Prevalence of Tissue BRCA Gene Mutation in Ovarian, Fallopian Tube and Primary Peritoneal Cancer: Thai Multi-institutional Study

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Abstract

Background:Ovarian, fallopian tube or primary peritoneal cancer patients with *BRCA* gene mutation have enhanced sensitivity to platinum-based regimens and PARP inhibitors. However, the knowledge regarding *BRCA* mutation in Thai patients are limited. This study is to identify the prevalence and characteristics of somatic and germline *BRCA1&2* mutations in Thai patients with these cancers.

Methods:The paraffin blocks of tumors that had histology of high grade serous or high grade endometrioid, or clear cell carcinoma which obtained between June 2016 and December 2017 were processed to evaluate *BRCA* mutation using next-generation sequencing system. Blood or normal tissue paraffin blocks of positive patients were further tested for germline *BRCA* mutation.

Results:Tissue paraffin blocks of 178 patients were collected. Only 139 patients whose paraffin-blocks could be processed. Positive *BRCA* mutation was identified in 24 cases (17.3%): *BRCA1* in 13 cases, *BRCA2* in 10 cases, and *BRCA1&2* in another. Germline mutation study in blood or normal tissue in 23 positive patients revealed *BRCA* mutation in 14 cases: *BRCA1* (8 cases) and *BRCA2* (6 cases). Overall, the prevalence of somatic and germline mutation were 6.5% (9 in 138 patients) and 8.7% (14 in 138 patients) respectively. The most common histology associated with *BRCA* mutation was high grade serous cancer (27.3%). No significant difference between stage, outcome, platinum status and survival outcome in patients with or without *BRCA* mutation.

Conclusion: *BRCA* mutation in Thai ovarian cancer patients was demonstrated in less than 10%. Higher rate of mutation was found in high grade serous cancer.

Background

Epithelial ovarian cancer (EOC) is the 6th most common cancer among Thai females with the age standardized rate of 6.0 per 100,000 females [1, 2]. The principal treatment for epithelial ovarian cancer (EOC), fallopian tube and peritoneal carcinoma is surgical resection of tumors along with uterus and retroperitoneal lymph node. The aim is to remove tumors as much as possible. Chemotherapy of paclitaxel and carboplatin which is the current standard regimen is given if indicated. With satisfactory surgical outcome or so called 'optimal debulking surgery' followed by this adjuvant chemotherapy regimen, response rate up to 70% can be achieved. However, the recurrence rate could be as high as 80% within 2 years especially in advanced stage [3].

Of all several prognostic factors for survival, stage is the most important: 2-year survival rates ranged from 90% in early and 40–50% in advanced stages [3]. Another important prognostic factor is the response to first-line chemotherapy or platinum-sensitivity status. If the recurrences occur either later than 6 months or sooner after the last therapy, the diseases are regarded as platinum-sensitive or platinum-resistant respectively. Platinum-based chemotherapy is usually used for platinum-sensitive disease whereas other non-platinum chemotherapies would be the option for platinum-resistant disease [3, 4].

Unfortunately, the patients with platinum-sensitive disease who have responded to platinum-based chemotherapy re-induction may have subsequent recurrences. The second-relapse generally have lower responses to treatment with platinum or other chemotherapeutic drugs [3, 4]. Hence, maintenance therapy after primary treatment has emerged in order to extend the progression-free period and survival.

Among drugs that are used as maintenance therapy, poly (adenosine diphosphate [ADP]) ribose polymerase (PARP) inhibitors (PARPi) is a recent agent with efficacy. PARP is an enzyme that repairs the single-strand break DNA in tumor cells. The mechanism of action of PARPi is the inhibition of this enzyme preventing DNA repair and leading to further damage to the other DNA strand or double-strand break DNA. The double-strand break DNA can be repaired to normal via homologous recombinant pathway by *BRCA1/2* gene. In the patients with *BRCA1/2* mutation, the repair mechanism cannot take place leading to cell death eventually [5–7]. Evidence-based data from previous studies showed that PARPi could prolong remission in patients especially those with platinum-sensitive recurrent ovarian cancer. This benefit of PARPi maintenance therapy on progression-free survival was evidenced especially in the patients with either germline or somatic *BRCA1/2* mutation [5–8]. Hence, knowing the status of *BRCA1/2* mutation in ovarian cancer patients is important in order to support a decision making of a clinician to select an appropriate treatment option for the patients.

The prevalence of germline *BRCA1/2* mutation from previous reports in Asia ranged from 14–29%[9–11]. Higher percentages of mutation were found in some types of EOC, such as, high grade serous cancer which was found to have *BRCA1/2* mutation as high as 28.5% [9].

With the possible ethnic influence, the prevalence of *BRCA1/2* mutation may differ across the countries. The genetic test including testing of *BRCA1/2* mutation in ovarian cancer patients had not been a standard practice in our country. Hence, the prevalence of this *BRCA1/2* gene mutation in our population remained unknown. The Thai Gynecologic Cancer Society is aware of the increasing role of PARPi in treatment for ovarian cancer, so this study was conducted among tertiary centers for cancer care in Thailand to determine the *BRCA1/2* mutation status in Thai patients with EOC.

Materials And Methods

The study was approved by local Ethic Committees of each participating institution. Inclusion criteria were: Thai patients who had EOC, fallopian tube cancer and primary peritoneal adenocarcinoma (PPA); had operation between June 1, 2016 and December 31, 2017; had histopathology of high grade serous, high grade endometrioid or clear cell adenocarcinoma; had available paraffin blocks for tissue processing; and had available clinical data. In any cases of mixed cell types, these aforementioned histopathologic components must be at least 10% for the pathological processing and examination.

Laboratory Data

The representative slides containing tumor from each institution were submitted for central pathologic review by a gynecologic pathologist (S.K.) to confirm tumor histopathology and grade. The paraffin

blocks of tumors were then randomly submitted to one of the two qualified genomic laboratories: 1) Center for Medical Genomics, Faculty of Medicine, Ramathibodi Hospital and 2) Chula GenePRO Center, Faculty of Medicine, King Chulalongkorn Memorial Hospital. Tumor cells percentage was reviewed by the pathologists (S.S). A cross-validation of the whole process from DNA extraction through data interpretation between both laboratories was executed in 10 samples before proceeding with the *BRCA1* and *BRCA2* mutation testing in the remaining cases which were equally distributed to both laboratories.

DNA extraction and quality assessment were performed using QIAamp DNA FFPE Tissue kit and GeneRead DNA QuantiMIZE kits according to manufacturer's recommendation (Qiagen, Hilden, Germany). *BRCA1* and *BRCA2* mutation were analyzed using GeneReader next-generation sequencing (NGS) system (Qiagen, Hilden, Germany). Quality of sequencing data was examined using unique molecular index (UMI) coverage including 100X > 90% and 60X > 95% of *BRCA1* and *BRCA2* coding regions. The samples that showed inadequate DNA quality or UMI coverage were discarded to avoid false positive and false negative results.

The variant classification was preliminarily evaluated by Ingenuity Variant Analysis (Qiagen) and manually reviewed according to the American College of Medical Genetics and Genomics (ACMG)/ the Association for Molecular Pathology (AMP) guidelines [12, 13]. The final result was made from discussion and mutual agreement of both laboratories in all specimens. The patients who had tissue *BRCA1/2* mutation were counselled for germline testing. The patients, who had agreed and signed inform consent, had 5 cc of blood drawn for germline testing using bidirectional direct sequencing. For those whose contact were not available or declined to have blood test, the genetic testing was performed using normal tissue taken from the paraffin blocks.

The prevalence of '*tissue BRCA mutation*' was calculated from the number of patients who had *BRCA* mutation from tumor tissue divided by the total number of patients who had tumor tissue testing. On the other hand, the prevalence of '*germline or somatic BRCA mutation*' was calculated different. This number would be divided by the total number of patients who had tumor tissue testing but excluded those patients with tissue *BRCA* mutation whose peripheral blood or the paraffin blocks with normal tissue were unavailable.

Clinical Data

Clinical data of the patients extracted from the patients' record files included age, stage of cancer according to the International Federation of Gynecology and Obstetrics (FIGO 2014), histopathology, dates of treatments, outcomes, status of disease and living status. The patients who developed progression during the course of chemotherapy or had recurrence within 6 months after the completion of chemotherapy were classified as platinum-refractory and -resistant, respectively or else were classified as platinum-sensitive. Progression-free survival (PFS) was calculated from the date of surgery or the date of start chemotherapy in patients who were administered neoadjuvant chemotherapy until the date of progression, recurrence, or last evaluation. Overall survival (OS) was obtained from the same date that

using for calculated PFS to date of death or last follow-up in patients who were alive at the end of the study.

Sample Size Calculation

A target minimum sample size was calculated from the previous publication that reported 10% prevalence of *BRCA1/2* mutation in EOC [14]. With alpha error at < 0.05 added with 10% loss of data, 160 patients were needed to be included in the study.

Statistical Analysis

Statistical analysis of the data was carried out using IBM SPSS statistics for Windows program (version 22; IBM Corporation, Armonk, NY, USA). Descriptive data were presented as number and percentages, mean with SD or median with range. Data between the patients with *BRAC 1/ 2* mutation or normal were compared using Chi-square or Fisher's Exact test as appropriate. Survival data was analyzed with Kaplan Meier and compared between groups with log-rank test. A p-value of < 0.05 was considered as statistical significance.

Results

A total of 178 cases from 5 cancer institutions were included in this study: Faculty of Medicine Ramathibodi Hospital, Mahidol University (n = 52), Chiang Mai University Hospital, Chiang Mai University (n = 44), King Chulalongkorn Memorial Hospital, Chulalongkorn University (n = 43), Faculty of Medicine and Vajira Hospital, Navamindradhiraj University (n = 31), and Chulabhorn Hospital, Chulabhorn Royal Academy (n = 8). All hospitals were in Bangkok, except for Chiang Mai University Hospital which is in the northern part of Thailand.

Basic features and clinical data of the patients are summarized in Table 1. The mean age of the patients was 56.9 ± 11.4 years. The majority diagnosis of the patients was cancer of ovary (86.5%) and more than half (57.3%) were in advanced stage. High grade serous cancer was the most common histopathology (56.7%). Approximately 11.2% of patients had neoadjuvant chemotherapy prior to surgery whereas almost all (96.1%) received adjuvant chemotherapy. The most common first-line chemotherapy was carboplatin plus paclitaxel (68.0%). Complete response after primary treatment were achieved in 118 patients (66.3%), and 55 patients (30.9%) later developed recurrence.

Table 1: Clinico-pathologic data of the patients and tumors (N=178)

Clinico-pathological features	N(n)
Diagnosis	
CA Ovary	154(86.5)
CA tube	17(9.6)
PPA	7(3.9)
Histology	
Serous	101(56.7)
Clear cell	69(38.8)
Endometrioid	4(2.2)
Mixed	4(2.2)
Stage	
I	52(29.2)
II	24(13.5)
III	80(44.9)
IV	22(12.4)
Neoadjuvant chemotherapy	20(11.2)
Adjuvant chemotherapy	171(96.1)
Regimen	
Carboplatin + paclitaxel	121(68.0)
Carboplatin	12(6.7)
Carboplatin + Pegylated liposomal doxorubicin	37(20.8)
Carboplatin + paclitaxel-Bevacizumab	1(0.6)
Outcome after primary chemotherapy treatment	
Responses	
Complete response	118(66.3)
Partial response	20(11.2)
Stable disease	4(2.2)
Progression	26(14.6)
Missing data	10(5.6)
Recurrence	55(30.9)
Progression after response to chemotherapy	23(12.9)
Platinum status	
Sensitive	129(72.5)
Refractory	18(10.1)
Resistant	21(11.8)
Data not available (loss to follow-up)	10(5.6)

Current status	
Alive with disease	55(30.9)
Alive without disease	88(49.4)
Death	27(15.2)
Data not available (loss to follow-up)	8(4.5)

Regarding *BRCA* results, there were only 139 patients whose paraffin-blocks could be further processed for the test. The others were disapproved due to suboptimal quality of DNA and sequencing data, and were excluded from the proceeding. Of 139 cases, the tissue *BRCA* gene mutation was found in 24 cases (17.3%): *BRCA* 1 mutation in 13 cases (9.5%), *BRCA* 2 mutation in 10 (7.2%), and both *BRCA* 1&2 mutation in 1 case (0.7%). The remaining 11 cases (7.9%) were reported to have variants of uncertain significance (VUS).

Table 2 shows *BRCA* gene mutation according to the histology. Only high grade serous cancer and clear cell carcinoma showed positive *BRCA* gene mutation: high grade serous cancer in 21 from 77 cases (27.3%) and clear cell carcinoma in 3 from 55 cases (5.5%). Of 24 patients with *BRCA* positive, all except one could be pursued to have germline *BRCA* gene mutation testing using peripheral blood in 18 cases and normal tissue of myometrium from paraffin block in the other 5 cases. The results showed germline positive in 14 cases, 8 *BRCA* 1 mutation and 6 *BRCA*2 mutation; 13 of which were high grade serous cancer and only 1 was clear cell carcinoma. Thus, among 138 cases who had the data of both germline and somatic, the percentages of germline *BRCA* gene mutation was 8.7% (14 in 138 cases) while the percentage of somatic *BRCA* gene mutation was 6.5% (9 in 138 cases). The detail of somatic *BRCA* mutation in all 9 patients were 4 *BRCA* 1 mutation, 4 *BRCA*2 mutation, and 1 *BRCA*1&2 mutation. The patients who had germline mutation was significantly younger than and the patients with only somatic

mutation (48.4±10.6 versus 61.6±12.9 years $P = 0.014$). Thus, at least the prevalence rates of germline and somatic *BRCA* mutation in our study were 8.7% and 6.5%, respectively.

Table 2: *BRCA* gene mutation according to the histology (N=139)

Histology	<i>BRCA</i> result (%)						
	Positive				Negative	VUS	Total
	<i>BRCA1</i>	<i>BRCA2</i>	<i>BRCA1&2</i>	Total			
Serous	13(16.9)	7(9.1)	1(1.3)	21(27.3)	49(63.6)	7(9.1)	77
Clear	-	3(5.5)	-	3(5.5)	48(87.3)	4(7.3)	55
Endometrioid	-	-	-	-	4(100)	-	4
Mixed	-	-	-	-	3(100)	-	3
Total	13(9.4)	10(7.2)	1(0.7)	24 (17.3)	104(74.8)	11(7.9)	139

VUS = Variant of Uncertain significance

Mixed histology included endometrioid caecinoma + clear cell carcinoma (2 cases), high grade serous carcinoma + clear cell carcinoma (1 case)

Table 3 summarizes the detail of *BRCA* gene mutation identified by next generation sequencing. Three mutation patterns were identified including 11 frameshifts, 9 nonsenses, and 2 missenses. Missense mutations were observed only in *BRCA2* genes while frameshift and nonsense were found in both *BRCA1* and *BRCA2*. Five novel mutations in 6 patients were observed whereas the others were known mutations reported in the NCBI database of genetic variation (dbSNP) [15].

Table 3 Detail of *BRCA* mutation in 24 patients

No.	Gene	Mutation				Histology	Age of diagnosis (years)	Germline / Somatic
		Nucleotide change	Amino acid change	Type of mutation	dbSNP			
1	<i>BRCA1</i>	c.624_625insAGGGATGAAATCAGGAACCA	p.(Pro209fsX)	Frameshift	rs397509302	Serous	53	Germline
2	<i>BRCA1</i>	c.697delG	p.(Val233Ter)	Nonsense	rs1555593298	Serous	64	Somatic
3	<i>BRCA1</i>	c.1265_1266dupAT	p.(Ser423IlefsX)	Frameshift	rs397508850	Serous	23	Germline
4**	<i>BRCA1</i>	c.1544_1550delAGGATTT	p.(Glu515fsX15)	Frameshift	-	Serous	31, 57	Germline, Germline
5	<i>BRCA1</i>	c.1789G>T	p.(Glu597Ter)	Nonsense	rs55650082	Serous	48	Germline
6**	<i>BRCA1</i>	c.1961delA	p.(Lys654SerfsX)	Frameshift	rs80357522	Serous	61	Somatic
7	<i>BRCA1</i>	c.2462dupA	p.(Asp821GlufsX2)	Frameshift	-	Serous	78	Somatic
8	<i>BRCA1</i>	c.2719G>T	p.(Glu907Ter)	Nonsense	rs876658593	Serous	47	Germline
9**	<i>BRCA1</i>	c.3037G>T	p.(Glu1013Ter)	Nonsense	-	Serous	58	Germline
10	<i>BRCA1</i>	c.3181delA	p.(Ile1061Ter)	Nonsense	rs80357702	Serous	54, 56	N.A***, Germline
11*,**	<i>BRCA1</i>	c.3769G>T	p.(Glu1257Ter)	Nonsense	-	Serous	58	Somatic
12**	<i>BRCA1</i>	c.4905_4914delGAAGCCAGAA	p.(Glu1635AspfsX)	Frameshift	-	Serous	45	Somatic
13*	<i>BRCA2</i>	c.145G>T	p.(Glu49Ter)	Nonsense	rs80358435	Serous	58	Somatic
14	<i>BRCA2</i>	c.755_758delACAG	p.(Asp252ValfsX24)	Frameshift	rs80359659	Serous	51	Germline
15	<i>BRCA2</i>	c.1321_1324delACTT	p.(Thr441GlufsX18)	Frameshift	rs1064793572	Serous	64	Germline
16	<i>BRCA2</i>	c.1399_1402delAAGA	p.(Lys467GlufsX17)	Frameshift	rs398122726	Clear cell	46	Germline
17	<i>BRCA2</i>	c.1813delA	p.(Ile605TyrfsX9)	Frameshift	rs80359306	Clear cell	56	Somatic
18	<i>BRCA2</i>	c.4222C>T	p.(Gln1408Ter)	Nonsense	rs80358663	Serous	69	Somatic
19	<i>BRCA2</i>	c.4593dupA	p.(Val1532SerfsX2)	Frameshift	rs397507731	Clear cell	43	Somatic
20	<i>BRCA2</i>	c.7090G>T	p.(Glu2364Ter)	Nonsense	rs80358940	Serous	80	Somatic
21	<i>BRCA2</i>	c.8009C>T	p.(Ser2670Leu)	Missense	rs80359035	Serous	50	Germline
22	<i>BRCA2</i>	c.9154C>T	p.(Arg3052Trp)	Missense	rs45580035	Serous	45, 48	Germline, Germline

Mutations reported conform to HGVS guidelines on mutation nomenclature and are named according to the reference sequencing.

NM_007294.3.LRG_292t1 and NM_000059.3.293t1 for *BRCA1* and *BRCA2*, respectively.

Serous; high grade serous cystadenocarcinoma

*, mutations in the same patient. N.A; not tested. **, novel mutations. ***; not tested due to patient death and no adequate specimen.

This study could not demonstrate any differences of age, type of cancer, stage, outcome after primary treatment, and platinum-sensitivity status of the patients with and without tissue *BRCA* gene mutation (Table 4). Figure 1& Fig. 2 also revealed no differences of 2-year PFS and 2-year OS between the two groups of patients. However, the OS in patients with pathogenic *BRCA* gene tended to be better with 2-

year OS of 95.0% (95% confidence interval 77.6–96.8%) compared to 87.2% (95% confidence interval 88.8–100%) in patients without pathogenic *BRCA* gene ($P = 0.077$).

Table 4: Clinical data of the patients according to *BRCA* results (N=139)

	BRCA		P value
	Pathogenic (N=24)	Non-pathogenic (N=115)	
Mean age	54.0	56.9	0.27*
Diagnosis			0.69#
Ovary	21(87.5)	103(89.6)	
Fallopian tube	3(12.5)	9(7.8)	
PPA	-	3(2.6)	
Stage			0.07#
I	2(8.3)	37(32.2)	
II	5(20.8)	15(13.0)	
III	12(50.0)	48(41.7)	
IV	5(20.8)	15(13.0)	
Outcome after primary treatment			0.88#
Complete response	18(75.0)	77(67.0)	
Partial response	2(8.3)	14(12.2)	
Stable disease	0	3(2.6)	
Progression	2(8.3)	15(13.0)	
Data not available	2(8.3)	6(5.2)	
Platinum-sensitivity status			0.28#
Sensitive	21(87.5)	85(73.9)	
Refractory	0	8(7.0)	
Resistant	1(3.3)	16(13.9)	
Data not available	2(8.3)	6(5.2)	

Non-pathogenic = *BRCA* negative - VUS (VUS = Variant of Uncertain significance)

#Fisher Exact test

*Chi-square test

Discussion

The present study found tissue *BRCA* mutation in high grade EOC, fallopian tube cancer and primary peritoneal adenocarcinoma in 24 from 139 patients (17.3%). Of 23 from 24 patients, 14 patients revealed germline *BRCA* 1/2 mutations. Thus, the prevalence of germline and somatic *BRCA* mutation in our study were at least 10.1% (14 in 138 cases) and 6.5% (9 in 138 cases), respectively. These rates corresponded to the Taiwanese's study. Chao et al. [16] investigated the occurrence of *BRCA* 1/2 mutation in 99 Taiwanese ovarian cancer patients from formalin-fixed paraffin-embedded tumor samples of tumor and normal tissue by using next-generation sequencing, and found *BRCA* 1 in 7 cases and *BRCA* 2 in 6 cases. Therefore, the prevalence rate of their study was 12.1%, and 4 cases (4%) were proved somatic mutation. Another study from Thailand by Manchana et al. [17] identified the frequency of *BRCA* mutation in 87 Thai high grade serous cancer and high grade endometrioid ovarian cancer, including the fallopian and peritoneal cancer. The authors used peripheral blood DNA samplers or DNA extracted from formalin-fixed paraffin embedded blocks (FFPE) or a fresh tumor specimen to analyze *BRCA* mutation via the next generation sequencing system. The results showed germline *BRCA* mutation detection in 19 patients

(21.8%), 14 of them (16.1%) with *BRCA1* mutation, and 5 of them (5.7%) with *BRCA2* mutation. All positive patients revealed histology as high grade serous cancer. The different detection rates of *BRCA* mutation between our study and Manchana's study were probably from the differed specimens. Our study used only FFPE that might decrease the detection rate due to the variability of tumor samples and intra-tumoral heterogeneity which probably compromised the representativeness of the sample [18] whereas Manchana et al. used fresh tumor specimen or blood samples aside from FFPE to analyze *BRCA* [17].

The most frequent histology in patients with germline *BRCA* mutation was high grade serous carcinoma in a range of 5.5–16.7%, followed by endometrioid carcinoma (4.3–13%) and clear cell carcinoma (6.3–9.1%) [18, 19]. However, in the present study, tissue *BRCA* mutation was found in 27.3% of high grade serous carcinoma and 5.5% of clear cell carcinoma, while none in endometrioid carcinoma. This non-similar outcome might be from very small number of patients with high grade endometrioid carcinoma in our study. However, *BRCA2* mutation was found only in clear cell carcinoma. This finding corresponded to the previous reports that suggested that *BRCA2* mutation are common in this cell type [20, 21]. However, 2 from 3 patients with clear cell carcinoma had somatic *BRCA2* mutation (87.7%) and only 1 patient (33.3%) had germline *BRCA2* mutation.

Due to variable from prevalence of *BRCA* mutation among various histology, the current recommendation of the American Society of Clinical Oncology (ASCO) guideline is to assess either germline or somatic *BRCA* gene mutation in all non-mucinous ovarian, fallopian tube and peritoneal cancer of high grade [22]. Improvement of treatment outcome is possible with PARPi [5–7, 18, 23]. Gori et al. [24] summarized an initial step of *BRCA* mutation gene investigation by studying *BRCA 1/2* mutation on tumor tissue. The test which could identify spectrum of genomic rearrangements (i.e., deletions or duplications of one or more exons, or of the whole gene) yielded high sensitivity. In the patients whose tissues were positive for *BRCA 1/2* mutation, genetic counseling and further investigation for germline mutation from their peripheral blood should be deferred as the next step of investigation. If the blood test was positive, these patients would benefit from PARPi therapy and should be under close surveillance for a possible development of second malignancy.

The major problem of tissue sample for testing pathogenic gene was the quality of FFPE clinical specimens. Although next generation sequencing that we used can sequence entire *BRCA 1/2* coding regions, epigenetic and structural change were limited to detect in this study. Thirty nine DNA samples (21.9%) were unable to obtain *BRCA* mutation status due to insufficient DNA quality. Various factors affected FFPE DNA quality in molecular genomics test such as tissue fixation time, storage time and archive temperature [25]. In this study, we selected FFPE tissues blocks during June 2016 to December 2017 and finished the DNA extraction within 2018 (< 3 years) to avoid long-term storage effect. Therefore, fixation time and archive temperature would be causes of low DNA quality since the samples were collected from 5 institutions and there might be deviation of FFPE tissue handling and collection.

Regarding clinical characteristics between the patients with and without *BRCA* gene mutation, the present study did not find any significant differences of age, disease, stage, primary outcome, and platinum-

sensitivity status, and survivals after treatment. Previous study by Kuberlac et al. [26] reported that their patients with both germline and somatic *BRCA* mutation had younger age and had significantly higher rate of complete pathologic response during the first and second platinum-sensitive relapse, and longer overall survival for advanced stage treated with neo-adjuvant chemotherapy when compared to 52 patients without *BRCA* mutation. Although this study also found younger age among *BRCA* mutation, the positive *BRCA* gene did not serve as a favorable prognostic factor. The small number of patients in this study may limit any meaningful clinical summary regarding the prognostic role of *BRCA* mutation.

In conclusion, tissue *BRCA* 1/2 mutation positive was presented in about 17% of high grade epithelial ovarian, fallopian and peritoneal cancer. The most frequent histology was the serous cancer. The quality of paraffin block preservation should be concerned in order to improve the detection rate of this *BRCA* mutation.

Conclusion

BRCA mutation in Thai ovarian cancer patients was demonstrated in less than 10%. Higher rate of mutation was found in high grade serous cancer

Declarations

Ethics approval

The study was approved by local Ethic Committees of each participating institution and had consent to participate.

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Consent for publication:

Not applicable

Availability of data and materials

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

Competing interests

All authors declare that they have no conflicts of interest to disclose

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Authors' contributions

P.S and A.Lconceived of the presented idea. PS,AL,TM,TK,NKdeveloped the theory and performed the computations. TC,SK,NPST and TL verified the analytical methods (Patho.) PS, CT,SS,NI,WC verified the analytical methods (LAB). ST,TM,AL, supervised the findings of this workfor PS. All authors discussed the results and contributed to the final manuscript.

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Figures

Median progression free survival:

Pathogenic *BRCA* gene = 31.8 months vs. non-pathogenic *BRCA* gene = 30 months

2 year progression free survival :

Pathogenic *BRCA* gene = 68.2% (95%CI 48.8-87.6%) vs. non- Pathogenic *BRCA* gene = 59% (95% CI 49.6-68.4)

Log rank test $P = 0.43$

CI = confidence interval

Figure 1

Progression – free survival in patients with and without pathogenic *BRCA* gene

Log rank test $P = 0.077$

2-yr overall survival : non-pathogenic BRCA gene = 87.2% (95% CI 88.8-100%), pathogenic BRCA gene = 95% (95% CI 77.6-96.8%)
 CI = confidence interval

Figure 2

Overall survival (OS) in patients with and without pathogenic BRCA gene

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