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Abstract

Familial pancreatic cancer (FPC) is broadly defined as two first-degree-relatives with pancreatic cancer (PC) and accounts for 4%-10% of PC. Several genetic syndromes, including Peutz-Jeghers syndrome, hereditary pancreatitis, hereditary breast-ovarian cancer syndrome (HBOC), Lynch syndrome, and familial adenomatous polyposis (FAP), also have increased risks of PC, but the narrowest definition of FPC excludes these known syndromes. When compared with other familial tumors, proven genetic alterations are limited to a small proportion (< 20%) and the familial aggregation is usually modest. However, an ethnic deviation (Ashkenazi Jewish > Caucasian) and a younger onset are com-

mon also in FPC. In European countries, "anticipation" is reported in FPC families, as with other hereditary syndromes; a trend toward younger age and worse prognosis is recognized in the late years. The resected pancreases of FPC kindred often show multiple pancreatic intraepithelial neoplasia (PanIN) foci, with various *K-ras* mutations, similar to colorectal polyposis seen in the FAP patients. As with HBOC patients, a patient who is a *BRCA* mutation carrier with unresectable pancreatic cancer (accounting for 0%-19% of FPC patients) demonstrated better outcome following platinum and Poly (ADP-ribose) polymerase inhibitor treatment. Western countries have established FPC registries since the 1990s and several surveillance projects for high-risk individuals are now ongoing to detect early PCs. Improvement in lifestyle habits, including non-smoking, is recommended for individuals at risk. In Japan, the FPC study group was initiated in 2013 and the Japanese FPC registry was established in 2014 by the Japan Pancreas Society.

Key words: Familial pancreatic cancer; Registry; High risk; Genetic; Surveillance

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Core tip: The incidence of pancreatic cancer increases with the number of family members with pancreatic cancer (PC). Familial pancreatic cancer (FPC) is defined as at least two first-degree relatives with PC that does not meet the criteria of other hereditary cancer syndromes. FPC has some epidemiological, pathological, and therapeutic characteristics. Since the 1990s, FPC registries have been established for use in studies to follow up high-risk individuals with family history of PC and hereditary cancer syndromes. Japan initiated a nationwide FPC registry in 2014, and several projects are expected at both the clinical and basic levels.

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INTRODUCTION

Today, in both Japan and United States, the number of patients with pancreatic cancer (PC) is gradually increasing^[1,2]. The nationwide cancer deaths due to PC is now total over 30000, so that PC ranks fourth among all human cancers (http://ganjoho.jp/reg_stat/

Table 1 Relative risk of pancreatic cancer in hereditary cancer syndromes

Inherited syndrome	Relative risk	Cumulative risk of PC	Responsible gene
Peutz-Jeghers syndrome ^[27]	132	11%-36%	<i>STK11</i>
Hereditary pancreatitis ^[28-31]	53-87	40%-55%	<i>PRSS1</i>
Familial atypical multiple mole melanoma ^[32,33]	13-22	17%	<i>CDKN2A</i>
Hereditary breast-ovarian cancer syndrome ^[34-37,73]	4-13	2%-7%	<i>BRCA1, BRCA2</i>
Lynch syndrome ^[38,39]	5-9	4%	<i>MLH1, MSH2, MSH6, PMS2</i>
Familial adenomatous polyposis ^[40]	5	-	<i>APC, MUTYH</i>

PC: Pancreatic cancer.

statistics/dl/index.html#mortality)^[1]. A survey by the Japanese Pancreas Society (2012) indicated an overall 5 year survival for PC patients of only 13.0%. However, when treated when the tumor size is ≤ 10 mm or within UICC-Stage 0, the 5 year survival increases to 80.4% and 85.8%, respectively^[2]. The best strategy for curing this deadly cancer is currently thought to be early detection by following high-risk individuals and resection at a suitable time.

The risk factors for PC include image-detectable pancreatic diseases and lifestyle factors. The former includes pancreatic cysts^[3,4], pancreatic duct dilation^[3], intraductal papillary mucinous neoplasm (IPMN)^[5], and chronic pancreatitis^[6,7], while the latter includes smoking^[8-10], diabetes mellitus^[10-12], obesity^[13,14], and low vitamin intake^[15], among others. A family history of PC is another known risk, and one that cannot be modified by individual effort or by medicine.

Various human cancers show family history as a risk of the same cancer developing in related family members^[16-18]. Several case-control studies and cohort studies have demonstrated an increased risk of PC in those who have a first degree relative (FDR) who is a PC patient [2.1^[19]-5.3^[20] of odds ratio (OR) and 1.5^[21]-1.7^[22] of relative risk (RR)^[23]. The incidence of PC increases with the number of family members with PC, so that persons with one FDR with PC have a 4.5 fold increased risk of PC, those with two FDRs have a 6.4 fold increased risk, and those with three or more FDRs have up to a 32 fold risk^[24]. The presence of two or more pancreatic cancer patients within FDRs, and without association with known hereditary genetic syndromes, is defined as familial pancreatic cancer (FPC).

The incidence of FPC among total cases of PC is 4%-10%. However, highly affected families are rare (*i.e.*, families with three or more PC cases within FDRs account for only 0.5% of all PC cases in Japan)^[10], and their inherited risk is not as high as that of other human malignancies (*e.g.*, melanoma, prostate cancer, ovarian cancer, and breast cancer) as confirmed by a study of a large number of twins in Nordic countries^[25]. Several environmental factors (tobacco smoke, asbestos, radon)^[10,26] have been reported in cases of FPC, and we must bear in mind that "familial PC" is not a synonym for "inherited PC". With the mentioned criteria, pathogenic germline mutation has been proven in less than 20% of FPC cases, and this is far

lower than is observed in other familial cancers associated with the pancreatic neoplasms, such as multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau disease.

Higher risks of PC are also associated with some inherited syndromes, such as Peutz-Jeghers syndrome (PJS)^[27], hereditary pancreatitis (HP)^[28-31], familial atypical multiple mole melanoma (FAMMM)^[32,33], hereditary breast-ovarian cancer (HBOC)^[34-37], hereditary nonpolyposis colorectal cancer [HNPCC, Lynch syndrome (LS)]^[38,39], familial adenomatous polyposis (FAP)^[40], and Werner syndrome^[41] (Table 1). However, these syndromes are excluded from the definition of FPC in its narrowest meaning. In western countries, high risk individuals (HRI) with a family history of PC and hereditary cancer syndromes have been participating in nationwide or institutional FPC registries^[42], and clinical surveillance and basic research have been performed to detect PC in its early stage. This review has focused on the concept and the current outcomes of surveillance of HRI.

CHARACTERISTICS OF FPC

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^[43]-68^[44], compared to sporadic PC (SPC): age 61^[43]-74^[44]] and an ethnic deviation (Ashkenazi Jewish > Caucasian)^[34]. The lifetime risk of PC also increases with decreasing age of onset of PC in family members^[44,45]. Meanwhile, similar to the sporadic cases, smoking (especially current smoking)^[10,26] and diabetes (recent onset of diabetes)^[10] are also risks for FPC.

A pedigree of FPC also incurs an increased risk of developing cancer or cancer death from diseases other than PC, such as in melanoma (OR = 16.8, $P < 0.0001$), endometrial cancer (OR = 5.26, $P = 0.034$), breast cancer [weighted standardized mortality ratio (wSMR): 1.7], ovarian cancer (wSMR: 2.1), and bile duct cancer (wSMR: 3.0)^[46]. Several studies have also demonstrated an unexplained worse prognosis in familial cases than in sporadic cases^[26,47], albeit some showed no difference^[48]. Surprisingly, two European registries (EUROPAC^[30] and FaPaCa^[49,50]) that analyzed 106 FPC families (264 affected individuals) through three

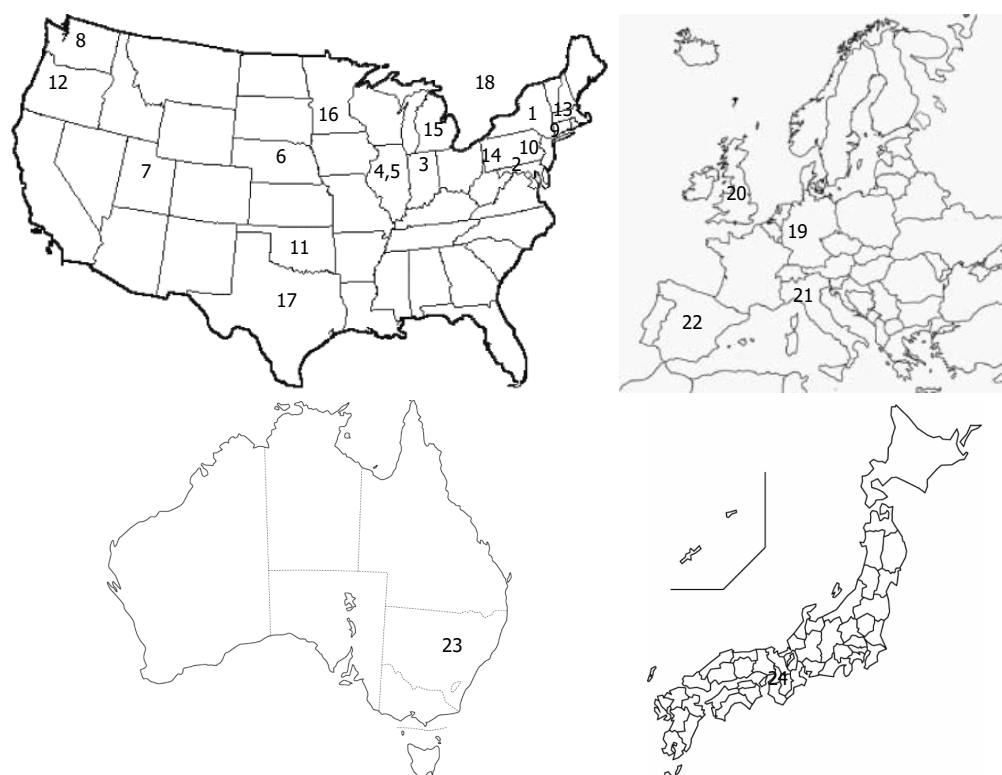


Figure 1 Worldwide mapping of the (familial) pancreatic cancer registries and genetic research institutions (1-24). 1: Memorial Sloan-Kettering Cancer Center, Familial Pancreatic Cancer Family Registry; 2: Johns Hopkins University, National Familial Pancreas Tumor Registry; 3: Indiana University, Familial Pancreatic Cancer Registry; 4: NorthShore University, Pancreatic Cancer Family Registry; 5: Northwestern University, Pancreatic Cancer Family Registry; 6: University of Nebraska Medical Center and Creighton University, Pancreatic Cancer Family Registry; 7: Huntsman Cancer Institute and University of Utah, Familial Pancreatic Cancer Registry; 8: University of Washington, Familial Pancreatic Cancer Registry; 9: Columbia University, Pancreatic Cancer Registry; 10: Thomas Jefferson University, Jefferson Pancreas Tumor Registry; 11: University of Oklahoma, National Pancreatic Cancer Registry; 12: Oregon Health & Science University, Oregon Pancreas Tumor Registry; 13: Dana-Farber Cancer Institute, Pancreatic Cancer Genes Study; 14: University of Pittsburgh, Pancreatic Adenocarcinoma Gene-Environment Risk Study and Registry; 15: Karmanos Cancer Center and Wayne State University, Pancreatic Cancer Genetic Study; 16: Mayo Clinic, Pancreatic Cancer Genetic Study; 17: University of Texas and MD Anderson Cancer Center, Pancreatic Cancer Genetic Study; 18: Mount Sinai Hospital, Toronto, Familial Gastrointestinal Cancer Registry; 19: Philipps University of Marburg, German National Case Collection Familial Pancreatic Cancer; 20: University of Liverpool, European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer; 21: National Registry for Familial Pancreatic Cancer in Italy; 22: Ramon y Cajal University Hospital, Madrid, Spanish Registry of Hereditary Pancreatic Cancer; 23: The Kinghorn Cancer Center, Australian Pancreatic Cancer Genome Initiative; 24: Kyoto University, Japanese Familial Pancreatic Cancer Registry.

generations [dates of birth: 1900-1919, 1920-1939, 1940-1969] observed “anticipation” in the affected kindred of FPC patients^[51]; that is, a trend existed toward younger age and worse prognosis in the latest generation.

Pathology and molecular biology

As is found with colorectal polyposis in numerous FAP patients, the pancreatic histology of FPC kindred often demonstrates multiple precancerous lesions^[48] or pancreatic intraepithelial neoplasias (PanINs)^[52,53]. PanINs with various mutations of *KRAS* codon 12 are frequently recognized in the vicinity of ordinary PC^[54], however, they are 2.75-fold more frequent in the FPC than in the SPC pancreas^[55]. These precursor lesions sometimes appear in the clinical image as small cystic lesions^[52,56] and are more often recognized in the pancreases of FPC families than in those of *CDKN2A/p16* mutation carriers (By contrast, PC is 10 times more frequent in the latter group)^[57]. These lesions in FPC kindred are associated with lobular parenchymal atro-

phy and chronic pancreatitis-like changes observable by endoscopic ultrasonography (EUS)^[53].

Despite the difference in the numbers of precursor lesions^[48,53], a blind review of histological observation of 519 FPCs and 561 SPCs by expert pathologists did not show any significant difference in terms of tumor size, location, neural invasion, angiolymphatic invasion, lymph nodal metastasis, and pathological stage^[58]. The genome-wide allelic status^[59,60], and genetic and epigenetic alterations^[61] are also similar between SPC and FPC.

GENETICS AND CLINICAL MANAGEMENT OF FPC

Familial pancreatic cancer registry

Figure 1 shows a global map of the institutional and nationwide pancreatic cancer registries, including FPC registries. The National Familial Pancreas Tumor Registry (NFPTR) (<http://pathology.jhu.edu/pancreas/nfptr/history.php>) was founded in 1994 at Johns

Hopkins University (Baltimore, United States)^[62]. This was followed by the European Registry of Hereditary Pancreatitis and Familial Pancreas Cancer (EUROPAC: <http://www.europac-org.eu/>)^[30] (1997) at Liverpool University (Liverpool, United Kingdom) and the German National Case Collection for Familial Pancreatic Carcinoma (FaPaCa: <http://www.fapaca.de/>)^[49,50] (1999) at Phillips University (Marburg, Germany). The NFPTC had enrolled 4322 families as of 2012; of these, 1376 families had one or more cases of PC in their FDRs. The FaPaCa had 452 registered FPC families as of 2009^[49]. National FPC registries have also been established in Italy (2007)^[63] and in Spain (2009)^[64]. In Japan, a kickoff meeting was held at Kyoto among international experts in October 2012^[65]. A committee was assembled in 2013 and the nationwide registry of FPC (Japanese Familial Pancreatic Cancer Registry: JFPCR: <http://jfpcr.com>) was officially established in 2014 by the Japan Pancreas Society.

Consortiums and symposiums have also been organized among several high volume centers and/or FPC registries in North America [Pancreatic Cancer Genetic Epidemiology Consortium (PACGENE) in 2002, funded from the National Cancer Institute]^[62] and across the globe [International Symposium on Inherited Diseases of the Pancreas^[66] initiated in 1997, Pancreatic Cancer Cohort Consortium (PanScan) in 2006^[8,67], and International Cancer of the Pancreas Screening Consortium (CAPS) in 2011^[68]]. The aim has been to gather information on patients and families of PC and to study the cause of PC, with the ultimate goal of improving the clinical practice of counseling and screening of the HRIs, and to devise new early detection methods for PC and better treatments. To date, a large number of clinical studies have been conducted under the FPC registries, mostly concerning risk assessment and screening of family members of FPC patients, in parallel with basic research on pancreatic carcinogenesis^[69].

Genetics associated with familial pancreatic cancer

The establishment of FPC registries was followed by a long period of basic research on FPC, as well as pursuit of its causative genes^[62]. As already mentioned, several hereditary cancer syndromes have increased risks for the development of PC (Table 1)^[23,70]. Genes responsible for FPC have included *ATM* (mutation rate: 2.4%)^[71], *BRCA1* (0-1%)^[72,73], *BRCA2* (8%-19%)^[35,74,75], *CHEK2* (2.9%)^[76], and *PALB2* (3.1%-3.7%)^[77,78]. However, the known germline mutations account for less than 20% of FPC cases. These genes all function in the homologous recombination of the double strand DNA repair system, or the so-called Fanconi anemia (FA) pathway^[79,80], and their germline mutations have also been reported in familial breast cancers^[81].

BRCA1/2 mutation carriers have a mild to moderate level of risk for PC (relative risks: 2-8, lifetime

risks: 2%-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 and the odds for having PC was 12.8^[82]. Similarly, the *BRCA2* K3326X mutation was detected in 5.6% (5/144) of American FPC cases^[83]. A murine model confirmed that a germline *BRCA2* mutation suffices to promote carcinogenesis by the *KRAS* mutation^[84], which is recognized in nearly 90% of PC cases^[54]. This may also explain the function of *BRCA2* mutation in FPC. Other genes working in conjunction with FA complementation groups, such as *FANCA*^[85], *FANCC*^[86], and *FANCG*^[86], have been reported to show very low incidences of mutation in FPC (0%-0.5%).

Most recently, the PACGENE study group, which included six American and Canadian institutions, used custom genotyping arrays (iSelect Collaborative Oncological Gene-Environment Study array: iCOGS array) to analyze a single nucleotide polymorphism of 985 PC cases [906 cases with a family history of PC and 79 cases with early-onset (≤ 50 years old)]. This group discovered evidence supporting an association of two genetic loci with PC: 7p21.1 (*HDAC9*) and 21q22.3 (*COL6A2*)^[87].

SURVEILLANCE OF HIGH RISK INDIVIDUALS

Surveillance conditions

Screening the high-risk population is thought to be an effective strategy for early diagnosis of PC; however, several issues concerning screening have been raised^[68]. These include the nature of the pathological lesion that represents the best target for surgical resection, the degree of risk expected for the screening, the best modality or combination of multiple modalities, the best age for initiating screening, the optimal screening interval, and the cost benefit and mental burden for the subjects.

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^[52] and IPMN^[88]) - UICC-stage I A PC (T1N0M0; limited to the pancreas and no more than 2 cm in size)^[68]. Today, the overall survival of UICC-stage I A 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%)^[2].

Screening candidates and lifestyle guidance at surveillance: A high predictive value can be obtained by surveillance if the conditions of the high-risk group enrolled in a screening protocol are well examined. This is important from the viewpoint of the advantage-

Table 2 Screening candidates with high risks¹

Individuals with ≥ 3 affected relatives, with ≥ 1 affected FDR
Individuals with ≥ 2 affected FDRs with PC, with ≥ 1 affected FDR, reaching a certain age
Individuals with ≥ 2 affected relatives with PC, with ≥ 1 affected FDR
Peutz-Jeghers syndrome patients, regardless of family history of PC
<i>CDKN2A</i> mutation carriers with one affected FDR
<i>BRCA2</i> mutation carriers with one affected FDR
<i>BRCA2</i> mutation carriers with two affected family member of PC
<i>PALB2</i> mutation carriers with one affected FDR
Mismatch repair gene mutation carrier (Lynch syndrome) with one affected FDR

¹Quoted from the reference^[69]. FDR: First-degree relative; PC: Pancreatic cancer.

disadvantage balance, especially concerning the economic and mental burden placed on the individuals who undergo this surveillance.

The risk level of the candidate individual is assessed based on the numbers of affected family members^[24] and hereditary syndromes (Table 1). "PancPro"^[89,90] is free software for estimating PC risk (based mainly on hereditary risk) that uses prospective data obtained from 961 families enrolled in the NFPTR; this software is actually applied to the screening programs in Italy^[90]. The international consortium recommended that an individual who had a 5^[68,91] to 10^[66,92-95] fold risk undergo PC screening. However, we must bear in mind that a complete view of the genetic susceptibility of PC is still unavailable and huge amounts of data from whole genome sequencing are needed for accurate assessment. 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^[68].

A screening strategy should also evaluate the risk factors of lifestyle and pancreatic diseases, such as smoking^[8,10,26,66,96], obesity^[13,14,66], physical inactivity^[14], diabetes^[10-12,66], chronic pancreatitis^[6,7,66], IPMN^[88], pancreatic cyst^[3,4], pancreatic duct ectasia^[3], *etc.* (Table 3). 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^[10]. The initial counseling should be used to present modifiable risks related to the lifestyle to HRIs and their improvement should be recommended; *i.e.*, smoking cessation, a healthy diet high in fruits and vegetables, higher intakes of vitamin D (> 600 IU)^[15], and regular exercise to control weight (body mass index: < 25 kg/m²)^[66].

Modalities of screening: Consensus could not be reached at the international consortium regarding the modality that is the most suitable for screening^[66]. Many institutions currently use EUS as their standard modality^[70], based on its ability to detect small pancreatic lesions (< 1 cm)^[97-100]. Kamata *et al.*^[100] prospectively compared the sensitivity of detecting a PC

Table 3 Non-genetic risk factors of pancreatic cancer

Factors	Risk level
Smoking ^[8-10]	OR = 1.5-2.2
Diabetes ^[11,12]	RR = 1.8-1.9
Obesity ^[13,14]	RR = 1.1-1.4
Chronic pancreatitis ^[6,7]	SIR = 13-14
Intraductal papillary mucinous neoplasm ^[5]	SIR = 16
Dilated main pancreatic duct ^[3]	HR = 6.4
Pancreatic cyst ^[3,4]	HR = 6.2; OR = 10.3

SIR: Standardized incidence ratio.

using EUS, enhanced computed tomography (CT), or magnetic resonance imaging (MRI) during the screening of 167 consecutive cases of IPMN; these authors concluded that EUS had the best sensitivity. EUS is also superior at detecting risk findings frequently seen in HRIs, such as duct ectasia, cysts^[3], and subtle parenchymal findings of the pancreas^[53,97,100-102]. However, agreement is poor in terms of these characteristic findings, even among expert endosonographers^[103]. First, visualization by EUS largely depends on the operator's skill^[104]. The choice of EUS scopes is also contentious^[105], as convex and radial types each have their own different peculiarities^[106]. Other drawbacks of EUS include the necessity for a relatively long-time fasting period and conscious sedation, 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 visualization of the pancreas is good without any blind spots^[3], for the subjects with slim abdominal trunk.

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^[3,4] and are actually frequently recognized in HRIs (cyst in 38.9% and duct ectasia in 2.3%)^[102], making MRCP a promising tool for assessing the risk level of HRIs. CT scans have a high spatial resolution; however, the healthy examiners are exposed to radiation. Long-term screening for breast cancer with low-dose radiation may possibly increase the incidence of cancer in *BRCA* mutation carriers (*BRCA1*: < 2%, *BRCA2*: < 4%)^[107]. This risk is especially high when radiation exposure occurs at age 20 or younger (OR = 2.0, 95%CI: 1.3-3.1) or is repeated five or more times (OR = 1.8, 95%CI: 1.1-3.0)^[108]. Excessive use of CT should be avoided in a *BRCA* mutant cohort. Endoscopic retrograde cholangiopancreatography (ERCP) is too invasive for routine screening and carries its own risk of procedure-associated pancreatitis; nevertheless, it is used for further investigation as it has the advantage of obtaining pathological samples^[42,109-111]. Repeated pancreatic juice cytology with placement of endoscopic nasopancreatic duct drainage is effective for detecting early pancreatic carcinoma or carcinoma in situ spreading within the pancreatic duct^[109]. EUS-guided fine needle

aspiration (EUS-FNA) can target small invasive carcinoma, although only limited tissues can be obtained from carcinoma *in situ*, and dissemination is a risk^[112].

In summary, EUS and MRI are considered the most accurate image tools^[100-102,113] with high agreement among the consortium experts (agreement, EUS: 83.7% and MRI/MRCP: 73.5%)^[68]. EUS-FNA and ERCP are applicable when abnormal findings or their changes are observed in other images^[42,97]. In addition to image analysis, serum tumor markers, including elevated carcinoembryonic antigen and CA19-9, should be checked each time^[42,49,50,68].

When to start screening: Screening in many institutions is started at 40 years of age^[64,97] or 10 years younger than the age of the youngest relative with PC^[42,49]. As PC develops in cases of PJS at a young age (40.8 years)^[27], screening is started at 30 years old^[97]. However, detection of pancreatic lesions increases after age 50-60^[102,114]. 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^[68].

Screening interval: Many institutions opt for yearly screening^[42,50,95,97,114] if the latest EUS and/or CT is normal (73.5% of agreement by CAPS consortium)^[68]. Once an abnormal finding is observed, subsequent screening is done every 3-6 mo^[50,97] or 3-12 mo^[42,68]. The endorsed screening interval for a non-suspicious cyst is 6-12 mo (agree: 83.7%), 3 mo for a newly detected solid lesion if surgery is not imminent (agree: 85.7%), and 3 mo for an indeterminate main pancreatic duct stricture (agree: 95.9%)^[68]. The natural history and progression of FPC still require study to determine the appropriate duration for screening intervals in relation to the risk level.

Surgical indications and procedures: As already mentioned, the characteristics of pancreatic histology in FPC kindred are multifocal PanINs or IPMNs^[55] associated with duct ectasia and parenchymal atrophy^[53]. The surgical indication for IPMN lesions can be determined according to established Fukuoka guidelines^[88]. However, detection of PanIN3 (carcinoma *in situ*) or minimally invasive cancer is difficult, as these cancers are tiny and do not form a solid mass or a nodule.

The extent of resection is controversial, depending on the therapeutic concept. The choices are to remove all precancerous lesions^[42] or to resect only a targeted area that includes nodular or cystic lesions^[97,115]. In cases of HBOC with the *BRCA* mutation, risk-reducing salpingo-oophorectomy is affordable and has an acceptable level of complications^[116]. However, for the pancreas, total pancreatectomy (TP) has severe complications, including a considerable level of postsurgical in-hospital mortality (cf. nationwide: 23%, high-volume hospital: 5%, in Germany)^[117,118] and subsequent serious glycemic control failure (mortality:

4%-8% per year)^[119]. A secondary pancreatectomy for the remnant pancreas can be conducted without increasing morbidity and mortality^[120], so resection of the target area, rather than TP, has been preferable thus far.

For many years, TP with pancreatic transplantation has been conducted in patients with type 1 diabetes^[119] and TP combined with islet autotransplantation has been performed on chronic pancreatitis patients with intractable pain^[121]. However, most recently, due to the improvements in post-surgical quality of life, these treatment procedures have been considered and actually indicated for FPC kindred with premalignant lesions^[119,122,123]. Further improvements are expected in the future.

Present outcomes of surveillance of high risk individuals

Several surveillance results have been reported from single or collaborated FPC registries in western countries; their protocol conditions and outcomes are summarized in Table 4^[42,50,91,92,94,95,97,101,114,124-127]. Some of the cases from the same registry may appear in more than one report; therefore, interpretation of cumulative data needs caution. About 5%-20% of the screened HRIs underwent surgery for suspected lesions. Roughly one third 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 (Table 4). A small proportion of PC was resected at an early phase (T1N0M0)^[94], but some PC cases were detected at the advanced unresectable stage. These outcomes testified to the difficulty of providing an accurate diagnosis of PCs at the curative stage.

Psychological and economical aspects of surveillance

Screening participants who are FPC kindred commonly express grief from the experience of family death due to PC^[128-130], and are distressed by the high mortality and uncertainty related to prevention and early detection^[128]. Their motivation for participating in surveillance is "possible early detection of (a precursor stage of) PC" (95%-100%)^[131], and they want to control their cancer risk by seeking information and resources to prevent PC^[128]. Research conducted by the Mayo Clinic indicated that 67% (238/361) of FPC kindred felt they had a higher lifetime risk of PC when compared to people of the same age, race, and gender, and 95% were likely to undergo blood test surveillance and 75% were likely to undergo EUS surveillance^[130]. A study at the University of Toronto revealed that the perception of PC risk was higher in FPC kindred than in *BRCA2* mutation carriers (42% vs 15%)^[129]. Most participants had anxiety and worry at the beginning, although only occasionally or sometimes^[128,130]; however, this gradually decreased as surveillance progressed (over

Table 4 Outcomes of pancreatic cancer surveillance of high risk individual

Ref.	Year	Country/registry	Entry period	Subjects conditions	Age (range), yr	n	Duration (mo)	Modality (surveillance → examination)	Ratio of surgical cases (n)	Pathology of the pancreatic lesion: Benign ¹ Border/CIS ² PC	Ratio of unresectable advanced PC (n)
Brentnall <i>et al</i> ^[12]	1999	United States	NA	FPC kindred	41 (28-65)	14	15	EUS, CT → ERCP	50.0% (7)	0	0 (0)
Canto <i>et al</i> ^[101]	2004	United States	1998-2001	FPC kindred, PJS	58 (NA)	38	22	EUS → CT, EUS-FNA, ERCP	18.4% (7)	2	0 (0)
Canto <i>et al</i> ^[97]	2006	United States	2001-2004	FPC kindred, PJS	52 (32-77)	78	12	EUS, CT → EUS-FNA, ERCP	9.0% (7)	3	1.3% (1)
Langer <i>et al</i> ^[50]	2009	FaPaCa	1999-2007	FPC kindred, BRCA2 (+) ¹ , CDKN2A (+) FAMMM family	60 (35-85)	76	NA	EUS, MRI → EUS-FNA	9.2% (7) ³	0	0 (0)
Poley <i>et al</i> ^[95]	2009	Netherlands	2005-2007	FPC kindred, HP, PJS, FAMMM, BRCA1/2 (+), TP53 (+)	50 (32-75)	44	Initial ⁶	EUS → CT, MRI	6.8% (3)	0	0 (0)
Verna <i>et al</i> ^[124]	2010	United States	2005-2008	FPC kindred, BRCA1/2 (+), LS, FAMMM	52 (29-77)	51	Initial	EUS, MRI → EUS-FNA, ERCP	9.8% (5)	0	2.0% (1)
Ludwig <i>et al</i> ^[114]	2011	United States	2002-2009	FPC kindred, BRCA1/2 (+)	54 (33-86)	109	Initial	MRI → EUS, EUS-FNA	5.5% (6)	2	0 (0)
Vasen <i>et al</i> ^[125]	2011	Netherlands	2000-2010	CDKN2A-Leiden (+)	56 (39-72)	79	48	MRI	6.3% (5)	0	2.5% (2)
Zubarik <i>et al</i> ^[126]	2011	United States	2006-2009	FDR of PC with sCA19-9 ¹	59 (NA)	26	NA	EUS → EUS-FNA	11.5% (3)	0	0 (0)
Al-Sukhni <i>et al</i> ^[127]	2012	Canada	2003-2011	FPC kindred, PJS, HP, CDKN2A (+), BRCA1/2 (+), STK11 (+)	54 (22-89)	262	50	MRI → MRI, EUS, EUS-FNA, ERCP	1.5% (4)	0	0.8% (2)
Sud <i>et al</i> ^[91]	2014	United States	2008-2011	FPC kindred, HP, CDKN2A (+), BRCA1/2 (+), PJS, LS	51 (20-75)	16	NA	EUS → EUS-FNA	18.8% (3)	1	0 (0)
Del Chiaro <i>et al</i> ^[92]	2015	Sweden	2010-2013	FPC kindred, individuals with increased genetic risk	50 (23-76)	40	13	MRI → EUS, EUS-FNA	12.5% (5)	2	0 (0)
Vasen <i>et al</i> ^[94]	2016	FaPaCa	2000-2015	FPC kindred, CDKN2A (+), BRCA1/2 (+), PALB2 (+)	46-56 (25-81)	411	16-53	MRI ± EUS → EUS, CT → EUS-FNA	7.3% (30)	15	1.0% (4)

¹Benign lesions included low-moderate grade of intra ductal papillary mucinous neoplasm (IPMN), grade 1-2 of pancreatic intraepithelial neoplasm (PanIN), serous cystadenoma, and neuroendocrine tumor; ²High-grade precursors and PanIN3; ³No lesion detected in one case of resected pancreas; ⁴(+): mutation carrier; ⁵Wide spread dysplasia; ⁶Evaluated only by the initial surveillance, one resectable pancreatic cancer case (T1N0M0) not resected because of metastatic melanoma. PC: Pancreatic cancer; FPC: Familial pancreatic cancer; PJS: Peutz-Jeghers syndrome; HP: Hereditary pancreatitis; FAMMM: Familial atypical multiple mole melanoma; LS: Lynch syndrome; FDR: First degree relative; FaPaCa: German national case collection for familial pancreatic cancer; NA: Not available; EUS: Endoscopic ultrasonography; EUS-FNA: EUS-guided fine needle aspiration; CT: Computed tomography; ERCP: Endoscopic retrograde cholangiopancreatography; MRI: Magnetic resonance imaging.

a 3-year period of follow-up)^[129,131]. This trend was significant in younger participants^[132]. The German FaPaCa registry showed that only 39% (80/205) of HRIs participated in the recommended surveillance. The psychological status of these non-participants is still unknown.

Several studies have analyzed the cost-effectiveness of HRI; however, they are not consistent in terms of the applied modality and the target group. For example, Ruyak *et al*^[133] evaluated a one-time screening by EUS and ERCP and reported an incremental cost-effectiveness ratio of \$16885/life-year saved. They concluded that surveillance remained cost-effective if the prevalence of dysplasia was at least 16% or if the sensitivity of EUS was at least 84%. Bruenderman *et al*^[134] estimated costs per year of life of MRI/MRCP surveillance for *CDKN2A (p16)-Leiden* mutation carriers at \$4545, and concluded it to be affordable. By contrast, Latchford *et al*^[135] estimated a life-saved cost of over \$350000 for total surveillance of PJS patients that followed the American Gastroenterology Association guidelines and recommended its performance only on a research basis. Rubenstein *et al*^[136] applied a Markov model to FPC kindred in a setting of 45-year-old-males with positive EUS findings of chronic pancreatitis and compared four different strategies: doing nothing, prophylactic TP, annual EUS surveillance, and annual EUS-FNA surveillance.

The “doing nothing” strategy provided the lowest cost, the greatest remaining years of life, and the best quality-adjusted life years, when compared to the smallest benefit in these aspects obtained with prophylactic TP.

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 mo and 6-9 mo, respectively)^[70]. However, in agreement with the response observed in HBOC patients^[137-139], PC patients with *BRCA1/2* mutation carriers respond well to platinum-based chemotherapy^[140] and poly (ADP-ribose) polymerase (PARP) inhibitors^[138,141], as determined in several studies. For example, Golan *et al.*^[140] 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 mo vs 9 mo, $P = 0.039$). A similar effect was confirmed in an experiment using xenografts by Lohse *et al.*^[142], who reported that PC xenografts harvested from *BRCA* mutation carriers and implanted into nude mice showed sensitivity to both gemcitabine and cisplatin. By contrast, xenografts from *BRCA* wild cases showed sensitivity only to gemcitabine. A joint study by Johns Hopkins University and the MD Anderson Cancer Center^[143] analyzed effectiveness of platinum-based chemotherapy in metastatic PC patients ($n = 549$) by familial cancer history, although germline *BRCA* status was not described, and demonstrated a superior OS in patients with family history of either breast, ovarian, or pancreatic cancer (HR = 0.49, $P = 0.003$). Survival was strongly associated with the number of relatives with *BRCA*-related malignancy ($P = 0.009$).

Kaufman *et al.*^[138] reported that a PARP inhibitor (PARPi) treatment induced a 22% response ratio with 4.6 mo of progression-free survival in *BRCA*-mutant PC patients who had already showed progression resistant to the gemcitabine treatment. PARPi is effective for PC cases with deficiency in the homologous recombination pathway; *i.e.*, in cases with either mutation of *ATM*, *BRCA1*, *BRCA2*, or *CHEK2*. 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^[139]. Currently, data are lacking with respect to PARPi use against FPC in causative mutation carriers. Future outcomes are expected.

CONCLUSION

In addition to classical risk factors, hereditary factors including family history of pancreatic cancer and some genetic syndromes must be taken into account when screening to detect early pancreatic cancer. Since the 1990s, basic and clinical research has accumulated much scientific data on FPC. However, to date, screening of HRIs has had unsatisfactory outcomes. In 2014, the JFPCR was established in Japan, and projects have just begun for early detection and better outcomes of PC. Success in this venture will depend on improvement of all aspects, including genetic medicine, screening and treatment methods, and better understanding of what determines a HRI.

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