REVIEW

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Familial Pancreatic Cancer and Surveillance of High-Risk Individuals

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Family history of pancreatic cancer (PC) is a risk factor for PC development, and the risk level correlates with the number of affected families. A case of PC with ≥1 PC cases in the first-degree relative is broadly defined as familial pancreatic cancer (FPC) and accounts for 5% to 10% of total PC cases. FPC possesses several epidemiological, genetic and clinicopathological aspects that are distinct from those of conventional PCs. In Western countries, FPC registries have been established since the 1990s, and high-risk individuals are screened to detect early PCs. For the pharmacotherapy of FPC, especially in cases with germline pathogenic *BRCA* mutations, regimens using platinum and poly (ADP-ribose) polymerase inhibitor have recently been studied for their effectiveness. To date, the concept of FPC has prevailed in Western countries, and it has begun to infiltrate into Eastern countries. As the genetic background and environmental conditions vary in association with ethnicity and living area, we need to establish our own FPC registries and accumulate data in Asian countries. **(Gut Liver 2019;13:498-505)**

Key Words: Familial pancreatic cancer; High risk; Genetic; Surveillance; Treatment

INTRODUCTION

Various human cancers show family history as a risk of the same cancer developing in related family members.[1-3] Several case-control studies and cohort studies have demonstrated an increased risk of pancreatic cancer (PC) in those who have a first-degree relative (FDR) who is a PC patient (odds ratio [OR], 2.1[4] to 5.3[5]; relative risk [RR], 1.5[6] to 1.7[7]).[8] The incidence of PC increases with the number of family members with PC (4.5-fold increased risk in a family with one case of PC, 6.4-fold in those with two FDRs, and 32-fold in those with ≥3 FDRs).[9] In a large sense, the presence of two or more PC patients within FDRs is defined as familial pancreatic cancer (FPC).[10] In a narrow sense, known genetic syndromes are excluded from it;[9] such as Peutz-Jeghers syndrome,[11] hereditary pancreatitis,[12] familial atypical multiple mole melanoma,[13,14] hereditary breast-ovarian cancer (HBOC),[15-17] Lynch syndrome,[18,19] and familial adenomatous polyposis (Table 1).[20] The incidence of FPC among total cases of PC is 5% to 10%. We must bear in mind that "familial PC" is not a synonym for "inherited PC," and pathogenic germline mutation has been proven in only <20% of FPC cases.[21]

CHARACTERISTICS OF FPC

1. Epidemiology

FPC has several epidemiological features that distinguish it from ordinary PC. Similar to other familial cancers, FPC shows a trend toward a younger onset (FPC age, 58 years[22] to 68 years[23]; compared to sporadic PC [SPC] age, 61 years[22] to 74 years[23]) and an ethnic deviation (Ashkenazi Jewish >Caucasian).[15] The lifetime risk of PC also increases with decreasing age of onset of PC in family members.[23,24] Similar to sporadic cases, smoking,[8,25] and diabetes[8] are risks for FPC. Surprisingly, two European FPC registries[26-28] analyzed 106 FPC families through three generations and observed "anticipation" in the affected kindred of FPC patients;[29] that is, a trend existed toward younger age and worse prognosis in the latest generation.

2. Pathology and molecular biology (somatic)

The pancreatic histology of FPC kindred often demonstrates multiple precancerous lesions,[30] such as intraductal papillary mucinous neoplasm (IPMN) or pancreatic intraepithelial neoplasias (PanINs).[31,32] Shi *et al*.[33] reported that these intraductal neoplasms were more frequently recognized in the FPC than in the SPC pancreas (2.8-fold, p<0.05). These lesions in FPC kindred

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Table 1. Risk Level of Pancreatic Cancer in Individuals with Hereditary Cancer Syndromes

Inherited syndrome	Causative gene	Relative risk	Cumulative risk (%)
Peutz-Jeghers syndrome[11]	*STK11*	132	11–36
Hereditary pancreatitis[12]	*PRSS1*	53–87	40–55
Familial atypical multiple mole melanoma[13,14]	*CDKN2A/p16*	13–22	17
Hereditary breast-ovarian cancer syndrome[15-17]	*BRCA1/2*	4–13	2–7
Lynch syndrome[18,19]	*MLH1*, *MSH2*, *MSH6*, *PMS2*	5–9	4
Familial adenomatous polyposis[20]	*APC*, *MUTYH*	5	-

are associated with lobular parenchymal atrophy and chronic pancreatitis-like changes observable by endoscopic ultrasonography (EUS).[32]

Despite the difference in these precursor lesions,[30,32] a blind histological observation of 519 FPCs and 561 SPCs by expert pathologists did not show significant difference in terms of tumor size, location, neural invasion, angiolymphatic invasion, lymph nodal metastasis, and pathological stage.[34] The genome-wide allelic status,[35,36] and genetic (*K-ras*, *TP53*, and *DPC4*) and epigenetic (*CDKN2A*, *NPTX2*, *ppENK*, *SPARC*, etc.) alterations frequently observed in PCs[37] were also similar between SPC and FPC.

3. Genetics (germline)

However, in a small proportion (<20%) of FPC, deleterious germline mutation of the genes functioning in the homologous recombination (HR) pathway has been reported from the Western countries; *ATM* (mutation rate: 2% to 4%),[38] *BRCA1* (0% to 7%),[39,40] *BRCA2* (4% to 17%),[16,41] *CHEK2* (1% to 6%),[42] *PALB2* (1% to 3%),[43,44] and *RAD51* (4%). In Asian countries, Takai *et al*.[45] reported the similar mutation pattern in Japanese FPC cases (mutated in eight [15%] of 54 analyzed FPC cases: *BRCA2*, three; *PALB2*, two; *ATM*, two; and *MLH1*, one). In Korea, although germline *BRCA1/2* mutation was recognized in 22% of the breast cancer patients with a family history of breast and ovarian cancers,[46] null pathogenic *BRCA2* mutation was detected in 60 PC patients.[47] Even other than *BRCA*, defects of these genes cause dysfunction of the double strand DNA repair system (BRCAness).[48]

BRCA1/2 mutation carriers have a mild to moderate level of risk for PC (RRs, 2 to 8; lifetime risks, 2% to 17%), but some specific mutation types may have further increased risks. For instance, *BRCA2* 6174delT, which is a Jewish founder mutation, was detected in 13% (3/23) of Jewish PC cases (odds for having PC, 12.8).[49] The *BRCA2* K3326X mutation was detected in 5.6% (5/144) of American FPC cases, significantly more frequently than in SPCs.[50] A murine model confirmed that a germline *BRCA2* mutation suffices to promote carcinogenesis by the *KRAS* mutation,[51] which is recognized in nearly 90% of PC cases,[52] explaining the function of *BRCA2* mutation in FPC.

CLINICAL MANAGEMENT OF FPC

1. Familial pancreatic cancer registry

The FPC registry system began from the establishment of The National Familial Pancreas Tumor Registry (http://pathology.jhu.edu/pancreas/nfptr/history.php) (1994) at Johns Hopkins University (Baltimore, MD, USA).[53] This was followed by the European Registry of Hereditary Pancreatitis and Familial Pancreas Cancer (https://www.lctu.org.uk/LCTU_NET/frontend/Default.aspx?Data=W1tiRzlqWVd4bF1dW09RPT1d) (1997)[26] at Liverpool University (Liverpool, UK) and the German National Case Collection for Familial Pancreatic Carcinoma (http://www.fapaca.de/) (1999)[27] at Phillips University (Marburg, Germany). National FPC registries have also been established in Italy (2007),[54] Spain (2009),[55] Australia (2011), and Japan (Japanese Familial Pancreatic Cancer Registry, JFPCR; http://jfpcr.com) (2014).[56] JFPCR aims prospective cohort study for FPCs and their relatives, basically to clarify the etiology of FPC and to research basic and clinical aspects of FPCs. At the initial organization, experts including clinicians, pathologists, basic researchers, statisticians, and genetic counselors from 20 nationwide nuclear hospitals gathered and formulated on the management system. Until the end of 2017, 66 families and 468 high risk individuals (HRIs) have been registered on the JFPCR.

2. Surveillance of high-risk individuals

Consortiums and symposiums have also been organized among several high volume centers and/or FPC registries across the globe, such as International Symposium on Inherited Diseases of the Pancreas (1997~)[57] and International Cancer of the Pancreas Screening Consortium (CAPS) (2011~).[58] Their aims have been to gather information on patients and families of PC and to study the cause of FPC, with the ultimate goal of improving the clinical practice of counseling and screening of the HRIs, and to devise early detection methods for PC and better treatments.

1) Targeted pathological lesions

The CAPS consortium summit held in Baltimore (2011) concluded that the success of a screening program for HRIs is defined as the detection and treatment of high-grade precursors

(PanIN[31] and IPMN[59])–UICC-stage IA PC (T1N0M0; limited to the pancreas and no more than 2 cm in size).[58] Today, the overall survival of UICC-stage IA cancer is unsatisfactory (5-year survival, 68.7%). The ideal for a targeted lesion is thought as high-grade precursors–UICC-stage 0 PC (5-year survival, 85.8%).[60]

2) Screening candidates and lifestyle guidance at surveillance

The risk level of the candidate individual is assessed based on the numbers of affected family members and hereditary syndromes (Table 1). The international consortiums recommended that an individual who had a 5-fold risk[58,61] to 10-fold risk[57] undergo PC screening. At present, the CAPS consortium has proposed nine conditions for candidate HRIs (Table 2), within a setting of greater than a 5-fold risk or a 5% of lifetime risk of PC.[58] A screening strategy should also evaluate the risk factors of lifestyle and pancreatic diseases, such as smoking,[8,62] obesity,[63,64] physical inactivity,[64] diabetes,[8,57,65] chronic pancreatitis,[57,66,67] IPMN,[59] pancreatic cyst,[68] pancreatic duct ectasia,[68] and so forth. For instance, a patient with diabetes mellitus and a smoking history and a patient with one FDR with PC each showed a 10-fold risk when compared with negative controls.[8] Therefore, the initial counseling should be used to present modifiable risks related to the lifestyle to HRIs and their improvement should be recommended; that is, smoking cessation, a healthy diet high in fruits and vegetables (vitamin), and regular exercise to control weight (body mass index <25 kg/m^2).[57]

3) Modalities of screening

Although not reaching complete consensus in the CAPS meeting,[58] EUS is though as the most suitable modality, based on its ability to detect small pancreatic lesions (<1 cm).[69,70] EUS is also superior at detecting risk findings frequently seen in HRIs, such as duct ectasia, cysts,[68] and parenchymal findings of the pancreas.[32] However, agreement is poor in terms of these characteristic findings, even among expert endosonographers.[71] Drawbacks of EUS include the necessity for a relatively long-time fasting period and conscious sedation, operator-dependent visualization and interpretation,[72] with a limited observation area in cases with a reconstructed upper gastrointestinal tract. In this sense, abdominal ultrasonography is a handy tool that may substitute for EUS if the pancreas is well visualized without any blind spots[68] for the Asian subjects with slim abdominal trunk. Magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) is good at visualization of the pancreatic ductal systems. Dilation of the pancreatic duct and cyst formation are risk factors for PC[68] and are actually frequently recognized in HRIs (cyst in 38.9% and duct ectasia in 2.3%),[73] making MRCP a promising tool for assessing the risk level of HRIs.

EUS and MRI are considered the most accurate image tools with high agreement among the consortium experts (agreement: EUS 83.7% and MRI/MRCP 73.5%).[58] EUS-guided fine needle aspiration and endoscopic retrograde cholangiopancreatography are applicable when abnormal findings or their changes are observed in other images.[69,74] In addition to image analysis, serum tumor markers, including carcinoembryonic antigen and carbohydrate antigen 19-9 should be checked each time.[58,74]

Table 2. Candidates for Screening According to Consensus of the International Cancer of Pancreas Screening Consortium

Individuals with ≥3 affected relatives, with ≥1 affected FDR
Individuals with ≥2 affected FDRs with PC, with ≥1 affected FDR
Individuals with ≥2 affected relatives with PC, with ≥l affected FDR
Peutz-Jeghers syndrome patients, regardless of family history of PC
Mutation carriers of *CDKN2A*, *BRCA*, *PALB2* or mismatch repair genes with 1 affected FDR
BRCA2 mutation carriers with 2 affected family members of PC

FDR, first-degree relative; PC, pancreatic cancer.

4) Timing to start screening and screening interval

Screening in many institutions is started at 40 years of age[69,75] or 10 years younger than the age of the youngest relative with PC.[27,74] As PC develops in cases of Peutz-Jeghers syndrome at a young age (40.8 years),[11] screening is started at 30 years old.[69] However, detection of pancreatic lesions increases after age 50 to 60 years old.[73] No consensus has been reached regarding the age to initiate screening and more than half (51%) of the experts in CAPS consortium voted the initial screening at age 50 years old.[58]

Many institutions opt for yearly screening if the latest EUS and/or computed tomography is normal.[58] Once an abnormal finding is observed, subsequent screening is done every 3 to 6 months[28,69,76] or 3 to 12 months.[58] The endorsed screening interval for a non-suspicious cyst is 6 to 12 months, 3 months for a newly detected solid lesion if surgery is not imminent, and 3 months for an indeterminate main pancreatic duct stricture. The natural history and progression of FPC still require study to determine the appropriate duration for screening intervals in relation to the risk level.

5) Surgical indications and procedures

The extent of resection is controversial, depending on the therapeutic concept. The choices are to remove all precancerous lesions[74] or to resect only a targeted area that includes nodular or cystic lesions.[69] In cases of HBOC with the *BRCA* mutation, risk-reducing salpingo-oophorectomy is affordable and has an acceptable level of complications.[77] However, for the pancreas, total pancreatectomy (TP) has severe complications, including a considerable level of postsurgical in-hospital mortality (5% to 23% in Germany)[78,79] and subsequent serious glycemic control failure (mortality, 4% to 8% per year).[80] A secondary pancreatectomy for the remnant pancreas can be conducted without increasing morbidity and mortality,[81] so resection of the target

Table 3. Representative Series of Pancreatic Cancer Surveillance in High-Risk Individuals*

Author	Year	Country /registry	No.	Subjects		Duration (mo)	Modality		Rate of surgical cases (n)	Pathology of the pancreatic lesion			Rate of unresectable advanced PC (n)
				Age (yr)	Conditions		Surveillance	Examination		Benign†	Border/CIS‡	PC	
Canto *et al.*[83]	2004	USA	38	58	FPC kindred, PJS	22	EUS	CT, EUS-FNA, ERCP	18.4 (7)	4	2	1	0
Canto *et al.*[69]	2006	USA	78	52	FPC kindred, PJS	12	EUS, CT	EUS-FNA, ERCP	9.0 (7)	4	3	0	1.3 (1)
Langer *et al.*[28]	2009	FaPaCa	76	60	FPC kindred, *BRCA2* (+),§ *CDKN2A* (+) FAMMM family	NA	EUS, MRI	EUS-FNA, ERCP	9.2 (7)‖	6	0	0	0
Poley *et al.*[84]	2009	Netherlands	44	50	FPC kindred, HP, PJS, FAMMM, *BRCA1/2* (+), *TP53* (+)	Initial¶	EUS	CT, MRI	6.8 (3)	0	0	3	0
Verna *et al.*[85]	2010	USA	51	52	FPC kindred, *BRCA1/2* (+), LS, FAMMM	Initial	EUS, MRI	EUS-FNA, ERCP	9.8 (5)	4	0	1	2.0 (1)
Ludwig *et al.*[86]	2011	USA	109	54	FPC kindred, *BRCA1/2* (+)	Initial	MRI	EUS, EUS-FNA	5.5 (6)	3	2	1	0
Vasen *et al.*[87]	2011	Netherlands	79	56	*CDKN2A-Leiden* (+)	48	MRI	MRI	6.3 (5)	0	0	5	2.5 (2)#
Al-Sukhni *et al.*[88]	2012	Canada	262	54	FPC kindred, PJS, HP, *CDKN2A* (+), *BRCA1/2* (+)	50	MRI	EUS, EUS-FNA, ERCP	1.5 (4)	3	0	1	0.8 (2)
Del Chiaro *et al.*[89]	2015	Sweden	40	50	FPC kindred, individuals with increased genetic risk	13	MRI	EUS, EUS-FNA	12.5 (5)	2	0	3	0
Vasen *et al.*[90]	2016	FaPaCa	411	46–56	FPC kindred, *CDKN2A* (+), *BRCA1/2* (+), *PALB2* (+)	16–53	MRI±EUS	EUS, CT, EUS-FNA	7.3 (30)	15	4	11	1.0 (4)#
Canto *et al.*[76]	2018	USA	354	56	FPC kindred, PJS, *BRCA1/2* (+), *PALB2*, *PRSS1*, *CDKN2A* (+), mismatch repair genes (+)	67	EUS, MRI, CT	EUS-FNA	12.4 (44)	20	10	14	1.1 (4)**

CIS, carcinoma *in situ*; PC, pancreatic cancer; FPC, familial pancreatic cancer; PJS, Peutz-Jeghers syndrome; EUS, endoscopic ultrasonography; CT, (enhanced) computed tomography; EUS-FNA, EUS-guided fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography; FaPaCa, German national case collection for familial pancreatic cancer; FAMMM, familial atypical multiple mole melanoma; NA, not available; MRI, magnetic resonance imaging; HP, hereditary pancreatitis; LS, Lynch syndrome.

*Only studies screening ≥30 high-risk individuals are listed; †Benign lesions included low-moderate grade of intraductal papillary mucinous neoplasm, grade 1 to 2 of pancreatic intraepithelial neoplasm (PanIN), serous cystadenoma, and neuroendocrine tumor; ‡High-grade precursors and PanIN3; §(+), Mutation carrier; ‖No lesion detected in one case of resected pancreas; ¶Evaluated only by the initial surveillance, one resectable pancreatic cancer case (T1N0M0) not resected because of metastatic melanoma; #Widespread dysplasia; **Advanced PC was detected outside surveillance are in 3 of 4 cases.

area, rather than TP, has been preferable thus far. However, most recently, due to the improvements in postsurgical quality of life, TP combined with islet autotransplantation have been considered and actually indicated for FPC kindred with premalignant lesions.[80,82] Further improvements are expected in the future.

6) Present outcome of surveillance

Several surveillance results have been reported from the Western FPC registries (Table 3).[21,28,69,76,83-90] About 2% to 18% of the screened HRIs underwent surgery for suspected lesions. Roughly 30% to 40% of the resected cases were benign lesions that underwent unnecessary treatment, and only less than one fifth were borderline precursors and carcinoma *in situ*, or definitive targets of the surveillance. A small proportion of PC was resected at an early phase (T1N0M0),[90] and some PC cases were detected at the advanced unresectable stage. These outcomes are still apart from the goal of the surveillance. However, a recent study from Johns Hopkins demonstrated that 3-year survival rate of 10 PC cases diagnosed during surveillance was 85% and was significantly longer than those detected outside the surveillance (p=0.0009). Also 10 cases with PanIN3 or high-grade IPMN were all alive after surgery (4.1 to 14.7 year). These data suggested that current surveillance system prolonged the PC-associated survival in HRIs.[76]

CHEMOTHERAPY FOR FAMILIAL PANCREATIC CANCER WITH *BRCA* MUTATION

For unresectable PC, on the basis of current evidence, FOLFIRINOX (fluorouracil, folic acid, irinotecan, and oxaliplatin) and gemcitabine-based regimens are standard choices of chemotherapy (median survival, 11 and 6–9 months, respectively).[91] However, in agreement with the response observed in HBOC patients,[92,93] PC patients with germline *BRCA1/2* mutation carriers respond well to platinum-based chemotherapy. Golan *et al*.[94] retrospectively compared overall survival (OS) of 43 patients with stage III-IV PC with *BRCA* mutation carriers in terms of their chemotherapy regimen—either platinum or non-platinum. Superior OS was observed for patients treated with platinum chemotherapy (n=22) than with non-platinum (n=21) (22 months vs 9 months; p=0.039). A similar effect was experimentally confirmed. PC xenografts harvested from *BRCA* mutation carriers and implanted into nude mice showed sensitivity to both gemcitabine and cisplatin, meanwhile, xenografts from *BRCA* wild cases demonstrated sensitivity only to gemcitabine.[95] A joint study by Johns Hopkins University and the MD Anderson Cancer Center[96] analyzed effectiveness of platinum-based chemotherapy in metastatic PC patients (n=549) by familial cancer history, although *BRCA* status was not described, and demonstrated a superior OS in patients with family history of either breast, ovarian, or PC (p=0.003). Survival was strongly associated with the number of relatives with *BRCA*-related malignancy (p=0.009). Kondo *et al*.[97] analyzed on the somatic mutations of HR-related genes (written in above) in 30 PC cases and reported longer progression-free survival after initiation of oxaliplatin-based chemotherapy in HR-related gene mutant group than in wild-type group (20.8 months vs 1.7 months, p=0.049).

Kaufman *et al*.[93] reported that a PARP inhibitor (PARPi) treatment induced a 22% response ratio with 4.6 months of progression-free survival in *BRCA*-mutant PC patients who had already showed progression resistant to the gemcitabine treatment. PARPi may be effective not only for breast and ovarian cancers[98] but also for PC cases with deficiency in the HR pathway; that is, as mentioned, in cases with either mutation of *ATM*, *CHEK2*, *BRCA1*, *BRCA2*, *PALB2*, or *Rad51*. This outcome is explained by a synthetic lethal theory, where apoptosis is induced by blocking both the single- and double-strand DNA break repair system.[99] Currently, data are lacking with respect to PARPi use against FPC in causative mutation carriers and several phase II/III studies are now ongoing (https://clinicaltrials.gov). Future outcomes are expected.

CONCLUSIONS

Family history of PC and some genetic syndromes need to be taken into account when screening to detect early pancreatic cancer. So far, basic and clinical researches on the basis of family registries have accumulated much scientific information of FPC in the Western countries. However, at present, outcome of screening of HRIs is still not satisfactory. As life style, food, ethnicity, and medical system are different between the Western and Eastern countries, to detect early PC, we need to establish our own FPC registries and surveillance programs in the Asian countries.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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