ORIGINAL ARTICLE

Refinement of screening for familial pancreatic cancer

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ABSTRACT

Objective Surveillance programmes are recommended for individuals at risk (IAR) of familial pancreatic cancer (FPC) to detect early pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC). However, the age to begin screening and the optimal screening protocol remain to be determined.

Methods IAR from non-*CDKN2A* FPC families underwent annual screening by MRI with endoscopic ultrasonography (EUS) in board-approved prospective screening programmes at three tertiary referral centres. The diagnostic yield according to age and different screening protocols was analysed.

Results 253 IAR with a median age of 48 (25–81) years underwent screening with a median of 3 (1–11) screening visits during a median follow-up of 28 (1–152) months. 134 (53%) IAR revealed pancreatic lesions on imaging, mostly cystic (94%), on baseline or follow-up screening. Lesions were significantly more often identified in IAR above the age of 45 years ($p<0.0001$). In 21 IAR who underwent surgery, no significant lesions (PDAC, pancreatic intraepithelial neoplasia (PanIN) 3 lesions, high-grade intraductal papillary mucinous neoplasia (IPMN)) were detected before the age of 50 years. Potentially relevant lesions (multifocal PanIN2 lesions, low/moderate-grade branch-duct IPMNs) occurred also significantly more often after the age of 50 years (13 vs 2, $p<0.0004$). The diagnostic yield of potentially relevant lesions was not different between screening protocols using annual MRI with EUS (n=98) or annual MRI with EUS every 3rd year (n=198) and between IAR screened at intervals of 12 months (n=180) or IAR that decided to be screened at ≥24 months intervals (n=30).

Conclusions It appears safe to start screening for PDAC in IAR of non-*CDKN2a* FPC families at the age of 50 years. MRI-based screening supplemented by EUS at baseline and every 3rd year or when changes in MRI occur appears to be efficient.

Significance of this study

What is already known on this subject?

- Individuals at risk (IAR) of familial pancreatic cancer (FPC) are recommended to participate in prospective screening programmes to detect early pancreatic cancer or its high-grade precursor lesions.
- The age at which screening should be initiated is uncertain. Almost all programmes start screening at the age of 40–45 years or 10 years below the youngest age of onset in the family.
- Endoscopic ultrasound (EUS) and MRI are used complementarily for pancreatic imaging in the majority of screening programmes, but it is unclear whether both are necessary at every screening visit.
- The optimal intervals for follow-up imaging need to be determined, although most experts recommend annual imaging, if the pancreas is normal at baseline screening.

What are the new findings?

- Screening of IAR for FPC rarely reveals significant and potentially relevant pancreatic lesions before the age of 50 years.
- MRI-based screening supplemented by EUS at baseline and every 3rd year or when changes in MRI occur appeared to be efficient.
- Screening intervals of 24 months may be justified in IAR with an unremarkable pancreas at baseline imaging.

How might it impact on clinical practice in the foreseeable future?

- Raising the age and changing the screening protocol can reduce the psychological distress of IAR and the costs of FPC screening programmes without losing efficiency.

INTRODUCTION

During a consensus conference in 2003 the attendees recommended to perform pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) screening under research protocol conditions for those individuals who are deemed to be at high risk of developing the disease.[1] Some years later the attendees to a subsequent consensus conference (Cancer of the Pancreas Screening study (CAPS) summit in 2011) stated that individuals at risk (IAR) for the development of PDAC should be screened, if eligible for potential surgical treatment.[2 3] A multidisciplinary approach combining screening and treatment at high-volume centres, preferably within research studies, was recommended. Individuals with an at least 5–10-fold increased risk for PDAC, such as members of familial pancreatic cancer (FPC) families with at least two affected first-degree relatives (FDRs), are felt to be good candidates for

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screening.[1 2] For the vast majority of experts at the CAPS-summit only the detection and surgical treatment of T1N0M0 adenocarcinoma and the high-grade precursor lesions pancreatic intraepithelial neoplasia 3 (PanIN3), main-duct intraductal papillary mucinous neoplasia (IPMN) and branch-duct (BD) IPMN with high-grade dysplasia was judged to be a success of screening.[2] Unfortunately, these lesions are asymptomatic and still difficult to diagnose with the current imaging procedures. Most centres currently consider screening based on MRI with MR cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) as the best approach to detect small solid pancreatic tumours and IPMNs ≤1 cm in size as well as irregularities of the pancreatic duct.[3–15] Although high-grade PanIN lesions cannot be detected reliably with the current imaging methods, cystic lesions, consistent with the diagnosis of BD-IPMNs, can be visualised in up to 42% of IAR of FPC families.[10]

The age at which screening should be initiated and stopped is uncertain.[1 2] Most published programmes start screening at the age of 40–45 years or 10 years below the youngest age of onset in the family.[3–15] The optimal intervals for follow-up imaging also need to be determined. Most experts recommend annual imaging, if the pancreas is normal at baseline screening.[2]

To identify the most effective protocol in the present study we determined the prevalence of significant and potentially relevant pancreatic lesions at the index examination and during follow-up with regard to age and different screening protocols in a large cohort of IAR for non-*CDKN2a* FPC. *CDKN2a*-positive patients with FPC were not included, since they represent a different cohort with a significantly higher PDAC risk.[16 17]

MATERIAL AND METHODS

Individuals at risk

The national case collection for familial pancreatic cancer in Germany (FaPaCa), the Leiden registry and the Madrid registry were established in 1996, 1999 and 2009, respectively, to prospectively collect FPC families.[13 18–20] Screening results of patient subgroups from the three centres, in particular MRI and pathological findings, were already reported previously.[8 16 17 20 21] As previously suggested[2 22] the diagnosis of FPC was based on the presence of two or more FDRs with a confirmed diagnosis of PDAC, and without evidence of any other inherited tumour syndrome. FPC families were included based on a three-generation family pedigree and confirmation of all cancer diagnoses in the family by review of medical and pathological records, death certificates, and by revision of the pathology slides whenever available. Members of families fulfilling the criteria of FPC were offered mutation analyses of the *BRCA1/2*, *PALB2* and *CDKN2a* genes as previously described.[17 23 24] All IAR underwent *BRCA1/BRCA2* and *PALB2* mutation analyses and the Marburg and Leiden cohorts also underwent *CDKN2a* mutation analysis. Analysis of mismatch repair genes or *STK11* genes was only performed when the family history was suspicious for hereditary non-polyposis colorectal cancer (HNPCC) or Peutz–Jeghers syndrome. *ATM* mutation analysis was not performed on any of the IAR. IAR of familial atypical multiple mole melanoma families with *CDKN2a* mutations were excluded from the analysis to reduce heterogeneity, since the development and precursor lesions of PDAC in this entity appears to be different.[16]

All IAR from the above defined FPC families were offered participation in board-approved PDAC screening programmes that were conducted exclusively at the three participating centres between July 2002 and May 2015. The following individuals were classified as IAR and encouraged to participate in PDAC screening:

- FDRs of affected patients that are members of FPC families;
- Mutation carriers of a *BRCA1/2* and *PALB2* germline mutation with at least one affected patient with PDAC in the family, independent of the degree of relationship.

IAR were considered at high risk, if they were members of a family with three or more affected relatives with PDAC, and at moderate risk, if they were members of a family with two affected FDRs (FDR is defined as a close blood relative which includes the individual's parents, full siblings or children). IAR were selected for PDAC screening, if they provided informed consent to participate in the study. Screening started 10 years before the youngest age of onset in the family or by the age of 40 years, whichever occurred earlier.

Screening protocols

The surveillance programme at the Philipps University in Marburg included annual screening with MRI with MRCP and EUS between 2002 and 2010 (protocol 1). Based on our initial analyses[8 21] that revealed a relatively low diagnostic yield of potentially relevant lesions, the screening protocol was modified. Since January 2011 follow-up imaging consisted of annual MRI with MRCP and EUS every 3rd year or when suspicious alterations were detected by MRI (protocol 2). If a suspicious lesion was identified, imaging was repeated after 4 weeks, possibly with EUS-guided fine needle aspiration cytology (FNAC). In case the lesions detected by imaging had a high probability to be malignant or premalignant, an interdisciplinary board discussion took place to decide whether to follow-up or to resect.

The surveillance programme in Madrid included annual EUS and MRI. IAR with pancreatic lesions suspicious to be premalignant or malignant were discussed by a multidisciplinary pancreas committee. The team then decided, whether a more intensive follow-up via imaging was necessary or whether surgery was required.

IAR of FPC families at the Leiden University Medical Centre were invited for an annual MRI with MRCP. Beginning in 2011, EUS was also offered as an option in addition to annual MRI. IAR with lesions suspicious for malignancy were additionally imaged with EUS and CT within the subsequent 2–3 weeks. In case the imaging workup was suggestive of malignancy, the IAR was discussed during a multidisciplinary team meeting and was eventually offered surgery.

Screening modalities

Endoscopic ultrasonography

EUS was in every institution performed by experienced endosonographers. Radial or linear echoendoscopes (Pentax FG 32 UA with a longitudinal 7.5 MHz and 5 MHz sector array (Pentax Medical Europe Headquarters, Hamburg, Germany) in combination with a Hitachi EUB 525 ultrasound processor (Hitachi Medical systems Europe, Zug, Switzerland) or Olympus GF-UE160 with an Aloka ultrasound processor (Olympus Europe, Hamburg)) and curvilinear (Olympus UCT/UCP 160 Olympus Europe, Hamburg, Germany) devices were used according to the personal preference of the endosonographer. Investigations were performed under conscious sedation with midazolam or propofol. The examination of the pancreas followed a standardised protocol according to institutional standard operating procedures.[16] In case a relevant lesion or an indeterminate lesion was identified, the lesion was described, measured in two dimensions and video recorded.

MRI (MRI+MR cholangiopancreatography)

MRI was performed using a 1.5 T or 3.0 T clinical MR scanner (Magnetom Sonata, Siemens, Erlangen, Germany) in one session. Axial T2-weighted as well as T1-weighted images with and without contrast agent (Magnevist, Bayer Schering Pharma, Berlin, Germany) were acquired. In addition, MRCP images were acquired prior and after stimulation with secretin (Secrelux, Sanochemia, Neuss, Germany). All MRIs were independently reviewed by an experienced radiologist. Images were analysed for focal lesions in the morphological T1-weighted and T2-weighted images. The MRCP images were evaluated for filling defects, duct dilatation, stenoses or duct interruption. Lesions were classified as solid, cystic or indeterminate with or without connection to pancreatic ducts. They were measured in two dimensions and described according to shape, heterogeneity and location.

Follow-up and treatment recommendations

In case the diagnostic workup was uneventful at baseline, a follow-up examination was recommended to the IAR after 12 months. When a pancreatic lesion suspicious of malignancy was identified in any of the imaging modalities, the findings were reviewed by an interdisciplinary board consisting of surgeons, radiologists, gastroenterologists and pathologists to determine further management, either intensified surveillance eventually including FNAC or surgery. Criteria to recommend surgery were solid lesions, cystic lesions >30 mm, cystic lesions <30 mm with a substantial solid component, indeterminate lesions with irregular boundaries, positive or highly suspicious EUS FNAC, significant change in size and morphology during follow-up. In addition, pros and cons of surgical intervention were discussed with IAR presenting with multiple small cystic lesions, especially if a strong family history or a predisposing mutation (eg, BRCA2) was present, since these small multiple 'imaging' BD IPMNs might be an indicator for concomitant high-grade PanIN lesions neoplasia in the setting of FPC.[25] IAR with suspicious lesions who did not undergo surgery were followed at 3-month intervals with EUS and MRI plus MRCP for 12 months. Further screening intervals depended on the imaging results.

Surgery

IAR who agreed to a recommended surgical exploration or insisted upon undergoing surgery due to carcinophobia underwent primarily a limited pancreatic resection (either pylorus-sparing partial duodenopancreatectomy or distal pancreatectomy), depending on the distribution of lesions in preoperative imaging. Intraoperative ultrasonography was routinely used to verify preoperatively imaged pancreatic lesions. After a limited pancreatic resection (distal pancreatectomy or partial pancreaticoduodenectomy) the specimen was sent for frozen section. In IAR with the intraoperative diagnosis of high-grade PanIN and/or IPMN or a PDAC based on frozen section, the procedure was extended to total pancreatectomy.

Pathology

Pancreatic resection specimens were assessed by the local pathologists and by a reference pathologist (Kloeppel G, Institute for General Pathology, Technical University Munich) with a special expertise in pancreatic pathology. Pancreatic lesions were classified according to Detlefsen *et al*[26] and Hruban *et al*.[27]

Outcomes considered success of screening

Histologically verified PDAC, PanIN3 lesions and IPMNs with high-grade dysplasia were considered as true significant lesions following the suggestions of the CAPS summit.[2] In addition, multifocal PanIN2 (>10) lesions in association with BD-IPMNs with low or moderate dysplasia and/or atypical flat lesions (AFL) and higher-grade pancreatic neuroendocrine tumour (pNET>G1) were judged to be health relevant for the patient and thus classified as potentially relevant lesions.

Statistics

Descriptive statistics of the relatives who enrolled were compiled. Variables included age, gender, number of relatives with PDAC, earliest age of onset in the family and underlying germline mutations. The age of diagnosis of PDAC was retrieved from the three-generation pedigrees and divided into 10-year categories. Early age of onset was defined as the occurrence of PDAC prior to the age of 50 years in a family. Significant lesions were defined as the presence of histologically verified PDAC, PanIN3 or IPMN with high-grade dysplasia. Potentially relevant lesions were defined as histologically verified multifocal PanIN2 lesions with/without BD-IPMN with low-grade and moderate-grade dysplasia and/or AFL and pNET. To compare the age of the IAR undergoing prospective screening with that of their youngest affected relative, we classified our subjects as to whether they were younger, in the same 5-year age range, or older than the youngest affected relative.

The number of patient years is the number of IARs multiplied by the median number of years in screening. The calculation of events per patient years was performed by dividing the number of events by the number of patient years.

The χ^2 test, Fisher's exact test, t test and Wilcoxon rank sum test were performed for categorical and numerical variables, where appropriate, to compare patient characteristics. Two-tailed p values <0.05 were considered to be statistically significant. Analyses were performed using Prism V.6 GraphPad Software.

RESULTS

Between July 2002 and June 2015 a total of 253 Caucasian IAR (210 Marburg, 30 Madrid, 13 Leiden) completed at least the baseline screening with a median of 3 (range 1–11) examination visits. The 253 IAR underwent a total of 813 MRI and 450 EUS, including FNAC in five IAR. The screened IAR cohort included 115 men (median age 48.5 years) and 138 women (median age 48 years). Ninety-six (38%) individuals were high-risk IAR from families with at least three affected family members (FPC3), 140 (55%) were moderate-risk IAR from families with at least two affected FDR (FPC2) and 17 (7%) IAR had predisposing germline mutations (3 BRCA1, 8 BRCA2, 6 PALB2) with at least 1 affected FDR. Demographics of IAR are shown in table 1.

Of the 253 IAR, 89 (35%) had prevalent abnormal findings at baseline imaging, in the majority small cystic lesions (90%). Another 45 (18%) IAR developed lesions, also mostly cystic, during a median follow-up of 28 (range 3–152) months. Thus, prospective screening identified pancreatic lesions in 134 (53%) IAR. Of those 125 were cystic, 3 solid and 6 indeterminate. The remaining 119 (47%) IAR had unremarkable imaging results at baseline and during follow-up as described above. Characteristics of pancreatic lesions identified are summarised in table 2.

No complications related to the contrast-enhanced MRI were observed and all IAR that received an EUS tolerated the

Table 1 Screening characteristics of 253 IAR from FPC families

Parameter	Total cohort (n=253)	High-risk IAR (n=96)	Moderate-risk IAR (n=140)	IAR with BRCA1/2, PALB2 mutation (n=17)
Median age (range), years at screening start	48 (25–81)	48 (28–71)	48 (26–81)	46 (25–70)
Gender (M/F)	115/138	43/53	68/72	4/13
Examination visits median/range	853 3 (1–11)	339 3 (1–11)	461 3 (1–11)	53 2 (1–9)
Number MRI/MRCP median/range	813 2 (1–11)	327 3 (1–11)	433 2 (1–11)	53 2 (1–9)
Number EUS median/range	450 1 (0–8)	139 1 (0–7)	280 1 (0–8)	31 1 (1–4)
Pancreatic lesions	134 (52.9%)	50 (52.1%)	74 (52.8%)	10 (59%)
IAR with significant lesions*	6 (2%)	3 (3.1%)	2 (1.4%)	1 (5.9%)
IAR with potentially relevant lesions†	15 (5.9%)	8 (8.3%)	4 (2.9%)	3 (17.6%)

*Includes PDAC, PanIN3 and IPMN with high-grade dysplasia.
†Also includes multifocal PanIN2, BD-IPMN with low/moderate dysplasia±AFL and pNET.
AFL, atypical flat lesion; BD, branch duct; EUS, endoscopic ultrasonography; FPC, familial pancreatic cancer; IAR, individuals at risk; IPMN, intraductal papillary mucinous neoplasia; MRCP, MR cholangiopancreatography; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumour.

procedure well and were discharged from hospital on the day of the procedure.

Evaluation of imaging results by the multidisciplinary team and counselling of IAR resulted in surgical intervention in 21 IAR, for 10 IAR after initial screening and for 11 during follow-up. The majority of these IAR had multiple small imaging BD-IPMN (n=12), the remaining IAR indeterminate (n=6) or solid lesions (n=3). In 16 IAR surgery was recommended, whereas 5 IAR insisted to undergo histological clarification of the pancreatic lesion(s) after counselling because of carcinophobia. These 21 IAR underwent 6 total pancreatectomies, 11 distal pancreatic resections and 4 partial pancreaticoduodenectomies. There was no perioperative mortality. Histopathological analysis identified six (2%) IAR with significant lesions (two PDAC (stage I and IIb), three PanIN3, one IPMN with high-grade dysplasia) as recently defined at the CAPS summit.[2] These included one PDAC (UICC stage IIB) diagnosed in a patient who, for personal reasons, omitted two scheduled screening visits after an initial imaging evaluation that revealed no pathological findings in MRI or EUS. Another nine IAR had potentially relevant lesions, including eight IAR with multifocal PanIN2 lesions with or without BD-IPMN and/or AFL and one IAR with a 12 mm pNET G2. The remaining six IAR had either serous cystadenomas up to 40 mm in size (n=3) or focal fibrosis with PanIN1b lesions (n=3) (table 3, see online supplementary table S1). The diagnostic yield in the whole cohort for potential relevant lesions was thus 5.9% (n=15/253), and for histopathological significant lesions 2% (n=6/253). Given a median follow-up of 28 (range 3–152) months, the incidence for histologically verified significant lesions and PDAC was 1 per 83 patient years and 1 per 250 patient years, respectively. Despite one IAR, who discontinued the screening for more than 2 years, none of the other 252 IAR developed a PDAC during surveillance that was not picked up by the screening programme. There was no excess of other cancers among IARs, only 2 of 253 IAR developed other cancers (1 breast cancer, 1 cholangiocarcinoma) during the surveillance period.

The median age of IAR with pancreatic lesions was 51 years ranging from 28 years to 81 years. Lesions were identified significantly more often in IAR above the age of 45 years ($p<0.0001$). However, no histopathological significant lesions (PDAC, PanIN3 and high-grade IPMN) were detected in IAR below the age of 50 years (table 4). Potentially relevant lesions (multifocal PanIN2 with low-grade IPMN and/or AFL, pNET) also were detected significantly more often in IAR over the age of 50 years (13 vs 2, $p<0.001$, table 4). There was no significant difference between moderate-risk (FPC2) and high-risk IAR (FPC3). This was also true for IAR with known germline mutations such as *BRCA2*. Even in the 45 families with a low age of PDAC onset (<50 years) and 25 families with a potential anticipation

Table 2 Characteristics of pancreatic lesions in IAR (n=134)

Parameter	All IAR with lesions (n=134)	IAR with lesions at first screening (n=89)	IAR with lesions during follow-up (n=45)
Type of lesion:* cystic/solid/indeterminate	125/3/6	83/1/5	42/2/1
Cystic lesions <10 mm	121 (90%)	80 (90%)	41 (91%)
Cystic lesions >10 mm	4 (3%)	3 (3.4%)	1 (2.2%)
Solid lesions	3 (2.2%)	1 (1.1%)	2 (4.4%)
Indeterminate lesions	6 (4.5%)	5 (5.6%)	1 (2.2%)
IAR with surgery	21 (16%)	10 (11%)	11 (24%)
Potentially relevant histology†	15/21 (71%)	7/10 (70%)	8/11 (73%)
Significant histology‡	6/21 (29%)	3/10 (30%)	3/11 (27%)

*As determined by MRI and EUS.
†Includes 2 PDAC, PanIN3, IPMN with high-grade dysplasia; multifocal PanIN2±BD-IPMN±AFL, IPMN with low/moderate-grade dysplasia, pNET.
‡Only includes PDAC, PanIN3 and IPMN with high-grade dysplasia.
AFL, atypical flat lesion; BD, branch duct; EUS, endoscopic ultrasonography; IAR, individuals at risk; IPMN, intraductal papillary mucinous neoplasia; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumour.

Table 3 Pancreatic lesions according to pathology in 21 IAR who underwent pancreatic resections

Histopathological lesions	All IAR (n=21)	Age at Dx (years)	FPC2 (n=7)	FPC3 (n=11)	IAR with PALB2 or BRCA2 mutations (n=3)
PDAC	2	53*, 68^{+}		1	1
pNET	1	48^	1		
Multifocal PanIN2+PanIN3	3	52*, 64*, 69*	1	2	
BD-IPMN with HGD	1	52^{+}	1		
Multifocal PanIN2+ BD-IPMN with LGD/MGD±AFL	6	47^{+}, 54^{+}, 57, 58*, 61, 70*	1	4	1
Multifocal PanIN2	2	53°, 67^{+}		1	1
Focal fibrosis+PanIN1b	3	49^, 54°, 60°	1	2	
Serous cystadenoma	3	42°, 61°, 61°	2	1	

Superscripts indicate previous references that reported imaging and pathological results of IAR: $^{+}$-17; *-16, 17; ^-17, 20; °-8, 16, 17.
FPC2, two affected first-degree relatives; FPC3, at least three affected relatives.
AFL, atypical flat lesion; BD-IPMN, branch-duct type intrapapillary mucinous neoplasia; FPC, familial pancreatic cancer; IAR, individuals at risk; LGD/MGD/HGD, low-grade, moderate-grade, high-grade dysplasia; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumour.

phenomenon, lesions were not diagnosed at a significantly earlier age (median age 48 years, range 28–71 years and median age 50 years, range 28–72 years, respectively). The age of IAR with histologically verified lesions is shown in table 3.

Although regular screening was recommended to IAR every 12 months, 30 of 253 (11.9%) IAR decided to extend their screening intervals to 24 months (20 IAR) or 36 months (10 IAR) for personal reasons. As mentioned above a female patient who missed the regular 12 months screening two times in a row was diagnosed with PDAC stage IIB 26 months after the last screening visit that revealed no pathological findings in MRI or EUS. This was the only IAR (1/30, 3.3%) in whom a significant pancreatic lesion was missed due to an extended screening interval >12 months.

The present study included a change of the screening protocol in the Marburg cohort (for 210 IAR) over time. Between 2003 and 2010 follow-up examination visits included MRI plus EUS every 12 months (protocol 1). As of January 2011 follow-up examination visits consisted of annual MRI, but included EUS only every 3 years or whenever a suspicious alteration occurred during MRI follow-up (protocol 2). Ninety-eight IAR were examined with protocol 1 and 175 IAR with protocol 2, whereas 63 of these IAR were screened with both protocols over the complete study period. This protocol change did not result in a significant change of the diagnostic yield since pancreatic lesions were detected in 47 (48%) IAR in protocol 1 and 73 (42%) IAR in protocol 2 (p=0.37, table 5). The detection of histologically confirmed potentially relevant pancreatic lesions was also not different (5 IAR in protocol 1 vs 6 IAR in protocol 2, p=0.53).

DISCUSSION

The International Cancer of the Pancreas Screening Consortium (CAPS) recommended PDAC screening for IAR of FPC families to detect relevant pancreatic lesions, although the underlying evidence to support this recommendation is restricted to level 3 evidence.[2] More evidence is needed regarding the age to initiate screening, screening intervals and the management of

Table 4 Prevalence of pancreatic lesions according to age (n=134 IAR)

Age at first screening (years)	IAR with any pancreatic lesions (%)	IAR with lesions at first screening (%)	IAR with lesions during follow-up (%)	IAR with significant lesions† detected by screening (%)	IAR with significant lesions† at first screening (%)	IAR with significant lesions† during follow-up (%)	IAR with relevant lesions‡ detected by screening (%)	IAR with relevant lesions‡ at first screening (%)	IAR with relevant lesions‡ during follow-up (%)
<40	16/48 (33%)	13 (27%)	3 (6%)	0/48 (0%)	0 (0%)	0 (0%)	0/48 (0%)	0 (0%)	0 (0%)
≥40	118/205 (57%)	76 (37%)	42 (20%)	6/205 (2.9%)	3 (1.45%)	3 (1.45%)	15/205 (7.3%)	6 (2.9%)	9 (4.4%)
<45	36/98 (37%)	26 (27%)	10 (10%)	0/98 (0%)**	0 (0%)	0 (0%)	0/98 (0%)	0 (0%)	0 (0%)
≥45	98/155 (63%)*	63 (41%)	35 (22%)	6/155 (3.8%)	3 (1.9%)	3 (1.9%)	15/155 (9.7%)	6 (3.9%)	9 (5.8%)
<50	67/152 (44%)	46 (30%)	21 (14%)	0/152 (0%)**	0 (0%)	0 (0%)	2/152 (1.3%)	0 (0%)	2 (1.3%)
≥50	67/101 (66%)	43 (42%)	24 (24%)	6/101 (6%)	3 (3%)	3 (3%)	13/101 (12.9%)***	6 (5.9%)	7 (7%)
<55	86/183 (47%)	56 (31%)	30 (16%)	3/183 (1.6%)	1 (0.5%)	2 (1.1%)	7/183 (3.8%)	1 (0.5%)	6 (3.3%)
≥55	48/70 (68%)	33 (47%)	15 (21%)	3/70 (4.2%)	2 (2.8%)	1 (1.4%)	8/70 (11.4%)	5 (7.1%)	3 (4.3%)
<60	107/217 (49%)	70 (32%)	37 (17%)	3/217 (1.4%)	1 (0.45%)	2 (0.95%)	9/217 (4.1%)	1 (0.4%)	8 (3.7%)
≥60	27/36 (75%)	19 (53%)	8 (22%)	3/36 (8.3%)	2 (5.6%)	1 (2.7%)	6/36 (16.6%)	5 (13.9%)	1 (2.7%)
Total with lesions	134/253 (52.9%)	89 (35%)	45 (18%)	6/253 (2.4%)	3 (1.2%)	3 (1.2%)	15/253 (5.9%)	6 (2.3%)	9 (3.6%)

*p=0.0001; **p<0.001; ***p=0.0004.
†Includes PDAC, PanIN3, high-grade IPMN.
‡Potentially relevant lesions: includes PDAC, multifocal PanIN2/3 lesions with/without low/moderate dysplastic BD-IPMN or AFL, pNET.
AFL, atypical flat lesion; BD, branch duct; IAR, individuals at risk; PanIN, pancreatic intraepithelial neoplasia; IPMN, intraductal papillary mucinous neoplasia; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumour.

Table 5 Diagnostic yield of different screening protocols in 210 IAR of the FaPaCa cohort

Screening protocol	N	IAR with pancreatic lesions	IAR with potentially relevant pancreatic lesions*	Missed PDAC
All IAR	210	120 (57%)	11	1
IAR in protocol 1†	98‡	47 (48%)	5	0
IAR in protocol 2§	175‡	73 (42%)	6	0
IAR with screening intervals ≥24 months	30/210 (14.3%)	17 (57%)	1/30 (3%)	1

*Includes PDAC, multifocal PanIN2/3 lesions with/without BD-IPMN or AFL, pNET.
†Protocol 1 included MRI+MRCP+EUS every 12 months.
‡63 IAR were also screened with the other protocol during the complete study time.
§Protocol 2 consisted of annual MRI+MRCP. EUS was performed at baseline and then every 3 years or in case of suspicious MRI findings.
AFL, atypical flat lesion; BD, branch duct; EUS, endoscopic ultrasonography; FaPaCa, the national case collection for familial pancreatic cancer in Germany; IAR, individuals at risk; IPMN, intraductal papillary mucinous neoplasia; MRCP, MR cholangiopancreatography; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumour.

asymptomatic pancreatic lesions in IARs. The present report provides the largest prospective baseline and follow-up screening study of a well defined cohort of 253 *CDKN2a*-negative asymptomatic IAR from FPC families. The screening was based on MRI plus MRCP and EUS imaging, as these are currently considered the best modalities to detect early pancreatic neoplasias.[4–15] In the present study 53% (134/253) of IAR revealed mostly cystic pancreatic lesions. This high prevalence of cystic lesions in IAR is in line with three previous MRI and EUS-based prospective studies that reported pancreatic lesions in 33–45% of IAR.[9 10 15]

In the recent CAPS summit,[2] there was a disagreement over the age to initiate screening. Fifty-one per cent of experts voted to recommend starting screening at age 50 years. However, most published programmes started screening at the age of 40–45 years or 10 years before the youngest age of onset in the family.[3–15] Screening age is a relevant issue with regard to the psychological burden of IARs as well as the costs for the health system, but the published data on the age of onset of PDAC in the setting of FPC are not conclusive. The pancreatic cancer genetic epidemiology consortium of the USA reported an average age of onset of 68 years which was the same age as for sporadic cases.[28] In contrast, the German FaPaCa registry reported a median age of onset of 63 years with 16% of patients younger than 50 years, which was about 5 years younger than reported age of onset for sporadic cases in Germany.[21] In addition, a European study reported the phenomenon of anticipation in 80% of FPC families, implying that the age of PDAC onset diminishes in consecutive generations of IAR.[29] In the present study imaging lesions of the pancreas were detected significantly more often in IAR over the age of 45 years (37% vs 63%, p=0.0001), both at baseline screening and during follow-up. This is line with the studies of Canto *et al*[10] and Ludwig *et al*[11] who also detected pancreatic lesions significantly more often in IAR older than 50 years or 55 years based on an EUS/MRI approach. In the present study all six IAR with histologically proven PDAC, PanIN3 and high-grade IPMNs were >50 years. In addition, potentially relevant lesions such as multifocal PanIN2 lesions with or without low-grade to moderate-grade BD-IPMNs and/or AFL also occurred significantly more often at an age over 50 years (13 vs 2, p=0.0004).

The results of the present study strongly suggest that the lower age limit of starting screening for PDAC in IAR of FPC families can be raised to 50 years. This observation is supported by the analysis of recent prospective multidisciplinary FPC screening programmes in the USA and Europe that screened a total of 1132 IAR from FPC families.[4–15] In the total cohort significant lesions were detected in 2.9% of the screened IAR (n=22 PDAC, 11 PanIN3 or high-grade IPMN), and only 3% of these lesions (n=1/33) were detected before the age of 50 years.[4–15] The total yield of screening compares positively with the 2% total yield described in our study. In terms of effectiveness of the presented screening programme, the yield of PDAC (0.8%) and significant precursor lesions (2.4%) was low. However, if surgical removal of multifocal PanIN2 and multifocal BD-IPMNs is regarded as beneficial, the diagnostic yield rises to 5.9% (15/253) and the presented surveillance strategy could be considered effective. However, at the present time we do not know if patients with these lesions will ever progress to PDAC, so that a final statement would be premature.

The recent CAPS consensus summit, as well as several other authors suggested that annual MRI plus MRCP and EUS are currently the best imaging tests for the detection of significant PDAC precursor lesions.[2 7 8 10 11 15] The present study also confirms the effectiveness of this screening approach. The present study is the first that used and compared two screening protocols (MRI+EUS every 12 months (protocol 1) versus annual MRI+EUS every 3 years or when suspicious alterations develop in follow-up MRIs (protocol 2)). There was no significant difference between the two screening protocols with regard to imaging yield and yield of histologically confirmed potentially relevant pancreatic lesions (five IAR protocol 1 vs six IAR protocol 2, p=0.53). Thus, we suggest that adding EUS to MRI at baseline and subsequently only every 3rd year or when a suspicious lesion develops in follow-up MRIs is sufficient for the screening of IAR from FPC families. Since EUS is stressful due to the required sedation, time- consuming and costly, confirmation of these findings in other long-term surveillance studies would be beneficial for PDAC screening.

The optimal intervals for follow-up screening need also to be determined. Most experts recommend that imaging should be repeated every 12 months, if the pancreas shows no lesions at baseline screening.[2] The present study had the opportunity to evaluate the effect of screening intervals of more than 12 months by chance. Due to personal reasons 30 (11.9%) of 253 IAR in the present study missed one or more scheduled annual visits and had at least one screening interval of 24 months (20 IAR) or even 36 months (10 IAR). Of these 30 IAR, only one IAR (3.3%) developed a PDAC 26 months after normal baseline imaging and none of the other 29 IAR showed significant progression at the next follow-up that required surgery. Although the presented data do not provide enough statistical power to come up with a definitive conclusion, it may be suggested that in IAR with an unremarkable pancreas at baseline

imaging, 2 year screening intervals are sufficient and safe. Therefore, we now consider extending the screening intervals to 24 months in IAR with an unremarkable pancreas at baseline screening. This approach is also underscored by the results of a quantitative analysis of the timing of the genetic evolution of PDAC, that indicate a time span of at least one decade between the occurrence of the cancer initiating mutation and cancer formation, providing a broad window of opportunity for the early detection of pancreatic cancer.[30] Recent studies suggest, however, that once a PDAC becomes detectable, clinical progression from low-stage to advanced-stage disease is rapid.[31] Thus, intensifying screening at baseline by using MRI plus EUS to exclude the presence of clinically detectable PDAC, and to de-escalate screening intensities and intervals thereafter appears as an option to be discussed.

The present study has some limitations. First, the majority of IAR (83%) were included from one centre resulting in some selection bias. Second, a definitive diagnosis of imaged pancreatic lesions was rarely verified by histopathology, since most IAR with lesions (84%) received no surgical treatment. Third, examiner-dependent results of EUS and interpretation of MRI images among the multiple physicians involved may have influenced the results of the present study. Fourth, due to the lack of evidence-based practice guidelines for recommending surgery, each of the three participating centres used an institution-specific individualised approach to recommend surgical treatment. Compared with some previous studies, the number of pancreatic resections and histologically analysed pancreatic lesions was relatively low.[3 5 6] Fifth, the results are only applicable for IARs from FPC families without CDKN2a mutations that have a lower risk than CDKN2a-positive pedigrees.

In summary, starting screening of IAR from non-*CDKN2a* FPC families at the age of 50 years appears to be safe and effective. A screening protocol with annual MRI plus MRCP and EUS every 3 years or whenever alterations are detected during MRI follow-up might be as effective as annual MRI plus EUS screening. Screening intervals of 24 months may be justified in IAR with an unremarkable pancreas at baseline imaging. The presented data should be considered during counselling to reduce the psychological distress of IAR and the costs of FPC screening programmes.

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