRCA wildtype, p=0.0002. Multivariate analysis confirmed an independent prognostic value of the BRCAness phenotype among the high-grade serous carcinoma subgroup, hazard ratio 0.65 (95% CI 0.47 to 0.92), p=0.014. Omole et al., (2022), stated that BRCA is an ovarian cancer predisposition gene that has been shown to have prognostic significance. They found a relationship between BRCA expression and patient outcomes.

However, Shawky et al., (2014) and Manchana et al., (2020) reported that there was no significant difference in disease free survival (DFS) and overall survival (OS) between BRCA immunohistochemically positive and negative patients.

A study by Kotsopoulos et al., (2016) confirms that the most important predictor of long-term survival is the absence of any residual tumor following primary debulking surgery, irrespective of other tumor characteristics. Despite a short-term survival advantage among *BRCA2* mutation carriers likely due to higher initial sensitivity to chemotherapy, BRCA mutation status does not confer a benefit for long-term survival.

Many studies stated the importance of the implementation of BRCA testing in the management and treatment pathways of ovarian cancer patients and their relatives. The identification of *BRCA1*/2 pathogenic variants have therapeutic implications in addition to cancer risk assessment. BRCA status allow to obtain the information to improve the outcome of medical treatments to promote specific strategies of risk reduction and finally to improve the survival of ovarian cancer patients and the incidence of the disease in the population (Eccleston et al., 2017; Gori et al., 2019; Wang et al., 2022).

A study by Menghi et al., (2022) also demonstrated a relationship between *BRCA1* expression and survival after chemotherapy treatment: patients with lower expression levels had a better response to platinum-based therapy whereas patients with higher expression responded better to taxanes and the overall survival rates for patients with higher *BRCA1* expression increased in the group chemotherapeutically treated with taxanes. *BRCA1* induces over 1,000-fold sensitivity to chemical factors that cause damage to the mitotic spindle.

In conclusion, *BRCA1* mutation was found in a relatively large number of ovarian serous carcinoma patients that had positive family history. Also, *BRCA1* expression had proven to be associated with advanced stage and high tumor grade as well as worsened prognostic survival parameters. So, incorporating genetic testing into cancer screening programs allows early detection and risk-reducing measures to be targeted to those at greatest risk. We also concluded that the initial survival advantage among women with BRCA mutations that reported in many studies may reflect a higher initial sensitivity of *BRCA* carriers to chemotherapy, but this response does not necessarily predict long-term survival.

Author Contribution Statement

All authors contributed to this study. Preparation, data collection, review of the slides and analysis were performed by Dr Nancy H. Amin. Monitoring of data collection, interpretation of results, revision and guidance were done by Dr Saad Eissa, Dr Amany A. Abou-Bakr, Dr Mai Gad, Dr Hanan R Nassar and Dr Mohab Eissa. The preliminary draft of the manuscript was written by Dr Nancy H. Amin and Dr. Bassant A. Ahmed. All authors revised and commented on primary version of the manuscript and approved the final one. Dr. Mohab Eissa helped in data analysis and revision of results..

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Ethical approval

The study was approved by the Institutional Review Board (IRB) no. IRB2206-306-012 of National Cancer Institute (NCI), Cairo University. Oral and written informed consents were obtained from all patients or from their eligible relatives.

Availability of data

The datasets are available from the corresponding author on reasonable request.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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