Review article

BRCA mutation in high grade epithelial ovarian cancers

Tarinee Manchanaa,⁎, Natacha Phoolcharoenb, Patou Tantbirojn

a Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand
b Division of Gynecologic Pathology and Cytology, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand

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ABSTRACT

Objective: To identify the frequency of BRCA mutation in patients with high grade epithelial ovarian cancer (EOC).

Methods: Patients with EOC included fallopian tube cancer or peritoneal cancer with high grade serous or high grade endometrioid were recruited. BRCA1 and BRCA2 mutations were tested and analyzed by next generation sequencing system.

Results: A total of 87 patients were recruited; majority of them (88.5%) were EOC, 5.7% fallopian tube cancer, 4.6% peritoneal cancer, and 1.1% synchronous primary ovarian and endometrial cancer. Seventy-four patients (85.1%) had high grade serous carcinoma and 13 patients (14.9%) had high grade endometrioid carcinoma. Germline BRCA mutation was detected in 19 patients (21.8%); 14 patients (16.1%) had BRCA1 mutation and 5 patients (5.7%) had BRCA2 mutation. All BRCA mutations were found in patients with high grade serous carcinoma (25.7%) but none in high grade endometrioid carcinoma. Six from 19 patients (31.6%) who had BRCA mutation had no family history of breast and ovarian cancers. Higher frequency of BRCA mutation was detected in patients with fallopian tube cancer; 3 in 5 patients (60%) followed by peritoneal cancer; 2 in 4 patients (50%), and EOC; 14 in 77 patients (18.2%).

Conclusion: The frequency of BRCA mutation in high grade serous carcinoma was 25.7%, none was found in high grade endometrioid carcinoma. High cost, unavailability of genetic testing, limited number of geneticists, may be barriers in limited resource countries. Selected patients especially high grade serous carcinoma should be considered initially.

1. Introduction

Approximately, 10–15% of epithelial ovarian cancer (EOC) patients carry germline mutation in BRCA1 or BRCA2. (Zhang et al., 2011; Alsop et al., 2012) 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%. (Hennessy et al., 2010; Ledermann et al., 2016) BRCA mutation was reported < 10% in endometrioid subtype and very low frequency in clear cell carcinoma and the other subtypes. (Arts-de Jong et al., 2016) The knowledge about molecular studies showed that EOC is heterogeneous disease. It can be classified into two groups as type I and type II. Different in genomic variation characterizes by different in clinical presentation and prognosis. Type I is low grade and usually have indolent clinical course. (Rojas et al., 2016) High grade is classified as type II, more aggressive and poor prognosis. Type II is considered to be more genomically instable than type I. Homologous recombination genes defect including BRCA genes are commonly detected in type II EOC. (Ledermann et al., 2016) Poly(ADP-ribose) polymerase (PARP) inhibitors have been reported to be a promising targeted therapy for BRCA deficient ovarian cancers. Phase 3 trials included recurrent platinum sensitive patients with high grade serous or high grade endometrioid EOC, primary peritoneal or fallopian tube carcinoma showed maintenance treatment with PARP inhibitors improved progression free survival. (Evans and Matulonis, 2017) The incidence of BRCA mutation might vary from one ethnicity and country to the others. The objective of this study was to identify the frequency of BRCA mutation in EOC Thai patients with high grade serous and high grade endometrioid subtype.

2. Materials and methods

Patients diagnosed with EOC included fallopian tube cancer or...
peritoneal cancer who had BRCA testing from January 2015 to December 2017 were reviewed. EOC patients with high grade subtypes included high grade serous carcinoma and high grade endometrioid carcinoma were included. Patients with clear cell, mucinous carcinoma, carcinosarcoma or borderline tumor were excluded. Pathological review was performed by gynecologic pathologist. This study was approved by the Institutional Review Board, the Faculty of Medicine, Chulalongkorn University.

BRCA1 and BRCA2 mutations were tested using peripheral blood DNA samples or DNA extracted from formalin-fixed paraffin embedded block (FFPE) or a fresh tumor specimen then analyzed by next generation sequencing system (The Illumina MiSeq System; Illumina). The variant pathogenicity was evaluated based on the American College of Medical Genetics and Genomics (ACMG) standard and guidelines for the interpretation of sequence variants. (Richards et al., 2015) The variants conform to the guidelines of human genome variation society (HGVIS) on mutation nomenclature and are referenced as sequence NM_007300.3 for BRCA1 and NM_000059.3 for BRCA2. The pathogenic and likely pathogenic variants were confirmed using bi-directional Sanger sequencing. Patients who had BRCA1 or BRCA2 mutation in their tumor specimens were investigated by bi-directional Sanger sequencing using peripheral blood DNA to confirm germline or somatic BRCA mutation.

Student’s t-test and Chi-square or Fisher’s exact test were used to compare the continuous and categorical data, respectively. Statistical significance was defined as p-value < .05.

3. Results

A total of 87 patients were recruited into this study. Majority of the patients (88.5%) were EOC. Five patients (5.7%) were fallopian tube cancer, 4 patients (4.6%) peritoneal cancer, and 1 patient (1.1%) synchronous primary ovarian and endometrial cancer. The mean age was 55.6 ± 10.1 years (range 33–80), only 19 patients were younger than 50 years (21.8%). Fifty-three patients (60.9%) were menopausal and 29 patients (33.3%) were nulliparous. Sixteen patients (18.4%) had family history of breast cancer and/or ovarian cancers. Six patients (6.9%) had personal history of breast cancer before diagnosis of EOC. Most patients presented at the advanced stage: stage 3 (63.2%) and stage 4 (11.5%). One-fourth of the patients had early stage cancer: 12.6% had stage 1 and 12.6% had stage 2 cancer. Seven-four patients (85.1%) had high grade serous carcinoma and 13 (14.9%) had high grade endometrioid carcinoma.

Germline BRCA mutation was detected in 17 from 54 peripheral blood samples (12 BRCA1 and 5 BRCA2) but only 2 pathogenic BRCA1 mutations were detected from 33 tumor specimens. As for both patients, BRCA1 mutations were confirmed and detected in the peripheral blood. Thus, the frequency of germline BRCA mutation was 19 in 87 patients (21.8%); 14 patients (16.1%) had BRCA1 mutation, and 5 patients (5.7%) had BRCA2 mutation. There was no somatic BRCA mutation in this study. Details of germline BRCA mutation in 19 patients were shown in Table 1. All BRCA mutations were found in 19 patients with high grade serous carcinoma (25.7%). None with high grade endometrioid carcinoma had BRCA mutation. Clinicopathological characteristics were not different between patients with or without BRCA mutation, except significantly higher frequency of family history of breast and ovarian cancer in patients with BRCA mutation. (Table 2) Based on age at diagnosis, 26.3% of patients who were younger than 50 years had BRCA mutation, compared with 32.4% of those older than 50 years (p = .78). BRCA mutation was found in 68.4% of patients with family history of cancer but only 4.4% in patients without family history (p < .001). About 6 from 19 patients (31.6%) who had BRCA mutation had no family history of breast and ovarian cancers. Highest frequency of BRCA mutation was detected in fallopian tube cancer: 3 in 5 patients (60%) followed by peritoneal cancer: 2 in 4 patients (50%), and EOC: 14 in 77 patients (18.2%).

4. Discussion

The worldwide incidence of BRCA mutations reported about 10–15%, and it was particularly high in high grade serous subtype, which was reported at about 20–30%. (Netwon, 2011; Mafficini et al., 2016) Our study reported 25.7% incidence of germline BRCA mutation in high grade serous carcinoma which is the most common subtype worldwide; its incidence is around 70%. (Lederman et al., 2016) In contrast, high grade serous carcinoma is much lower in Thailand; the incidence is only 22%. (Chirasophon et al., 2017; Manchana and Kobwitaya, 2018) The proportion of endometrioid and clear cell carcinoma are more frequent, up to 50%, whereas mucinous carcinoma was reported about 18% of them. (Manchana and Kobwitaya, 2018) Our previous study reported the frequency of germline BRCA mutation about 11.4% in selected EOC patients with risk factors. However, higher frequency of BRCA mutation was reported in 18.2% of EOC patients with high grade serous subtype. (Chirasophon et al., 2017) Thus, the frequency of BRCA mutation might be lower in unselected EOC patients in Thailand. The incidence of BRCA mutation might vary from one ethnicity and country to the others. Few studies reported the incidence of germline BRCA mutation in Asian countries, it was between 12 and 29%. (Choi et al., 2015; Chao et al., 2016; Hasmad et al., 2016; Sakamoto et al., 2016; Wu et al., 2017). Highest incidence was reported in the Chinese (29%) and Koreans (26%). The incidence of high grade serous subtype in these two countries is similar to the western countries which was 73% and 63%, respectively. Most patients with BRCA mutation in those studies had high grade serous subtype. Incidence of BRCA mutation in high grade serous subtype were reported as high as 30–40%. (Choi et al., 2015; Wu et al., 2017) This incidence is slightly higher than our study, which showed about 25.7%. Previous systematic review showed lower probability of having germline BRCA mutation in endometrioid subtype, which was reported about 7.7% (95%CI 4.8–10.6). (Arts-de Jong et al., 2016) However, no BRCA mutation was found in patients with high grade endometrioid carcinoma in our study.

The incidence of BRCA mutation in patients without family history of breast and/or ovarian cancers was reported about 10%. (Lim et al., 2009) In contrast, 60–70% of patients with family history of cancers had BRCA mutation. (Wu et al., 2017; Pal et al., 2005) This finding is in concordance with finding that showed 4.4% and 68.4% of patients without and with family history of cancers who had BRCA mutation. If patients were selected based on family history of cancers, at least 30% of patients may be missed.

Age of onset below 50 years is one important factor associated with BRCA status. Almost 50% of Israeli EOC patients younger than 50 years carried BRCA mutation. (Helpman et al., 2017) Jewish is a specific ethnicity associated with increased rate of BRCA mutation. As this result, this number is much higher than the other studies which reported 22–33% of patients younger than 50 years carried BRCA mutation. (Alsop et al., 2012; Wu et al., 2017; Choi et al., 2018) This number was concordance to our finding which reported about 26.3%.

In general, BRCA testing is recommended to offer in all patients with EOC including fallopian tube and peritoneal cancer. Fallopian tube is believed to be the original site for development of pelvic serous cancers. There is evidence that fallopian tube and peritoneal cancer also relate to BRCA mutations. The prevalence of BRCA mutation in fallopian tube and peritoneal cancer was reported to be higher than EOC. Previous studies showed 20–40% of patients with these cancers had BRCA mutation. (Choi et al., 2018; Levine et al., 2003) Although there were limited number of patients, BRCA mutation tended to be higher in fallopian tube and peritoneal cancers, 60% and 50%, respectively.

The limitation in this study was BRCA testing did not test in both tumor tissue and peripheral blood in all patients. Therefore, the exact incidence of somatic BRCA mutation can not be identified. However, 2 in 33 patients who found BRCA mutation in tumor tissue also had BRCA mutation in peripheral blood. Germline BRCA mutation was diagnosed.
The incidence of germline mutation in high grade subtype in this small subset of patients especially high grade serous carcinomas can get barriers in limited resource countries. From our previous survey, only 25% of patients knew that ovarian cancer may be inherited and only 16% of them knew that there is a test to evaluate. Interestingly, high rate of acceptance for genetic testing was reported up to 75% of them. (Chirasophon et al., 2017) It is one major challenge to improve knowledge and increase patient awareness. Although, increasing centers in both public and private sectors provide genetic testing service, limited number of geneticists and high cost are still important barriers. The expense for genetic testing is not covered by the Universal Coverage Scheme yet, only government or state enterprise officers can get partial reimbursement. Selected patients especially high grade serous subtype and/or patients who had strong family history of breast and/or ovarian cancers should be considered initially in Thailand.

**Author contribution section**

TM did conception and study design, acquisition of data, analysis, interpretation of data, drafting and revision of the manuscript. NP did acquisition of data and revision of the manuscript. PT did pathological revision and revision of the manuscript.

**Declaration of Competing Interest**

The authors declare no conflicts of interest.

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| Age (years) | Gene | Mutation | Nucleotide change | Protein change | Variant classification | Cancer | Family history of cancer | Synchronous cancers |
|------------|------|----------|-------------------|---------------|-----------------------|--------|-------------------------|-------------------|
| 64         | BRCA1| c.981_982delAT| p.Cys328Ter | Frameshift | Pathogenic | Ovarian cancer IIB | Ovarian cancer (sister) | – |
| 59         | BRCA1| c.981_982delAT| p.Cys328Ter | Frameshift | Pathogenic | Ovarian cancer IIC | Breast cancer (sister) | – |
| 72         | BRCA1| c.3049G > T | p.Glu1017Ter | Nonsense | Pathogenic | Ovarian cancer IIA | Breast cancer (2 sisters) | – |
| 45         | BRCA1| c.3049G > T | p.Glu1017Ter | Nonsense | Pathogenic | Ovarian cancer IVC | Endometrial cancer (mother) | – |
| 46         | BRCA1| c.2059C > T | p.Gln687Ter | Nonsense | Pathogenic | Ovarian cancer (grandmother) | – |
| 63         | BRCA1| c.1899delA | p.Asn630IlefsTer2 | Frameshift | Pathogenic | Ovarian cancer (sister) | – |
| 57         | BRCA1| c.3770_3771delAG | p.Glu1027GlyfsTer9 | Frameshift | Pathogenic | Ovarian cancer (IEC) | Breast cancer (aunt) | – |
| 51         | BRCA1| c.1426delC | p.His476MetfsTer2 | Frameshift | Pathogenic | Ovarian cancer IVC | Breast cancer (Niece) | – |
| 35         | BRCA1| c.3020C > A | p.Ser1007Ter | Nonsense | Pathogenic | Peritoneal cancer IIB | Breast cancer (daughter) | – |
| 62         | BRCA1| c.4327C > T | p.Arg1443 | Frameshift | Pathogenic | BRCA1/2 germline and somatic mutations in Taiwanese patients with ovarian cancer. Ovarian cancer (sister) | Breast and ovarian cancer (sister) | – |

| Age (years) | Gene | Mutation | Nucleotide change | Protein change | Variant classification | Cancer | Family history of cancer | Synchronous cancers |
|------------|------|----------|-------------------|---------------|-----------------------|--------|-------------------------|-------------------|
| 52         | BRCA1| c.3748G > T | p.Glu1250Ter | Nonsense | Pathogenic | Peritoneal cancer IIE | Breast cancer (mother) | – |
| 56         | BRCA1| c.5072C > A | p.Thr1691Iys | Missense | Likely pathogenic | Tubal cancer IIA | Breast cancer | – |
| 63         | BRCA1| c.3181delA | p.Ile1061Ter | Frameshift | Pathogenic | Tubal cancer IIB | Breast cancer (2 sisters) | Breast cancer |
| 69         | BRCA1| c.1155G > A | p.Trp385Ter | Nonsense | Pathogenic | Tubal cancer IC | – | – |
| 60         | BRCA1| c.3109C > T | p.Gln1037Ter | Nonsense | Pathogenic | Ovarian cancer IVC | Breast cancer (2 sisters) | Breast cancer |
| 56         | BRCA2| c.758C > T | p.Arg252Ter | Nonsense | Pathogenic | Ovarian cancer IIC | Breast cancer (2 sisters) | Breast cancer |
| 49         | BRCA2| c.1397_1398delAG | p.Lys467GlufsTer4 | Frameshift | Pathogenic | Ovarian cancer IIC | Breast cancer (sister) | Breast cancer |
| 49         | BRCA2| c.4126G > T | p.Glu5176Ter | Nonsense | Pathogenic | Ovarian cancer IIC | Breast cancer (sister) | Breast cancer |

| Table 1 Details of epithelial ovarian cancer patients with germline BRCA mutation. |
| Age (years) | Gene | Mutation | Nucleotide change | Protein change | Variant classification | Cancer | Family history of cancer | Synchronous cancers |
|------------|------|----------|-------------------|---------------|-----------------------|--------|-------------------------|-------------------|
| 64         | BRCA1| c.981_982delAT| p.Cys328Ter | Frameshift | Pathogenic | Ovarian cancer IIB | Ovarian cancer (sister) | – |
| 59         | BRCA1| c.981_982delAT| p.Cys328Ter | Frameshift | Pathogenic | Ovarian cancer IIC | Breast cancer (sister) | – |
| 72         | BRCA1| c.3049G > T | p.Glu1017Ter | Nonsense | Pathogenic | Ovarian cancer IIA | Breast cancer (2 sisters) | – |
| 45         | BRCA1| c.3049G > T | p.Glu1017Ter | Nonsense | Pathogenic | Ovarian cancer IVC | Endometrial cancer (mother) | – |
| 46         | BRCA1| c.2059C > T | p.Gln687Ter | Nonsense | Pathogenic | Ovarian cancer (grandmother) | – |
| 63         | BRCA1| c.1899delA | p.Asn630IlefsTer2 | Frameshift | Pathogenic | Ovarian cancer (sister) | – |
| 57         | BRCA1| c.3770_3771delAG | p.Glu1027GlyfsTer9 | Frameshift | Pathogenic | Ovarian cancer (IEC) | Breast cancer (aunt) | – |
| 51         | BRCA1| c.1426delC | p.His476MetfsTer2 | Frameshift | Pathogenic | Ovarian cancer IVC | Breast cancer (Niece) | – |
| 35         | BRCA1| c.3020C > A | p.Ser1007Ter | Nonsense | Pathogenic | Peritoneal cancer IIB | Breast cancer (daughter) | – |
| 62         | BRCA1| c.4327C > T | p.Arg1443 | Frameshift | Pathogenic | BRCA1/2 germline and somatic mutations in Taiwanese patients with ovarian cancer. Ovarian cancer (sister) | Breast and ovarian cancer (sister) | – |

| Table 2 Clinicopathologic characteristics. |
| Age (years) | BRCA positive | BRCA negative | p-Value |
|------------|---------------|---------------|--------|
| (N = 19)  | (N = 68)      |               |        |
| Nulliparous | 56.2 ± 9.2    | 55.4 ± 10.4   | 0.49   |
| Menopause  | 12 (63.2%)    | 41 (60.3%)    | 1.00   |
| Family history of breast and ovarian cancer | 13 (68.4%) | 3 (4.4%) | < 0.001 |
| Personal history of breast cancer | 3 (15.8%) | 3 (4.4%) | 0.12 |
| Type of cancer |  |  | 0.07 |
| Epithelial ovarian cancer | 14 (73.7%) | 63 (92.6%) |  |
| Fallopian tube cancer | 3 (15.8%) | 2 (2.9%) |  |
| Peritoneal cancer | 2 (10.5%) | 2 (2.9%) |  |
| Synchronous ovarian and endometrial cancer | 0 (0%) | 1 (1.5%) |  |
| Histology |  |  | 0.06 |
| High grade serous | 19 (100%) | 55 (80.9%) |  |
| High grade endometrioid | 0 (0%) | 13 (19.1%) |  |
| Stage |  |  | 0.35 |
| I | 1 (5.3%) | 10 (14.7%) |  |
| II | 3 (15.8%) | 8 (11.8%) |  |
| III | 11 (57.9%) | 44 (64.7%) |  |
| IV | 4 (21.1%) | 6 (8.8%) |  |
| Platinum sensitive | 18 (94.7%) | 55 (80.9%) | 0.29 |
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