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TOPICS

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Clinical importance of Familial Pancreatic Cancer Registry in Japan: a report from kick-off meeting at International Symposium on Pancreas Cancer 2012

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Abstract Pancreatic cancer is still a highly lethal disease with a 5-year survival rate of approximately 5 %. Early detection offers one of the best hopes for improving survival. Previous cohort studies and case–control studies showed that 4–10 % of pancreatic cancers have a hereditary basis, and individuals with a family history have an increased risk of developing pancreatic and extra-pancreatic malignancies. Since individuals with a family history of pancreatic cancer and those with a known genetic syndrome that predisposes to pancreatic cancer will be the first to benefit from early detection tests as they become available, familial pancreatic cancer (FPC) registries have been established in the US and Europe, but not yet in Japan. Such registries form the basis for epidemiological studies, clinical trials, and basic research on familial pancreatic cancer. There is a need for FPC registries in Japan as cancer risk varies among different populations and discoveries made in Western populations may not translate to the Japanese population. These registries in Japan will align with ongoing international efforts and add to a better understanding of the natural history, risk factors, screening strategies, and responsible genes, for improving survival of this dismal disease.

Keywords Familial pancreatic cancer · Risk factors · Screening

Introduction

Pancreatic cancer (PC) is the 5th leading cause of cancer-related death (>28,000 per year) in Japan, and the

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incidence is increasing [1]. According to the 30-year experience of the Japan Pancreatic Cancer Registry, the overall survival rate has been improving decade by decade for both resected and non-resected cases, with an overall 5-year survival of 18.8 % for resected cased registered between 2001 and 2007 [2]. These improvements are believed to be due to better patient selection, refinements in surgical techniques, and better postoperative patient care, in addition to effective adjuvant therapies. However, given the low incidence of resectable PC (20–30 % in general), the overall 5-year survival can be estimated at around 5 % at best, which is still the worst among gastrointestinal (GI) and non-GI solid malignancies [3].

Early detection and prevention offer the best hopes for reducing the mortality from pancreatic cancer. The survival rate of invasive PC is stage-dependent, and the survival for early disease is favorable [2, 3]. It is reported that small tumors $\leq$10 mm in diameter (T1a) have a favorable prognosis of >80 % at 5 years [2]. Furthermore, many invasive pancreatic cancers arise from non-invasive precursor lesions, such as intraductal papillary mucinous neoplasms (IPMN), and these non-invasive lesions are completely curable. These observations suggest that screening for pancreatic cancer may save lives, but screening the general population is problematic given the low incidence of PC in the general population (8.5–12 per 100,000 per year) [4, 5]. Hence, the identification of high-risk individuals (HRIs) is crucial for screening programs in PC.

Several environmental and genetic risk factors for developing PC have been identified and are summarized in Table 1 [6–19] and Table 2 [20–37]. Cigarette smoking is the strongest environmental risk factor for PC, with an increased odds ratio (OR) of 1.7–2.2 [6–9]. Diabetes mellitus and chronic pancreatitis also both increase risk, and both can also be a sign of the disease. Although most PC cases are sporadic in nature, up to 10 % of cases can be attributed to genetic predisposition [38, 39]. Familial pancreatic cancer (FPC) is a term once widely used to describe a general clustering of PC in a family, but FPC is now more specifically defined as a family in which at least two first-degree relatives (FDR) have been diagnosed with PC. In some FPC kindreds the disease appears to have an autosomal dominant inheritance with variable penetrance [40, 41]. Although less well-established, it has also been suggested in some, but not all, studies that some patients with FPC have a younger onset (by 5 years) [42–44], anticipation [45, 46], and worse prognosis [45, 47].

Registries of kindreds with FPC have proven invaluable for epidemiological studies, clinical trials, and basic research, but such registries have not been established in Japan. This is particularly problematic because the gene or genes responsible for the aggregation of pancreatic cancer in the Japanese population may be different from those responsible for FPC in the Western population.

Based on the above mentioned background, a kick-off meeting was held during the International Symposium on Pancreas Cancer 2012 which took place in October 4–6, 2012 in Kyoto, Japan. In this article, the history and current status of FPC is described while emphasizing the emerging necessity for a FPC registry in Japan.

Table 1 Non-genetic factors associated with pancreatic cancer

Risk factors	Risk level	References
Smoking	OR 1.7–2.2	[6–9]
Obesity	RR 1.1–1.4	[10, 11]
Alcohol abuse	OR 1.2–1.6	[12, 13]
Diabetes	RR 1.8–1.9	[14–16]
New onset type II diabetes	OR 2.1	[14, 15]
Chronic pancreatitis	SIR 13–14	[17, 18]
IPMN	SIR 16	[19]

OR odds ratio, *RR* relative risk, *SIR* standardized incidence ratio

Epidemiology of familial pancreatic cancer

Adenocarcinoma-prone families, including families predisposed to PC, were reported by Henry Lynch [48] as early as in 1967, and MacDarmott and Kramer [49]

Table 2 Hereditary cancer syndromes associated with an increased risk of pancreatic cancer

Syndrome	Gene	Inheritance	Relative risk	Risk by age 70	References
Peutz–Jegers syndrome (PJS)	*SKT11*, *LKB1*	AD	132	11–36 %	[20, 21]
Hereditary pancreatitis (HP)	*PRSS1*, *SPink1*, *CTFR*	AD	50–70	40–55 %	[22–24]
Familial atypical multiple mole melanoma (FAMMM)	*p16INK4a/MTS1*	AD	34–39	17 %	[25–28]
Hereditary breast ovarian cancer (HBOC)	*BRCA1*, *BRCA2*	AD	4.5	2–7 %	[29–33]
Hereditary nonpolyposis colon cancer (HNPCC)	*MSH2*, *MLH1*, *MSH6*, etc.	AD	4.7–8.6	<5 %	[34–37]
Familial Pancreatic Cancer (FPC)	*PALB2*, *ATM*	AD	Not known	Not known	[100, 101]

AD autosomal dominant

described a pedigree in which 4 of 6 siblings were diagnosed with PC in 1973. These early reports were followed by several more case series [50–53]. Since then population-based, case–control studies and cohort studies have been conducted, and a family history of PC is recognized as a risk factor for PC, with 4–10 % of patients with PC reporting a family history of the disease [38, 39]. In 1991 Ghadirian and colleagues [54] reported the result of a Canadian population-based case–control study showing that 7.8 % of patients with PC and only 0.6 % of controls had a family history of PC, a 13-fold difference between cases and controls. Larger case–control studies have also shown an increased risk level, with an OR of 2.1–3.8 among individuals with a family history of PC compared with those without such a history [55–57]. Similarly, prospective cohort studies showed a relative risk (RR) of 1.5–1.7 [58–61], indicating that having a single close relative with PC doubles one's risk of developing PC.

The Pancreatic Cancer Genetic Epidemiology (PACGENE) consortium, which is a FPC consortium of multiple centers in North America, reported that mean age ± SD at diagnosis among 369 FPC probands and 429 relatives was 65.4 ± 11.6 years, which was significantly younger than the mean age at diagnosis in the Surveillance, Epidemiology and End Result (SEER) population (70.0 ± 12.1 years; $P < 0.001$) [43]. Other studies from a European registry have suggested genetic anticipation, which refers to younger onset in successive generations in familial disease [45, 46]. Similarly, a registry-based prospective study from the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) and the German National Case Collection for Familial Pancreatic Cancer (FaPaCa) reported on 80 affected child–parent pairs, and found that the children died of their disease a median of 10 years earlier than did their parents. The median age of death from PC was 70, 64, and 49 years in Generations G1, G2, and G3 [45]. These observations are important for determining the most appropriate age at which to commence screening for PC in individuals at high-risk.

FPC is currently defined as kindred in whom at least a pair of first-degree relatives have been diagnosed with pancreatic cancer. In most instances the gene responsible for this clustering is not known, although a few cancer-predisposing syndromes are known and are summarized in Table 2. Klein and colleagues prospectively followed more than 5,000 individuals from 838 kindreds enrolled in the National Familial Pancreas Tumor Registry (NFPTR) at Johns Hopkins University [61]. A standardized incidence rate (SIR) was calculated by comparing the numbers of observed PC cases with those expected using SEER rates. The SIR for developing PC was significantly elevated in members of FPC kindreds [SIR = 9.0; 95 % confidence interval (CI), 4.5–16.1], but not in the sporadic PC kindreds [SIR = 1.8; 95 % CI, 0.22–6.4] or in the unrelated kindreds [SIR = 2.4, 95 %CI, 0.06–13.5]. This risk in FPC kindreds was elevated in individuals with two affected FDRs with PC who had a 6.4-fold increased risk (95 % CI, 1.8–16.4), and individuals with 3 or more FDRs with PC who had a 32.0-fold increased risk (95 % CI, 10.4–74.7), as summarized in Table 3 [61]. By using these observations Wang and colleagues established risk prediction software, called PancPRO, that can be used to quantify an individual's risk of developing PC based on the family history of PC [62]. This software is publicly available.

Table 3 Risk and incidence of pancreatic cancer in familial pancreatic cancer kindreds [42]

Number of FDRs with pancreatic cancer	SIR (95 % CI)	Incidence (per 100,000) in the general US population
3 or more FDRs	32 (10.4–74.7)	288
2 FDRs	6.4 (1.8–16.4)	58
1 FDR	4.5 (0.54–16.3)	41
General population	1	9

FDR first-degree relative, *SIR* standardized incidence rate, *CI* confidence interval

Individuals having a strong family history of PC also have an increased risk of developing extra-pancreatic cancer. Wang and colleagues reported elevated cancer mortality in the relatives of patients with PC, showing that cancer mortality was increased in the relatives of both sporadic and familial PC probands. Relatives of familial probands had a significantly increased risk of dying from breast cancer, ovarian cancer, and bile duct cancers [47]. The Pancreatic Cancer Cohort Consortium (PanScan) study, an international collaborative nested case–control study investigating the association between a family history of 5 types of cancer (pancreas, prostate, ovarian, breast, and colorectal) and risk of PC, found that a family history of PC and prostate cancer was associated with increased risk of PC [60].

Familial pancreatic cancer registries and consortiums

There are a number of established FPC registries in the US, Canada, Europe, and Australia, but not in Japan. The National Familial Pancreas Tumors Registry (NFPTR) at Johns Hopkins Hospital is the first and largest registry in the world (http://pathology.jhu.edu/pc/nfptr/index.php), and was established by Dr. Ralph H. Hruban in 1994. The primary goals of the registry were three-fold: understanding the risk of PC, identifying genetic and non-genetic causes of PC, and facilitating the early detection of PC. As of February 2013, more than 4,569 families with at least one PC have been enrolled in the NFPTR, of which 1,447

meet criteria for FPC. A number of pivotal research studies have been conducted using this registry. It was followed by other high-volume centers in the US. In Europe, the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) at Liverpool University (Liverpool, UK) and the German National Case Collection for Familial Pancreatic Carcinoma (FaPaCa) at Phillips University (Marburg, Germany) were established in 1999, followed by a National Registry for Familial Pancreatic Cancer in Italy, the Spanish National Hereditary Pancreatic Cancer Registry (PanFAM) in Spain, the Australian Familial Pancreatic Cancer Cohort (AFPaCC) in Australia, etc.

In 2002 the Pancreatic Cancer Genetic Epidemiology (PACGENE) consortium was organized with funding from the National Cancer Institute and data collection is ongoing in high-volume centers in the US and Canada, including the Dana–Farber Cancer Institute (Boston, MA, USA), Sol Goldman Pancreatic Cancer Research Center at Johns Hopkins University (Baltimore, MD, USA), Karmanos Cancer Institute–Wayne State University (Detroit, MI, USA), Mayo Clinic (Rochester, MN, USA), Creighton University (Omaha, NE, USA), and University of Toronto (ON, Canada) [43]. The objective of this consortium is to identify susceptibility genes for PC using linkage analysis in order to improve risk assessment, aid in the early detection of PC, and help point to new strategies for screening, prevention, and treatment. In Europe, the European PANGEN PC case–control study is also organized for an EU-wide multicenter case collection.

Currently, epidemiological studies, risk analysis, basic research, and clinical trials on early detection are being conducting based on the abovementioned FPC registries and consortia, which necessitates an FPC registry in Japan.

Screening in familial pancreatic cancer registries and consortia

The goal of the screening of PC is to detect curable high-grade precursor lesions such as pancreatic intraepithelial neoplasia (PanIN) [63–67], intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasms (MCN) [68–73], as well as early small adenocarcinomas [2]. When found, these lesions can be surgically resected and lives saved. Despite recent improvements in imaging modalities allowing the detection of small cystic and solid lesions, it is still uncertain whether or not PanIN lesions can be detected. However, over the past two decades, screening of individuals at high risk based on FPC registries has provided increasing insights into the precursor lesions in patients with a family history of pancreatic cancer [74, 75].

One of the first reports on screening FPC kindreds came from the University of Washington in 1999 [76]. Brentnall and colleagues studied 14 individuals from three families with strong family histories of PC, using computed tomography (CT), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP). Of note, multiple family members were affected in one of the three families (Family X). In this family, nine family members have died of PC without any evidence of hereditary pancreatitis, hereditary nonpolyposis colon cancer, or *p16* germline mutation. On EUS findings, ten out of 14 screened family members (71 %) had abnormal results including heterogeneous parenchyma with 1- to 2-mm scattered echogenic foci, hypoechoic nodules 2–4 mm in diameter, hyperechoic main-duct walls, discrete masses, and findings similar to those of chronic pancreatitis. Findings on ERCP showed focal side-branch duct irregularities, main-duct strictures, and grapelike clusters of saccules in seven out of 13 patients (54 %). Seven patients (50 %) underwent pancreatectomy on the basis of abnormal ERCP findings and family history. All 7 patients had widespread ductal epithelial dysplasia (PanIN 1-3); no patient had invasive cancer [76]. The same group subsequently reported another larger series which included 43 individuals from 24 families. In this study EUS was used as first-line imaging modality and ERCP was selectively performed for patients with EUS abnormalities. Twelve patients (28 %) with imaging abnormalities underwent pancreatectomy, two had distal pancreatectomy, and ten had total pancreatectomy. None had evidence of invasive cancer, but all of the cases revealed widespread PanIN lesions involving small and medium-sized ducts [77]. The authors concluded that screening of individuals at high risk using EUS and ERCP is an effective method of identifying precursor lesions before the onset of invasive PC. Of note, such screening is not without its side effects, as pancreatic surgery is associated with significant morbidity, and in $\sim$2 % of the patients even mortality.

The Johns Hopkins group has been conducting a prospective PC screening program on kindred enrolled in NFPTR, called "Cancer of the Pancreas Screening (CAPS)" [78–80]. The first report from this group consisted of 38 patients from FPC kindreds with mostly more than 2 affected relatives or individuals with Peutz–Jegers syndrome (PJS). The initial approach was EUS and CT scan, while ERCP was selectively used for EUS abnormalities. As a result, six pancreatic masses were found on EUS: 1 invasive ductal adenocarcinoma, 1 benign IPMN, 2 serous cystadenomas, and 2 non-neoplastic masses, resulting in a diagnostic yield for detecting clinically significant pancreatic neoplasms of 5.3 % (2 of 38) [78]. Subsequently, another prospective trial (CAPS-2) was performed with 78 high-risk individuals (72 from FPC

kindreds and 6 PJS), using annual CT and EUS. If EUS abnormalities were found EUS–fine needle aspiration (FNA) and ERCP was indicated, and surgery was offered when potentially neoplastic lesions were found. Among 78 individuals at high risk who were screened, 17 patients (22 %) had positive imaging, 7 received surgery, and 1 had pathological diagnosis by FNA, resulting in a diagnostic yield of 10 % (8/78) for histologically-proven pancreatic neoplasms; 6 patients had 8 benign IPMNs, 1 had malignant invasive IPMN, and 1 had PanIN. They also noted that many patients with a strong family history of pancreatic cancer have multi-focal PanIN lesions, and that these multifocal PanIN lesions can produce EUS findings similar to those associated with chronic pancreatitis [79, 81].

There have been a number of clinical trials, either single-institution or multicenter, screening individuals at high risk based on FPC registry or hereditary PC-predisposing syndromes, as summarized in Table 4. To date the experience is limited, and there is significant variability among these studies in terms of inclusion criteria, diagnostic modalities, targeted pancreatic lesions for surgical resection, types of surgical resection, etc. The significant questions that remain include:

Who should be screened?

Inclusion criteria for screening have not been consistent. Not surprisingly, diagnostic yield as well as pathological yield has varied among studies as they are highly dependent on the risk level of the individuals screened, sensitivity of the diagnostic imaging, and indication for surgical resection. According to the Fourth International Symposium of Inherited Diseases of the Pancreas [74], a surveillance program is recommended for individuals having more than a 10-fold greater risk for developing PC as compared with the general population. Others have proposed screening for those having a lifetime risk of PC that is $\geq$16 % [82]. A recent international consensus meeting proposed that the following are candidates for screening: first-degree relatives (FDRs) of patients with PC from a familial PC kindred with at least two affected FDRs; patients with Peutz–Jeghers syndrome; and p16, BRCA2, and hereditary nonpolyposis colorectal cancer (HNPCC) mutation carriers with one or more affected FDR [75].

At what age should screening begin?

There is no consensus recommendation on the age to begin screening for individuals at high risk. Screening too early will produce more false positives, while screening too late risks missing a chance to detect and treat curable lesions. Most suggest that screening should be initiated 10 years before the youngest affected family member with PC. In a report from the Memorial Sloan–Kettering Cancer Center, the yield was highly dependent on the age of the screened relatives, with those $\geq$65 years having a significantly higher yield than those <65 years [83].

What is the best modality for screening?
And how to follow those patients?

Previous studies have employed different modalities, as shown in Table 4. EUS is very sensitive for detecting PC [84], has a negative predictive value of 99–100 %, and has the ability to obtain tissue via FNA [85], which improves the positive predictive value to 99.4 % [85]. On the other hand, EUS is operator-dependent and has a high inter-observer variation [86], and requires sedation. Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) has the advantage over CT of avoiding radiation exposure, and it is particularly useful for visualizing cystic lesions such as IPMN [87], as small cysts (branch-duct IPMNs) are the most common abnormality detected in screening [80]. According to the recent guidelines, initial screening should include EUS and MRI/MRCP and ionizing radiation should be limited [75]. These recommendations are based on the prospective CAPS-3 study comparing between CT, MRI/MRCP, and EUS for one-time baseline screening in a blinded fashion [80]. This study found that EUS and MRI/MRCP are better than CT at detecting pancreatic lesions, predominantly cystic lesions [80]. For follow-up, both EUS and MRI/MRCP are modalities preferred by experts, with a 12-month interval [75].

What kind of lesions should be resected? And what type of surgery should be performed?

There is little consensus on making decisions regarding surgical indications for asymptomatic individuals at high risk. This is the most challenging part in a screening program for individuals at high risk to select premalignant lesions for "preventive" surgery, since it is also a potentially unnecessary intervention and clearly can do harm. Given the potential risk of prophylactic pancreatectomy, removing a "still healthy" organ in relatively young asymptomatic patients is not acceptable. Two surgical approaches have been reported (Table 4). The radical approach has been performed by the University of Washington group, conducting total pancreatectomy aiming to remove all precursors involving the pancreas shown by EUS and ERCP, while it has been suggested that a laparoscopic distal pancreatectomy should be performed upfront, and if pathological examination shows abnormal findings then proceed with a complete pancreatectomy [76, 77, 88]. Total pancreatectomy produces brittle diabetes,

Table 4 Summary of screening programs of pancreatic cancer for individuals at high risk

References	Author (year)	Institution	Country	Study period	*N*	Criteria for high risk	Imaging tests	Diagnostic yield[†] (%)	Resection (%)	Pathological yield[¶] (%)
[76]	Brentnall (1999)	UW	USA	N/A	14	FPC	EUS + ERCP + CT	7[‡] (50)	7 (50)	7 (50)
[77]	Kimmey (2002)	UW	USA	5 years	46	FPC	EUS ± ERCP	24[‡] (52)	12 (26)	12 (26)
[78]	Canto (2004)	JHH	USA	1998–2001	38	FPC, PJS	EUS + CT ± ERCP, EUS-FNA	12 (32)	7 (21)	2 (5.3)
[79]	Canto (2006)	JHH	USA	2001–2004	78	FPC, PJS	EUS + CT ± ERCP, EUS-FNA	17 (22)	7 (9)	8** (10)
[90]	Langer (2009)	FaPaCa	Germany	1999–2007	76	FPC, MPCS	EUS + MRI/MRCP	25 (33)	6 (8)	1 (1.3)
[91]	Poley (2009)	Dutch	Netherlands	2005–2007	44	FPC, FAMMM, PJS, BRCA1/2,	EUS	10 (23)	10 (23)	10 (23)
[92]	Verna (2010)	Columbia U	USA	2005–2008	51	FPC, BRCA1/2, HNPCC, FAMMM	EUS + MRI ± ERCP, EUS-FNA	14 (27)	5 (10)	6** (12)
[83]	Ludwig (2011)	MSKCC	USA	2002–2009	109	FPC, BRCA1/2	MRI/MRCP ± EUS-FNA	9 (8.3)	6 (5.5)	6 (5.5)
[93]	Vasen (2011)	Dutch multi-center	Netherlands	2000–2010	79	FAMMM	MRI/MRCP	16 (20)	5 (6.3)	5 (6.3)
[94]	Zubarik (2011)	UVM/DHMC	USA	2006–2009	27	FPC* w/elevated CA19-9	EUS	7 (26)	3 (11)	2 (7.4)
[46]	Schneider (2011)	FaPaCa	Germany	1999–2009	72	FPC	EUS + MRI/MRCP	10 (14)	9 (13)	6 (8.3)
[95]	Al-Sukhni (2012)	Canada multi-center	Canada	2003–2011	262	FPC, p16, STK11, RCA1/2, PJS, HP	MRI/MRCP ± CT, EUS	19 (7.3)	4 (1.5)	6 (2.3)
[80]	Canto (2012)	US multi-center	USA	N/A	225	FPC, PJS	CT, MRI, EUS	92 (42)	5 (2.2)	5 (2.2)

UW University of Washington, *JHH* Johns Hopkins Hospital, *FaPaCa* German national case collection for familial pancreatic cancer, *MSKCC*, Memorial Sloan–Kettering Cancer Center, *UVM* University of Vermont, *DHMC* Dartmouth–Hitchcock Medical Center, *FPC* familial pancreatic cancer, *PJS* Peutz–Jegers syndrome, *MPCS* melanoma pancreatic cancer syndrome, *FAMMM* familial atypical multiple mole melanoma, *LS* Lynch syndrome, *LFS* Li–Fraumeni syndrome, *HNPCC* hereditary nonpolyposis colon cancer, *HP* hereditary pancreatitis, *EUS* endoscopic ultrasound, *ERCP* endoscopic retrograde cholangiopancreatography, *FNA* fine-needle aspiration, *CT* computed tomography, *MRI* magnetic resonance imaging, *MRCP* magnetic resonance cholangiopancreatography

[†] Only includes pancreatic mass, nodule, and cyst and/or focally dilated pancreatic duct

[‡] Includes "chronic pancreatitis-like" lesion

[¶] Defined as pathologically proven (pre)malignant lesion (pancreatic adenocarcinoma, IPMN, MCN, PanIN-2/3, and neuroendocrine tumor)

* In this series FPC was defined as at least 1 FDR with PC

** Also included biopsy results

and death has been reported in a patient who underwent total pancreatectomy [76, 89]. On the other hand, because of the real risks associated with total pancreatectomy, the Johns Hopkins group and following series support partial pancreatectomy, targeting the removal of solid (nodular) or cystic lesions detected by EUS or MRI/MRCP [46, 78–80, 83, 90–95]. Whichever approach is chosen, pancreatectomy should be performed at a center experienced in pancreatic disease involving a multi-disciplinary team including gastroenterology, surgery, radiology, and pathology.

The majority of lesions detected by screening programs to date include small branch-duct IPMNs and PanINs [46, 76–80, 83, 90–95]. In the international consensus guidelines for cystic neoplasms (Sendai guidelines), it is widely accepted that surgical resection for branch-duct IPMN is recommended if the tumor size is over 3 cm or if a mural nodule (solid component) is observed [69, 73]. There remains no consensus on whether smaller branch-duct IPMNs in individuals at high risk should be resected or not.

Finally, like other malignancies [96, 97], screening of PC for individuals at high risk will not be justified unless survival benefit and cost–effectiveness is proven; this requires a large-scale multicenter study with long-term follow-up.

Basic research based on the Familial Pancreatic Cancer Registry

A number of familial pancreatic cancer genes have been identified. These genes account for some, but not all of the familial aggregation of pancreatic cancer. Germline *BRCA2* mutations cause up to 17–19 % of FPC, making *BRCA2* the most common genetic abnormality among FPC kindreds [32, 98]. Germline *BRCA2* gene mutations are particularly common in the Ashkenazi Jewish population. Recently the *PALB2* gene, partner and localizer of breast cancer 2 gene, was identified as a FPC susceptibility gene by sequencing of all protein-coding genes in a single FPC patient and their cancer [99]. Subsequent studies suggest that *PALB2* accounts for about 3 % of FPC [100]. Whole-exome sequencing of relatives with pancreatic cancer enrolled in the NFPTR led to the discovery of *ATM* as a FPC gene [101].

As next-generation sequencing technology improves in speed and cost, it will certainly add to our understanding of the genes responsible for the familial clustering of PC. The best way to ensure that individuals of Japanese heritage are included in these exciting studies, and that genes responsible for the aggregation of PC in Japanese patients are discovered, is to establish FPC registries in Japan.

Familial Pancreatic Cancer Registry in Japan and future direction

Formal FPC registries have not yet been established in Japan, but case reports and case–control studies suggest that the incidence of FPC in Japan is similar to that in the USA and European countries [102–104]. Recently, Matsubayashi and colleague [104] conducted a case–control study comparing 577 patients with PC and the same number of age-matched controls, showing that the incidence of having a first-degree relative with PC is significantly higher in patients with PC (6.9 %) than controls (2.9 %), with an odds ratio of 2.5 ($P = 0.02$).

There is obviously a need for a FPC registry in Japan in order to align pancreatic cancer research in Japan with international efforts to study familial pancreatic cancer. Establishing such registries in Japan is critical, as it will lead to a better understanding of the natural history, risk factors, and responsible genes in the Japanese population. These advances, in turn, will improve survival by allowing effective screening programs to be applied to individuals at high risk. Although there are very many questions that must be answered in this subject, the initial step is full awareness of the clinical importance of family history in patients with PC by individual physicians and medical staff, as well as the patients themselves and their families.

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