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SHORT REPORT

Germline *BRCA* mutations in Asian patients with pancreatic adenocarcinoma: a prospective study evaluating risk category for genetic testing

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Summary *Introduction* Germline *BRCA* mutations may have therapeutic implications as surrogate markers of DNA-damage repair status in pancreatic ductal adenocarcinoma (PDAC). We performed a prospective study to evaluate the efficiency of risk criteria based on personal or family history of breast and ovarian cancer for determining germline *BRCA* mutations in PDAC patients with Asian ethnicity. *Methods* Between November 2015 and May 2016, we screened consecutive PDAC patients with locally advanced unresectable or metastatic disease who were referred for systemic chemotherapy. Analyses for germline *BRCA* mutations were performed if patients had one or more first-degree or second-degree relatives with breast or ovarian cancers or had a personal medical history of these diseases. DNA was extracted from whole blood, and all coding exons and their flanking intron regions of *BRCA1* and *BRCA2* were sequenced. *Results* A total of 175 patients were screened for personal and family history and 10 (5.7%) met the inclusion criteria for genetic sequencing. Pathogenic germline *BRCA2* mutation [c.7480C>T (p.Arg2494*)] was identified in one male patient, resulting in a frequency of 10% for the risk-stratified patients and 0.6% for the unselected PDAC population. Two patients had germline *BRCA2* variants of uncertain significance [c.1744A>C (p.Thr582Pro) and c.68-7T>A]. *Conclusion* Personal or family history of breast or ovarian cancers is a feasible, cost-effective risk categorization for screening germline *BRCA* mutations in Asian PDAC patients as 10% of this population had the pathogenic mutation herein. Future validation from a large, prospective cohort is needed.

Keywords *BRCA1* · *BRCA2* · Pancreatic ductal adenocarcinoma · Genetic testing

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a well-known disease with poor prognosis, having a 5-year survival rate of <6% [1]. At the time of diagnosis, 10%–20% patients with PDAC are categorized as potentially curable with surgical resection [2]. However, the overall survival (OS) of patients as reported in large phase 3 trials for adjuvant chemotherapy ranges between 20 and 25 months even after resection and postoperative chemotherapy [3–5].

In recent years, the efficacy of systemic chemotherapy for PDAC has been enhanced using combination chemotherapy regimens, such as FOLFIRINOX (fluorouracil [5-FU],

leucovorin, irinotecan, and oxaliplatin) and gemcitabine plus *nab*-paclitaxel [6, 7]. Despite these improvements, overall prognosis for metastatic PDAC is still dismal as median OS is <1 year.

Approximately 5%–10% patients with PDAC are regarded to have hereditary predisposition [8, 9]. Among the inherited cancer susceptibility syndromes, germline mutations in *BRCA1* or *BRCA2* have been well defined for increased risk of PDAC development compared to the general population (2-fold with *BRCA1* and 3.5-fold with *BRCA2*) [10, 11]. The population frequency of pathogenic *BRCA1* and *BRCA2* mutations is estimated at 1 in 400 to 1 in 800, with exceptionally high prevalence in the Ashkenazi Jewish population (approximately 2%), but it varies depending on ethnicity [12–14].

DNA-damage repair deficiency status is well known for susceptibility to platinum-based chemotherapy or a poly (ADP-ribose) polymerase (PARP) inhibitor [15]. A recent study revealed that genomic instability and *BRCA* mutational signature status can be identified using whole-genome sequencing and did not necessarily require germline *BRCA1* and *BRCA2* in pancreatic cancer [16]. However, tests for germline *BRCA1* and *BRCA2* mutations are still the most widely used surrogate measures of DNA maintenance deficiencies in daily practice. As a previous Israeli retrospective analysis showed that platinum-based chemotherapy was associated with improved survival compared to non-platinum-based chemotherapies in PDAC patients with germline *BRCA1* and *BRCA2* mutations [17], *BRCA* mutations may be the valuable biomarker in patients with PDAC.

Previous studies have revealed that the prevalence of germline *BRCA1* and *BRCA2* mutations in overall PDAC patients ranged between 3% and 21% [18–22]. However, most of these data were from Western populations and limited data is available from Asian populations. Considering that *BRCA* mutation prevalence is higher in patients with Ashkenazi Jewish ancestry, the frequency of *BRCA* mutation in the Asian PDAC patient population may be less than previous studied populations. A previous Korean study, which evaluated germline *BRCA2* mutation for 60 unselected patients with PDAC, could not find any patient with pathogenic mutation [23].

Given the high cost and low positive rate, genetic tests for germline *BRCA1* and *BRCA2* mutations are not currently recommended for unselected PDAC patients in the daily practice setting. In contrast that several criteria have been suggested for *BRCA* mutations in patients with breast or ovarian cancer [24], but no such criteria exist for patients with PDAC. Therefore, we performed a prospective study to evaluate the efficiency of risk criteria based on personal and family history of breast and ovarian cancer in PDAC patients of Asian ethnicity.

Patients and methods

Patients

Between November 2015 and May 2016, we screened consecutive patients with locally advanced unresectable or metastatic PDAC who were referred for systemic chemotherapy to the Department of Oncology, Asan Medical Center, Seoul, Korea. Analyses for germline *BRCA1* and *BRCA2* mutations were performed if patients had one or more first-degree or second-degree relatives with breast or ovarian cancers or had a personal medical history of breast or ovarian cancer.

Participants provided informed consent, a cancer family history and personal medical history, and allowed access to current and previous cancer treatment records. This study was approved by the Institutional Review Board of the Asan Medical Center and conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

BRCA mutation analysis

DNA was extracted from EDTA-anticoagulated whole blood using the QIAamp DSP DNA Mini Kit according to the manufacturer's instructions (Qiagen, Hilden, Germany). The concentration of extracted DNA was measured using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Carlsbad, CA, USA). All coding exons and their flanking intron regions of *BRCA1* and *BRCA2* were amplified by polymerase chain reaction using primer pairs designed by Primer3 software (Whitehead Institute for Biomedical Research, Cambridge, MA). Relevant regions were sequenced using a BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems) and an ABI 3730 Genetic Analyzer (Applied Biosystems Foster City, CA).

We classified the variants in accordance with the American College of Medical Genetics and Genomics guidelines. The mutation status was assessed using the Human Genome Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), or UMD (http://www.umd.be/BRCA1/, http://www.umd.be/BRCA2/). Functional effects of variants of unknown significance (VUSs) were predicted by sorting intolerant from tolerant, polymorphism phenotyping-2 (PolyPhen), LRT, FATHMM, MutationTaster, MutationAssesor, MaxEnt, and Genomic Evolutionary Rate Profiling score. The allele frequency (AF) of the VUSs were estimated on the basis of the 1000 Genome Project (1000GP, http://browser.1000genomes.org/index.html), the Exome Sequencing Project (ESP6500, http://evs.gs.washington.edu/EVS/), and the Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org/). Sequences were visualized for analysis using Sequencher 4.10.1 (Gene Codes Corporation, Ann Arbor, MI). The "A" of the ATG translation initiation codon is

described as position number 1 in *BRCA1* (NM_007294.3) and *BRCA2* (NM_000059.3).

Response evaluation and treatment

Baseline radiological tumor evaluations were performed at diagnosis and the response was evaluated every 6 or 8 weeks of treatment by the same imaging techniques used at baseline. Additional imaging was performed if disease progression was suspected Tumor response was determined according to the Response Evaluation Criteria in Solid Tumor version 1.1. In this study, treatment was not prespecified and was administered at the discretion of the attending physicians.

Statistical analysis

Progression-free survival (PFS) was defined as the duration from the first day of chemotherapy to disease progression or death from any cause, whichever occurred first. OS was calculated from the date of first chemotherapy to the date of death because of any cause. Data were censored if the disease had not progressed on last evaluation or patients were still alive at the time of analysis (December 31, 2016). PFS and OS were estimated using the Kaplan–Meier method. All statistical analyses, including descriptive statistics, were performed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp).

Results

Patient characteristics

During the study period, a total of 175 patients received systemic chemotherapy for locally advanced unresectable or metastatic PDAC. Among them, 10 (5.7%) patients met the prespecified criteria for analysis of germline *BRCA1* and *BRCA2* mutations. Of these 10, six (60%) patients had family history of breast or ovarian cancers and four (40%) patients had previous medical history of breast cancer. All patients agreed to undergo the genetic testing for germline *BRCA1* and *BRCA 2*.

Patient characteristics and treatment outcomes are listed in Table 1. The median age was 60 years (range 49–72 years) and five patients (50%) were male. All patients received chemotherapy for locally advanced unresectable ($n = 3$, 30%) and metastatic or recurrent disease ($n = 7$, 70%). FOLFIRINOX was most commonly used ($n = 6$, 60%), followed by gemcitabine-based regimens ($n = 3$, 30%) and FOLFOX ($n = 1$, 10%).

Germline BRCA mutations

Among 10 patients undergoing germline variant evaluation, pathogenic variants and VUSs were found in one (10%) and two (20%) patients, respectively (Table 1). These three variants have been previously reported in cancer patients. The pathogenic variant detected in our study was *BRCA2* c.7480C > T (p.Arg2494*) and VUSs were *BRCA2* c.1744A > C (p.Thr582Pro) and c.68-7 T > A, a single-nucleotide variant. The frequency data, including ExAC, ESP6500, and 1000GP, showed that the AF of these two VUSs was <0.1% in the general population. According to in silico analyses, they were predicted to have benign or neutral effects. Recent updates indicate that these two variants have benign or uncertain effects according to ClinVar.

Clinical outcomes

In overall patients, median PFS and OS were 4.2 months (95% confidence interval [CI], 0.8–7.7) and 9.3 months (95% CI, 6.0–12.5), respectively (Table 1). Partial response was observed in 2 patients (20%) and progressive disease was the best response in 2 patients (20%). The patient with pathogenic *BRCA2* mutation showed partial response and median PFS of 4.6 months with modified FOLFIRINOX and median OS was 9.3 months. This patient had exposure to cisplatin after failure of FOLFIRINOX. Two patients with VUSs of BRCA2 showed median PFS of 2.2 with modified FOLFIRINOX and 5.5 months with *nab*-paclitaxel plus gemcitabine.

Clinical courses of patients with BRCA-mutant PDAC

The patient (No.3, Table 1) with pathogenic germline *BRCA2* mutation was a 63-year-old male with pancreatic head adenocarcinoma and liver metastases. His younger sister was diagnosed with breast cancer. He had a nonsense mutation (p.Arg2494*) in *BRCA2*. He received modified FOLFIRINOX as first-line chemotherapy. Although a partial response was achieved after four cycles, the response duration was only 10 weeks (Fig. 1). As second-line chemotherapy, a combination of gemcitabine and cisplatin was administered. Despite a slight decrease in pancreas and liver tumor sizes after 6 weeks of gemcitabine plus cisplatin, the tumors progressed after 3 months of treatment. Although the patient received subsequent third-line S-1, an oral fluoropyrimidine, disease progressed very rapidly, and he died 9 months after being diagnosed with PDAC.

Two patients, found to have *BRCA2* VUSs, were both women previously diagnosed and treated for breast cancer. The patient harboring a *BRCA2* c.1744A > C (p.Thr582Pro) mutation (No.4) received modified FOLFIRINOX, but PFS was only 2.2 months. The patient with *BRCA2* c.68-7 T > A mutation (No.9) was treated with *nab*-paclitaxel plus gemcitabine. For this patient, partial response was achieved

Table 1 Summary of findings and treatment of 10 patients meeting the classification for germline *BRCA* tests

No.	Sex	Age, years	Stage	Metastatic site	Family history	Personal history	*BRCA* Mutation result	1st line therapy	Best response on 1st line chemotherapy	PFS (months)	2nd line therapy	Survival	OS (months)
1	M	57	IV	Liver	Sister, breast cancer	No	No	Modified FOLFIRINOX	SD	2.3	Gemcitabine/*nab*-paclitaxel	Death	6.6
2	F	49	III		Sister, breast cancer	No	No	Modified FOLFIRINOX	SD	12.8		Alive	16.1+
3	M	63	IV	Liver	Sisters (2), breast cancer	No	*BRCA2* (7480C > T)	Modified FOLFIRINOX	PR	4.6	Gemcitabine/Cisplatin	Death	9.3
4	F	52	IV	Liver, bone	No	Breast cancer	*BRCA2* VUS (1744A > C)	Modified FOLFIRINOX	SD	2.2	Gemcitabine	Death	10.5
5	F	65	IV	Liver, lung	No	Breast cancer	No	Modified FOLFIRINOX	SD	4.2	Gemcitabine	Death	7.0
6	F	72	III		No	Breast cancer	No	Modified FOLFIRINOX	PD	1.3	Gemcitabine	Death	7.6
7	M	55	III		Mother, ovarian cancer	No	No	Gemcitabine	SD	7.2		Alive	7.3+
8	M	54	IV	Peritoneum	Mother, breast cancer	No	No	Gemcitabine	PD	1.6	XELOX	Alive	7.9+
9	F	69	IV	Liver	No	Breast cancer	*BRCA2* VUS (68-7 T > A)	Gemcitabine/ *nab*-paclitaxel	PR	5.5		Alive	7.1+
10	M	65	IV	Liver	Sister, breast cancer	No	No	FOLFOX	SD	5.4	S-1	Death	14.5

PFS = progression-free survival, OS = overall survival, VUS = variants of unknown significance, PR = partial response, SD = stable disease, PD = progressive disease

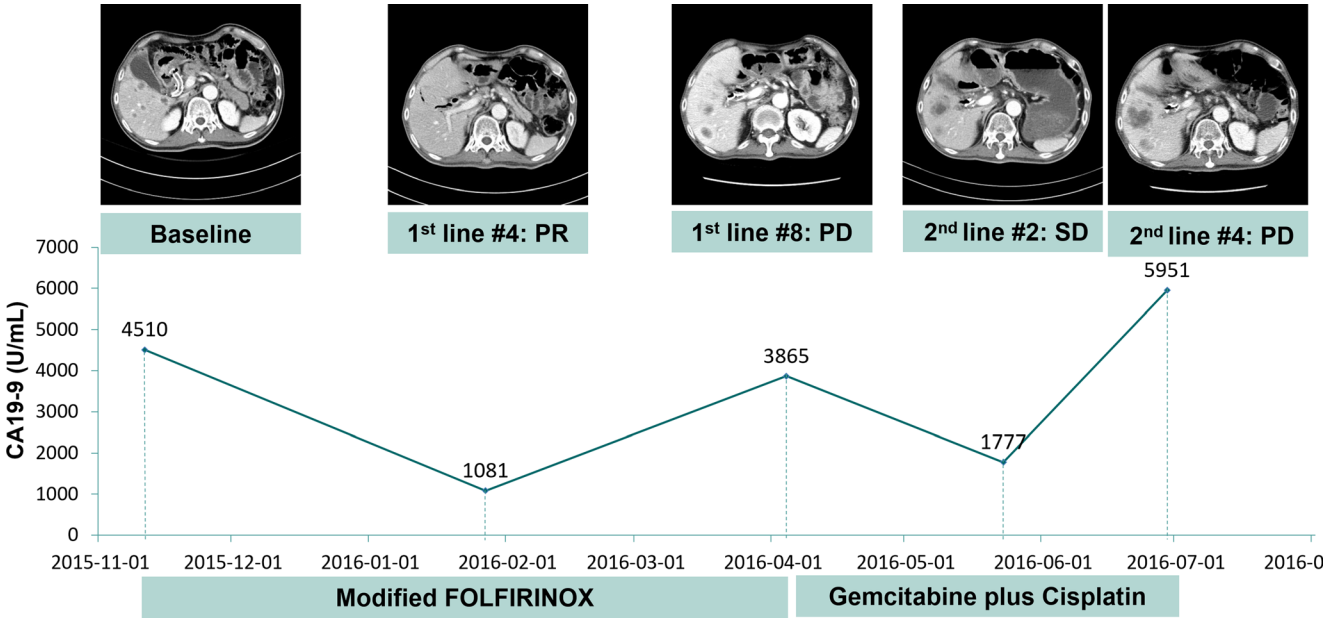

Fig. 1 Clinical course and outcomes of the patient with a pathogenic *BRCA*2 mutation (patient No.3)

and the disease remained stable at the time of analysis (7.1 months after the start of chemotherapy).

Discussion

Our study prospectively evaluated the frequency of germline *BRCA1* and *BRCA2* mutations in advanced PDAC patients with Asian ethnicity screened by personal and family cancer history. We screened 175 patients for personal and family cancer history and found 10 patients who met the prespecified criteria—a personal history of breast or ovarian cancers or one first-degree or second-degree relative with breast or ovarian cancers—and underwent genetic testing for *BRCA1* and *BRCA2* mutations. There was one patient with pathogenic mutation of *BRCA2*, indicating a frequency of 10% in the risk-stratified patient group and 0.6% in the unselected patient population. Our findings suggest that determining germline *BRCA* mutation risk category using personal and family history of breast or ovarian cancer might be feasible in the Asian population.

Although previous studies reported a *BRCA* mutation prevalence in patients with PDAC of up to 21%, most recent large cohort studies have reported approximately a 3% *BRCA* mutation prevalence in PDAC patients overall [22, 25, 26]. The discrepancy in *BRCA* mutation prevalence among the studies may be because of the proportion of PDAC patients with Ashkenazi Jewish ancestry, as this population has a high reported prevalence of *BRCA* mutations (10%–14%) [22, 27]. In

Table 2 Prevalence of *BRCA1/BRCA2* mutations in patients with pancreatic cancer

	Current study	Takai et al. [28]	Salo-Mullen et al. [27]	Holter et al. [22]
Nationality	Korea	Japan	United States	Canada
Number of patients	175	63	175	306
Proportion of AJ ancestry	0	0	98 (56.0%)	33 (10.8%)
Risk category for genetic tests	Yes	Yes	Yes	No
	Personal history or ≥1 FDR or SDR with breast and ovarian cancers	(1) Familial pancreatic cancer (2) Personal history of breast and ovarian cancers	Patients who underwent clinical genetic counseling	
Number of patients with testing for *BRCA* mutation	10	(1) 54 (2) 13	151	306
Frequency of pathogenic *BRCA1* and *BRCA2* mutations	1 (10.0%)	(1) 3 (5.6%) (2) 2 (15.4%)	13 (13.7%) in AJ ancestry 4 (7.1%) in non-AJ ancestry	4 (12.1%) in AJ ancestry 10 (3.7%) in non-AJ ancestry

AJ = Ashkenazi Jewish, FDR = first-degree relative, SDR = second-degree relative

these studies, mostly using a Western patient population, the *BRCA* mutation prevalence ranged from 4 to 7% in PDAC patients with non-Ashkenazi Jewish ancestry (Table 2).

Until recently, only a few studies have evaluated the prevalence of *BRCA* mutations in PDAC patients with Asian ethnicity. In a previous Korean study testing *BRCA2* mutation only, no pathogenic mutation was found in 60 unselected patients with PDAC [23]. A recently published Japanese study reported the prevalence of germline mutations in familial PDAC patients with at least one first-degree relative with PDAC [28]. In this study, targeted deep sequencing of peripheral blood was performed for 21 genes known to be associated with hereditary predispositions to pancreatic, breast, and ovarian cancers, including *BRCA1* and *BRCA2*. *BRCA2* mutations were detected in three (5.6%) of 54 patients with familial pancreatic cancer. The results of these Asian studies, including ours, indicate that germline *BRCA* mutations may be less frequent in Asian PDAC patients. However, because there was no large cohort study evaluating all unselected patients with PDAC, the exact prevalence of *BRCA1* and *BRCA2* mutations in Asian PDAC patients remains unclear.

Because *BRCA1* and *BRCA2* mutations may have therapeutic implications for patients with PDAC, relevant risk criteria for genetic testing are needed considering their low prevalence in PDAC patients, except those with Ashkenazi Jewish ancestry. Our study suggests that personal and family history of breast and ovarian cancer might be a good indicator for genetic screening for *BRCA1* and *BRCA2* mutations in PDAC patients with non-Ashkenazi Jewish ancestry, at least in terms of cost effectiveness. Our results are consistent with those in previous studies. A study conducted in the United States showed that prevalence of *BRCA1* and *BRCA2* mutation prevalence was 9% (4 of 44) in PDAC patients with non-Ashkenazi Jewish ancestry and ≥1 first-degree or second-degree relatives with breast, ovarian, or pancreatic cancer [27]. A large Canadian cohort study showed that BRCA mutation positive rates were 13.3% (2 of 15) in patients with a personal history of breast cancer, 10% (5 of 50%) in patients with ≥1 first-degree relatives with breast cancer, and 22.2% (2 of 9) in patients with ≥1 first-degree relatives with ovarian cancer, although there was only marginal significance ($p = 0.06$) for increased *BRCA* mutation frequency compared to those without family history of breast or ovarian cancers [22]. A Japanese study also showed that BRCA positive rates were 15.4% (2 of 13) in patients with a personal history of breast or ovarian cancers [28]. Although familial history of pancreatic cancer has also been regarded as potential risk category for genetic testing of *BRCA1* and *BRCA2* mutations, frequency of BRCA mutations were 5.4% (2 of 35 patients) in a Canadian study and 5.6% (3 of 54) in a Japanese study, which are much lower positive rates than categorization by family history of breast or ovarian cancers. [22, 28].

Despite the potential feasibility of using personal or family history of breast or ovarian cancer to determine genetic testing of *BRCA1* and *BRCA2* mutations, there are some issues to be globally accepted. The most important one is that this risk category can determine only a subset of patients with *BRCA* mutations, as only 30%–40% *BRCA* mutation carriers met various definitions for family breast/ovarian cancer history in a previous Canadian study [22]. This indicates that our study may miss the subgroup of patients with *BRCA*-mutated PDAC. Nevertheless, because there were no other predictive factors for *BRCA* mutations in PDAC patients, except Ashkenazi Jewish ancestry [22, 27], personal or family history of breast or ovarian cancer may be a reasonable and cost-effective option for finding *BRCA* mutation in PDAC patients.

The prospective design of this study was beneficial for determining the risk category for detection of *BRCA* mutation carriers in PDAC patients with Asian ethnicity. However, the number of patients who met the prespecified criteria for genetic testing was too small, as only 10 of 175 patients were included. Because personal and family cancer history were based on the patients' self-reports, our study may underestimate the number of patients qualifying for our risk category. Some patients, particularly those with old age, may have had difficulty recalling family cancer history. Moreover, the number of patients with pathogenic *BRCA* mutation was too small to investigate the clinical phenotype of *BRCA*-mutated PDAC, such as the association between clinical characteristics and *BRCA* mutations, prognostic implication of *BRCA* mutation in PDAC, and efficacy of platinum-based treatment in *BRCA*-mutated PDAC.

In conclusion, personal or family history of breast or ovarian cancers is a feasible and reasonable risk categorization for germline *BRCA1* and *BRCA2* mutations in Asian PDAC patients. Despite of our results, as recent whole-genome study suggested that *BRCA* mutation signatures, potential biomarkers for platinum or PARP inhibitors, in PDAC are not limited in patients with germline *BRCA* mutation carriers [16], further studies are needed to define the subgroup of PDAC patients with this phenotype.

Compliance with ethical standards

Funding This study was supported by a grant (2015–0753) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea.

Conflict of interest The authors indicate no potential conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Institutional Review Board of the Asan Medical Center and informed consent was obtained from all individual participants included in the study.

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