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ORIGINAL RESEARCH

Association Between Germline *BRCA1/2* Gene Variants and Clinicopathological Features of Ovarian Cancer

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Objective: To investigate the relationship between *BRCA1/2* gene mutation and clinicopathological features in ovarian cancer patients, so as to develop precise individualized treatment plan for patients.

Methods: Patients diagnosed with ovarian cancer between January 2018 and July 2023 who underwent *BRCA1/2* genetic testing were retrospectively analyzed. The clinicopathological characteristics (age, body mass index (BMI), family history of ovarian cancer, pregnancy history, menopause status, tumor size, histopathology, Federation of Gynecology and Obstetrics (FIGO) staging, and ascites) of non-carriers and *BRCA1/2* variant carriers were compared. Logistic regression analysis was used to explore the relationship between *BRCA1/2* variants and clinicopathological characteristics of ovarian cancer.

Results: A total of 284 ovarian cancer patients were collected, and the subjects were divided into two groups, 197 non-carriers and 87 *BRCA1/2* variants carriers. The proportion of serous ovarian carcinoma in *BRCA1/2* variant carriers is higher than that in non-*BRCA* variant carriers (78.2% vs 60.9%, p=0.015). There were 51 patients with *BRCA* pathogenic or likely pathogenic variant, 22 patients with *BRCA* likely benign variant, and 14 patients with *BRCA* variants of uncertain significance (VUS). The proportion of serous ovarian carcinoma in patients with *BRCA* pathogenic/likely pathogenic variant is higher than that in patients with *BRCA* likely benign variant and *BRCA* VUS (94.1% vs 50.0% and 64.3%. p<0.001). There were no statistically significant differences in BMI, family history of ovarian cancer, pregnancy history, menopause status, maximum diameter of the tumor lesion, FIGO stage, and ascites among patients with different grades of variants. Multivariate logistic regression analysis showed that serous ovarian carcinoma was related to *BRCA* mutation (Serous carcinoma vs non-serous carcinoma: OR 2.145, 95% CI: 1.044–4.407) (p=0.038).

Conclusion: Patients with *BRCA1* variant develop ovarian cancer at a younger age than those with the *BRCA2* variant. The proportion of FIGO stage III–IV in patients with *BRCA* pathogenic + likely pathogenic variant was significantly higher than those in patients with other variants. Germline *BRCA1/2* variants were most frequently identified in serous ovarian carcinoma patients.

Keywords: ovarian cancer, *BRCA1*, *BRCA2*, clinicopathological characteristics

Background

Ovarian cancer is one of the most common gynecological cancers worldwide. According to global cancer statistics, ovarian cancer makes up 1.6% of all new cancer cases, accounting for 2.1% of all cancer deaths in 2020.[1] Ovarian cancer was the eighth most common causes of cancer-associated death among women, accounting for 4.7% of female mortality rates worldwide.[1] In China, an estimated 45,000 new cases and almost 29,000 deaths of ovarian cancer occurred in 2019, and the burden of ovarian cancer increased in women over 40 years old, especially in postmenopausal women.[2] Ovarian cancer burden in China is expected to continue to rise with a higher rate than the global level in the next decade.[2] Due to the lack of disease-specific symptoms in ovarian cancer, most patients are diagnosed at advanced stages, giving rise to a greatly increased risk of cancer metastasis and

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early mortality.[3,4] Although advances are being made, ovarian cancer remains the most fatal female gynecologic cancer, so that further research into the characteristics of these patients should be performed for early control.

The symptoms of ovarian cancer are non-specific compared with other female cancers that have early warning symptoms.[5] Therefore, it is very important to effectively judge the disease development status and severity of ovarian cancer through some predictable indicators. Various risk factors are described to be associated with ovarian cancer, including older age, genetics, family history, nulliparity, and so on.[6] Studies have shown that more than 20% of ovarian cancer have a genetic susceptibility, and about 70% of these genetic abnormalities are germline mutations in the breast cancer susceptibility gene, *BRCA* gene.[7] Breast cancer susceptibility gene 1 (*BRCA1*) and breast cancer susceptibility gene 2 (*BRCA2*) are two distinct tumor suppressor genes, which play an integral role in response to cellular stress via the activation of DNA repair processes.[8–10] *BRCA1* gene is located on chromosome 17q21, including 24 exons that encodes 1863 amino acids.[11] BRCA1 has two tandem repeat C-terminal domain of BRCA1 (BRCT) domains at the C terminus, including BRCT1 and BRCT2, which are important signaling and protein targeting domains in the DNA damage repair system and are closely related to the important functions of BRCA1.[12,13] *BRCA2* gene is localized at 13q12-13 with 27 exons and encodes 3418 amino acids.[13,14] The C terminal of BRCA2 protein contains five domains, and studies have shown that missense mutations involved in tumorigenesis mainly occur in these five domains in the C terminus of the BRCA2 protein, which play a key role in tumor suppressor function.[15] Carriers of mutations in the *BRCA1* and *BRCA2* genes have an increased risk of ovarian cancer.[16–18] In addition, some studies have found that the *BRCA1/2* germline mutations are associated with prognosis of ovarian cancer.[19,20]

Few studies have reported the correlation between *BRCA* gene mutations and clinicopathological features of ovarian cancer.[5,21,22] However, another study has found no correlation of them.[23] It is unclear whether *BRCA* gene mutations are associated with clinicopathological features in ovarian cancer patients, and whether they can guide treatment and early prevention. Therefore, this article explores the clinical and pathologic characteristics, menstruation, and reproductive conditions in germline *BRCA1/2* variant carriers, which helps to better understand the tumor characteristics of patients with germline *BRCA1/2* variants in the patients with ovarian cancer.

Materials and Methods

Participants

We conducted a retrospective analysis of 284 ovarian cancer patients from our institute who were tested for *BRCA1/2* gene mutations between January 2018 and July 2023. The inclusion criteria were as follows: (1) patients diagnosed with ovarian cancer; (2) undergoing *BRCA* gene testing; and (3) complete clinical data. Exclusion criteria: the genetic test result was of uncertain significance. The clinicopathological and demographic data extracted from the medical records of the patients, including age, body mass index (BMI) of patients, family history of ovarian cancer, pregnancy history, menopause status, maximum diameter of the tumor lesion, histopathology, Federation of Gynecology and Obstetrics (FIGO) staging, and whether the patient is accompanied by ascites. This study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital, Meizhou Academy of Medical Sciences. All participants signed informed consent in accordance with the Declaration of Helsinki.

BRCA1/2 Testing

Approximately 2 mL of peripheral blood was collected in a tube containing EDTA, and genomic DNA was extracted according to the QIAamp DNA Blood Mini Kit instructions (Qiagen, Germany). The genomic DNA samples were sent to CapitalBio (Beijing, China) and subjected to next-generation sequencing on the Ion Proton instrument (Life Technologies). All procedures were performed according to the standard operating procedures of the Life Technology Company. The sequencing results were compared with the *BRCA1* (NM_007294.3) and *BRCA2* (NM_000059.3) reference sequences for variant detection. According to the Human Genome Variation Society (HGVS) guidelines, there are five grades of variants: pathogenic variants, likely pathogenic variants, variants of uncertain significance (VUS), likely benign variants, and benign variants.[13]

This study divided ovarian cancer patients who had been tested for *BRCA1/2* gene variants into two groups: (1) *BRCA1/2* variant/variants carriers, (2) non-*BRCA1/2* variant/variants carriers. The demographic data and clinicopathological characteristics of the two groups of patients were tabulated, and the two groups of patients were compared.

Statistical Analysis

SPSS statistical software version 26.0 was used for data analysis. Qualitative variables were presented using frequencies and percentages (N, %). The χ^2 test or Fisher' s exact test was used to compare frequencies of qualitative variables. Univariate and multivariate logistic regression analyses were performed to evaluate the relationship between clinical and pathological parameters of ovarian cancer and *BRCA* mutation. Values of odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to measure the strength of the associations by logistic regression. All *p* values were two-sided, and $p<0.05$ was considered statistically significant.

Results

Clinical and Pathological Characteristics of Ovarian Cancer Patients

All clinical and pathological data of the 284 ovarian cancer patients are summarized in Table 1. There were 139 (48.9%) and 145 (51.1%) patients with <55 years old and ≥55 years old, respectively. Most of the patients were diagnosed after with pregnancy history (95.1%) or in a menopausal status (about 64.1%). The patients with maximum diameter of tumor

Table 1 Clinical Characteristics in *gBRCA1/2* Variant/Variants Carriers and Non-Carriers

Categories	Total (n=284)	Non-Carriers (n=197)	*BRCA1/2* Variant/Variants Carriers (n=87)	*p* value
Age (years)				
<55	139 (48.9%)	92 (46.7%)	47 (54.0%)	0.303
≥55	145 (51.1%)	105 (53.3%)	40 (46.0%)	
BMI				
18.5–23.9	156 (54.9%)	105 (53.3%)	51 (58.6%)	0.415
<18.5	31 (10.9%)	20 (10.2%)	11 (12.6%)	
≥24	97 (34.2%)	72 (36.5%)	25 (28.7%)	
Family history of ovarian cancer				
No	282 (99.3%)	196 (99.5%)	86 (98.9%)	0.520
Yes	2 (0.7%)	1 (0.5%)	1 (1.1%)	
Pregnancy history				
No	14 (4.9%)	9 (4.6%)	5 (5.7%)	0.767
Yes	270 (95.1%)	188 (95.4%)	82 (94.3%)	
Menopause				
No	102 (35.9%)	71 36.0%)	31 (35.6%)	1.000
Yes	182 (64.1%)	126 (64.0%)	56 (64.4%)	
Maximum diameter of the tumor lesion				
<5cm	57 (20.1%)	43 (21.8%)	14 (16.1%)	0.218
≥5cm	193 (68.0%)	133 (67.5%)	60 (69.0%)	
Unknown	34 (12.0%)	21 (10.7%)	13 (14.9%)	
Histological types				
Non-serous carcinoma	81 (28.5%)	64 (32.5%)	17 (19.5%)	0.015
Serous carcinoma	188 (66.2%)	120 (60.9%)	68 (78.2%)	
Unknown	15 (5.3%)	13 (6.6%)	2 (2.3%)	
FIGO stage				
I–II	79 (27.8%)	58 (29.4%)	21 (24.1%)	0.383
III–IV	184 (64.8%)	124 (62.9%)	60 (69.0%)	
Unknown	21 (7.4%)	15 (7.6%)	6 (6.9%)	
Ascites				
No	104 (36.6%)	72 (36.5%)	32 (36.8%)	1.000
Yes	180 (63.4%)	125 (63.5%)	55 (63.2%)	

Note: BMI, Body mass index; FIGO, The International Federation of Gynecology and Obstetrics.

lesion ≥ 5cm accounted for 68.0%. Most of the patients were diagnosed at stage III–IV (184/284, 64.8%), while 79 patients were diagnosed at stage I–II (79/284, 27.8%). There were 180 (63.4%) patients with ascites. The proportion of serous ovarian carcinoma in *BRCA1/2* variant carriers is higher than that in non-*BRCA* variant carriers (78.2% vs 60.9%, p=0.015). There were no statistically significant differences in age, BMI, family history of ovarian cancer, pregnancy history, menopause status, maximum diameter of the tumor lesion, FIGO stage, and ascites between non-*BRCA1/2* variant/variants carriers and *BRCA1/2* variant/variants carriers.

Comparison of the Clinical Characteristics of *BRCA* Variant Carriers According to Different Grades of Variants

In this study, there were 51 patients with *BRCA* pathogenic or likely pathogenic variant, 22 patients with *BRCA* likely benign variant, and 14 patients with *BRCA* VUS. The proportion of serous ovarian carcinoma in patients with *BRCA* pathogenic or likely pathogenic variant is higher than that in patients with *BRCA* likely benign variant and *BRCA* VUS (94.1% vs 50.0% and 64.3%. p<0.001). The proportion of FIGO stage III–IV in patients with *BRCA* pathogenic + likely pathogenic variant was significantly higher than those in patients carried *BRCA* likely benign variant and *BRCA* VUS (82.4% vs 54.5% and 42.9%. p=0.009). There were no statistically significant differences in BMI, family history of ovarian cancer, pregnancy history, menopause status, maximum diameter of the tumor lesion, and ascites among patients with different grades of variants (Table 2). In this study, 45 patients carried the *BRCA1* variant, 38 patients carried the *BRCA2* variant, and 4 patients carried both the *BRCA1* and *BRCA2* gene variants. The patients with *BRCA1* variant were younger than the patients with *BRCA2* variant, accounting for 66.7% (30/45) and 42.1% (16/38) in patients younger than 55 years, respectively. Patients with the *BRCA1* gene variant had a higher proportion of cases younger than 55 years of age than those with the *BRCA2* gene variant (p=0.021). The histological subtypes were classified into serous ovarian cancer and non-serous ovarian cancer. In the patients with *BRCA1* variant, the histological subtype was mainly serous ovarian carcinoma (91.1%) compared with patients with *BRCA2* variant (60.5%). There were no statistically significant

Table 2 Comparison of the Clinical Characteristics of *BRCA* Variant Carriers According to Different Grades of Variants

Categories	*BRCA* Pathogenic + Likely Pathogenic Variant (n=51)	*BRCA* Likely Benign Variant (n=22)	*BRCA* VUS (n=14)	*p* value	*BRCA1* Variant Carriers (n=45)	*BRCA2* Variant Carriers (n=38)	*p* value
Age (years)							
<55	25 (49.0%)	10 (45.5%)	12 (85.7%)	0.031	30 (66.7%)	16 (42.1%)	0.021
≥55	26 (51.0%)	12 (54.5%)	2 (14.3%)		15 (33.3%)	22 (57.9%)	
BMI							
18.5–23.9	29 (56.9%)	12 (54.5%)	10 (71.4%)	0.913	26 (57.8%)	24 (63.2%)	0.768
<18.5	7 (13.7%)	3 (13.6%)	1 (7.1%)		5 (11.1%)	5 (13.2%)	
≥24	15 (29.4%)	7 (31.8%)	3 (21.4%)		14 (31.1%)	9 (23.7%)	
Family history of ovarian cancer							
No	50 (98.0%)	22 (100.0%)	14 (100.0%)	1.000	44 (97.8%)	38 (100.0%)	1.000
Yes	1 (2.0%)	0 (0)	0 (0)		1 (2.2%)	0 (0)	
Pregnancy history							
No	2 (3.9%)	1 (4.5%0)	2 (14.3%)	0.341	3 (6.7%)	2 (5.3%)	1.000
Yes	49 (96.1%)	21 (95.5%)	12 (85.7%)		42 (93.3%)	36 (94.7%)	
Menopause							
No	18 (35.3%)	7 (31.8%)	6 (42.9%)	0.821	18 (40.0%)	12 (31.6%)	0.495
Yes	33 (64.7%)	15 (68.2%)	8 (57.1%)		27 (60.0%)	26 (68.4%)	

(*Continued*)

Table 2 (Continued).

Categories	*BRCA* Pathogenic + Likely Pathogenic Variant (n=51)	*BRCA* Likely Benign Variant (n=22)	*BRCA* VUS (n=14)	*p* value	*BRCA1* Variant Carriers (n=45)	*BRCA2* Variant Carriers (n=38)	*p* value
Maximum diameter of the tumor lesion							
<5cm	8 (15.7%)	4 (18.2%)	2 (14.3%)	1.000	8 (17.8%)	5 (13.2%)	0.556
≥5cm	34 (66.7%)	17 (77.3%)	9 (64.3%)		30 (66.7%)	28 (73.7%)	
Unknown	9 (17.6%)	1 (4.5%)	3 (21.4%)		7 (15.6%)	5 (13.2%)	
Histological types							
Non-serous carcinoma	2 (3.9%)	10 (45.5%)	5 (35.7%)	<0.001	4 (8.9%)	13 (34.2%)	0.005
Serous carcinoma	48 (94.1%)	11 (50.0%)	9 (64.3%)		41 (91.1%)	23 (60.5%)	
Unknown	1 (2.0%)	1 (4.5%)	0 (0)		0 (0)	2 (5.3%)	
FIGO stage							
I–II	7 (13.7%)	9 (40.9%)	5 (35.7%)	0.009	9 (20.0%)	12 (31.6%)	0.311
III–IV	42 (82.4%)	12 (54.5%)	6 (42.9%)		32 (71.1%)	24 (63.2%)	
Unknown	2 (3.9%)	1 (4.5%)	3 (21.4%)		4 (8.9%)	2 (5.3%)	
Ascites							
No	18 (35.3%)	8 (36.4%)	6 (42.9%)	0.907	16 (35.6%)	14 (36.8%)	1.000
Yes	33 (64.7%)	14 (63.6%)	8 (57.1%)		29 (64.4%)	24 (63.2%)	

Abbreviation: BMI, Body mass index; VOUS, variants of uncertain significance; FIGO, The International Federation of Gynecology and Obstetrics.

differences in BMI, family history of ovarian cancer, pregnancy history, menopause status, maximum diameter of the tumor lesion, FIGO stage, and ascites between patients with *BRCA1* variant and *BRCA2* variant (Table 2).

Comparison of the Clinical Characteristics of *BRCA* Variant Carriers According to Different Grades of Variants of *BRCA1* and *BRCA2*, Respectively

In the patients with *BRCA1* variant, the proportion of serous ovarian carcinoma in patients with pathogenic or likely pathogenic variant is higher than that in patients with likely benign variant and VUS (97.1% vs 60.0% and 87.5%. p=0.030). The proportion of III–IV stage in patients with pathogenic or likely pathogenic variant is higher than those in patients with likely benign variant and VUS (82.9% vs 60.0% and 37.5%. p=0.037). In the patients with *BRCA2* variant, patients with the *BRCA2* VUS had a higher proportion of cases younger than 55 years of age than those with other grades of *BRCA2* variants (p=0.046). The proportion of serous ovarian carcinoma in patients with pathogenic or likely pathogenic variant is higher than that in patients with likely benign variant and VUS (87.5% vs 47.1% and 33.3%. p=0.005). There were no statistically significant differences in BMI, family history of ovarian cancer, pregnancy history, menopause status, maximum diameter of the tumor lesion, FIGO stage, and ascites among patients with different grades of variants in *BRCA1* and *BRCA2*, respectively (Table 3).

Logistic Regression of Clinical Characteristics Related to *BRCA* Gene Variant in Ovarian Cancer

Logistic regression analysis was performed to determine which clinical features are associated with *BRCA* mutation. Univariate logistic regression showed that serous ovarian carcinoma was related to *BRCA* mutation (serous carcinoma vs non-serous carcinoma: odds ratio (OR) 2.133, 95% confidence interval (CI): 1.157–3.934) (p=0.015). Univariate logistic regression analysis showed no correlation between the other clinical characteristics and *BRCA* variant. Multivariate logistic regression analysis showed that serous ovarian carcinoma was related to *BRCA* mutation (serous carcinoma vs non-serous carcinoma: OR 2.145, 95% CI: 1.044–4.407) (p=0.038) (Table 4). That is to say, germline *BRCA1/2* variants were most frequently identified in serous ovarian carcinoma patients.

Table 3 Comparison of the Clinical Characteristics of *BRCA* Variant Carriers According to Different Grades of Variants of *BRCA1* and *BRCA2*, Respectively

Categories	*BRCA1* Pathogenic + Likely Pathogenic Variant (n=35)	*BRCA1* Likely Benign Variant (n=5)	*BRCA1* VUS (n=8)	*p* Value	*BRCA2* Pathogenic + Likely Pathogenic Variant (n=16)	*BRCA2* Likely Benign Variant (n=17)	*BRCA2* VUS (n=6)	*p* Value
Age (years)								
<55	21 (60.0%)	2 (40.0%)	7 (87.5%)	0.236	4 (25.0%)	8 (47.1%)	5 (83.3%)	0.046
≥55	14 (40.0%)	3 (60.0%)	1 (12.5%)		12 (75.0%)	9 (52.9%)	1 (16.7%)	
BMI								
18.5–23.9	16 (45.7%)	4 (80.0%)	6 (75.0%)	0.248	13 (81.3%)	8 (47.1%)	4 (66.7%)	0.155
<18.5	5 (14.3%)	1 (20.0%)	0 (0)		2 (12.5%)	2 (11.8%)	1 (16.7%)	
≥24	14 (40.0%)	0 (0)	2 (25.0%)		1 (6.3%)	7 (41.2%)	1 (16.7%)	
Family history of ovarian cancer								
No	34 (97.1%)	5 (100.0%)	8 (100.0%)	1.000	16 (100.0%)	17 (100.0%)	6 (100.0%)	–
Yes	1 (2.9%)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Pregnancy history								
No	1 (2.9%)	0 (0)	2 (25.0%)	0.093	1 (6.3%)	1 (5.9%)	0 (0)	1.000
Yes	34 (97.1%)	5 (100.0%)	6 (75.0%)		15 (93.8%)	16 (94.1%)	6 (100.0%)	
Menopause								
No	13 (37.1%)	3 (60.0%)	3 (37.5%)	0.640	5 (31.3%)	4 (23.5%)	3 (50.0%)	0.466
Yes	22 (62.9%)	2 (40.0%)	5 (62.5%)		11 (68.8%)	13 (76.5%)	3 (50.0%)	
Maximum diameter of the tumor lesion								
<5cm	8 (22.9%)	0 (0)	1 (12.5%)	0.691	0 (0)	4 (23.5%)	1 (16.7%)	0.195
≥5cm	22 (62.9%)	4 (80.0%)	5 (62.5%)		12 (75.0%)	13 (76.5%)	4 (66.7%)	
Unknown	5 (14.3%)	1 (20.0%)	2 (25.0%)		4 (25.0%)	0 (0)	1 (16.7%)	
Histological types								
Non-serous carcinoma	1 (2.9%)	2 (40.0%)	1 (12.5%)	0.030	1 (6.3%)	8 (47.1%)	4 (66.7%)	0.005
Serous carcinoma	34 (97.1%)	3 (60.0%)	7 (87.5%)		14 (87.5%)	8 (47.1%)	2 (33.3%)	
Unknown	0 (0)	0 (0)	0 (0)		1 (6.3%)	1 (5.9%)	0 (0)	
FIGO stage								
I–II	4 (11.4%)	2 (40.0%)	3 (37.5%)	0.037	3 (18.8%)	7 (41.2%)	2 (33.3%)	0.318
III–IV	29 (82.9%)	3 (60.0%)	3 (37.5%)		13 (81.3%)	9 (52.9%)	3 (50.0%)	
Unknown	2 (5.7%)	0 (0)	2 (25.0%)		0 (0)	1 (5.9%)	1 (16.7%)	
Ascites								
No	14 (40.0%)	1 (20.0%)	3 (37.5%)	0.887	4 (25.0%)	7 (41.2%)	3 (50.0%)	0.491
Yes	21 (60.0%)	4 (80.0%)	5 (62.5%)		12 (75.0%)	10 (58.8%)	3 (50.0%)	

Notes: BMI, body mass index; in this study, there were 51 patients with disease-causing and potentially disease-causing variants, 22 patients with potentially benign variants, and 14 patients with VOUS.US, variants of uncertain significance; FIGO, The International Federation of Gynecology and Obstetrics.

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Table 4 Multivariate Logistic Regression of Clinical Characteristics Related to *BRCA* Gene Variant in Ovarian Cancer

Clinical Characteristics		Univariate OR (95% CI)	*p* Values	Multivariate OR (95% CI)	*p* Values
Age (≥55 vs <55 years)		0.746(0.450–1.237)	0.256	0.627(0.344–1.144)	0.128
BMI					
	18.5–23	1.000(reference)		1.000(reference)	
	<18.5	1.132(0.505–2.541)	0.763	0.841(0.310–2.283)	0.734
	≥23.2	0.715(0.406–1.257)	0.244	0.927(0.481–1.788)	0.822
Family history of ovarian cancer (Yes vs No)		2.279(0.141–36.861)	0.562	1.551(0.092–26.179)	0.761
Pregnancy history (Yes vs No)		0.785(0.255–2.415)	0.673	0.699(0.177–2.757)	0.609
Menopause (Yes vs No)		1.018(0.601–1.723)	0.947	0.964(0.509–1.829)	0.911
Maximum diameter of the tumor lesion (≥5cm vs <5cm)		1.386(0.705–2.723)	0.344	1.585(0.760–3.304)	0.219
Histological types (Serous carcinoma vs Non-serous carcinoma)		2.133(1.157–3.934)	0.015	2.145(1.044–4.407)	0.038
FIGO stage (III–IV vs III–IV)		1.336(0.743–2.403)	0.333	1.313(0.665–2.595)	0.433
Ascites (Yes vs No)		0.990(0.587–1.671)	0.970	0.875(0.459–1.668)	0.684

Discussion

The risk of ovarian cancer in female lifetime is about 2% and is the leading cause of death from any gynecologic malignancy.[24] The prognosis of ovarian cancer remains relatively poor, especially in low-resource settings. Therefore, it is important to continuously examine the burden of ovarian cancer to identify domain differences.[25] Therefore, it is important to educate women and health care providers about the risk factors for ovarian cancer. However, the signs and symptoms of ovarian cancer historically have been nonspecific and vague. Studies have indicated that there have multiple environmental and genetic factors for ovarian cancer. The most intensively studied risk factors have been family history, pregnancy history, oral contraceptive use, menopause, body mass index (BMI), and number of pregnancies.[26–28]

Moreover, mutations of *BRCA1* and *BRCA2* are mainly associated with a genetic risk of ovarian cancer, and can increase the risk of ovarian cancer from 1.6% to 40% and 18%, respectively.[29,30] *BRCA1* and *BRCA2* are autosomal dominant genes that are the most studied genes among mutations associated with hereditary ovarian cancer syndrome.[11,31] Mutations in *BRCA1* and *BRCA2* account for hereditary breast and ovarian cancer syndrome in a majority of families and 14% of epithelial ovarian cancer cases.[32] Different populations may have different characteristics of *BRCA1/2* gene variants. Zhang et al found that the prevalence and spectrum of variants in *BRCA1/2* genes in the population which this study was conducted were different from those of other nationalities.[33] *BRCA1* and *BRCA2* are the tumor suppressor genes, and highly penetrating mutations in these genes result in a loss of tumor suppressor function and thus an increased risk of ovarian cancer.[34] Understanding whether the unique clinical and pathological features of ovarian cancer are associated with the *BRCA1/2* gene mutation is essential to mitigate prognosis differences in the female population.

As far as the current literature reports are concerned, the relationship between *BRCA* gene and ovarian cancer is mostly studied in the aspects of treatment effect, prognosis, and recurrence of ovarian cancer.[19,35] There is relatively little research on the relationship between *BRCA* germline variants and clinicopathological features of ovarian cancer patients. In this study, germline *BRCA1/2* variants were most frequently identified in serous ovarian carcinoma patients. Vera M Witjes et al showed that germline *BRCA1/2* pathogenic variants were most frequently identified in high-grade serous ovarian carcinoma patients.[36] A study from an Israeli population showed that *BRCA* variant carriers had a higher rate of serous cancer than non-carriers.[37] Patients with germline *BRCA* variants were frequently observed in ampulla type and FIGO I/II stage fallopian tube cancers in Japanese women.[22] In addition, the age of patients carried *BRCA* variant was significantly lower than that of *BRCA* wild-type patients.[38] *BRCA1/2* variants were significantly associated with age, family history, and FIGO stage, according to a study from China.[39] But this study did not get similar results. However, Li et al found no significant differences in age-of-onset, FIGO stage, pathological type, and family disease history between patients with *BRCA1/2* mutation and others.[40]

Ovarian serous carcinoma is the most common histological type of ovarian epithelial carcinoma, accounting for 30–70% of the entire ovarian cancer, and has a high degree of clinical malignancy.[41] Norquist et al studied p53 imprinted and tubal intraepithelial carcinoma in patients with inherited *BRCA1* mutation, and found that there was loss of heterozygosity of wild-type allele *BRCA1* in tubal intraepithelial carcinoma, but not in p53 imprinted, suggesting loss of *BRCA* gene function after TP53 gene mutation, and it may be a key event that drives cells to become cancerous.[42] Chromosome instability is one of the causes of tumorigenesis and plays an important role in the occurrence and development of ovarian tumors. Singer et al performed a single nucleotide polymorphism (SNP) analysis on the DNA of serous ovarian tumors and found that there was an imbalance of the upper genes of chromosomes 1p, 5q, 8p, 18q, 22q and Xp.[43] The insufficiency or absence of BRCA function can lead to the defect of homologous recombination (DHR) repair, which leads to chromosome instability.[44,45]

The study has some limitations. First, the number of research objects in this study is relatively small, which leads to some deviations in the results. Second, we only studied the germline variants of *BRCA* genes in ovarian cancer patients, and did not compare the variants of *BRCA* genes in somatic cells of these patients. Third, this study was limited to the relationship between *BRCA1/2* gene variants and clinicopathological features of ovarian cancer patients, and the association between *BRCA1/2* gene variants and treatment response and prognosis in patients with ovarian cancer was not analyzed. Therefore, future studies need to collect more cases for comprehensive analysis.

Conclusions

This study analyzed the relationship of *BRCA1/2* variants and clinical and pathological characteristics of ovarian cancer patients. Patients with *BRCA1* variant develop ovarian cancer at a younger age than those with the *BRCA2* variant, and *BRCA2* VUS carriers develop the disease at a younger age than other grades of *BRCA2* variant carriers. The proportion of FIGO stage III–IV in patients with *BRCA* pathogenic + likely pathogenic variant was significantly higher than those in patients with other variants. It should be mentioned that germline *BRCA1/2* variants were most frequently identified in serous ovarian carcinoma patients. *BRCA1/2* mutation detection should be performed in patients with serous ovarian carcinoma to evaluate the prognosis of clinical treatment.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals and the study obtained written informed consent from all the participants. We confirm that all methods were performed in accordance with relevant guidelines and regulations. This study was approved by the Human Ethics Committees of Meizhou People's Hospital (Clearance No.: MPH-HEC 2022-C-100).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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