Familial pancreatic cancer: Concept, management and issues

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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 pancreaticitis, 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 common 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

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.

INTRODUCTION

Today, in both Japan and Unites 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/...
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\(^3,6\), 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\(^{19,20}\), 5.3\(^{20}\) of odds ratio (OR) and 1.5\(^{21,22}\)-1.7\(^{22}\) of relative risk (RR)\(^{223}\)]. The incidence of PC increases with the number of family members with PC, so that persons with one FDR 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)\(^1\), 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 (HNPC), 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\(^{33,68}\), compared to sporadic PC (SPC): age 61\(^{43-74}\) 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\(^34,49\). 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\(^28,47\), albeit some showed no difference\(^48\). Surprisingly, two European registries (EUROPAC\(^{38}\) and FePaCa\(^{40,51}\)) that analyzed 106 FPC families (264 affected individuals) through three

| Inherited syndrome                                      | Relative risk | Cumulative risk of PC | Responsible gene |
|---------------------------------------------------------|--------------|-----------------------|-----------------|
| Peutz-Jeghers syndrome\(^{27}\)                        | 132          | 11%-36%               | STK11           |
| Hereditary pancreatitis\(^{30}\)                        | 53-87        | 40%-55%               | PRSS1           |
| Familial atypical multiple mole melanoma\(^{22,30}\)    | 13-22        | 17%                   | CDKN2A          |
| Hereditary breast-ovarian cancer syndrome\(^{24-27,74}\)| 4-13         | 2%-7%                 | BRCA1, BRCA2    |
| Lynch syndrome\(^{38,39}\)                             | 5-9          | 4%                    | MLHI, MSH2, MSH6, PMS2 |
| Familial adenomatous polyposis\(^{94}\)                | 5            | -                     | APC, MUTYH      |

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generations [dates of birth: 1900-1919, 1920-1939, 1940-1969] observed “anticipation” in the affected kindred of FPC patients; 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 or pancreatic intraepithelial neoplasias (PanINs) \[^{48,53}\]. 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 \[^{45}\]. These precursor lesions sometimes appear in the clinical image as small cystic lesions \[^{55,56}\] 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 atrophy 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 (NFPTPR) (http://pathology.jhu.edu/pancreas/nfptr/history.php) was founded in 1994 at Johns...
This was followed by the European Registry of Hereditary Pancreatitis and Familial Pancreatic 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 NFPTR 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)[61] 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[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[68].

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[64]. As already mentioned, several hereditary cancer syndromes have increased risks for the development of PC (Table 1)[23,30]. Genes responsible for FPC have included ATM (mutation rate: 2.4%)[72], 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[85]. This may also explain the function of BRCA2 mutation in FPC. Other genes working in conjunction with FA complementation groups, such as FANCA[86], 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 (Select 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[54] 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-
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 and hereditary syndromes (Table 1). *PancPro* 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. The international consortiums recommended that an individual who had a $\geq 1$ affected FDR, $\geq 2$ affected FDRs with PC, $\geq 1$ affected FDR reaching a certain age, Individuals with $\geq 2$ affected relatives with PC, with $\geq 1$ affected FDR, Peutz-Jeghers syndrome patients, regardless of family history of PC. CDKN2A mutation carriers with one affected FDR. BRCA2 mutation carriers with one affected FDR. BRCA2 mutation carriers with two affected family member pf PC. PALB2 mutation carriers with one affected FDR. Mismatch repair gene mutation carrier (lynch syndrome) with one affected FDR.

A screening strategy should also evaluate the risk factors of lifestyle and pancreatic diseases, such as smoking, obesity, physical inactivity, diabetes, chronic pancreatitis, IPMN, pancreatic cyst, pancreatic duct ectasia, 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. 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), and regular exercise to control weight (body mass index: $<25$ kg/m²).

**Table 2** Screening candidates with high risks

| Individuals with $\geq 3$ affected relatives, with $\geq 1$ affected FDR |
| Individuals with $\geq 2$ affected FDRs with PC, with $\geq 1$ affected FDR, reaching a certain age |
| Individuals with $\geq 2$ affected relatives with PC, with $\geq 1$ affected FDR |
| Peutz-Jeghers syndrome patients, regardless of family history of PC |
| CDKN2A mutation carriers with one affected FDR |
| BRCA2 mutation carriers with one affected FDR |
| BRCA2 mutation carriers with two affected family member pf PC |
| PALB2 mutation carriers with one affected FDR |
| Mismatch repair gene mutation carrier (lynch syndrome) with one affected FDR |

| Quoted from the reference. |

| Table 3 Non-genetic risk factors of pancreatic cancer |

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

SIR: Standardized incidence ratio.
area that includes nodular or cystic lesions on the therapeutic concept. The choices are to remove however, detection of PanIN3 (carcinoma associated with duct ectasia and parenchymal atrophy in FPC kindred are multifocal PanINs or IPMNs mentioned, the characteristics of pancreatic histology in relation to the risk level.

When to start screening: Screening in many institutions is started at 40 years of age (40.8 years)\cite{107} or 10 years younger than the age of the youngest relative with PC\cite{42,49}. As PC develops in cases of PJS at a young age (4.9 years)\cite{114}, screening is started at 30 years old\cite{57}. However, detection of pancreatic lesions increases after age 50-60\cite{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\cite{68}.

Screening interval: Many institutions opt for yearly screening\cite{42,50,95,114} if the latest EUS and/or CT is normal (73.5% of agreement by CAPS consortium)\cite{68}. Once an abnormal finding is observed, subsequent screening is done every 3-6 mo\cite{50,97} or 3-12 mo\cite{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%)\cite{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\cite{55} associated with duct ectasia and parenchymal atrophy\cite{53}. The surgical indication for IPMN lesions can be determined according to established Fukuoka guidelines\cite{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\cite{62} or to resect only a targeted area that includes nodular or cystic lesions\cite{97,115}. In cases of HBOC with the BRCA mutation, risk-reducing salpingo-oophorectomy is affordable and has an acceptable level of complications\cite{110}. 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)\cite{117,118} and subsequent serious glycemic control failure (mortality: 4%-8% per year)\cite{119}. A secondary pancreatectomy for the remnant pancreas can be conducted without increasing morbidity and mortality\cite{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\cite{119} and TP combined with islet autotransplantation has been performed on chronic pancreatitis patients with intractable pain\cite{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\cite{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\cite{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)\cite{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\cite{128-130}, and are distressed by the high mortality and uncertainty related to prevention and early detection\cite{128}. Their motivation for participating in surveillance is “possible early detection of (a precursor stage of) PC” (95%-100%)\cite{131}, and they want to control their cancer risk by seeking information and resources to prevent PC\cite{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\cite{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%)\cite{128}. Most participants had anxiety and worry at the beginning, although only occasionally or sometimes\cite{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: n | Ratio of unresectable advanced PC (n) |
|-----------------------|------|-----------------|--------------|---------------------|----------------|---|--------------|-------------------------------------|----------------------------------|--------------------------------------|--------------------------------------|
| Brentnall et al[43]   | 1999 | United States   | NA           | FPC kindred         | 28-65(14)      | 15 | 14           | EUS, CT → ERCP                      | 0.0% (7)                         | 0                                    | 0% (0)                              |
| Camo et al[101]       | 2004 | United States   | 1998-2001    | FPC kindred, PJS    | 58 (NA)        | 22 | 38           | EUS → CT, EUS-FNA, ERCP             | 18.4% (7)                        | 2                                    | 1% (0)                              |
| Camo et al[95]        | 2006 | United States   | 2001-2004    | FPC kindred, PJS    | 52 (32-77)     | 12 | 78           | EUS, CT, EUS-FNA, ERCP              | 9.0% (7)                         | 3                                    | 0% (1)                              |
| Langer et al[78]      | 2009 | FaPaCa          | 1999-2007    | FPC kindred, BRCA2 (+), CDKN2A (+), FAMMM family | 60 (35-85)     | 76 | NA           | NA                                  | 9.2% (7)                         | 0                                    | 0% (0)                              |
| Ley et al[90]         | 2009 | Netherlands     | 2005-2007    | FPC kindred, HP, PJS, FAMMM, BRCA1/2 (+), TP53 (+) | 50 (32-75)     | 44 | Initial      | EUS, CT, MRI                        | 6.8% (3)                         | 0                                    | 0% (0)                              |
| Verma et al[52]       | 2010 | United States   | 2005-2008    | FPC kindred, BRCA1/2 (+), LS, FAMMM | 52 (29-77)     | 51 | Initial      | EUS, MRI, EUS-FNA                   | 9.8% (5)                         | 4                                    | 2% (1)                              |
| Ludwig et al[40]      | 2011 | United States   | 2002-2009    | FPC kindred, BRCA1/2 (+) | 54 (33-86)     | 109 | Initial      | EUS, MRI, EUS-FNA, ERCP             | 5.5% (6)                         | 3                                    | 2% (0)                              |
| Veen et al[38]        | 2011 | Netherlands     | 2000-2010    | Cdkn2A-Leiden (+)   | 56 (39-72)     | 79 | 48           | EUS, MRI, EUS-FNA                   | 6.3% (5)                         | 0                                    | 5% (2)                               |
| Zuberik et al[41]     | 2012 | United States   | 2011         | FDR of PC with SCA9-9 [91] | 59 (NA)        | 26 | NA           | EUS, MRI, EUS-FNA                   | 11.5% (3)                        | 2                                    | 0% (0)                              |
| Al-Sukhni et al[72]   | 2012 | Canada          | 2003-2011    | FPC kindred, PJS, HP, CDKN2A (+), BRCA1/2 (+), STK11 (+) | 54 (22-89)     | 262 | 50           | EUS, MRI, EUS-FNA                   | 1.5% (4)                         | 3                                    | 0% (2)                               |
| Sud et al[40]         | 2014 | United States   | 2008-2011    | FPC kindred, HP, CDKN2A (+), BRCA1/2 (+), PJS, LS | 51 (20-75)     | 16 | NA           | EUS, MRI, EUS-FNA, ERCP             | 18.8% (3)                        | 1                                    | 0% (0)                              |
| Del Chiaro et al[41]  | 2015 | Sweden          | 2010-2013    | FPC kindred, individuals with increased genetic risk | 50 (23-76)     | 40 | 15           | EUS, MRI, EUS-FNA                   | 12.5% (5)                        | 2                                    | 0% (0)                              |
| Veen et al[38]        | 2016 | FaPaCa          | 2000-2015    | FPC kindred, CDKN2A (+), BRCA1/2 (+), PALI2 (+) | 46-56 (25-81)  | 411 | 16-53       | EUS, MRI, EUS, CT                   | 7.3% (30)                        | 15                                   | 4% (1)                               |

1Benign lesions included low-moderate grade of intraductal 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 (T1 N0 M0) 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). This trend was significant in younger participants. 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 the PC surveillance of HRIs; however, they are not consistent in terms of the applied modality and the target group. For example, Rulyak et al[23] 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 94%. Brunenderman 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[92] 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[135] 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, folinic 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 HOBPC patients[127–130], 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[139] 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.

REFERENCES

1 American Cancer Society. Cancer Facts and Figures 2016. Available from: URL: http://www.cancer.org/research/cancerfactsstatistics/2016

2 Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, Maguchi H, Hayagisawa A, Tanaka M. Japanese Pancreatic Cancer Registry. 30th year anniversary: Japan Pancreas Society. Pancreas 2012; 41: 985-992 [PMID: 22750974 DOI: 10.1097/MPA.0b013e318258055c]

3 Tanaka S, Nakao M, Ioka T, Takakura Y, Tsukuma H, Uchihara H, Suzuki K, Fukuda J. Slight dilatation of the main pancreatic duct and presence of pancreatic cysts as predictive signs of pancreatic cancer: a prospective study. Radiology 2010; 254: 965-972 [PMID: 20177107 DOI: 10.1148/radiol.09090992]

4 Matsushita Y, Tada M, Akahe M, Yagioka H, Kogure H, Sasaki T, Arizumi T, Togawa O, Nakai Y, Sasahira N, Hiranoe K, Tsujino T, Isayama H, Toda N, Kawabe T, Ohtomo K, Omata M. Incidental pancreatic cysts found by magnetic resonance imaging and their relationship with pancreatic cancer. Pancreas 2012; 41: 1241-1246 [PMID: 22699201 DOI: 10.1097/MPA.0b013e31824f5970]

5 Tanno S, Nakano Y, Koizumi K, Sugiyama Y, Nakamura K, Sasajima J, Nishikawa T, Mizukami Y, Yanagawa N, Fujii T, Okumura T, Obara T, Kohyo Y. Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary mucinous neoplasms. Pancreas 2010; 39: 36-40 [PMID: 19745777 DOI: 10.1097/MPA.0b013e3181b91cd0]

6 Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dumagno EP, Andren-Sandberg A, Domellof L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993; 328: 1433-1437 [PMID: 8479461]

7 Talalmin G, Falconi M, Bassi C, Sartori N, Salvia R, Caldiron E, Frulloni L, Di Francesco V, Vaona B, Bovo P, Vantini I, Pederzoli P, Cavallini G. Incidence of cancer in the course of chronic pancreatitis. Am J Gastroenterol 1999; 94: 1253-1260 [PMID: 10235203]

8 Lynch SM, Vielting L, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, Canzian F, Stepnovski E, Arslan AA, Gross M, Helzlsouer K, Jacobs EJ, LaCroix A, Petersen G, Zheng W, Albanes D, Amundadottir L, Bingham SA, Boffette P, Boutron-Ruault MC, Chanock SJ, Clipp S, Hoover RN, Jacobs K, Johnson KC, Kooperberg C, Luo J, Messina C, Palli D, Patel AV, Riboli E, Shu XO, Rodriguez Suarez L, Thomas G, Tjeadlal A, Tobias GS, Tong E, Trichopoulos D, Virtano J, Ye W, Yu K, Zeleniuch-Jacquette A, Bueno-de-Mesquita HB, Stolzenberg-Solomon RZ. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009; 170: 403-413 [PMID: 19561064 DOI: 10.1093/aje/kwp134]

9 Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Bi JT, Negri E, Lu D, Rischi HA, Olson SH, Gallinger S, Miller
Vitamin D for the treatment and prevention of pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4). Am. J. Epidemiol. 2012; 23: 1880-1888 [PMID: 22120457 DOI: 10.1093/aje/knm541]

Matsubayashi H, Aida M, Kanemoto H, Uesaka K, Yamazaki S, Lockett T, Boussioutas A, Hopper JL, Jenkins P, Maisonneuve P, DiMagno EP, Elitsur Y, Gates MA, Aarnio M, Scheike T, Graff RE, Holst K, Möller S, Unger RH, McIntosh C, Mucci LA, Matsubayashi H, Klein AP, Lowenfels AB, Brose MS, Braxton RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF. Life-style risk factors for pancreatic cancer in Louisianans: a case-control study. Am. J. Epidemiol. 1988; 128: 324-336 [PMID: 3394699]

Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF. Lifestyle risk factors for pancreatic cancer in Louisianans: a case-control study. Am. J. Epidemiol. 1988; 128: 324-336 [PMID: 3394699]

Coughlin SS, Callie EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 2000; 11: 915-923 [PMID: 11142526]

Hemminki K, Li X. Familial and second primary pancreatic cancers: a nationwide epidemiologic study from Sweden. Int. J. Cancer 2003; 103: 525-530 [PMID: 12476670 DOI: 10.1002/ijc.10863]

Matsubayashi H, Amin M, Kanemoto H, Uesaka K, Yamazaki S, Lockett T, Boussioutas A, Hopper JL, Jenkins P, Maisonneuve P, DiMagno EP, Elitsur Y, Gates MA, Aarnio M, Scheike T, Graff RE, Holst K, Möller S, Unger RH, McIntosh C, Mucci LA, Matsubayashi H, Klein AP, Lowenfels AB, Brose MS, Braxton RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF. Life-style risk factors for pancreatic cancer in Louisianans: a case-control study. Am. J. Epidemiol. 1988; 128: 324-336 [PMID: 3394699]

Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Griff in C, Cameron JL, You CJ, Kern S, Hruban RH. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 2004; 64: 2634-2638 [PMID: 15059921]

Mucci LA, Jhemborg JB, Harris JR, Czene K, Havelick DJ, Scheitek T, Graff RE, Holit K, Möller S, Unger RH, McIntosh C, Nuttall E, Brandt I, Penney KL, Hartman M, Kraft P, Parmigiani G, Christensen K, Koskenvuo M, Holm NV, Heikkilä K, Pukkala E, Skytthe A, Adami HO, Kaprio J. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. JAMA 2016; 315: 1170-1177 [PMID: 26935459 DOI: 10.1001/jama.2015.17703]

Matsubayashi H, Aida M, Kanemoto H, Uesaka K, Yamazaki S, Lockett T, Boussioutas A, Hopper JL, Jenkins P, Maisonneuve P, DiMagno EP, Elitsur Y, Gates MA, Aarnio M, Scheike T, Graff RE, Holst K, Möller S, Unger RH, McIntosh C, Mucci LA, Matsubayashi H, Klein AP, Lowenfels AB, Brose MS, Braxton RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF. Life-style risk factors for pancreatic cancer in Louisianans: a case-control study. Am. J. Epidemiol. 1988; 128: 324-336 [PMID: 3394699]

Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Griff in C, Cameron JL, You CJ, Kern S, Hruban RH. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 2004; 64: 2634-2638 [PMID: 15059921]
Early diagnosis and treatment of pancreatic cancer in patients with a family history of pancreatic cancer. *Ann Intern Med* 1999; 131: 247-255 [PMID: 10454945] 

James TA, Sheldon DG, Raajput A, Kuvshinoff BW, Javle MM, Navar HR, Smith JL, Gibbs JP. Risk factors associated with earlier age of onset in familial pancreatic carcinoma. *Cancer* 2004; 101: 2722-2726 [PMID: 15534880] 

Brune KA, Lau B, Palmissano E, Canto M, Goggins MG, Hruban RH, Klein AP. Importance of age of onset in pancreatic cancer kindreds. *J Natl Cancer Inst* 2010; 102: 119-126 [PMID: 20668195] 

Del Chiaro M, Zerbi A, Falconi M, Bertaccia L, Polese M, Sartori N, Boggi U, Casari G, Longoni BM, Salvia R, Caligo MA, Di Carlo V, Pederzoli P, Presiccutti S, Mosca F. Cancer risk among the relatives of patients with pancreatic ductal adenocarcinoma. *Pancreatology* 2007; 7: 459-469 [PMID: 17912101] 

Wang L, Brune KA, Visvanathan K, Laheru D, Herman J, Greenhalf W, Earl J, Howes N, Neoptolemos JP, Ishida H, Ali SZ, Goggins M, Canto M, Wolfgang CL, Meriden Z, Roberts N, Klein AP, Hruban RH. A histomorphologic comparison of familial and sporadic pancreatic cancers. *Pancreatology* 2015; 15: 387-391 [PMID: 25599245 DOI: 10.1016/j.pan.2014.04.003] 

Abu T, Fukushima N, Brune K, Boelhm C, Sato N, Matsuyashiki H, Canto M, Petersen GM, Hruban RH, Goggins M. Genome-wide allelotypes of familial pancreatic adenocarcinomas and familial and sporadic intraductal papillucious neoplasms. *Clin Cancer Res* 2007; 13: 6019-6025 [PMID: 17947463] 

North RS, Roberts NJ, Jones S, Wheelan SJ, Papadopoulos N, Vogelstein B, Kinzler KW, Hruban RH, Klein AP, Eshleman JR. Familial and sporadic pancreatic cancer share the same molecular pathogenesis. *Fam Cancer* 2015; 14: 95-103 [PMID: 25240578 DOI: 10.1007/s10689-014-9755-y] 

Brune K, Hong SM, Li A, Yachida S, Abe T, Griffith M, Yang D, Oomura N, Eshleman J, Canto M, Schucki R, Klein AP, Hruban RH, Iacobuzio-Donohue C, Goggins M. Genetic and epigenetic alterations of familial pancreatic cancers. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 3536-3542 [PMID: 19064560] 

Petersen GM, de Andrade M, Goggins M, Hruban RH, Boddy M, Korczak JF, Gallinger S, Lynch HT, Syngal S, Rabe KG, Seminara D, Klein AP. Pancreatic cancer genetic epidemiology consortium. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 704-710 [PMID: 16614112 DOI: 10.1158/1055-9965.EPI-05-0734] 

Del Chiaro M, Zerbi A, Capurro G, Zamboni G, Maisonneuve P, Presiccutti S, Arcidiacono PG, Callicelli L, Falconi M; Italian Registry for Familial Pancreatic Cancer. Familial pancreatic cancer in Italy. Risk assessment, screening programs and clinical approach: a position paper from the Italian Registry. *Dig Liver Dis* 2010; 42: 597-605 [PMID: 20627831 DOI: 10.1016/j.dld.2010.04.016] 

Mocci E, Guillen-Ponce C, Earl J, Marquez M, Solera J, Salazar-Lopez MT, Calcedo-Arnáiz C, Vázquez-Sequeiros E, Montans J, Muñoz-Beltrán M, Vicente-Bártulos A, González-Gordaliza C, Sanjuanbenito A, Guerrero C, Mendía E, Lisa E, Lobo E, Martínez JC, Real FX, Malats N, Carrato A. PanGen-Fam: Spanish registry of hereditary pancreatic cancer. *Cancer* 2015; 51: 1911-1917 [PMID: 26212471 DOI: 10.1007/s10564-015-2907-6] 

Wada K, Takada K, Traverso LW, Hruban RH, Furukawa T, Brentnall TA, Hatori T, Sano K, Takada T, Majitama Y, Shimosegawa T. Clinical importance of Familial Pancreatic Cancer Registry in Japan: a report from kick-off meeting at International Symposium on Pancreas Cancer 2012. *J Hepatobiliary Pancreat Sci* 2013; 20: 557-566 [PMID: 23604538 DOI: 10.1002/jhbp.3-0611-5] 

Brand RE, Lerc MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, Brentnall TA, Lynch HT, Canto MI. Advances in counselling and surveillance of patients at risk for pancreatic cancer. *Cancer* 2007; 56: 1460-1469 [PMID: 17872573 DOI: 10.1111/j.1055-9965.2006.09856] 

Jacobs EJ, Chanock SJ, Fuchs CS, Lacroix A, McWilliams RR, Steplekosi E, Stolzenberg-Solomon RZ, Arslan AA, Bueno-Desmesquita HB, Gross M, Helzlsouer K, Petersen G, Zheng W, Agulliu I, Allen NE, Amundadottir L, Boutron-Ruault MC, Buring JE, Canzian F, Clipp S, Dorrornsoo M, Gaziano JM, Giovanniacchi EL, Hankinson SE, Hartge P, Hooever PN, Huner DJ, Jacobs KB, Jenab M, Kraft P, Koopbercg C, Lynch SM, Sund M, Mendelosh JB, Mouw T, Newton CC, Overad K, Palli D, Peeters PH, Rajkovic A, Shu XO, Thomas G, Tobias GS, Trichopoulos D, Virtamo J, Wactawski-Wende J, Wolpin BM, Yu K, Zeleniuch-Jacquotte A. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Int J Cancer* 2010; 127: 1421-1428 [PMID: 20049842 DOI: 10.1002/ijc.25148] 

Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, Nio Y, Schucki RS, Bassi C, Khijit I, Levy MJ, Chak A, Fockens P, Goggins M, Bruno M; International Cancer of Pancreas Screening (CAPS) Consortium, International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 2013; 62: 339-347 [PMID: 23135763 DOI: 10.1136/gutjnl-2012-303108]
Hruban RH, Canto MI, Goggins M, Schilicke R, Klein AP. Update on familial pancreatic cancer. Adv Surg 2010; 44: 293-311 [PMID: 20991528]

Kamisawa T, Wood LD, Itji T, Takaori K. Pancreatic cancer. Cancer 2016; 138: 73-85 [PMID: 26830752 DOI: 10.1016/S0008-5472(16)00141-0]

Roberts NJ, Yeo J, Yu J, Kopelovich L, Petersen GM, Bondy ML, Gallinger S, Schwartz AG, Syngal S, Cote ML, Axilbund J, Schulick R, Ali SZ, Ishelman JR, Velucelske V, Goggins M, Vogelstein B, Papadopoulos N, Hruban RH, Kinzler KW, Klein AP. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov 2012; 2: 41-46 [DOI: 10.1158/2155-2265.CD-11-0194]

Axilbund JE, Argami P, Kamiyama M, Palmisanos E, Raben M, Borge M, Brune KA, Goggins M, Hruban RH, Klein AP. Absence of germine BRCA1 mutations in familial pancreatic cancer patients. Cancer Biol Ther 2009; 8: 131-135 [PMID: 19029836]

Lynch HT, Deters CA, Snyder CL, Lynch JF, Villeneuve P, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Verbeke CS, Kartalis N, Pozzi Mucelli R, Kluijt I, Gouma DJ, Harinck F, Wagner A, Aalfs C, Figer A. The rate of the 6174delT founder Jewish mutation in BRCA2 in individuals with familial pancreatic cancer. J Med Genet 2004; 41: e126 [PMID: 15591268 DOI: 10.1136/jmg.2004.028451]

Roger CD, van der Heijden MS, Brune K, Yeo CJ, Hruban RH, Kern SE, Goggins M. The genetics of the FANCA gene in familial pancreatic cancer. J Med Genet 2004; 41: e126 [PMID: 15591268 DOI: 10.1136/jmg.2004.028451]

Children EJ, Chaffee KG, Gallinger S, Syngal S, Schwartz AG, Cote ML, Bondy ML, Hruban RH, Chanock SJ, Hooven RR, Fuchu CS, Rider DN, Amundadottir LT, Stolzenberg-Solomon R, Wolpin BM, Risch HA, Goggins MG, Petersen GM, Klein AP. Association of Common Susceptibility Variants of Pancreatic Cancer in Higher-Risk Patients: A PAGENE Study. Cancer Epidemiol Biomarkers Prev 2016; 25: 1185-1191 [PMID: 27197284 DOI: 10.1158/1055-9965.EPI-15-1217]

Takanaka M, Femandez-del Castillo A, Asay V, Chari S, Falconi M, Jang YJ, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamauchi K, Yamao K. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012; 12: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]

Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol 2007; 25: 1417-1422 [PMID: 17416862 DOI: 10.1200/JCO.2006.09.2452]

Leonardi G, Marchi S, Falconi M, Zerbì A, Ussia V, de Bortoli N, Mosca F, Presciutti S, Del Chiaro M. “PancPro” as a tool for selecting families eligible for pancreatic cancer screening: an Italian study of incident cases. Dig Liver Dis 2012; 44: 585-588 [PMID: 22821375 DOI: 10.1016/j.dld.2011.12.019]

Sud A, Wham D, Catalano M, Guda NM. Promising outcomes of screening for pancreatic cancer by genetic testing and endoscopic ultrasound. Pancreas 2014; 43: 458-461 [PMID: 24620797 DOI: 10.1097/MPA.0000000000000520]

Del Chiaro M, Verbeke CS, Kartalis N, Pozzi mucelli R, Gustafsson P, Hansson J, Haas SL, Segersvård R, Andren-Sandberg Å, Löhr JM. Short-term Results of a Magnetic Resonance Imaging-Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer. JAMA Surg 2015; 150: 512-518 [PMID: 25853361 DOI: 10.1001/jamasurg.2014.3852]

Harinck F, Konings IC, Kluitj J, Polev JW, van Hooft JE, van Dulmen HM, Nio CY, Krak NC, Hermans JI, Aafsl CM, Wagner A, Sijmons RH, Biermann K, van Eijck CH, Gouma DJ, Dijkgraaf MG, Fockens P, Bruno MJ. A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. Gut 2016; 65: 1505-1513 [PMID: 25986944 DOI: 10.1136/gutjnl-2014-308008]

Vasen H, Ibrahim I, Ponce CG, Slater EP, Matthai E, Carrato A, Earl J, Robbers K, van Mil AM, Potter B, Bonsing BA, de Vos Tot Nederveen Cappel WH, Bergman W, Massé M, Morreau H, Klöppel G, Schicker C, Steinkamp M, Figiel J, Esposito I, Mocci E, Vazquez-Sequeiros E, Sanjuanbenito A, Muñoz-Beltran M, Montans J, Langer P, Hendrikz V, Bartsch DK. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From the 6174delT Founder Jewish Mutation in BRCA2 in Patients with non-colonic gastrointestinal tract tumours in Israel. Br J Cancer 2001; 84: 478-481 [PMID: 11207041]

Martin ST, Matsubayashi H, Rogers CD, Phillips J, Couch FJ, Brune K, Yeo CJ, Kern SE, Hruban RH, Goggins M. Increased prevalence of the BRCA2 polymorphic stop codon K3326X among individuals with familial pancreatic cancer. Oncogene 2005; 24: 3652-3656 [PMID: 15806175]

Skoulidis F, Cassidy LD, Pisupati V, Jonasson JG, Bjarnason H, Eyfjord JE, Karreth FA, Lim M, Barber LM, Clawahorthy SA, Davies SE, Olive KP, Tuveson DA, Venkitaraman AR. Germline Brca2 heterozygosity promotes Kras(G12D)-driven carcinogenesis in a murine model of familial pancreatic cancer. Cancer Cell 2010; 18: 499-509 [PMID: 21050012]

Rogers CD, Van der Heijden MS, Brune K, Yeo CJ, Hruban RH, Kern SE, Goggins M. The genetics of the FANCA gene in familial pancreatic cancer. J Med Genet 2004; 41: e126 [PMID: 15591268 DOI: 10.1136/jmg.2004.028451]

Rogers CD, van der Heijden MS, Brune K, Yeo CJ, Hruban RH, Kern SE, Goggins M. The genetics of the FANCC and FANCG in familial pancreatic cancer. Cancer Biol Ther 2004; 3: 167-169 [PMID: 14726760]

Lowenkels AB, Masionneuve P, Whitcomb DC, Lerch MM,
Matsubayashi H et al. Familial pancreatic cancer

DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA 2001; 286: 169-170 [PMID: 11448279]

Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo CJ, Fishman EK, Brune K, Axilbund J, Griffin C, Ali S, Richman J, Jagannath S, Kantsevoy SV, Kalloo AN. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol 2006; 4: 766-781; quiz 665 [PMID: 16682259]

Greenhalf W. Neoptolemos JP. Increasing survival rates of patients with pancreatic cancer by earlier identification. Nat Clin Pract Oncol 2006; 3: 346-347 [PMID: 16826198 DOI: 10.1038/ncponc0483]

Yasuda I, Iwashita T, Doi S, Nakashima M, Moriwaki H. Role of EUS in the early detection of small pancreatic cancer. Dig Endosc 2011; 23 Suppl 1: 22-25 [PMID: 21535195 DOI: 10.1111/j.1443-1661.2011.01113.x]

Kamata K, Kitano M, Kudo M, Sakamoto H, Kadosaka K, Miyata T, Imaizumi H, Maekawa K, Chikugo T, Kumanoh M, Hyodo T, Murakami T, Chiha Y, Takeyama Y. Value of EUS in early detection of pancreatic ductal adenocarcinomas in patients with intraductal papillary mucinous neoplasms. Endoscopy 2014; 46: 22-29 [PMID: 24218310 DOI: 10.1055/s-0033-1353603]

Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund J, Brune K, Ali SZ, Jagannath S, Petersen GM, Fishman EK, Piantadosi S, Giardiello FM, Hruban RH. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol 2004; 2: 606-621 [PMID: 15224285]

Canto MI, Hruban RH, Fishman EK, Kamel JR, Schuller R, Zhang Z, Topazian M, Takakisi N, Fleisher J, Petersen G, Klein AP, Axilbund J, Griffin C, Syngal S, Saltzman JR, Mortele KJ, Lee J, Tamm E, Vikram R, Bho-sale P, Margolis D, Farrell J, Goggins M. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology 2012; 142: 796-804; quiz e14-e15 [PMID: 22245846 DOI: 10.1053/j.gastro.2012.01.005]

Topazian MD, Enners F, Kimmey M, Brand R, Chak A, Clain J, Cunningham JH, Eloubeidi MA, Meldes H, Gress F, Jagannath S, Kantsevoy S, LeBlanc JK, Levy M, Lighthall C, Romagnuolo J, Saltzman JR, Savides T, Wiersema M, Woodward T, Petersen G, Canto M. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. Gastrointest Endosc 2007; 66: 62-67 [PMID: 17382940 DOI: 10.1016/j.gie.2006.09.018]

Eisen GM, Dominitz JA, Faigel DO, Goldstein JA, Petersen BT, Raddawi HM, Ryan ME, Vargo JJ, Young HS, Wheeler-Harbaugh J, Hawes RH, Brugge WR, Carrougher JG, Chak A, Faigel DO, Kochman ML, Savides TJ, Wallace MB, Wiersema MJ, Erickson RA. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc 2001; 54: 811-814 [PMID: 11726873]

Kanazawa K, Imaizumi H, Mori N, Ikega K, Kakutani H, Sumiyama K, Hino S, Ang TL, Omar S, Tajiri H. A comparison of electronic endoscopic ultrasonography and retrograde pancreatography for early detection of pancreatic ductal adenocarcinoma concomitant with intraductal papillary mucinous neoplasm of the pancreas. J Hepatobiliary Pancreat Sci 2013; 20: 356-361 [PMID: 22878836 DOI: 10.1002/jhh.20541-0547-1]

Maguchi H, Takahashi K, Osanai M, Katanuma A. Small pancreatic lesions: is there need for EUS-FNA preoperatively? What to do with the incidental lesions? Endoscopy 2006; 38 Suppl 1: S53-S56 [PMID: 16802225 DOI: 10.1055/s-2006-946653]

Kittano M, Kudo M, Yamao K, Takagi T, Sakamoto H, Komaki T, Kamata K, Imaizumi H, Chiha Y, Okada M, Murakami T, Takeyama Y. Characterization of small solid tumors in the pancreas: the value of contrast-enhanced harmonic endoscopic ultrasonography. Am J Gastroenterol 2012; 107: 303-310 [PMID: 22008892 DOI: 10.1038/ajg.2011.354]

Ludwig E, Olson SH, Bayuga S, Simon J, Schattner MA, Gerdes H, Allen PJ, Jarnagin WR, Kurtz RC. Feasibility and yield of screening in relatives from familial pancreatic cancer families. Am J Gastroenterol 2011; 106: 946-954 [PMID: 21468009 DOI: 10.1038/ajg.2011.65]

Davis B, Lowy AM. Surgical management of hereditary pancreatic cancer. Med Clin North Am 2000; 84: 749-759 [PMID: 10872430]

Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in BRCA1 or BRCA2. J Clin Oncol 2007; 25: 2921-2927 [PMID: 17617523 DOI: 10.1200/JCO.2007.11.3449]

Nimptsch U, Krautz C, Weber GF, Mansky T, Grützmann R. Nationwide In-hospital Mortality Following Pancreatic Surgery in Germany is Higher than Anticipated. Ann Surg 2016; 264: 1082-1090 [PMID: 26978570 DOI: 10.1097/SLA.0000000000001693]

Müller MW, Friess H, Kleeff J, Dahmen R, Wagner H, Hinzl U, Breisch-Girbig D, Ceyhan GO, Büchler MW. Is there still a role for total pancreatectomy? Islet transplantation alone. J Hepatobiliary Pancreat Sci 2012; 19: 101-109 [PMID: 22666366 DOI: 10.1002/jhh.20541-0547-1]

Mehraei A, Gofrini M, Adili-Aghdam F, Hafezi M, Ashrafi M, Morath C, Zeier M, Hackert T, Schemmer P. Expanding the indications of pancreatic transplantation alone. Pancreas 2014; 43: 1190-1193 [PMID: 25333402 DOI: 10.1097/MPA.0000000000001811]

Miyazaki M, Yoshitomi H, Shinzui H, Otsuka M, Yoshidome H, Furukawa K, Takayasaki T, Kuboki S, Okamura D, Suzuki D, Nakajima M. Repeat pancreatectomy for pancreatic ductal cancer recurrence in the remnant pancreas after initial pancreatectomy: is it worthwhile? Surgery 2014; 155: 58-66 [PMID: 24238124 DOI: 10.1016/j.surg.2013.06.050]

Bellin MD, Gelrud A, Arrea-Rubín G, Dunn TB, Humar A, Morgan KA, Naziruddin B, Rastellini C, Rickels MR, Schwarzenberg SJ, Andersen DK. Total pancreatectomy with islet transplantation: a single-center experience of 46 cases. Ann Surg 2007; 246: 966-974; discussion 974-975 [PMID: 18043098]

Heidt DG, Burant C, Simeone DM. Total pancreatectomy: indications, operative technique, and postoperative sequelae. J Gastrointest Surg 2007; 11: 209-216 [PMID: 17390175 DOI: 10.1007/s11617-005-0025-7]

Wu W, Dodson R, Makary MA, Weiss MJ, Hirose K, Cameron
Matsubayashi H et al. Familial pancreatic cancer

JL, Ahuja N, Pawlik TM, Wolfgang CL, He J. A Contemporary Evaluation of the Cause of Death and Long-Term Quality of Life After Total Pancreatectomy. World J Surg 2016; 40: 2513-2518 [PMID: 27177647 DOI: 10.1007/s00268-016-3552-8]

124 Verna EC, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, Prince MA, Chung WK, Fine RL, Chatbot JA, Frucht H. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. Clin Cancer Res 2010; 16: 5028-5037 [PMID: 20876795 DOI: 10.1186/1078-0432-CRR-09-3209]

125 Vasa HF, Wasser M, van Mil A, Tollenara RA, Konstantinovski M, Gruis NA, Bergman W, Hes FJ, Hommes DW, Offerhaus GJ, Morreau H, Bonsing BA, de Vos tot Nederveen Cappel WH. Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation. Gastroenterology 2011; 140: 850-856 [PMID: 21129377 DOI: 10.1053/j.gastro.2010.11.048]

126 Zubarik R, Gordon SR, Lidosky SF, Anderson SR, Pipas JM, Badger G, Ganguly E, Vecchio J. Screening for pancreatic cancer in a high-risk population with serum CA 19-9 and targeted EUS: an eight-year experience. Gastrointest Endosc 2015; 74: 87-95 [PMID: 21704809 DOI: 10.1016/j.gie.2011.03.1235]

127 Al-Sukhni W, Borgida A, Rothenmund H, Holter S, Semotiuk K, Grant R, Wilson S, Moore M, Narod S, Jhaveri K, Haider MA, Gallinger S. Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. J Gastrointest Surg 2012; 16: 771-783 [PMID: 22127781 DOI: 10.1007/s11605-011-1781-6]

128 Underhill M, Berry D, Dulton E, Schienda J, Syngal S. Patient experiences living with pancreatic cancer risk. Hered Cancer Clin Pract 2015; 13: 13 [PMID: 26029287 DOI: 10.1186/s13053-015-0034-1]

129 Maheu C, Vodermaier A, Rothenmund H, Gallinger S, Ardiles P, Semotiuk K, Holter S, Thayalan S, Esplen MJ. Pancreatic cancer risk counselling and screening: impact on perceived risk and psychological functioning. Fam Cancer 2010; 9: 617-624 [PMID: 20623197 DOI: 10.1007/s10689-010-9354-5]

130 Breitkopf CR, Sinicrope FS, Rabe KG, Brockman TA, Patten CA, McWilliams RR, Ehlers S, Petersen GM. Factors influencing receptivity to future screening options for pancreatic cancer in those with and without pancreatic cancer family history. Hered Cancer Clin Pract 2012; 10: 8 [PMID: 22738386 DOI: 10.1186/1869-4278-10-8]

131 Konings IC, Sidharta GN, Harinck F, Aalffs CM, Poley WJ, Kieffer JM, Kuenen MA, Smets EM, Wagner A, van Hooff JE, van Rens JGM, Aderka D, Paluch-Shimon S, Kaufman B, Gershoni-Baruch R, Hedley D, Moore MJ, Friedman E, Gallinger S. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer 2014; 111: 1132-1138 [PMID: 25072261 DOI: 10.1038/bjc.2014.418]

132 Oza AM, Cihula D, Benzaken AO, Poole C, Mathijssen RH, Sonke GS, Colombo N, Špáček J, Vuylsteke P, Hirte H, Mahner S, Plante M, Schuinfeldt B, Mackay H, Rowbottom J, Lowe ES, Dougherty B, Barrett JC, Friedlander M, Olaripar monoethersynthesis in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33: 244-250 [PMID: 25366685 DOI: 10.1200/JCO.2014.56.2728]

133 Ashworth A. Synthetic lethal therapy approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 2008; 26: 3785-3790 [PMID: 18591545 DOI: 10.1200/JCO.2008.16.0812]

134 Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, Aderka D, Paluch-Shimon S, Kaufman B, Gershoni-Baruch R, Hedley D, Moore MJ, Friedman E, Gallinger S. Peutz-Jeghers syndrome and screening for pancreatic cancer kindreds. Gastrointest Endosc 2003; 57: 23-29 [PMID: 12518126]

135 Bruenderman E, Martin RC. A cost analysis of a pancreatic cancer screening protocol in high-risk populations. Am J Surg 2015; 210: 409-416 [PMID: 26003200 DOI: 10.1016/j.amjsurg.2014.11.017]

136 Latchford A, Greenhall W, Vitone LJ, Neoptolemos JP, Lancaster GA, Phillips RK. Peutz-Jeghers syndrome and screening for pancreatic cancer. Br J Surg 2006; 93: 1446-1455 [PMID: 17115408]

137 Rubenstein JH, Scheiman JM, Anderson MA. A clinical and economic evaluation of endoscopic ultrasound for patients at risk for familial pancreatic adenocarcinoma. Pancreatology 2007; 7: 514-525 [PMID: 17912015 DOI: 10.1159/000108069]

138 Alop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, Friedlander M, Fox, S, Bowtell D, Mitchell G. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012; 30: 2654-2663 [PMID: 22711857 DOI: 10.1200/JCO.2011.39.8545]

139 Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaha J, Mitchell G, Fried G, Stemmer SM, Hubert A, Rosengarten O, Steinier M, Loman N, Bowen K, Fielding A, Donchek SM. Olaripar monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33: 244-250 [PMID: 25366685 DOI: 10.1200/JCO.2014.56.2728]

140 Ashworth A. Synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 2008; 26: 3785-3790 [PMID: 18591545 DOI: 10.1200/JCO.2008.16.0812]

141 Oza AM, Cihula D, Benzaken AO, Poole C, Mathijssen RH, Sonke GS, Colombo N, Špáček J, Vuylsteke P, Hirte H, Mahner S, Plante M, Schuinfeldt B, Mackay H, Rowbottom J, Lowe ES, Dougherty B, Barrett JC, Friedlander M. Olaripar combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol 2015; 16: 87-97 [PMID: 25481791 DOI: 10.1016/S1470-204X(14)71135-0]

142 Lohse I, Borgida A, Cao P, Cheung M, Pintilie M, Bianco T, Holter S, Ibrahimov E, Kunareshwar R, Bristow RG, Tsao MS, Gallinger S, Hedley DW. BRCA1 and BRCA2 mutations sensitize to chemotherapy in patient-derived pancreatic cancer xenografts. Br J Cancer 2015; 113: 425-432 [PMID: 26180923 DOI: 10.1038/bjc.2015.220]

143 Fogelman D, Sugar EA, Oliver G, Shah N, Klein A, Alewine C, Wang H, Javle M, Shroff R, Wolff RA, Abbruzzese JL, Laheru D, Diaz LA. Family history as a marker of platinum sensitivity in pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2015; 76: 489-498 [PMID: 26126726 DOI: 10.1007/s00280-015-2788-6]
