BRCA1 and *TP53* mutations in ovarian cancer: Molecular genetic insights and updated situations in Thailand

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ABSTRACT

Ovarian cancer is the second most common gynecologic cancer among Thai women. It is the most lethal gynecologic cancer worldwide. The incident rate increases in women over 45 years old. Several genetic factors linked to ovarian cancer have been identified. Previous reports have shown that women with deleterious mutations in the *BRCA1* gene had a high risk of developing ovarian tumors during their lifetime. *TP53* mutation is also recognized as one of genetic factors associated with ovarian cancer. Around 50% of ovarian cancer patients contain various mutations in the *TP53* gene resulting in the overexpression of the mutated proteins. Additionally, mutations of *BRCA1* together with *TP53* are found in the most aggressive subtype high-grade serous ovarian cancer (HGSOC). The prevalence of *BRCA1* and *TP53* mutations in breast and ovarian cancers has been reported in many populations. However, the mutation types seem to be different depending on ethnicity. In Thailand, the significance of both *BRCA1* and *TP53* gene mutations on ovarian cancer initiation and progression has not been completely elucidated. This review points out the incidence and association between *BRCA1* as well as *TP53* mutations and ovarian cancer. Cumulative data obtained from Thai population are shown. The knowledge may help improve genetic screening, prognosis and treatment selection for ovarian cancers in our country in the near future.

Keywords: ovarian cancer; *BRCA1*; *TP53*; mutations; Thailand

INTRODUCTION

Over the past decade, there have been reports of the increasing incidence of ovarian cancer in Thailand. The age-standardized rate (ASR) has been rising continuously from 5.1 to 6.0 per 100,000 female population within twelve years (2001 to 2012). The prevalence appears to be highest in Bangkok (Khuhaprema *et al.*, 2010; 2012; 2013; Imsamran *et al.*, 2015). Ovarian cancer is the seventh most common cancer among women worldwide and is the most harmful gynecological malignancies. The occurrence of ovarian cancer in women worldwide was more than 200,000 cases in 2012 which resulting in 152,000 deaths (Prat and Franceschi, 2014). Many ovarian cancer risk factors have been identified. However, truly biologic events that lead to ovarian cancer remain unknown. Approximately 10% of cases are related to inherited genetic risk. Women with mutation in *BRCA1* genes (MIM# 113705) have around 40% chance of developing ovarian cancer by the age of 70 (Antoniou *et al.*, 2003; Chen and Parmigiani, 2007; Prat and Franceschi, 2014). Previously, there has been report of *BRCA1* mutations associated with familial breast and ovarian cancers in Thai patients by Patmasiriwat and colleagues. More than half of ovarian cancer cases (4 out of 6) appeared to have *BRCA1* mutations (Patmasiriwat *et al.*, 2002). The mutations identified in this study were different from those reported in other countries in Asia, Europe and North America (Liede and Narod, 2002; Patmasiriwat *et al.*, 2002; Janavičius, 2010; Narod and Salmena, 2011). The other study has shown that almost 30% of high-risk epithelial ovarian cancer patients had germline mutations (Chirasophon *et al.*, 2017). Among these, 8.6% of mutations were detected in *BRCA1* which is the most common mutated-gene found in this study. Moreover, genetic changes in the untranslated region (UTR) of *BRCA1* were also proposed to be associated with ovarian cancer risk in Thai patients (Pongsavee *et al.*, 2009).

TP53 (MIM# 191170) is a tumor suppressor gene encoding for p53 protein that regulates normal growth and suppresses neoplastic development. The major role of p53 is to maintain genetic stability by preventing genome mutation. *TP53* gene inactivation mutations have been identified in more than 50% of cancer cases, thus makes it be the most frequently mutated gene in human cancers (Hollstein *et al.*,

1991; Levine *et al.*, 1991; May and May, 1999; Surget *et al.*, 2013). As in other cancers, the *TP53* gene is one of the genetic factors contributes to abnormal growth of ovarian cells. Mutant *TP53* frequently affects and is detected in human epithelial ovarian cancers. The presence of the mutation in *TP53* gene is negatively correlated with their protein expression in ovarian carcinomas. The *TP53* mutations are most common in high-grade serous cancers (Yemelyanova *et al.*, 2011; Cole *et al.*, 2016; Ma *et al.*, 2016). Arg72Pro is the most common alteration found in many types of cancer. Many studies have investigated a genetic link between this variation and cancer susceptibility (Petitjean *et al.*, 2007; Rivlin *et al.*, 2011). In Thailand, only one study of *TP53* mutation and ovarian cancer was reported in 2002. Three point mutations and one insertion in exon 5 of *TP53* were identified (Neungton *et al.*, 2002). However, the number of cases was still low and the finding of 18% of *TP53* mutation was lower than the average of about 50% from many reported data.

Somatic mutations in the *TP53* gene often accompany *BRCA1/2*-associated tumors. The *TP53* polymorphisms Arg72Pro and Ins16 have been proposed to increase risk of *BRCA1/2*-associated breast cancer. Some studies have demonstrated that patient who carried both a mutation in *TP53* and in *BRCA1* or *BRCA2* increased the risk of breast cancer than those who did not have mutation in *BRCA1/2* coding region (Osorio *et al.*, 2006; Cavallone *et al.*, 2008; Yarden *et al.*, 2010). Ovarian cancers are divided into five tumor types including the predominant high-grade serous carcinomas which tend to harbor *BRCA1* and *TP53* mutations. This highly aggressive tumor relates with disturbance of molecular mechanisms leading to genomic instability and severe mutability (Köbel *et al.*, 2008; Prat and Franceschi, 2014).

Since ethnic and geographic differences contribute to difference in *BRCA1* as well as *TP53* mutation spectrum and prevalence. The information of *BRCA1* and *TP53* mutations in Thailand is not clearly classified. This article focuses on collecting the incidence of *BRCA1* and *TP53* mutations found in Thais with ovarian cancer. The information might be used for the purpose of surveillance or risk management of ovarian cancer in Thailand.

Ovarian cancer and the incidence in Thailand

Cancer has been the common cause of death in Thailand since many years ago. During 2010-2012, the ASR of cancer at all sites was 143.3 per 100,000 in male and 131.9 per 100,000 in female. The highest incidence fell in to liver and bile duct cancer (33.9/100,000) and breast cancer (28.5/100,000) in male and female, respectively. Ovarian cancer is the second gynecologic cancer in Thailand following cervical cancer. The incidence has gradually increased during the past decade. It was shown to be 6.0 per 100,000 Thai females by 2012. Approximately 239,000 new cases of ovarian cancer were estimated worldwide in 2012, which represented 4% of all cancers in women. The highest incidence peak of ovarian cancer is falling in between the age group of 45-70, while the typical age of diagnosis is around 63 years old. Ovarian cancer associated death tends to be more common in North America and Europe than in Africa and Asia (Prat and Franceschi, 2014; Imsamran *et al.*, 2015; Wilailak and Lertchaipattanakul, 2016).

Staging of ovarian cancer is relied on the International Federation of Gynecology and Obstetrics (FIGO) staging system which needs information obtained after surgery including the extent of primary tumor, the absence or presence of metastasis to nearby lymph nodes and the absence or presence of distant metastasis (Suh *et al.*, 2013). There are four stages of ovarian cancers; stage I: cancer is located only within the ovary or fallopian tube and has not spread to other organs and tissues, stage II: cancer is in one or both ovaries or fallopian tubes and has spread to other organs within the pelvis, stage III: cancer is in one or both ovaries or fallopian tubes and has spread outside the pelvis and/or to retroperitoneal lymph nodes, stage IV: cancer has spread to the inside of the spleen, liver, lungs, or other organs located outside the peritoneal cavity. The most common stage of ovarian cancer at the time of diagnosis is stage III. Ovarian cancers show different prognosis at a particular stage and are treated differently. Hence it makes staging procedure very important. Inaccurate staging may cause misdiagnosis and leave cancer cells that have spread outside the ovary untreated (Suh *et al.*, 2013; Paik *et al.*, 2015). Based on histopathology, ovarian cancers are divided into five main types: high-grade serous, low-grade serous, mucinous, endometrioid, and clear cell carcinomas. The two most common types found in Thai patients are serous and mucinous carcinomas (Prat and Franceschi, 2014; Wilailak and Lertchaipattanakul, 2016). Molecular events during oncogenesis are different depending on histological types and thence give different outcomes and prognosis. The high-grade serous carcinomas which usually found in advance stage appear to have abnormalities in p53 and pRb pathways and have poor prognosis (Prat and Franceschi, 2014).

There are several risk factors associated with ovarian cancers. The risk increases in nulliparous women. Other risk factors include hormone therapy, fertility medication, and obesity. The risk is reduced in women with suppressed ovulation, typically by pregnancy or oral contraceptives as well as breast feeding (Luan *et al.*, 2013; Prat and Franceschi, 2014; Kotsopoulos *et al.*, 2015; Liu *et al.*, 2015). Exposure to certain occupational and environmental agents such as pesticides, herbicides, talc and nitrates may increase risk of ovarian cancer (Srivastava *et al.*, 2017). Family history is one of essential factors to be considered. Woman who has one or more first-degree relatives with this disease will have higher risk of getting ovarian cancer when compared with those without such a history (Stratton *et al.*, 1998). Genetic factor is normally related with family history. Generally, genetic cause is accounted for 5-10% of ovarian cancer cases. Genes that have been reported to be involved with ovarian cancer include *BRCA1/2*, *TP53*, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, *RAD51D* and *BARD1* (Petitjean *et al.*, 2007; Kuusisto *et al.*, 2011; Hoffman *et al.*, 2012; Norquist *et al.*, 2016). In Thai patients with ovarian cancer, mutations have been observed in *TP53*, *BRCA1/2*, *CHECK2*, *RAD1C*, *MLH1*, *MSH2* and *MUTYH*. *BRCA1* and *TP53* are the two most common genes that have found to be mutated. Among those 21 reported mutations, 9 mutations (42.9%) were in *BRCA1* and 5 mutations (23.8%) were in *TP53* (Figure 1) (Neungton *et al.*, 2002; Patmasiriwat *et al.*, 2002; Chirasophon *et al.*, 2017).

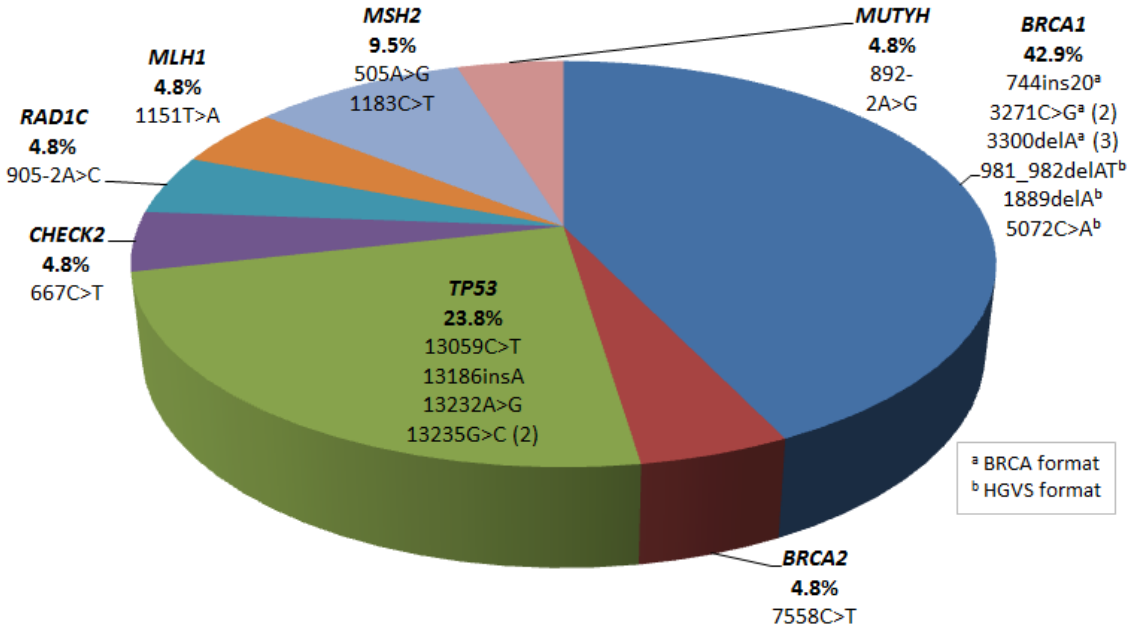

Figure 1 Gene mutations observed in Thai ovarian cancer patients.

***BRCA1* mutations in ovarian cancer**

BRCA1 is a tumor suppressor gene which locates on chromosome 17q21. Like many other tumor suppressor genes, *BRCA1* regulates cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way. BRCA1 protein contains several functional domains which are important in their tumor suppressive activity. RING finger, nuclear localization signal (NLS), DNA binding, SQ-cluster domains (SCDs), and BRCT domains participate in BRCA1 functions (Narod and Foulkes, 2004). The protein encoded by the *BRCA1* gene is directly involved in the repair of damaged DNA. Carboxyl-terminal of BRCA1 protein interacts with RAD51 protein to repair breaks in DNA (Zhou *et al.*, 2005). These breaks can be caused by natural radiation, chemical exposure or chromosomal crossover during cell division. The BRCA2 protein, which has a function similar to that of BRCA1, also interacts with the RAD51 protein. These three proteins play a role in maintaining human genome stability. When DNA is damaged, both BRCA1 and RAD51 localize to the damaged region, and BRCA1 is phosphorylated during this process (Welcsh *et al.*, 2000; Venkitaraman, 2002).

Interactions between BRCA1 and other proteins such as BARD1, RB, p53, RNA pol.II, CtIP etc. also implicate in other molecular functions of BRCA1 protein (Venkitaraman, 2002). The BRCA1-

BARD1 complex functions in the ubiquitylation process of several proteins including progesterone receptor while BRCA1-p53 complex plays a role in checkpoint control (Narod and Foulkes, 2004; Scully *et al.*, 2004). Mammary glands of nulliparous BRCA1/p53-deficient mice accumulate lateral branches and undergo extensive alveologenesis, since they cannot ubiquitinate progesterone receptor (PR) (Poole *et al.*, 2006).

Mutations in the *BRCA1* gene lead to an increased risk for breast and ovarian cancer. It is the gene most commonly associated with high-grade serous ovarian cancer (Prat and Franceschi, 2014). A mutated *BRCA1* usually makes a protein that does not function properly. Defective BRCA1 protein cannot perform its DNA repair function and is unable to help fixing mutations that occur in other genes. These defects accumulate and may allow cells to grow and divide uncontrollably to form a tumor (Tutt and Ashworth, 2002). Approximately 750 mutations in the *BRCA1* gene have been identified, many of which are associated with an increased risk of cancer. The germline *BRCA1/2* mutation spectrum is varied among certain countries and ethnic communities (Karakasis *et al.*, 2016). *BRCA1* mutations found in Thai ovarian cancer patients are shown in Table 1.

Numbers of mutations have been found throughout the entire coding and non-coding sequence. Two novel mutations, the *BRCA1* 3300delA and *BRCA1* 744ins20 have been identified as cancer-related mutation in Thai familial and early-onset breast and ovarian cancers. On the other hand, *BRCA1* C3271G was thought to be a non-cancer associated mutation. Another missense mutation, *BRCA1* T320G was detected in three breast cancer patients from two unrelated families and one sporadic case. Interestingly, one of the cases has another two family members diagnosed with ovarian cancer. And thus it was predicted to be breast and ovarian cancer-related mutation (Patmasiriwat *et al.*, 2002). Recently, three more pathogenic *BRCA1* mutations in Thai ovarian cancer patients were reported by Chirasophon and colleagues. Those mutations are *BRCA1* 981_982delAT, *BRCA1* 1889delA and *BRCA1* C5072A. All mutations were found in high-grade serous carcinomas. Patients with *BRCA1* 981_982delAT and with *BRCA1* 1889delA had significant family history of ovarian cancer but patients with *BRCA1* C5072A did not report the evidence (Chirasophon *et al.*, 2017).

The significance of variation in non-coding region was also stated. In previous study, nine *BRCA1* splice forms were characterized supposing that alternative splicing of *BRCA1* possibly plays a major role in the tumorigenesis of breast and/or ovarian cancers (Lixia *et al.*, 2007). From one study in Thai patients, the 5711+421T/T_5711+1286T/T genotype in *BRCA1* 3'-UTR was believed to be a risk factor of breast and ovarian cancers. The prevalence of this gene variant in the group of *BRCA1/2* negative cancer patients was three times higher than that has seen in healthy individuals (Pongsavee *et al.*, 2009). Hypermethylation of *BRCA1* promoter is one of important molecular mechanisms accounts for reduction of *BRCA1* transcripts in non-familial cancers. About 7% to 31% of sporadic cases have been found hypermethylation in *BRCA1* promoter. Methylated *BRCA1* resulted in molecular and clinicopathologic phenotype similar to that of hereditary *BRCA1*-associated breast and ovarian cancers (Catteau and Morris, 2002).

Although mutations in the *BRCA1* gene have been proposed as a major risk factor for familial breast and ovarian cancer, it does not directly result in tumor formation. *BRCA1* gene mutations cause genetic instability, contributing cell susceptibility to cancer. Additional cooperation of other oncogenes and tumor suppressor genes implicate in cancer progression (Ingvarsson, 1999).

Table 1 *BRCA1* mutations identified in Thai ovarian cancer patients.

***BRCA1* mutation**		**Exon**	**Variation type**	**Age of onset**	**No. of cases**	**References**
Nucleotide change	**Amino acid change**					
744ins20[a]	240Ter	10	NS	42	1	Patmasiriwat *et al.*, 2002
3271C>G[a]	Thr1051Ser	11	MS	42, 64	2	
3300delA[a]	1061Ter	11	NS	42, 64, 50	3	
981_982delAT[b]	328Ter	11	NS	64	1	Chirasophon *et al.*, 2017
1889delA[b]	631Ter	11	NS	63	1	
5072C>A[b]	Thr1691Lys	17	MS	56	1	

NS, nonsense; MS, missense

[a] Nucleotide number = BRCA format (A of start codon ATG is #120)

[b] Nucleotide number = HGVS format (A of start codon ATG is #1)

***TP53* mutations in ovarian cancer**

TP53 is a tumor suppressor gene which locates on the short arm of chromosome 17 (17p13.1) (Isobe *et al.*, 1986). This gene contains 20 kb with a non-coding exon 1. The coding sequence comprises of five regions showing a high degree of conservation in vertebrates, especially in exons 2, 5, 6, 7 and 8 (May and May, 1999). The *TP53* encodes for p53 which is a 53 kDa protein that binds to DNA and regulates gene expression to maintain genomic stability (Talos and Moll, 2010). This transcription factor protein consists of 393 amino acids with four distinct functional domains. Transactivation domain (TD) and proline-rich domain (PD) are located at the N-terminus, DNA-binding domain (DBD) at the central, whereas oligomerization domain (OD) and regulatory domain (RD) at the C-terminus. Anticancer function of p53 is contributed by many mechanisms involving in genomic stability, apoptosis, and inhibition of angiogenesis. Those mechanisms are cell cycle arrest, DNA repair and apoptosis initiation (Wang and Sun, 2010; Saha *et al.*, 2015). In a normal situation, p53 is inactivated by its negative regulator, mdm2. Once the cell has DNA damage or other stresses, the dissociation of the p53 and mdm2 complex will be occurred. This event leads p53 to be activated. The active p53 will either induce cell cycle arrest to allow DNA repair and continue growing or initiate apoptosis to get rid of the damaged cell. Growth arrest induced by p53 is mainly mediated by up-regulation of cell cycle control genes such as p21, Gadd45, and 14-3-3σ through a direct DNA binding and transactivation (Harris and Levine, 2005; Wang and Sun, 2010).

In cancer, mutations that deactivate p53 usually occur in the DNA-binding domain which can abrogate the binding ability of the protein to its target DNA sequences, and thus prevent gene transcriptional activation (Wang and Sun, 2010; Rivlin *et al.*, 2011). Mutational inactivation of p53 tumor suppressor is the most frequent genetic lesions found in human cancers including ovarian, breast, adrenal cortical carcinomas and brain tumor (Saha *et al.*, 2015). The mutations are distributed throughout the coding exons of the *TP53* gene, predominantly in exons 4 to 9. Most of the mutations in *TP53* gene cluster in the mutation hotspot in between codons 125 and 300 (Olivier *et al.*, 2010; Wang and Sun, 2010; Rivlin *et al.*, 2011). While the Arg72Pro mutation exhibits the most prevalence mutation found in many regions, this type of mutation has not been observed in Thailand. According to the previous study, four mutations *TP53* Ser127Phe, Ser185Gly, Asp186His and Met169frameshift were recognized in the Thai ovarian cancer patients (Table 2) (Neungton *et al.*, 2002; Petitjean *et al.*, 2007; Rivlin *et al.*, 2011). As already mentioned, the *TP53* mutations are normally detected in high-grade serous ovarian carcinomas (HGSOC). Recent study demonstrated that more than 90% of HGSOC had mutation in *TP53*. Missense mutations showed high p53 expression by immunohistochemistry while low p53 expression was observed in non-missense mutations. Wild-type *TP53* tumors tended to display intermediate p53 levels (Prat and Franceschi, 2014; Cole *et al.*, 2016).

Current trends in mutation-based treatment of ovarian cancer

BRCA1 mutations have been reported to be more common than other genes in young patients with early onset ovarian cancer. The mutation rate was as high as 33.3% in patients under the age of 40. Most of the patients carrying mutations in this gene were diagnosed with advance (stage III-IV) ovarian cancer and had high-grade serous histology (Rudaitis *et al.*, 2014; Bernards *et al.*, 2016; Norquist *et al.*, 2016). Patients with mutations in *BRCA* tend to be more sensitive to platinum compound chemotherapy such as cisplatin and carboplatin than the non-carrier patients. This characteristic resulted from the loss of platinum-induced double-strand break repair ability. It also increased sensitivity to PARP (poly(ADP)-ribose polymerase) inhibitor and other DNA-damaging chemotherapeutic agents including pegylated liposomal doxorubicin. However, the mutation carrier group seemed to have neutropenia risk after the first cycle of chemotherapy and increased risk of radiation toxicity (Dann *et al.*, 2012; Huszno *et al.*, 2013; Tan and Kaye, 2015). Olaparib, the PARP inhibitor, is a tumor-specific cytotoxic agent that provides minimal side effects than the platinum-based compound. It has been proposed to be used in patients with platinum-sensitive relapsed as monotherapeutic maintenance treatment or in combination with cisplatin, in order to reduce the toxicity and prolong the progression-free survival of high-grade serous ovarian cancer with a *BRCA1/2* mutation (Balmaña *et al.*, 2014; Ledermann, 2016; De Jaeghere *et al.*, 2017).

Predictive role of *TP53* mutations on chemoresistance has also been studied. However, an intricate role of mutated *TP53* in the response to chemotherapy is still unclear (Laframboise *et al.*, 2000; Gadducci *et al.*, 2006; He *et al.*, 2016). Many therapeutic approaches have been proposed to overcome

TP53-associated carcinomas. Those of which include p53 targeting compounds that have the ability to 1) activate or restore the wild-type function of p53; 2) reactivate and rescue the mutant p53; or 3) kill the cancer cells carrying mutant p53 by synthetic lethal mechanism. The compounds that activate or restore p53 function are suitable for wild-type p53 containing patients. In contrast, the compounds that reactivate or kill mutant p53 cells are suitable for patients harboring p53 mutation. Moreover, gene therapy using wild-type *TP53*, *Mdm2* siRNA for inhibiting the function of Mdm2 (p53 negative regulator), and p53-based vaccines were also noted (Lane *et al.*, 2010; Wang and Sun, 2010; Duffy *et al.*, 2017).

Table 2 *TP53* mutations identified in Thai ovarian cancer patients.

***TP53* mutation**		**Exon**	**Variation type**	**Age of onset**	**No. of cases**	**References**
Nucleotide change	**Amino acid change**					
13059C>T	Ser127Phe	5	MS	56	1	Neungton *et al.*, 2002
13186insA	Met169frameshift	5	FS	45	1	
13232A>G	Ser185Gly	5	MS	37	1	
13235G>C	Asp186His	5	MS	30, 40	2	

MS, missense; FS, frameshift

Importance of genetic testing and their applications

Nowadays, the role of *BRCA1/2* mutation screening in prediction and prognosis of ovarian cancer is established. Several screening and primary prevention options such as prophylactic mastectomy/oophorectomy and chemoprevention have been suggested for those individuals who have *BRCA1/2* mutation. Once the *BRCA* mutation has been identified in a family, it is recommended that *BRCA1/2* mutation screening should be performed in other family members in order to decrease risk by early intervention before cancer is diagnosed (Petrucelli *et al.*, 2010). The risk-reducing salpingo–oophorectomy is offered to women who have known to be at high risk for developing ovarian cancer based on *BRCA1/2* mutation carrier status. This prevention procedure can reduce the risk of ovarian cancer by 71–96%. In addition, knowing the *BRCA* status provides patient opportunity to be managed with targeted treatment using a PARP inhibitor (Smith *et al.*, 2015; Karakasis *et al.*, 2016). Olaparib is used for treatment advanced epithelial ovarian cancer patients who have mutations in the *BRCA* genes. Some recent studies indicated that *BRCA*-associated ovarian cancer patients with olaparib maintenance had better progression-free survival when compared with those who receiving chemotherapy alone (Ledermann *et al.*, 2014; Oza *et al.*, 2015). Hence, the *BRCA* mutations are recommended to be checked as predictive markers in ovarian cancer for selection of the most suitable regimen for the patients.

Not only *BRCA1* but *TP53* mutations were also detected in high-grade serous ovarian cancer (HGSOC) (Prat and Franceschi, 2014; Cole *et al.*, 2016). Due to the severity of *TP53*-associated ovarian cancer, many studies tried to cope with this problem by creating p53 targeted therapy. Knowing the *TP53* status including mutational sites and expression level are required for therapeutic targeting of p53 (Lane *et al.*, 2010; Wang and Sun, 2010; Duffy *et al.*, 2017). Taken together, testing for *BRCA1* and *TP53* mutations along with appropriate genetic counseling could provide valuable information for ovarian cancer patients and their family members, and thus the data can directly impact clinical care.

CONCLUSION

The incidence of ovarian cancer is increasing continuously. Ovarian cancer associated death tends to be more common in developed country than others. Same phenomenon is also found in Thailand where the data showed that incidence rate of ovarian cancer in female is higher in the capital city, Bangkok, than other provinces. (Imsamran et al., 2015; Prat and Franceschi, 2014). Even though the real risk factors are difficult to be identified, genetic factor is shown to be one that implicates in ovarian tumorigenesis and progression. *BRCA1* and *TP53* mutations are commonly found in ovarian tumors especially in high-grade serous ovarian cancer. Many findings have been demonstrated that abnormality in both *BRCA1* and *TP53* genes increases the risk of developing aggressive cancer. (Cavallone et al., 2008; Prat and Franceschi, 2014; Yarden et al., 2010). Since BRCA1 and p53 are tumor suppressor proteins serve in the DNA damage repair process, the mutated proteins could not reserve their ability to maintain genetic stability thus leading cells to divide uncontrollably (Köbel et al., 2008). Mutations of *BRCA1* and *TP53* have been studied among ovarian cancer patients in

many population groups. The mutations were different depending on their ethnicity. In Thai patients, six pathogenic *BRCA1* mutations and four *TP53* mutations have been reported. The *BRCA1* 3300delA and *TP53* G13235C were observed in more than one ovarian cancer patients hence it believed to be cancer associated mutations in Thai group (Chirasophon et al., 2017; Neungton et al., 2002; Patmasiriwat et al., 2002). However, the number of studied cases was still low. In order to get the real founder mutations, more studies are needed. As mentioned above, targeted treatments are available for ovarian cancer patients with mutations in *BRCA1* and *TP53* (Duffy et al., 2017; Ledermann et al., 2014). Information regarding *BRCA1* and *TP53* mutations will help to develop genetic screening test which is important for primary prevention and treatment selection.

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