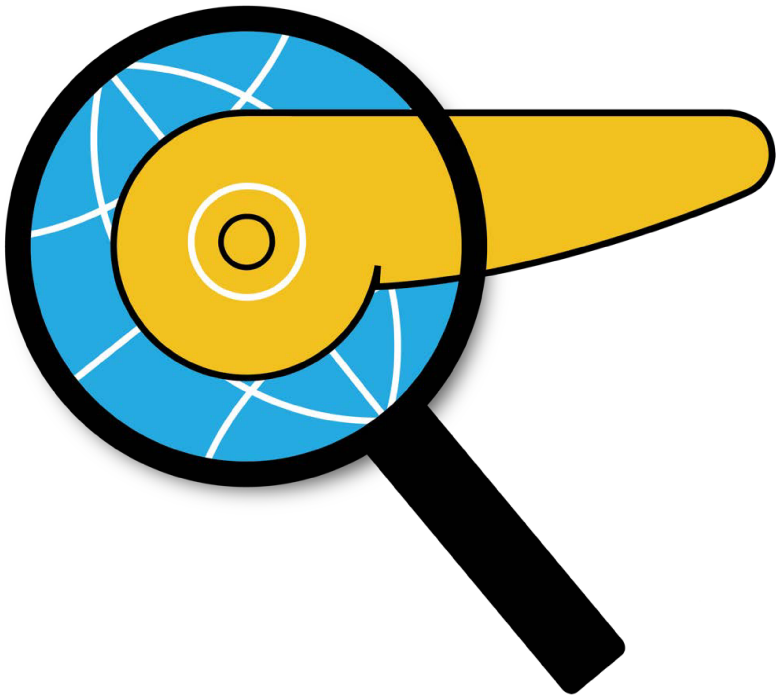

CAncer of the Pancreas Surveillance (CAPS)

LITERATURE OVERVIEW

2011-2018

for the revision of the CAPS consortium consensus guidelines

20 APRIL 2018

Updated 19 JANUARY 2019

Note to reader
This literature overview contains a selection of relevant and impactful publications in the field of pancreas surveillance of individuals at high risk for pancreatic cancer, published since the previous CAPS consortium summit in 2011. Articles not specifically regarding this field, such as papers on biomarkers for sporadic pancreatic cancer, management of pancreatic cysts in the general population, and surgery of pancreatic cancer in general, are beyond the scope of this overview but may still have relevance for the consensus guidelines revisions.

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CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

Contents

Goggins M, *et al. Gut* 2019; 69:7–17. doi: 10.1136/gutjnl-2019-319352

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

Literature search build

MeSH database:

Pancreas	Neoplasm	Surveillance
Pancreas	Pancreatic neoplasms (and subheadings)	Early detection of cancer
		Primary prevention

Title/abstract:

Pancreas	Neoplasm	Surveillance
Pancreas	Neoplas*	Surveill*
Pancreatic	Cyst	Screening
	Cysts	
	Cystic	
	Cancer*	
	"Precursor lesion*"	
	Tumour*	
	Tumor*	
	Malign*	
	Carcinoma*	
	Adenocarcinoma*	

Search: on determinant (surveillance) and outcome (pancreatic neoplasm)
Database: Medline (PubMed)
Filter: human studies
Filter: since 2011

(((((((Pancreas[MeSH Terms]) OR Pancreas[Title/Abstract]) OR Pancreatic[Title/Abstract])) AND ((((((((((((((pancreatic neoplasms[MeSH Terms]) OR pancreatic neoplasm[MeSH Terms]) OR neoplas*[Title/Abstract]) OR cancer*[Title/Abstract]) OR precursor lesion*[Title/Abstract]) OR tumour*[Title/Abstract]) OR tumor*[Title/Abstract]) OR malign*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract])))) OR cyst[Title/Abstract]) OR cysts[Title/Abstract]) OR cystic[Title/Abstract])))) AND (((((early detection of cancer[MeSH Terms]) OR early detection of disease[MeSH Terms]) OR primary prevention[MeSH Terms]) OR surveill*[Title/Abstract]) OR screening[Title/Abstract]))

Goggins M, *et al. Gut* 2019; 69:7–17. doi: 10.1136/gutjnl-2019-319352

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

Summary of recent literature (2011 -2018)

1. When to screen, who to screen (Risk)

a. Non-modifiable risk factors

GENETICS

Bruenderman et al. J Surg Res 2014[1]

METHODS: A **systematic review** was conducted of the literature regarding identification of and screening in high-risk groups.

RESULTS: Those with the highest genetic risk of developing PC include those with **hereditary pancreatitis (87 times** more likely at age 55), **Peutz-Jehgers syndrome (132 times** more likely at age 50), **p16-Leiden mutations (48 times** more likely), and **familial pancreatic cancer (FPC) kindreds (32 times** more likely). Those with the highest risk of developing **sporadic PC** include those with **new-onset diabetes older than 50 y and smoking history.** CONCLUSIONS: Given that sporadic PC is the single largest patient population effected with this devastating disease, some form of screening should be initiated. Currently, the medical community does nothing to attempt early detection of PC. However, sufficient evidence now exists to begin a screening protocol in a high-risk cohort, which would be patients with new-onset diabetes older than 50 y and a smoking history.

Moran et al. Fam Cancer 2012[2]

Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations

We assessed risks of "other cancers" in 268 BRCA1 families and 222 BRCA2 families using a person years at risk analysis from 1975 to 2005. There was **no overall increase in risk for BRCA1** carriers although oesophagus had a significant increased RR of 2.9 (95% CI 1.1-6.0) and stomach at 2.4 (95% CI 1.2-4.3), these were based mainly on unconfirmed cases. For **BRCA2 increased risks for cancers of the pancreas (RR 4.1, 95% CI 1.9-7.8)** and prostate (RR 6.3, 95% CI 4.3-9.0) and uveal melanoma (RR 99.4, 95% CI 11.1-359.8) were confirmed.

The present study strengthens the known links between BRCA2 and pancreatic and prostate cancer, but throws further doubt onto any association with BRCA1. New associations with upper gastro-intestinal malignancy need to be treated with caution and confirmed by large prospective studies.

Mersch et al. Cancer 2015[3]

Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian

BACKGROUND: The purpose of this study was to evaluate the incidence of cancers other than breast and ovarian cancer in known mutation carriers.

METHODS: An institutional review board-approved study identified 1072 patients who had genetic counseling at the authors' institution and tested positive for a deleterious BRCA mutation. The expected number of cancer cases was calculated from the number of individuals in the study sample multiplied by the cancer incidence rates for the general population. The expected and observed numbers of cases were calculated in 5-year intervals to accommodate different age-related incidence rates. Standardized incidence ratios (SIRs) for each cancer type were calculated.

RESULTS: Among the 1072 mutation carriers, 1177 cancers of 30 different cancer types were identified. Individuals with a **BRCA1 mutation did not have a significant increase in cancers other than breast and ovarian cancer**; however, a trend in melanoma was observed. Individuals with a **BRCA2 mutation had significantly higher numbers of observed cases versus expected cases for pancreatic cancer in both men and women** (SIR, 21.7; 95% confidence interval [CI], 13.1-34.0; P < .001) and for prostate cancer in men (SIR, 4.9; 95% CI, 2.0-10.1; P = .002). CONCLUSIONS: The results of this study uphold the current recommendations for hereditary breast and ovarian cancer screening of cancers other than breast and ovarian cancer by the National Comprehensive Cancer Network. Larger cohorts and collaborations are needed to further verify these findings.

Lucas et al. Cancer 2014[4]

BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts

In the current study, the authors attempted to determine the **diagnostic yield of testing for BRCA1/2 germline mutations in a PDAC screening cohort and a PDAC cohort referred for genetic testing**. METHODS: Patients in a high-risk PDAC prevention and genetics program or those with a personal history of PDAC who were referred

for genetic evaluation underwent testing for BRCA1/2 germline mutations. Clinical BRCA1/2 genetic testing included testing for the 3 Ashkenazi Jewish founder mutations or BRCA1/2 comprehensive testing. RESULTS: A total of 37 patients without PDAC underwent BRCA1/2 testing at the study institution. **Genetic testing identified 7 patients who were BRCA1/2 carriers for a yield of 18.9%.** Six patients carried Ashkenazi Jewish founder mutations (3 with BRCA1 and 3 with BRCA2), and 1 patient was found to have a BRCA2 mutation on comprehensive testing. Thirty-two patients with PDAC underwent BRCA1/2 genetic testing. Five patients had Ashkenazi Jewish founder mutations (2 with BRCA1 and 3 with BRCA2), and 2 patients were found to have BRCA2 mutations on comprehensive testing. **The diagnostic yield was 7 of 32 patients** (21.9%). CONCLUSIONS: BRCA1/2 testing is useful in PDAC risk stratification and alters risk assignment and screening recommendations for mutation-positive patients and their families. **Clinical BRCA1/2 testing should be considered in patients of Ashkenazi Jewish descent with a personal history or family history of PDAC, even in the absence of a family history of breast and ovarian cancer.**

Grant et al. Gastroenterology 2015[5]

Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer

BACKGROUND & AIMS: We investigated the prevalence of germline mutations in APC, ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, PRSS1, STK11, and TP53 in patients with pancreatic cancer. METHODS: The Ontario Pancreas Cancer Study enrolls consenting participants with pancreatic cancer from a province-wide electronic pathology database; 708 probands were enrolled from April 2003 through August 2012. To improve the precision of BRCA2 prevalence estimates, 290 probands were selected from 3 strata, based on family history of breast and/or ovarian cancer, pancreatic cancer, or neither. Germline DNA was analyzed by next-generation sequencing using a custom multiple-gene panel. Mutation prevalence estimates were calculated from the sample for the entire cohort. RESULTS: **Eleven pathogenic mutations were identified: 3 in ATM, 1 in BRCA1, 2 in BRCA2, 1 in MLH1, 2 in MSH2, 1 in MSH6, and 1 in TP53**. The prevalence of mutations in all 13 genes was 3.8% (95% confidence interval, 2.1%-5.6%). Carrier status was associated significantly with breast cancer in the proband or first-degree relative (P < .01), and with colorectal cancer in the proband or first-degree relative (P < .01), **but not family history of pancreatic cancer**, age at diagnosis, or stage at diagnosis. Of patients with a personal or family history of breast and colorectal cancer, 10.7% (95% confidence interval, 4.4%-17.0%) and 11.1% (95% confidence interval, 3.0%-19.1%) carried pathogenic mutations, respectively. CONCLUSIONS: **A small but clinically important proportion of pancreatic cancer is associated with mutations in known predisposition genes**. The heterogeneity of mutations identified in this study shows the value of using a multiple-gene panel in pancreatic cancer.

Win et al. J Clin Oncol 2012[6]

Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study

PATIENTS AND METHODS: We prospectively followed a cohort of 446 unaffected carriers of an MMR gene mutation **(MLH1, n = 161; MSH2, n = 222; MSH6, n = 47; and PMS2, n = 16**) and 1,029 their unaffected relatives who did not carry a mutation every 5 years at recruitment centers of the Colon Cancer Family Registry. For comparison of cancer risk with the general population, we estimated country-, age-, and sex-specific standardized incidence ratios (SIRs) of cancer for carriers and noncarriers.
RESULTS: Over a median follow-up of 5 years, mutation carriers had an increased risk of colorectal cancer (CRC; SIR, 20.48; 95% CI, 11.71 to 33.27; P < .001), endometrial cancer (SIR, 30.62; 95% CI, 11.24 to 66.64; P < .001), ovarian cancer (SIR, 18.81; 95% CI, 3.88 to 54.95; P < .001), renal cancer (SIR, 11.22; 95% CI, 2.31 to 32.79; P < .001), **pancreatic cancer (SIR, 10.68; 95% CI, 2.68 to 47.70; P = .001)**, gastric cancer (SIR, 9.78; 95% CI, 1.18 to 35.30; P = .009), urinary bladder cancer (SIR, 9.51; 95% CI, 1.15 to 34.37; P = .009), and female breast cancer (SIR, 3.95; 95% CI, 1.59 to 8.13; P = .001). **We found no evidence of their noncarrier relatives having an increased risk of any cancer**, including CRC (SIR, 1.02; 95% CI, 0.33 to 2.39; P = .97). CONCLUSION: We confirmed that carriers of an MMR gene mutation were at increased risk of a wide variety of cancers, including some cancers not previously recognized as being a result of MMR mutations, and found no evidence of an increased risk of cancer for their noncarrier relatives.

McWilliams et al. Eur J Hum Gen 2011[7]

Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling

Germline mutations in CDKN2A have been reported in pancreatic cancer families, but genetic counseling for pancreatic cancer risk has been limited by lack of information on CDKN2A mutation carriers outside of selected

pancreatic or melanoma kindreds. Among 1537 cases, 9 (0.6%) carried germline mutations in CDKN2A, including three previously unreported mutations. **CDKN2A mutation carriers were more likely to have a family history of pancreatic cancer (P=0.003) or melanoma (P=0.03),** and a personal history of melanoma (P=0.01). **Among cases who reported having a first-degree relative with pancreatic cancer or melanoma, the carrier proportions were 3.3 and 5.3%, respectively.** Penetrance for mutation carriers by age 80 was calculated to be 58% for pancreatic cancer (95% confidence interval (CI) 8-86%), and 39% for melanoma (95% CI 0-80). **Among cases who ever smoked cigarettes, the risk for pancreatic cancer was higher for carriers compared with non-carriers** (HR 25.8, P=2.1 x 10(-)(1)(3)), but **among nonsmokers, this comparison did not reach statistical significance**. Germline mutations in CDKN2A among unselected pancreatic cancer patients are uncommon, although notably penetrant, especially among smokers. **Carriers of germline mutations of CDKN2A should be counseled to avoid tobacco use to decrease risk of pancreatic cancer in addition to taking measures to decrease melanoma risk.**

Potjer et al. Eur Human Genet 2015[8]

Prospective risk of cancer and the influence of tobacco use in carriers of the p16-Leiden germline variant

The aims of this study were to assess the risk of developing other cancers and to determine whether tobacco use would alter cancer risk in carriers of such a variant. We therefore prospectively evaluated individuals with a p16-Leiden germline variant, participating in a pancreatic surveillance programme, for the occurrence of cancer (n=150). Tobacco use was assessed at the start of the surveillance programme. We found a **significantly increased risk** for melanoma (relative risk (RR) 41.3; 95% confidence interval (CI) 22.9-74.6) **and pancreatic cancer (RR 80.8; 95% CI 44.7-146).** In addition, increased risks were found for cancers of the lip, mouth and pharynx (RR 18.8; 95% CI 6.05-58.2) and respiratory tumours (RR 4.56; 95% CI 1.71-12.1). **Current smokers** developed significantly **more cancers** of the lip, mouth and pharynx, respiratory system and pancreas compared with former and never-smokers. In conclusion, this study shows that carriers of a p16-Leiden variant have an increased risk of developing various types of cancer, and smoking significantly increases the risk of frequently occurring cancers. **Smoking cessation should be an integral part of the management of p16-Leiden variant carriers.**

Yang et al. Fam Cancer 2011[9]

Lack of germline PALB2 mutations in melanoma-prone families with CDKN2A mutations and pancreatic cancer

The presence of pancreatic cancer (PC) in melanoma-prone families has been consistently associated with an increased frequency of CDKN2A mutations, the major high-risk susceptibility gene identified for melanoma. However, **the precise relationship between CDKN2A, melanoma and PC remains unknown**. We evaluated a recently identified PC susceptibility gene PALB2 using both sequencing and tagging to determine whether PALB2 might explain part of the relationship between CDKN2A, melanoma, and PC. No disease-related mutations were identified from sequencing PALB2 in multiple pancreatic cancer patients or other mutation carrier relatives of PC patients from the eight melanoma-prone families with CDKN2A mutations and PC. In addition, no significant associations were observed between 11 PALB2 tagging SNPs and melanoma risk in 23 melanoma-prone families with CDKN2A mutations or the subset of 11 families with PC or PC-related CDKN2A mutations. **The results suggested that PALB2 does not explain the relationship between CDKN2A, melanoma, and pancreatic cancer in these melanoma-prone families.**

Yang et al. Hum Genetics 2016[10]

Multiple rare variants in high-risk pancreatic cancer-related genes may increase risk for pancreatic cancer in a subset of patients with and without germline CDKN2A mutations

The risk of pancreatic cancer (PC) is increased in melanoma-prone families but **the causal relationship between germline CDKN2A mutations and PC risk is uncertain,** suggesting the existence of non-CDKN2A factors. One genetic possibility involves patients having mutations in multiple high-risk PC-related genes; however, no systematic examination has yet been conducted. We used next-generation sequencing data to examine 24 putative PC-related genes in 43 PC patients with and 23 PC patients without germline CDKN2A mutations and 1001 controls. For each gene and the four pathways in which they occurred**, we tested whether PC patients (overall or CDKN2A+ and CDKN2A- cases separately) had an increased number of rare nonsynonymous variants**. Overall, we identified **35 missense variants in PC patients,** 14 in CDKN2A+ and 21 in CDKN2A- PC cases. We found nominally significant associations for mismatch repair genes (MLH1, MSH2, MSH6, PMS2) in all PC patients and for ATM, CPA1, and PMS2 in CDKN2A- PC patients. Further, nine CDKN2A+ and four CDKN2A- PC patients had rare potentially deleterious variants in multiple PC-related genes. Loss-of-function variants were only

observed in CDKN2A- PC patients, with ATM having the most pathogenic variants. Also, ATM variants (n = 5) were only observed in CDKN2A- PC patients with a family history that included digestive system tumors. Our results suggest that **a subset of PC patients may have increased risk because of germline mutations in multiple PC-related genes.**

Korsse et al. J Med Genet 2013[11]

Pancreatic cancer risk in Peutz-Jeghers syndrome patients: a large cohort study and implications for surveillance

We therefore aimed to determine the PC risk in a large cohort of Dutch PJS patients. METHODS: PJS was defined by diagnostic criteria recommended by the WHO, a proven LKB1 mutation, or both. All patients with a presumptive diagnosis of pancreatic, ampullary or distal bile duct cancer were identified. Cases were reviewed clinically, radiologically and immunohistochemically. Cumulative PC risks were calculated by Kaplan-Meier analysis and relative risks by Poisson regression analysis. RESULTS: We included 144 PJS patients (49% male) from 61 families (5640 person years follow-up). Seven (5%) patients developed PC at a median age of 54 years. Four patients (3%) were diagnosed with distal bile duct (n=2) or ampullary cancer (n=2) at a median age of 55 years. **The cumulative risk for PC was 26%** (95% CI 4% to 47%) **at age 70 years and relative risk was 76** (95% CI 36 to 160; p<0.001). The cumulative risk for pancreatico-biliary cancer was 32% (95% CI 11% to 52%) at age 70 years, with a relative risk of 96 (95% CI 53 to 174; p<0.001). CONCLUSIONS: PJS patients have a highly increased risk for pancreatico-biliary cancer. Therefore, patients are eligible for surveillance within well defined research programmes to establish the benefit of such surveillance.

Potjer, Vasen et al. Clin Cancer Res 2012.[12]

Variation in precursor lesions of pancreatic cancer among high-risk groups

We assessed differences in frequency and behavior of precursor lesions and PDAC between two high-risk groups. EXPERIMENTAL DESIGN: Individuals with a p16-Leiden germline mutation (N = 116; median age 54 years) and individuals from familial pancreatic cancer (FPC) families (N = 125; median age 47 years) were offered annual surveillance by MRI and magnetic resonance cholangiopancreatography (MRCP) with or without endoscopic ultrasound (EUS) for a median surveillance period of 34 months (0-127 months) or 36 months (0-110 months), respectively. Detailed information was collected on pancreatic cystic lesions detected on MRCP and precursor lesions in surgical specimens of patients who underwent pancreatic surgery. RESULTS: **Cystic lesions were more common in the FPC cohort (42% vs. 16% in p16-Leiden cohort), whereas PDAC was more common in the p16-Leiden cohort (7% vs. 0.8% in FPC cohort). Intraductal papillary mucinous neoplasm (IPMN) was a common finding in surgical specimens of FPC-individuals, and was only found in two patients of the p16-Leiden cohort. In the p16-Leiden cohort, a substantial proportion of cystic lesions showed growth or malignant transformation during follow-up, whereas in FPC individuals most cystic lesions remain stable.** CONCLUSION: In p16-Leiden mutation carriers, cystic lesions have a higher malignant potential than in FPC-individuals. On the basis of these findings, a more intensive surveillance program may be considered in this high-risk group.

Konings et al. Pancreas 2016.[13]

Prevalence and Progression of Pancreatic Cystic Precursor Lesions Differ Between Groups at High Risk of Developing Pancreatic Cancer

OBJECTIVES: The aim of this study was to compare the prevalence of cystic pancreatic lesions and their natural behavior in 2 distinct high-risk groups for developing pancreatic ductal adenocarcinoma (PDAC): (1) carriers of a mutation that predisposes to PDAC and (2) individuals without a known gene mutation but with a family history of PDAC (familial pancreatic cancer [FPC]). METHODS: Pancreatic surveillance by annual magnetic resonance imaging and endoscopic ultrasound was performed in individuals with an estimated lifetime risk of developing PDAC of 10% or greater**. Progression of a lesion was defined as growth 4 mm or greater or the development of worrisome features.** RESULTS: We included 186 individuals: 98 mutation carriers and 88 FPC individuals (mean follow-up, 51 months). **Individuals with FPC were significantly more likely than mutation carriers to have a pancreatic cyst 10 mm or greater** (16% vs 5%, P = 0.045). **Pancreatic cysts detected in mutation carriers, however, were significantly more likely to progress than those in FPC individuals** (16% vs 2%, P = 0.050). CONCLUSIONS: This study provides evidence that the prevalence and growth characteristics of pancreatic cysts differ between distinct high-risk groups: individuals with FPC have a higher prevalence of pancreatic cysts 10 mm or greater, whereas cysts in mutation carriers are more likely to progress. These observations may help to develop more optimally tailored surveillance strategies in specific high-risk populations.

Harinck et al. Eur J Hum Gen 2012[14]

Routine testing for PALB2 mutations in familial pancreatic cancer families and breast cancer families with pancreatic cancer is not indicated

PALB2-mutation carriers not only have an increased risk for breast cancer (BC) but also for pancreatic cancer (PC). Thus far, PALB2 mutations have been mainly found in PC patients from families affected by both PC and BC. As it is well known that the prevalence of gene mutations varies between different populations, we studied the prevalence of PALB2 mutations in a Dutch cohort of non-BRCA1/2 familial PC (FPC) families and in non-BRCA1/2 familial BC (FBC) families with at least one PC case. Mutation analysis included direct sequencing and multiplex ligation-dependent probe amplification (MLPA) and was performed in a total of 64 patients from 56 distinct families (28 FPC families, 28 FBC families). In total, 31 patients (48%) originated from FPC families; 24 were FPC patients (77%), 6 had a personal history of BC (19%) and 1 was a suspected carrier (3.2%). The remaining 33 patients (52%) were all female BC patients of whom 31 (94%) had a family history of PC and 2 (6.1%) had a personal history of PC. In none of these 64 patients a PALB2 mutation was found. **Therefore, PALB2 does not have a major causal role in familial clustering of PC and BC in non-BRCA1/2 families in the Dutch population**.

Ghiorzo et al. Journal of Medical Genetics[15]

CDKN2A is the main susceptibility gene in Italian pancreatic cancer families

Patients and methods A series of **225 consecutively enrolled patients with PC** were tested for CDKN2A mutations. After personal and family cancer histories of all the patients had been reviewed, a subset of the patients were classified as FPC and were also tested for mutations in PALLD, PALB2, BRCA1 and BRCA2 as FPC candidate genes. Results The **CDKN2A mutation rate in the 225 PC cases was 5.7%.** The CDKN2A founder mutations, p.E27X and p.G101W, were predominant, but the mutation spectrum also included p.L65P, p.G67R and two novel, potentially pathogenic variants, promoter variant c.-201ACTC>CTTT and p.R144C. **None of the patients with FPC harboured germline mutations in PALLD, PALB2 or BRCA2.** One family was positive for the BRCA1 UV variant p.P727L. Strikingly, five of 16 patients with FPC (31%) carried CDKN2A mutations. Conclusion These findings suggest that a sizeable subset of Italian FPC families may carry CDKN2A mutations. This result may be of value for identifying the best candidates for future PC screening trials in Italy.

Yu et al. PloS one 2016[16]

Development and Validation of a Prediction Model to Estimate Individual Risk of Pancreatic Cancer

The goal of this study was to develop an individualized risk prediction model that can be used to screen for asymptomatic pancreatic cancer in Korean men and women. MATERIALS AND METHODS: Gender-specific risk prediction models for pancreatic cancer were developed using the Cox proportional hazards model **based on an 8-year follow-up of a cohort study of 1,289,933 men and 557,701 women in Korea** who had biennial examinations in 1996-1997. The performance of the models was evaluated with respect to their discrimination and calibration ability based on the C-statistic and Hosmer-Lemeshow type chi2 statistic. RESULTS: A total of 1,634 (0.13%) men and 561 (0.10%) women were newly diagnosed with pancreatic cancer. **Age, height, BMI, fasting glucose, urine glucose, smoking, and age at smoking initiation were included in the risk prediction model for men. Height, BMI, fasting glucose, urine glucose, smoking, and drinking habit were included in the risk prediction model for women.** Smoking was the most significant risk factor for developing pancreatic cancer in both men and women. The risk prediction model exhibited good discrimination and calibration ability, and in external validation it had excellent prediction ability. CONCLUSION: Gender-specific risk prediction models for pancreatic cancer were developed and validated for the first time. The prediction models will be a useful tool for detecting high-risk individuals who may benefit from increased surveillance for pancreatic cancer.

Ibrahim et al. Eur J Hum Genet. 2018[17]

Risk of multiple pancreatic cancers in CDKN2A-p16-Leiden mutation carriers

CDKN2A-p16-Leiden mutation carriers have a substantial risk of developing pancreatic ductal adenocarcinoma (PDAC). One of the main clinical features of hereditary cancer is the development of multiple cancers. Since 2000, we have run a surveillance program for CDKN2A-p16-Leiden mutation carriers. The patients are offered a yearly MRI with optionally endoscopic ultrasound. In patients with a confirmed lesion, usually, a partial resection of the pancreas is recommended. A total of 18 PDAC (8.3%) were detected in 218 mutation carriers. In this report, we describe two CDKN2A-p16-Leiden patients with a synchronous and metachronous PDAC. Including two previously-reported cases, we identified four patients with multiple PDAC: two of 18 patients within the

surveillance program (11%) and two patients with a proven CDKN2A-p16-Leiden mutation not participating in the surveillance program. In conclusion, **this study demonstrated a high risk of developing multiple PDAC in CDKN2A-p16-Leiden mutation carriers. After detecting a primary tumor, it is very important to exclude the presence of a second synchronous tumor.** Moreover, after a partial pancreatectomy for PDAC, close surveillance is necessary. In view of the current findings, offering a total pancreatectomy might be an appropriate option in patients with an early PDAC.

Kim et al. Hered Cancer Clin Pract. 2019[18]

The association between non-breast and ovary cancers and BRCA mutation in first- and second-degree relatives of high-risk breast cancer patients: a large-scale study of Koreans

Background: As a large-scale study of Koreans, we evaluated the association between BRCA mutation and the prevalence of non-breast and ovary cancers in first- and second-degree relatives of high-risk breast cancer patients. Methods: We organized familial pedigrees of 2555 patients with breast cancer who underwent genetic screening for BRCA1/2 in Samsung Medical Center between January 2002 and May 2018. Families with a member that had a history of cancer other than of the breast or ovary were regarded positive for other primary cancer. Results: The median age of the population was 40 years (range, 19 to 82 years). BRCA mutation was detected in 377 (14.8%) of the patients. The BRCA-positive group had a higher frequency of family history of breast or ovarian cancer ($p < 0.001$), bilateral breast cancer ($p = 0.021$), and the male gender ($p = 0.038$). There were 103 (27.3%) patients who had multiple risk factors in the BRCA-positive group, while there were 165 (7.6%) patients who had multiple risk factors in the BRCA-negative group ($p < 0.001$). BRCA mutation was detected in 215 (11.7%) of the 1841 families without history of other primary cancers. Among the 714 families with histories of other primary cancers, 162 (22.7%) had BRCA mutation, and this was significantly more frequent ($p < 0.001$) than in those without a history. The occurrence of other primary cancers in families of high-risk patients was associated with a younger age at diagnosis ($p = 0.044$), bilateral breast cancer ($p = 0.006$), and BRCA mutations ($p < 0.001$). The most common site for the occurrence of another type of primary cancer was the stomach. **In the BRCA-positive group, the proportional incidences of stomach, pancreas, colorectal, lung, and uterine cancer were 13.8, 4.0, 7.7, 8.8, and 5.0%, respectively; these were all relatively higher than those in the BRCA-negative group.** Conclusions: We confirmed that BRCA mutation was associated with having multiple risk factors and an increased prevalence of non-breast and ovary cancers in first- and second-degree relatives of high-risk breast cancer patients. Due to the possibility of inherited cancer risk, genetic counseling with options for risk assessment and management should be provided to both patients and families of BRCA mutation carriers.

Roch et al. J Surg Oncol 2019[19]

Are BRCA1 and BRCA2 gene mutation patients underscreened for pancreatic adenocarcinoma?

Screening is currently recommended only for patients with one first-degree relative or two family members with PDAC. We hypothesized that screening all BRCA1/2 patients would identify a higher rate of pancreatic abnormalities. METHODS: **All BRCA1/2 patients at a single academic center were retrospectively reviewed** (2005-2015). Pancreatic abnormalities were defined on cross-sectional imaging as pancreatic neoplasm (cystic/solid) or main-duct dilation. RESULTS: **Two hundred and four patients were identified with BRCA mutations**. **Forty-seven (40%) had abdominal imaging** (20 computerized tomography and 27 magnetic resonance imaging). **Twenty-one percent had pancreatic abnormalities** (PDAC [n = 2] and intraductal papillary mucinous neoplasm [IPMN; n = 8]). The **prevalence of pancreatic abnormalities and IPMN was higher in BRCA2 patients than in the general population** (21% vs 8% and 17% vs 1%; P = 0.0007 and P < 0.0001, respectively), with no influence of family history. Similarly, BRCA1 patients had an increased prevalence of IPMN (8.3% vs 1%; P < 0.0001). CONCLUSIONS: In this series, 4% and 17% of BRCA2 patients developed PDAC and IPMN, respectively. Eight percent of BRCA1 patients developed IPMN. Under current recommended screening, 60% of BRCA1/2 patients had incompletely pancreatic assessment. With no influence of family history, this study suggests all BRCA1/2 patients should undergo a high-risk screening protocol that will identify a higher rate of precancerous pancreatic neoplasms amenable to curative resection.

Tucker et al. J Invest Dermatol[20]

Risks of Melanoma and Other Cancers in Melanoma-Prone Families over 4 Decades

Since 1976, melanoma-prone families have been followed at the National Cancer Institute to identify etiologic factors for melanoma**. We compared risks of melanoma and other cancers in 1,226 members of 56 families followed for up to 4 decades with population rates in the Surveillance, Epidemiology, and End Results program**. All families were tested for mutations in CDKN2A and CDK4; 29 were mutation-positive and 27 mutation-negative. We compared rates of invasive melanomas, both first and second, by family mutation status,

with Surveillance, Epidemiology, and End Results program. Comparing three calendar periods of the study, risk of first primary melanoma decreased slightly. Risks of melanoma after first examination, however, were approximately one-third the risks prior to the first examination in both mutation-positive and mutation-negative families. Among patients with melanoma, risk of a second melanoma was increased 10-fold in all families; risk was somewhat higher in mutation-positive families. **Risks of other second cancers were increased only for pancreatic cancer after melanoma in mutation-positive families.** Over 4 decades, prospective risk of melanoma has decreased substantially in both mutation-positive and mutation-negative families, when melanoma has greatly increased in the general population.

FAMILIAL PANCREATIC CANCER

Antwi et al. J Natl Cancer Inst 2018[21]

Risk of Different Cancers Among First-degree Relatives of Pancreatic Cancer Patients: Influence of Probands' Susceptibility Gene Mutation Status

We assessed **risk for 15 cancers among FDRs of unselected PC probands**. Methods: Data on 17 162 FDRs, with more than 336 000 person-years at risk, identified through 2305 sequential PC probands enrolled at Mayo Clinic (2000-2016) were analyzed. Family history data were provided by the probands. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated, **comparing malignancies observed among the FDRs with that expected using Surveillance, Epidemiology, and End Results (SEER) data**. Genetic testing was performed among a subset of probands (n = 2094), enabling stratified analyses among FDRs based on whether the related proband tested positive or negative for inherited mutation in 22 sequenced cancer susceptibility genes. All statistical tests were two-sided. Results: Compared with SEER, **PC risk was twofold higher among FDRs of PC probands (SIR = 2.04, 95% CI = 1.78 to 2.31, P < .001).** Primary liver cancer risk was elevated among female FDRs (SIR = 2.10, 95% CI = 1.34 to 3.12, P < .001). **PC risk was more elevated among FDRs of mutation-positive probands (SIR = 4.32, 95% CI = 3.10 to 5.86) than FDRs of mutation-negative probands (SIR = 1.77, 95% CI = 1.51 to 2.05, between-group P < .001). FDR PC risk was higher when the related proband was younger than age 60 years at diagnosis and mutation-positive (SIR = 5.24, 95% CI = 2.93 to 8.64) than when the proband was younger than age 60 years but mutation-negative (SIR = 1.76, 95% CI = 1.21 to 2.47, between-group P < .001).** Breast (SIR = 1.29, 95% CI = 1.01 to 1.63) and ovarian (SIR = 2.38, 95% CI = 1.30 to 4.00) cancers were elevated among FDRs of mutation-positive probands. Conclusions: Our study substantiates twofold risk of PC among FDRs of PC patients and suggests increased risk for primary liver cancer among female FDRs. FDRs of susceptibility mutation carriers had substantially increased risk for PC and increased risk for breast and ovarian cancers.

RACE AND ETHNIC DESCENT

Risch et al. Am J of Epidemiology 2015[22]

Detectable Symptomatology Preceding the Diagnosis of Pancreatic Cancer and Absolute Risk of Pancreatic Cancer Diagnosis

We combined US Surveillance Epidemiology and End Results (SEER) incidence data from 2008 to 2010 with regression models from representative case-control data from Connecticut (2005-2009) to estimate age- and sex-specific 5-year absolute risks of pancreatic cancer diagnosis. Our risk model included current **cigarette smoking** (adjusted odds ratio (OR) = 3.3, 95% confidence interval (CI): 2.1, 5.0), **current use of proton pump-inhibitor antiheartburn medications** (OR = 6.2, 95% CI: 1.7, 23), **recent diagnosis of diabetes mellitus** (OR = 4.8, 95% CI: 2.2, 11), **recent diagnosis of pancreatitis** (OR = 19, 95% CI: 3.1, 120), **Jewish ancestry** (OR = 1.8, 95% CI: 1.1, 3.1), **and ABO blood group other than O** (OR = 1.3, 95% CI: 1.0, 1.8). In total, 0.87% of controls with combinations of these factors had estimated 5-year absolute risks greater than 5%, and for some, the risks reached more than 10%. Combining risk factors for pancreatic cancer with detectable prediagnostic symptomatology can allow investigators to begin to identify small segments of the population with risks sufficiently high enough to make screening efforts among them potentially useful.

AGE (what age to start and stop surveillance)

Canto et al. Gastroenterology 2012.[23]

Frequent detection of pancreatic lesions in asymptomatic high-risk individuals

METHODS: We screened 225 asymptomatic adult HRIs at 5 academic US medical centers once, using computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). We compared results in a blinded, independent fashion.
RESULTS: Ninety-two of 216 HRIs (42%) were found to have at least 1 pancreatic mass (84 cystic, 3 solid) or a dilated pancreatic duct (n = 5) by any of the imaging modalities. Fifty-one of the 84 HRIs with a cyst (60.7%) had multiple lesions, typically small (mean, 0.55 cm; range, 2-39 mm), in multiple locations. **The prevalence of pancreatic lesions increased with age; they were detected in 14% of subjects younger than 50 years old, 34% of subjects 50-59 years old, and 53% of subjects 60-69 years old (P < .0001)**.

Bartsch et al. Gut 2016[24]
Refinement of screening for familial pancreatic cancer
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.

BLOOD TYPE

Risch et al. Am J of Epidemiology 2015[22]
Detectable Symptomatology Preceding the Diagnosis of Pancreatic Cancer and Absolute Risk of Pancreatic Cancer Diagnosis
We combined US Surveillance Epidemiology and End Results (SEER) incidence data from 2008 to 2010 with regression models from representative case-control data from Connecticut (2005-2009) to estimate age- and sex-specific 5-year absolute risks of pancreatic cancer diagnosis. Our risk model included current **cigarette smoking** (adjusted odds ratio (OR) = 3.3, 95% confidence interval (CI): 2.1, 5.0), **current use of proton pump-inhibitor antiheartburn medications** (OR = 6.2, 95% CI: 1.7, 23), **recent diagnosis of diabetes mellitus** (OR = 4.8, 95% CI: 2.2, 11), **recent diagnosis of pancreatitis** (OR = 19, 95% CI: 3.1, 120), **Jewish ancestry** (OR = 1.8, 95% CI: 1.1, 3.1), **and ABO blood group other than O** (OR = 1.3, 95% CI: 1.0, 1.8). In total, 0.87% of controls with combinations of these factors had estimated 5-year absolute risks greater than 5%, and for some, the risks reached more than 10%. Combining risk factors for pancreatic cancer with detectable prediagnostic symptomatology can allow investigators to begin to identify small segments of the population with risks sufficiently high enough to make screening efforts among them potentially useful.

Risch et al. Am J of Epidemiology 2013[25]
ABO blood group and risk of pancreatic cancer: a study in Shanghai and **meta-analysis**
Studies over 5 decades have examined ABO blood groups and risk of pancreatic cancer in Western, Asian, and other populations, though no systematic review has been published. We studied data from 908 pancreatic cancer cases and 1,067 population controls collected during December 2006-January 2011 in urban Shanghai, China, and reviewed the literature for all studies of this association. Random-effects meta-analysis provided summary odds ratio estimates according to blood group and by populations endemic versus nonendemic for cytotoxin-associated gene A (CagA)-positive Helicobacter pylori. In our Shanghai study, **versus group O, only ABO group A was associated with risk** (odds ratio (OR) = 1.60, 95% confidence interval (CI): 1.27, 2.03). In 24 pooled studies,

group A showed increased risk in both CagA-nonendemic and -endemic populations (ORpooled = 1.40, 95% CI: 1.32, 1.49). **In nonendemic populations, groups B and AB were also associated** with higher risk (OR = 1.38, 95% CI: 1.16, 1.64; and OR = 1.52, 95% CI: 1.24, 1.85, respectively). However**, in CagA-endemic populations, groups B and AB were not associated with risk** (OR = 1.05, 95% CI: 0.92, 1.19; and OR = 1.13, 95% CI: 0.92, 1.38, respectively). These population differences were significant. One explanation for contrasts in associations of blood groups B and AB between CagA-endemic and -nonendemic populations could involve gastric epithelial expression of A versus B antigens on colonization behaviors of CagA-positive and CagA-negative H. pylori strains.

b. Modifiable risk factors

SMOKING

Bosetti et al. Ann Oncol 2012.[26]

Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4).

METHODS: We analyzed data from 12 case-control studies within the International Pancreatic Cancer Case-Control Consortium (PanC4), including 6507 pancreatic cases and 12 890 controls. We estimated summary odds ratios (ORs) by pooling study-specific ORs using random-effects models.

RESULTS: Compared with never smokers, the OR was 1.2 (95% confidence interval [CI] 1.0-1.3) for former smokers and **2.2 (95% CI 1.7-2.8) for current cigarette smokers**, with a significant **increasing trend in risk with increasing number of cigarettes** among current smokers (OR=3.4 for >/=35 cigarettes per day, P for trend<0.0001). Risk increased in relation to duration of cigarette smoking up to 40 years of smoking (OR=2.4). No trend in risk was observed for age at starting cigarette smoking, whereas **risk decreased with increasing time since cigarette cessation, the OR being 0.98 after 20 years.**

CONCLUSIONS: This uniquely large pooled analysis confirms that current cigarette smoking is associated with a twofold increased risk of pancreatic cancer and that the risk increases with the number of cigarettes smoked and duration of smoking. Risk of pancreatic cancer reaches the level of never smokers approximately 20 years after quitting.

ALCOHOL

Wang et al. BMC Cancer 2016[27]

Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies.

BACKGROUND: The purpose of this study was to summarize and examine the evidence regarding the association between alcohol intake and pancreatic cancer risk based on results from prospective cohort studies.

RESULTS: We included 19 prospective studies (21 cohorts) reporting data from 4,211,129 individuals. **Low-to-moderate alcohol intake had little or no effect on the risk of pancreatic cancer**. **High alcohol intake was associated with an increased risk of pancreatic cancer** (risk ratio [RR], 1.15; 95 % CI: 1.06-1.25). Pooled analysis also showed that high liquor intake was associated with an increased risk of pancreatic cancer (RR, 1.43; 95 % CI: 1.17-1.74). Subgroup analyses suggested that high alcohol intake was associated with an increased risk of pancreatic cancer in North America, when the duration of follow-up was greater than 10 years, in studies scored as high quality, and in studies with adjustments for smoking status, body mass index, diabetes mellitus, and energy intake.. CONCLUSIONS: Low-to-moderate alcohol intake was not significantly associated with the risk of pancreatic cancer, whereas high alcohol intake was associated with an increased risk of pancreatic cancer. Furthermore, liquor intake in particular was associated with an increased risk of pancreatic cancer.

OBESITY

Genkinger et al. Int J Cancer 2011[28]

A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk.

RESULTS: Compared to individuals with a body mass index (BMI) at baseline between 21-22.9 kg/m(2) , pancreatic cancer **risk was 47% higher** (95%CI:23-75%) **among obese** (BMI >/= 30 kg/m(2)) individuals. A positive association was observed for BMI in early adulthood (pooled multivariate [MV]RR = 1.30, 95%CI = 1.09-1.56 comparing BMI >/= 25 kg/m(2) to a BMI between 21 and 22.9 kg/m(2)). Compared to individuals who were not

overweight in early adulthood (BMI < 25 kg/m(2)) and not obese at baseline (BMI < 30 kg/m(2)), pancreatic cancer risk was 54% higher (95%CI = 24-93%) for those who were overweight in early adulthood and obese at baseline. We observed a 40% higher risk among individuals who had gained BMI >/= 10 kg/m(2) between BMI at baseline and younger ages compared to individuals whose BMI remained stable.
CONCLUSION: **BMI is positively associated with pancreatic cancer risk.**

Stolzenberg-Solomon et al. Am J Clin Nutr 2013.[29]

OBJECTIVE: We determined **the association for body mass index (BMI) at different ages and adiposity duration and gain with incident pancreatic adenocarcinoma** in the NIH-AARP Diet and Health Study cohort.
DESIGN: Participants aged 50-71 y completed questionnaires at baseline (1995-1996) and 6 months later that queried height and weight history. We calculated HRs and 95% CIs by using Cox proportional hazards models adjusted for age, smoking, sex, and intakes of energy and total fat.
RESULTS: Over an average follow-up of 10.5 y, **1206 and 2122 pancreatic cancer cases were identified in the subcohort who completed the second questionnaire (n = 273,975) and the baseline cohort (n = 501,698),** respectively. Compared with normal weight, **overweight or obesity at ages 18, 35, 50, or >50 y** (baseline BMI) **was significantly associated with pancreatic cancer, with HRs ranging from 1.15 to 1.53**. **A longer duration of BMI (in kg/m(2)) >25.0 was significantly associated with pancreatic cancer (overall HR per 10-y increment of duration: 1.06; 95% CI: 1.02, 1.09), with individuals who reported diabetes having the greatest risk (HR per 10-y increment of duration: 1.18; 95% CI: 1.05, 1.32; P-interaction = 0.01) and rates**. A substantial gain in adiposity (>10 kg/m(2)) after age 50 y was significantly associated with increased pancreatic cancer risk. The etiologic fraction of pancreatic cancer explained by adiposity at any age was 14% overall and 21% in never smokers.
CONCLUSION: Overweight and obesity at any age are associated with increased pancreatic cancer.

DIET

Jansen et al. Cancer Causes Control 2011[30]

Fruit and vegetable consumption is inversely associated with having pancreatic cancer
Comparing highest to lowest quintiles, we observed significant inverse associations (OR < 0.8) with significant trends (p (trend) < 0.05) for citrus, melon, and berries, other fruits, dark green vegetables, deep yellow vegetables, tomato, other vegetables, dry bean and pea, insoluble fiber, soluble fiber, whole grains, and orange/grapefruit juice, and an increased association with non-whole grains. Results were similar after adjusting for diabetes or total sugar intake.
Conclusion: **Lower consumption of fruits, vegetables, whole grains, and fiber is associated with having pancreatic cancer.**

Larsson et al. Br J Cancer 2012[31]

Red and processed meat consumption and risk of pancreatic cancer: **meta-analysis** of prospective studies.
Eleven prospective studies, with 6643 pancreatic cancer cases, were included in the meta-analysis. An increase in **red meat consumption of 120 g per day was associated with an overall relative risk (RR) of 1.13** (95% confidence interval (CI)=0.93-1.39; P(heterogeneity)<0.001). **Red meat consumption was positively associated with pancreatic cancer risk in men** (RR=1.29; 95% CI=1.08-1.53; P(heterogeneity)=0.28; five studies), but **not in women (**RR=0.93; 95% CI=0.74-1.16; P(heterogeneity)=0.21; six studies).

Jansen et al. Int J Cancer 2014[32]

Fatty acids found in dairy, protein and unsaturated fatty acids are associated with risk of pancreatic cancer in a case-control study
We evaluated the association between intake of meat, fish, dairy, specific FAs and related nutrients and pancreatic cancer. In our American-based Mayo Clinic case-control study 384 cases and 983 controls frequency matched on recruitment age, race, sex and residence area (Minnesota, Wisconsin or Iowa, USA) between 2004 and 2009. All subjects provided demographic information and completed 144-item food frequency questionnaire. Logistic regression-calculated odds ratios (ORs) and 95% confidence intervals (95% CIs) were adjusted for age, sex, cigarette smoking, body mass index and diabetes mellitus. Significant inverse association (trend p-value < 0.05) between pancreatic cancer and the groupings (highest vs. lowest consumption quintile OR [95% CI]) was as follows: meat replacement (0.67 [0.43-1.02]), total protein (0.58 [0.39-0.86]), vitamin B12 (0.67 [0.44, 1.01]), zinc (0.48 [0.32, 0.71]), phosphorus (0.62 [0.41, 0.93]), vitamin E (0.51 [0.33, 0.78]), polyunsaturated FAs (0.64 [0.42, 0.98]) and linoleic acid (FA 18:2) (0.62 [0.40-0.95]). Increased risk associations were observed for saturated FAs

(1.48 [0.97-2.23]), butyric acid (FA 4:0) (1.77 [1.19-2.64]), caproic acid (FA 6:0) (2.15 [1.42-3.27]), caprylic acid (FA 8:0) (1.87 [1.27-2.76]) and capric acid (FA 10:0) (1.83 [1.23-2.74]). Our study suggests that **eating a diet high in total protein and certain unsaturated FAs is associated with decreased risk of developing pancreatic cancer in a dose-dependent manner, whereas fats found in dairy increase risk.**

Piper et al. Am J Clin Nutr 2015[33]

Vitamin D-binding protein and pancreatic cancer: a nested case-control study

OBJECTIVE: The objective was to examine the association between DBP and pancreatic cancer risk in an American population.

DESIGN: We conducted a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Cancer screening trial cohort of men and women aged 55-74 y at baseline. Between 1993 and 2010, 295 incident pancreatic adenocarcinoma cases were reported (follow-up to 15.1 y). Two controls (n = 590) were matched to each case by age, race, sex, and month of blood draw. We calculated smoking- and diabetes-adjusted ORs and 95% CIs with the use of conditional logistic regression.

RESULTS: **DBP concentration was not significantly associated with pancreatic cancer overall** [highest (>/=7149.4 nmol/L) vs. lowest (<3670.4 nmol/L) quintile; OR: 1.75; 95% CI: 0.91, 3.37; P-trend = 0.25]. For serum 25(OH)D compared with the referent (50 to <75 nmol/L), individuals in the highest group had a significantly higher risk (>/=100 nmol/L; OR: 3.23; 95% CI: 1.24, 8.44), whereas those in the lowest group had no significant association (<25 nmol/L; OR: 2.50; 95% CI: 0.92, 6.81). Further adjustment for DBP did not alter this association.

CONCLUSION: Our results **do not support the hypothesis that serum DBP or 25(OH)D plays a protective role in pancreatic cancer**. This trial was registered at clinicaltrials.gov as NCT00339495.

c. Diabetes

Batabyal et al. Ann Surg Oncol 2014.[34]

Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies

METHODS: A systematic review of the association between DM and PDAC was undertaken by searching electronic databases and journal references from 1973 to 2013.

RESULTS: A total of 88 independent studies, including 50 cohort and 39 case-control studies were examined. The overall summary-combined RR was 1.97 (95 % CI 1.78-2.18) with marked heterogeneity that could not be clearly attributed to any subgroup analyses. **The risk of PDAC was greatest early after the diagnosis of DM but remained elevated long after the diagnosis**. The individual-level RR ranged from **6.69 at less than 1 year** to 1.36 at 10 years.

CONCLUSION: The results demonstrate a strong association between PDAC and recently diagnosed DM, which may be attributed to a paraneoplastic effect. However, the presence of diabetes also remains a modest risk factor for the development of PDAC long-term. Selective screening of patients with new-onset DM for PDAC needs to be considered.

Aggarwal et al. Pancreas 2013[35]

Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers

We compared the prevalence and characteristics of DM in lung, breast, prostate, and colorectal cancers with PaC and noncancer controls. METHODS: We retrospectively reviewed the medical records of 500 consecutive patients with cancer (100 each with lung, breast, prostate, and colorectal cancers and PaC) and 100 noncancer controls.

RESULTS: **Patients with PaC (mean age +/- SD, 71.6 +/- 9.4 years; 53% men) had a significantly (P < 0.0001) higher prevalence of DM (68%)** compared to age-matched patients with lung (mean age +/- SD, 71.6 +/- 9.4 years; 59% men; and 19.6% DM), breast (mean age +/- SD, 71.6 +/- 9.6 years; 100% women; and 19.4% DM), prostate (mean age +/- SD, 71.3 +/- 9.4 years; 100% men; and 14.8% DM), and colorectal cancer (mean age +/- SD, 71.6 +/- 9.5 years; 56% men; and 20.7% DM), and noncancer controls (mean age +/- SD, 70.7 +/- 9.2 years; 57% men; and 23.5% DM). **Among the patients with PaC, 40% developed DM in the 36 months preceding the diagnosis of PaC** compared with 3.3% to 5.7% in the other groups (P < 0.0001).

CONCLUSIONS: Whereas the prevalence of DM in PaC is very high, DM prevalence in other common cancers is no different from that in noncancer controls. In particular, new-onset DM is a phenomenon that is unique to PaC.

Sasazuki et al. Cancer Sci 2013[36]

Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

We conducted a comprehensive assessment of the association between pre-existing diabetes and total and site-specific cancer risk based on a pooled analysis of eight cohort studies in **Japan** (>330 000 subjects). **A statistically increased risk** was observed for cancers at specific sites, such as colon (hazard ratio; HR = 1.40), liver (HR = 1.97), **pancreas (HR = 1.85)** and bile duct (HR = 1.66; men only). Increased risk was also suggested for other sites, and diabetes mellitus was associated with an overall 20% increased risk in total cancer incidence in the Japanese population. The association between these two diseases has important implications for reiterating the importance of controlling lifestyle factors and may suggest a possible strategy for cancer screening among patients with diabetes. Studies continuously investigating the risk factors for diabetes are also important.

Goggins M, *et al. Gut* 2019; 69:7–17. doi: 10.1136/gutjnl-2019-319352

Liao et al. BMJ 2015[37]

Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis

OBJECTIVE: To evaluate potential linear and non-linear dose-response relations between blood glucose and risk of pancreatic cancer.

DESIGN: Systematic review and dose-response meta-analysis of prospective observational studies.

RESULTS: Nine studies were included for analysis, with a total of 2408 patients with pancreatic cancer. There was a **strong linear dose-response association** between fasting blood glucose concentration and the rate of pancreatic cancer across the range of prediabetes and diabetes. No non-linear association was detected. **The pooled rate ratio of pancreatic cancer per 0.56 mmol/L (10 mg/dL) increase in fasting blood glucose was 1.14** (95% confidence interval 1.06 to 1.22; P<0.001) without significant heterogeneity. Sensitivity analysis excluding blood glucose categories in the range of diabetes showed similar results (pooled rate ratio per 0.56 mmol/L increase in fasting blood glucose was 1.15, 95% confidence interval 1.05 to 1.27; P=0.003), strengthening the association between prediabetes and pancreatic cancer.

CONCLUSIONS: Every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in the rate of pancreatic cancer. As prediabetes can be improved or even reversed through lifestyle changes, early detection of prediabetes coupled with lifestyle changes could represent a viable strategy to curb the increasing incidence of pancreatic cancer.

Sadr-Azodi et al. Acta Oncol 2015[38]

Pattern of increasing HbA1c levels in patients with diabetes mellitus before clinical detection of pancreatic cancer - a population-based nationwide case-control study

METHODS: This was a nested case-control population-based study assessing the pattern of glycated hemoglobin (HbA1c) change before clinical detection of pancreatic cancer in a population of individuals with diabetes mellitus. All patients registered in the Swedish National Diabetes Register **with a prescription of an anti-diabetic drug** between 2005 and 2011 were identified. For each case of pancreatic cancer, 10 controls were randomly selected, matched for age, sex, and factors related to diabetes mellitus. Multivariable conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between HbA1c and pancreatic cancer.

RESULTS: In total, 391 cases and 3910 matched controls were identified. The risk of pancreatic cancer was **increased more than two-fold in individuals with the highest HbA1c quartile compared with the lowest** (OR 1.96, 95% CI 1.40-2.75). The risk of pancreatic cancer remained elevated when comparing the highest HbA1c quartile measured within five years from the clinical detection of pancreatic cancer to the lowest HbA1c quartile (p-value for trend < 0.05). **No association was found between HbA1c and pancreatic cancer if HbA1c was measured > 5 years before the clinical detection of pancreatic cancer**. CONCLUSIONS: **The pattern of increasing HbA1c in patients with diabetes mellitus preceded the clinical detection of pancreatic cancer by up to five years.** These findings indicate that there is a lead time of several years during which the development of pancreatic cancer might be detectable through screening in patients with diabetes mellitus.

Mizuno et al. J of Gastroenterology 2013[39]

Risk factors and early signs of pancreatic cancer in diabetes: screening strategy based on diabetes onset age

METHODS: Forty diabetic patients with PaC were identified and compared with 120 diabetic patients without any malignancies. **We analyzed risk factors for and early signs of PaC, focusing on the DM-onset age**. RESULTS: As there were peaks at 40-45 years and 60-65 years in the distribution of DM-onset age, we analyzed the clinical characteristics of and risk factors for PaC according to DM-onset age: i.e., early-onset (< 55 years) and late-onset (>/= 55 years). PaC was diagnosed within 2 years of DM onset (new-onset) in 0% of the patients with early-onset DM, and in 33% of those with late-onset DM. The mean duration of DM in patients with early-onset DM with PaC was longer than that in the late-onset patients (26 vs. 9 years; P < 0.01). **A family history of DM (odds ratio [OR] 3.60) and use of insulin (OR 3.52) were significant risk factors in patients with early-onset DM**, while the **onset age of DM (OR 1.12) and multiple diabetic patients in the family (OR 6.13) were risk factors in those with late-onset DM**. Body weight loss and exacerbation of DM were seen 12 months prior to PaC diagnosis in both groups. CONCLUSIONS: Our study revealed specific risk factors for and similar early signs of PaC in early-onset and late-onset DM. Thus, we could develop a screening strategy, combining these risk factors specific for DM-onset age with early signs of disease.

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

Goggins M, *et al. Gut* 2019; 69:7–17. doi: 10.1136/gutjnl-2019-319352

Illes et al. Pancreatology 2016[40]

New-onset type 2 diabetes mellitus - A high-risk group suitable for the screening of pancreatic cancer? OBJECTIVE: To determine the incidence of pancreatic cancer in new-onset type 2 diabetic patients by measuring the serum level of CA 19-9 and performing abdominal ultrasonography (US). PATIENTS AND METHODS: **Consecutive type 2 diabetic patients in whom diabetes was diagnosed within 36 months** were included in this prospective study. **Serum CA 19-9 measurement and US were performed in all patients**. If any of two was positive, abdominal computer tomography (CT) was carried out. Endoscopic ultrasound-guided fine needle aspiration or direct surgical referral was performed on patients with CT-identified lesions. RESULTS: A total of 115 patients were enrolled. **CA 19-9 was elevated in 10 patients but pancreatic cancer diagnosed in neither of them.** Pancreatic **cancer was revealed by morphological means in three patients without elevated CA 19-9 level**. The sensitivity, specificity, positive-, negative predictive values and validity were 0%, 90.4%, 0%, 97.9% and 87.9% for CA 19-9, 66.7%, 100%, 100%, 99% and 99% for US, respectively. The value of the Standardized Incidence Ratio for pancreatic cancer in new-onset type-2 diabetic patients was 198.6 (95% CI = 6.25-46.9). CONCLUSIONS: **The prevalence of pancreatic cancer in patients with new-onset type-2 diabetes is significantly higher than that in the general population and screening is beneficial for detecting PaC in this patient population**. **CA 19-9 and US is not reliable** screening modality for pancreatic cancer screening in this population.

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

2. Imaging

Best, Pereira, et al. Cochrane 2017[41] ***COCHRANE SYSTEMATIC REVIEW***

OBJECTIVES: To determine and **compare the diagnostic accuracy of various imaging modalities in detecting cancerous and precancerous lesions in people with focal pancreatic lesions.**

MAIN RESULTS: We included 54 studies involving a total of 3,196 participants evaluating the diagnostic accuracy of various index tests. In these 54 studies, eight different target conditions were identified with different final diagnoses constituting benign, precancerous, and cancerous lesions**. None of the studies was of high methodological quality.** None of the comparisons in which single studies were included was of sufficiently high methodological quality to warrant highlighting of the results. **For differentiation of cancerous lesions from benign or precancerous lesions, we identified only one study per index test**. The **second analysis, of studies differentiating cancerous versus benign lesions, provided three tests in which meta-analysis could be performed**. The sensitivities and specificities **for diagnosing cancer were: EUS-FNA: sensitivity 0.79** (95% confidence interval (CI) 0.07 to 1.00), **specificity 1.00** (95% CI 0.91 to 1.00); **EUS: sensitivity 0.95** (95% CI 0.84 to 0.99), **specificity 0.53** (95% CI 0.31 to 0.74); **PET: sensitivity 0.92** (95% CI 0.80 to 0.97), **specificity 0.65** (95% CI 0.39 to 0.84). The **third analysis, of studies differentiating precancerous or cancerous lesions from benign lesions, only provided one test (EUS-FNA) in which meta-analysis was performed. EUS-FNA had moderate sensitivity for diagnosing precancerous or cancerous lesions (sensitivity 0.73 (95% CI 0.01 to 1.00) and high specificity 0.94 (95% CI 0.15 to 1.00),** the extremely wide confidence intervals reflecting the heterogeneity between the studies). The **fourth analysis, of studies differentiating cancerous (invasive carcinoma) from precancerous (dysplasia) provided three tests in which meta-analysis was performed**. The sensitivities and specificities for diagnosing invasive carcinoma were: **CT: sensitivity 0.72** (95% CI 0.50 to 0.87), **specificity 0.92** (95% CI 0.81 to 0.97); **EUS: sensitivity 0.78** (95% CI 0.44 to 0.94), **specificity 0.91** (95% CI 0.61 to 0.98); **EUS-FNA: sensitivity 0.66** (95% CI 0.03 to 0.99), **specificity 0.92** (95% CI 0.73 to 0.98). The **fifth analysis**, of studies **differentiating cancerous** (high-grade dysplasia or invasive carcinoma) **versus precancerous** (low- or intermediate-grade dysplasia) provided six tests in which meta-analysis was performed. The sensitivities and specificities for diagnosing cancer (high-grade dysplasia or invasive carcinoma) were: **CT: sensitivity 0.87** (95% CI 0.00 to 1.00), **specificity 0.96** (95% CI 0.00 to 1.00); **EUS: sensitivity 0.86** (95% CI 0.74 to 0.92), **specificity 0.91** (95% CI 0.83 to 0.96); **EUS-FNA: sensitivity 0.47** (95% CI 0.24 to 0.70), **specificity 0.91** (95% CI 0.32 to 1.00); **EUS-FNA carcinoembryonic antigen 200 ng/mL: sensitivity 0.58** (95% CI 0.28 to 0.83), **specificity 0.51** (95% CI 0.19 to 0.81); **MRI: sensitivity 0.69** (95% CI 0.44 to 0.86), **specificity 0.93** (95% CI 0.43 to 1.00); **PET: sensitivity 0.90** (95% CI 0.79 to 0.96), **specificity 0.94** (95% CI 0.81 to 0.99). The **sixth analysis**, of studies differentiating **cancerous (invasive carcinoma) from precancerous (low-grade dysplasia)** provided **no tests** in which meta-analysis was performed. The seventh analysis, of studies **differentiating precancerous or cancerous (intermediate- or high-grade dysplasia or invasive carcinoma)** from **precancerous (low-grade dysplasia)** provided **two tests** in which meta-analysis was performed. The sensitivity and specificity for diagnosing cancer were: **CT: sensitivity 0.83** (95% CI 0.68 to 0.92), **specificity 0.83** (95% CI 0.64 to 0.93) and **MRI: sensitivity 0.80** (95% CI 0.58 to 0.92), **specificity 0.81** (95% CI 0.53 to 0.95), respectively. The eighth analysis, of studies differentiating **precancerous or cancerous (intermediate- or high-grade dysplasia or invasive carcinoma) from precancerous (low-grade dysplasia) or benign lesions** provided **no test** in which meta-analysis was performed. There were no major alterations in the subgroup analysis of cystic pancreatic focal lesions (42 studies; 2086 participants). None of the included studies evaluated EUS elastography or sequential testing.

CONCLUSIONS: **We were unable to arrive at any firm conclusions because of the differences in the way that study authors classified focal pancreatic lesions into cancerous, precancerous, and benign lesions; the inclusion of few studies with wide confidence intervals for each comparison; poor methodological quality in the studies; and heterogeneity in the estimates within comparisons.**

Goggins M, *et al. Gut* 2019; 69:7–17. doi: 10.1136/gutjnl-2019-319352

Tang et al. Eur J Radiol 2011.[42]

Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis.

Results: The pooled sensitivity estimate for combined PET/CT (90.1%) was significantly higher than PET (88.4%) and EUS (81.2%). The pooled specificity estimate for EUS (93.2%) was significantly higher than PET (83.1%) and PET/CT (80.1%).

Conclusion: PET/CT was a high sensitive and EUS was a high specific modality in diagnosing patients with pancreatic cancer. PET/CT and EUS could play different roles during different conditions in diagnosing pancreatic carcinoma.

Canto et al. Gastroenterology 2012.[23]

Frequent detection of pancreatic lesions in asymptomatic high-risk individuals

METHODS: We screened 225 asymptomatic adult HRIs at 5 academic US medical centers once, using computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). We compared results in a blinded, independent fashion.

RESULTS: Ninety-two of 216 HRIs (42%) were found to have at least 1 pancreatic mass (84 cystic, 3 solid) or a dilated pancreatic duct (n = 5) by any of the imaging modalities. Fifty-one of the 84 HRIs with a cyst (60.7%) had multiple lesions, typically small (mean, 0.55 cm; range, 2-39 mm), in multiple locations. The prevalence of pancreatic lesions increased with age; they were detected in 14% of subjects younger than 50 years old, 34% of subjects 50-59 years old, and 53% of subjects 60-69 years old (P < .0001). **CT, MRI, and EUS detected a pancreatic abnormality in 11%, 33.3%, and 42.6% of the HRIs, respectively**. Among these abnormalities, proven or suspected neoplasms were identified in 85 HRIs (82 intraductal papillary mucinous neoplasms and 3 pancreatic endocrine tumors). Three of 5 HRIs who underwent pancreatic resection had high-grade dysplasia in less than 3 cm intraductal papillary mucinous neoplasms and in multiple intraepithelial neoplasias.

CONCLUSIONS: Screening of asymptomatic HRIs frequently detects small pancreatic cysts, including curable, noninvasive high-grade neoplasms. **EUS and MRI detect pancreatic lesions better than CT.**

Chen et al. Pancreatology 2013[43]

Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for pancreatic cancer: a meta-analysis

BACKGROUND AND OBJECTIVE: EUS-FNA of pancreatic lesion has been put into clinical use widely in many centers. The present meta-analysis was conducted to study the diagnostic role of EUS-FNA in pancreatic cancer.

RESULTS: Thirty-one articles were eligible for the meta-analysis. **The pooled sensitivity, specificity, PLR, NLR and DOR of EUS-FNA in the diagnosis of pancreatic cancer were 0.89 (95% CI: 0.88-0.90), 0.96 (95% CI: 0.95-0.97), 16.88 (95% CI: 10.63-26.79), 0.13 (95%CI: 0.10-0.16) and 150.80 (95%CI: 95.94-237.03) respectively**. In subgroup meta-analysis of the prospective studies, the pooled sensitivity, specificity, PLR, NLR and DOR were 0.91 (95% CI: 0.90-0.93), 0.94 (95% CI: 0.91-0.96), 11.19 (95% CI: 6.36-19.69), 0.10 (95% CI: 0.07-0.15) and 125.22 (62.37-251.41). The area under the curve (AUC) was 0.97, indicating a good performance of overall accuracy. CONCLUSION: EUS-FNA has the high sensitivity and specificity in differentiating pancreatic cancer. Moreover, it is also a safe diagnostic modality with little complications.

Harinck et al. Gut 2015[44]

A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals

We aimed to compare the efficacy of EUS and MRI in their ability to detect clinically relevant lesions in HRI. Multicentre prospective study. The results of 139 asymptomatic HRI (>10-fold increased risk) undergoing first-time screening by EUS and MRI are described. Clinically relevant lesions were defined as solid lesions, main duct intraductal papillary mucinous neoplasms and cysts ≥10 mm. Results were compared in a blinded, independent fashion. Two solid lesions (mean size 9 mm) and nine cysts ≥10 mm (mean size 17 mm) were detected in nine HRI (6%). Both solid lesions were detected by EUS only and proved to be a stage I PDAC and a multifocal pancreatic intraepithelial neoplasia 2. Of the nine cysts ≥10 mm, six were detected by both imaging techniques and three were detected by MRI only. The agreement between EUS and MRI for the detection of clinically relevant lesions was 55%. Of these clinically relevant lesions detected by both techniques, there was a good agreement for location and size**. EUS and/or MRI detected clinically relevant pancreatic lesions in 6% of HRI. Both imaging techniques were complementary rather than interchangeable: contrary to EUS, MRI was found to be very**

sensitive for the detection of cystic lesions of any size; MRI, however, might have some important limitations with regard to the timely detection of solid lesions.

Lu et al. World Journal of Gastroenterology 2015[45]

Screening for pancreatic cancer in familial high-risk individuals: A systematic review

AIM: To analyze the benefits and harms of pancreatic cancer screening in familial high-risk individuals (HRIs).

METHODS: Studies were identified by searching PubMed, EBSCO, ClinicalTrials.gov and the Cochrane database from database inception to June 2014. We also obtained papers from the reference lists of pertinent studies and systematic reviews. However, anticipating only a few of these studies, we also included observational studies with or without control groups. We also included studies concerning the anxiety associated with pancreatic cancer risk and other psychological changes in familial HRIs.

RESULTS: Sixteen studies on pancreatic cancer screening were included. Five studies included control groups, nine were observational studies without control groups, and the other two studies investigated the worry associated with pancreatic cancer risk. **We found that pancreatic cancer screening resulted in a high curative resection rate** (60% vs 25%, P = 0.011), **longer median survival time** (14.5 mo vs 4 mo, P < 0.001), and **higher 3-year survival rate** (20% vs 15.0%, P = 0.624). We also found that **familial HRIs had a higher diagnostic rate of pancreatic tumors than controls** (34% vs 7.2%, P < 0.001). In patients who underwent regular physical examinations, more stage I pancreatic cancers were observed (19% vs 2.6%, P = 0.001). In addition, **endoscopic ultrasonography, which was the main means of detection, diagnosed 64.3% of pancreatic cancers**. In **comparison, endoscopic retrograde cannulation of the pancreas, magnetic resonance imaging, and computed tomography diagnosed 28.6%, 42.9%, and 21.4%, respectively.** For mass lesions, instant surgery was recommended because of the beneficial effects of post-operative chemotherapy. However, in patients with intraductal papillary mucinous neoplasms, we did not find a significant difference in outcome between surgery and follow-up without treatment. Moreover, pancreatic cancer screening in familial HRIs had a greater perceived risk of pancreatic cancer (P < 0.0001), higher levels of anxiety regarding pancreatic cancer (P < 0.0001), and increased economic burden.

Toft et al. Eur J Radiol 2017[46]

Imaging modalities in the diagnosis of pancreatic adenocarcinoma: A systematic review and meta-analysis of sensitivity, specificity and diagnostic accuracy

METHODS: A systematic review was undertaken to identify studies reporting sensitivity, specificity and/or diagnostic accuracy for the diagnosis of PDAC with MRI, CT, PET, EUS or TAUS. Proportional meta-analysis was performed for each modality.

RESULTS: A total of 5399 patients, 3567 with PDAC, from 52 studies were included. The sensitivity, specificity and diagnostic accuracy were 93% (95% CI=88-96), 89% (95% CI=82-94) and 90% (95% CI=86-94) for MRI; 90% (95% CI=87-93), 87% (95% CI=79-93) and 89% (95% CI=85-93) for CT; 89% (95% CI=85-93), 70% (95% CI=54-84) and 84% (95% CI=79-89) for PET; 91% (95% CI=87-94), 86% (95% CI=81-91) and 89% (95% CI=87-92) for EUS; and 88% (95% CI=86-90), 94% (95% CI=87-98) and 91% (95% C=87-93) for TAUS.

CONCLUSION: **This review concludes all modalities, except for PET, are equivalent within 95% confidence intervals for the diagnosis of PDAC.**

3. Biomarkers

Kisiel et al. Cancer 2012[47]

Stool DNA testing for the detection of pancreatic cancer: assessment of methylation marker candidates

The authors aimed to select discriminant **methylated genes and to assess accuracy of these and mutant KRAS in stool** to detect PanC. METHODS: Nine target genes were assayed by real-time methylation-specific polymerase chain reaction (MSP) in bisulfite-treated DNA from microdissected frozen specimens of 24 PanC cases and 30 normal colon controls. Archived stools from 58 PanC cases and 65 controls matched on sex, age, and smoking were analyzed. Target genes from fecal supernatants were enriched by hybrid capture, bisulfite-treated, and assayed by MSP. KRAS mutations were assayed using the QuARTS technique. RESULTS: Areas under the receiver operating characteristics curves (AUCs) for tissue BMP3, NDRG4, EYA4, UCHL1, MDFI, Vimentin, CNTNAP2, SFRP2, and TFPI2 were 0.90, 0.79, 0.78, 0.78, 0.77, 0.77, 0.69, 0.67, and 0.66, respectively. The top 4 markers and mutant KRAS were evaluated in stool. **BMP3 was the most discriminant methylation marker in stool**. At 90% specificity, methylated BMP3 alone detected 51% of PanCs, mutant KRAS detected 50%, and combination detected 67%. AUCs for methylated BMP3, mutant KRAS, and combination in stool were 0.73, 0.75, and 0.85,

respectively. CONCLUSIONS: This study demonstrates **that stool assay of a methylated gene marker can detect PanC**. Among candidate methylated markers discriminant in tissue, BMP3 alone performed well in stool. Combining methylated BMP3 and mutant KRAS increased stool detection over either marker alone.

Zubarik et al. Gastrointest Endoscopy 2011[48]

Screening for pancreatic cancer in a high-risk population with serum CA 19-9 and targeted EUS: a feasibility study

BACKGROUND: Earlier detection of pancreatic adenocarcinoma is needed. OBJECTIVE: To determine whether early pancreatic neoplasia can be detected in a high-risk population by using CA 19-9 followed by targeted EUS. SETTING: Two academic medical centers. PATIENTS: Eligible patients met age criteria and had at least 1 first-degree relative with pancreatic adenocarcinoma. INTERVENTIONS: A **serum CA 19-9 was performed on all patients. EUS was performed if the CA 19-9 level was elevated**. **FNA of identified lesions was performed.** Patients with pancreatic cancer detected by using this screening protocol were compared with patients presenting off-protocol for staging data. Medicare reimbursement rates were used to derive cost data. MAIN OUTCOME MEASUREMENTS: Detection of early pancreatic neoplasia. RESULTS: A total of 546 patients were enrolled. **CA 19-9 was elevated in 27 patients** (4.9%, 95% CI, 3.2%-7.1%). **Neoplastic or malignant findings were detected in 5 patients** (0.9%, 95% CI, 0.3%-2.1%), **and pancreatic adenocarcinoma in 1 patient** (0.2%, 95% CI, 0.005%-1.02%). The patient with pancreatic cancer detected as part of this protocol was 1 of 2 patients presenting to the University of Vermont with stage 1 cancer. The cost to detect 1 pancreatic neoplasia was $8431. The cost to detect 1 pancreatic adenocarcinoma was $41,133. LIMITATIONS: **The sample size is adequate only to demonstrate the feasibility of this approach.** CONCLUSIONS: Potentially curative pancreatic adenocarcinoma can be identified with this screening protocol. Stage 1 pancreatic cancer is more likely to be detected by using this screening protocol than by using standard means of detection.

Li, Wolfgang, Canto, Hruban, Goggins et al. Clin Cancer Res 2013[49]

MicroRNA array analysis finds elevated serum miR-1290 accurately distinguishes patients with low-stage pancreatic cancer from healthy and disease controls.

EXPERIMENTAL DESIGN: We measured 735 miRNAs in pancreatic cancer case and control sera by QRTPCR using TaqMan MicroRNA Arrays. After array analysis, we selected 18 miRNA candidates for validation in an independent set of cases and control samples.

RESULTS: Of the significantly elevated circulating miRNAs in patients with pancreatic cancer compared with controls, **miR-1290 had the best diagnostic performance: receiver operating characteristic (ROC) analysis on miR-1290 serum level yielded curve areas (AUC) of 0.96** [95% confidence interval (CI), 0.91-1.00], **0.81** (0.71-0.91), and **0.80** (0.67-0.93), for subjects with **pancreatic cancer** (n = 41) relative to **healthy controls** (n = 19), subjects with **chronic pancreatitis** (n = 35), and **pancreatic neuroendocrine tumors** (n = 18), respectively. Serum miR-1290 levels were also significantly higher than healthy controls among patients with intraductal papillary mucinous neoplasm (IPMN; n = 20; AUC = 0.76, 0.61-0.91). Serum miR-1290 levels distinguished patients with low-stage pancreatic cancer from controls better than CA19-9 levels, and like CA19-9, higher miR-1290 levels predicted poorer outcome among patients undergoing pancreaticoduodenectomy. Greater numbers of miR-1290 transcripts were detected by FISH in primary pancreatic cancer and IPMN than normal pancreatic duct cells. miR-1290 influenced in vitro pancreatic cancer cell proliferation and invasive ability. Several other circulating miRNAs distinguished sera of patients with pancreatic cancer from those of healthy controls with AUCs >0.7, including miR-24, miR-134, miR-146a, miR-378, miR-484, miR-628-3p, and miR-1825. CONCLUSIONS: The detection of elevated circulating miR-1290 has the potential to improve the early detection of pancreatic cancer.

Huang et al. Tumour Biol 2014.[50]

Diagnostic value of serum carbohydrate antigen 19-9 in pancreatic cancer: a meta-analysis

Therefore, we performed a meta-analysis to evaluate the sensitivity and specificity of CA19-9 in the diagnosis of pancreatic cancer. A total of 11 studies that included 2,316 individuals who fulfilled all of the inclusion criteria were considered for analysis. The summary estimates for serum CA19-9 in the diagnosis of pancreatic cancer in these studies were **pooled sensitivity 0.80** (95 % confidence interval [CI] 0.77-0.82), **specificity 0.80** (95 % CI 0.77-0.82), and DOR 14.79 (95 % CI 8.55-25.59), and the **area under the curve was 0.87**. Our meta-analysis showed that serum CA19-9 plays important role in the diagnosis of pancreatic cancer.

Eshleman, Topazian, Farrell, Syngal, Hruban, Canto, Goggins et al. Clin Gastroenterol Hepatol 2014.[51]

KRAS and guanine nucleotide-binding protein mutations in pancreatic juice collected from the duodenum of patients at high risk for neoplasia undergoing endoscopic ultrasound
METHODS: Secretin-stimulated juice samples were collected from the duodenum of 272 subjects enrolled in Cancer of the Pancreas Screening studies; 194 subjects were screened because of a family history of, or genetic predisposition to, pancreatic cancer, and 78 subjects were evaluated for pancreatic cancer (n = 30) or other disorders (controls: pancreatic cysts, pancreatitis, or normal pancreata, n = 48).
RESULTS: **KRAS mutations were detected in pancreatic juice from larger percentages of subjects with pancreatic cancer (73%) or undergoing cancer screening (50%) than controls (19%) (P = .0005).** A greater proportion of patients with pancreatic cancer had at least 1 KRAS mutation detected 3 or more times (47%) than screened subjects (21%) or controls (6%, P = .002). Among screened subjects, mutations in KRAS (but not guanine nucleotide-binding protein alpha-stimulating) were found in similar percentages of patients with or without pancreatic cysts. However, a greater proportion of patients older than age 50 years had KRAS mutations (54.6%) than younger patients (36.3%) (P = .032); the older subjects also had more mutations in KRAS (P = .02).
CONCLUSIONS: Mutations in KRAS are detected in pancreatic juice from the duodenum of 73% of patients with pancreatic cancer, and 50% of asymptomatic individuals with a high risk for pancreatic cancer. However, KRAS mutations were detected in pancreatic juice from 19% of controls. Mutations detected in individuals without pancreatic abnormalities, based on imaging analyses, likely arise from small pancreatic intraepithelial neoplasia lesions. ClinicalTrials.gov no: NCT00438906 and NCT00714701.

Kisiel et al. Clin Cancer Res 2015[52]
New DNA Methylation Markers for Pancreatic Cancer: Discovery, Tissue Validation, and Pilot Testing in Pancreatic Juice
EXPERIMENTAL DESIGN: At a referral center, we conducted four sequential case-control studies: discovery, technical validation, biologic validation, and clinical piloting. Candidate markers were identified using variance-inflated logistic regression on reduced-representation bisulfite DNA sequencing results from matched pancreatic cancers, benign pancreas, and normal colon tissues. Markers were validated technically on replicate discovery study DNA and biologically on independent, matched, blinded tissues by methylation-specific PCR. **Clinical testing of six methylation candidates and mutant KRAS was performed on secretin-stimulated pancreatic juice samples from 61 patients with pancreatic cancer, 22 with chronic pancreatitis, and 19 with normal pancreas on endoscopic ultrasound**. Areas under receiver-operating characteristics curves (AUC) for markers were calculated. RESULTS: Sequencing identified >500 differentially hyper-methylated regions. On independent tissues, AUC on 19 selected markers ranged between 0.73 and 0.97. Pancreatic juice AUC values for CD1D, KCNK12, CLEC11A, NDRG4, IKZF1, PKRCB, and KRAS were 0.92*, 0.88, 0.85, 0.85, 0.84, 0.83, and 0.75, respectively, for pancreatic cancer compared with normal pancreas and 0.92*, 0.73, 0.76, 0.85*, 0.73, 0.77, and 0.62 for pancreatic cancer compared with chronic pancreatitis (*, P = 0.001 vs. KRAS). CONCLUSIONS: We identified and validated novel DNA methylation markers strongly associated with pancreatic cancer. On pilot testing in pancreatic juice, best markers (especially CD1D) highly discriminated pancreatic cases from controls.

Hata et al. Pancreatology 2016[53]
Telomerase activity in pancreatic juice differentiates pancreatic cancer from chronic pancreatitis: A meta-analysis
BACKGROUND/OBJECTIVE: To evaluate the usefulness **of genetic markers in pancreatic juice** (PJ), and the combination of these markers with telomerase activity in the differential diagnosis of pancreatic ductal adenocarcinoma (PDAC) from chronic pancreatitis.
RESULTS: Thirty-nine studies fulfilled the inclusion criteria. Pooled estimates of **KRAS analysis** were as follows: **sensitivity was 0.67** (95% CI, 0.63-0.71) **and specificity, 0.82** (95% CI, 0.79-0.85). For **telomerase activity** analysis, **sensitivity was 0.82** (95% CI, 0.76-0.87) and **specificity, 0.96** (95% CI, 0.90-0.99). The other three tumor suppressors demonstrated low sensitivity. The data did not suggest any publication bias. A combined analysis of KRAS and telomerase activity showed a higher diagnostic sensitivity (0.94; 95% CI, 0.83-0.99) than KRAS alone. A combined analysis of telomerase activity and cytology revealed more reliable diagnostic accuracy than telomerase activity alone, with high sensitivity (0.88; 95% CI, 0.74-0.96) and specificity (1.00; 95% CI, 0.91-1.00).
CONCLUSIONS: The most reliable marker in PJ samples for diagnosis of PDAC was telomerase activity. Telomerase activity can play a central role in diagnostic analysis using PJ samples, and can increase diagnostic accuracy when combined with KRAS mutations or cytological examination.

Yu et al. Gut 2016[54]

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

Digital next-generation sequencing identifies low-abundance mutations in pancreatic juice samples collected from the duodenum of patients with pancreatic cancer and intraductal papillary mucinous neoplasms
DESIGN: We employed digital next-generation sequencing ('digital NGS') to detect low-abundance mutations in secretin-stimulated juice samples collected from the duodenum of subjects enrolled in Cancer of the Pancreas Screening studies at Johns Hopkins Hospital. For each juice sample, digital NGS necessitated 96 NGS reactions sequencing nine genes. The study population included 115 subjects (53 discovery, 62 validation) (1) with pancreatic ductal adenocarcinoma (PDAC), (2) intraductal papillary mucinous neoplasm (IPMN), (3) controls with non-suspicious pancreata. RESULTS: **Cases with PDAC and IPMN were more likely to have mutant DNA detected in pancreatic juice than controls (both p<0.0001); mutant DNA concentrations were higher in patients with PDAC than IPMN (p=0.003) or controls (p<0.001)**. TP53 and/or SMAD4 mutations were commonly detected in juice samples from patients with PDAC and were not detected in controls (p<0.0001); mutant **TP53/SMAD4 concentrations could distinguish PDAC from IPMN cases with 32.4% sensitivity, 100% specificity** (area under the curve, AUC 0.73, p=0.0002) and controls (AUC 0.82, p<0.0001). Two of four patients who developed pancreatic cancer despite close surveillance had SMAD4/TP53 mutations from their cancer detected in juice samples collected over 1 year prior to their pancreatic cancer diagnosis when no suspicious pancreatic lesions were detected by imaging. CONCLUSIONS: The detection in pancreatic juice of mutations important for the progression of low-grade dysplasia to high-grade dysplasia and invasive pancreatic cancer may improve the management of patients undergoing pancreatic screening and surveillance.

Yang et al. Pancreatology 2016[55]
A meta-analysis of the diagnostic value of detecting K-ras mutation in pancreatic juice as a molecular marker for pancreatic cancer
BACKGROUND: K-ras codon 12 mutation is one of the earliest genetic changes in the development of pancreatic cancer (PC) and accurate detection of K-ras mutations is gaining increasing attention in the field of molecular diagnosis. RESULTS: We assessed 16 studies from 15 published articles. **The pooled sensitivity and specificity were 59% (95%CI: 54%-64%) and 87% (95%CI: 84%-89%), respectively**. The pooled positive likelihood ratio and negative likelihood ratio were 4.13 (95%CI: 2.73-6.25) and 0.42 (95%CI: 0.32-0.56), respectively, and the pooled diagnostic odds ratio was 13.66 (95% CI: 7.25-25.74). CONCLUSIONS: Our results indicate that the analysis of K-ras mutations in pancreatic juice has a considerable diagnostic value in PC. Further studies with rigorous design, large sample size, and multi-regional co-operation are needed.

Cohen et al. Science 2018[56]
Detection and localization of surgically resectable cancers with a multi-analyte blood test
Earlier detection is key to reducing cancer deaths. Here, we describe a blood test that can detect eight common cancer types through assessment of the levels of **circulating proteins and mutations in cell-free DNA**. We applied this test, called **CancerSEEK**, to 1005 patients with nonmetastatic, clinically detected cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, or breast. CancerSEEK tests were positive in a median of 70% of the eight cancer types. **The sensitivities ranged from 69 to 98%** for the detection of five cancer types (ovary, liver, stomach, pancreas, and esophagus) for which there are no screening tests available for average-risk individuals. The **specificity** of CancerSEEK **was greater than 99%**: only 7 of 812 healthy controls scored positive. In addition, CancerSEEK localized the cancer to a small number of anatomic sites in a median of 83% of the patients.

Kim et al. Sci Transl Med 2017[57]
Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers
Starting with a PDAC cell reprogramming model that recapitulated the progression of human PDAC, we identified secreted proteins and tested a subset as potential markers of PDAC. We optimized an enzyme-linked immunosorbent assay (ELISA) using plasma samples from patients with various stages of PDAC, from individuals with benign pancreatic disease, and from healthy controls. A phase 1 discovery study (n = 20), a phase 2a validation study (n = 189), and a second phase 2b validation study (n = 537) revealed that **concentrations of plasma thrombospondin-2 (THBS2) discriminated among all stages of PDAC consistently**. The receiver operating characteristic (ROC) c-statistic was 0.76 in the phase 1 study, 0.84 in the phase 2a study, and 0.87 in the phase 2b study. The plasma concentration of THBS2 was able to discriminate **resectable stage I cancer as readily as stage III/IV PDAC tumors.** THBS2 plasma concentrations **combined with those for CA19-9**, a previously identified PDAC marker, yielded a **c-statistic of 0.96 in the phase 2a study and 0.97 in the phase 2b study**.

THBS2 data improved the ability of CA19-9 to distinguish PDAC from pancreatitis. With a specificity of 98%, the combination of THBS2 and CA19-9 yielded a sensitivity of 87% for PDAC in the phase 2b study. A THBS2 and CA19-9 blood marker panel measured with a conventional ELISA may improve the detection of patients at high risk for PDAC.

Schonemeier et al. Pancreas 2016[58]

Urinary Peptide Analysis Differentiates Pancreatic Cancer From Chronic Pancreatitis

OBJECTIVES: Differentiation of pancreatic cancer (PCA) from chronic pancreatitis (CP) is challenging. We searched for peptide markers in urine to develop a diagnostic peptide marker model. METHODS: Capillary electrophoresis-mass spectrometry was used to search for peptides in urine of patients with PCA (n = 39) or CP (n = 41). Statistical different peptides were included in a peptide multimarker model. Peptide markers were sequence identified and validated by immunoassay and immunohistochemistry (IHC). RESULTS: Applied to a validation cohort of **54 patients with PCA and 52 patients with CP**, the peptide model correctly classified 47 patients with PCA and 44 patients with CP **(area under the curve, 0.93; 87% sensitivity; 85% specificit**y). All 5 patients with PCA with concomitant CP were classified positive. Urine proteome analysis outperformed carbohydrate antigen 19-9 (area under the curve, 0.84) by a 15% increase in sensitivity at the same specificity. From 99 healthy subjects, only four were misclassified. Fetuin-A was the most prominent peptide marker source for PCA as verified by immunoassay and IHC. In silico protease mapping of the peptide markers' terminal sequences pointed to increased meprin-A activity in PCA, which in IHC was associated with neoangiogenesis. CONCLUSIONS: **Urinary proteome analysis differentiates PCA from CP and may serve as PCA screening tool.**

Suenaga et al. Clin Cancer Res[59]

Pancreatic Juice Mutation Concentrations Can Help Predict the Grade of Dysplasia in Patients Undergoing Pancreatic Surveillance

Purpose: The measurement of mutations in pancreatic juice samples collected from the duodenum during endoscopic ultrasound (EUS) may improve the diagnostic evaluation of patients undergoing pancreatic surveillance. Our aim was to evaluate the accuracy of using pancreatic juice mutation concentrations to predict the presence and histologic grade of neoplasia in the pancreas.Experimental Design: **Digital next-generation sequencing (NGS) of pancreatic juice DNA using a targeted 12-gene panel was performed on 67 patients undergoing pancreatic evaluation during EUS**, including patients with pancreatic ductal adenocarcinoma, patients who subsequently underwent pancreatic resection for precursor lesions, patients undergoing surveillance for their familial/inherited susceptibility to pancreatic cancer, and normal pancreas disease controls.Results: **Patients with pancreatic cancer or high-grade dysplasia as their highest grade lesion had significantly higher pancreatic juice mutation concentrations than all other subjects** (mean/SD digital NGS score; 46.6 +/- 69.7 vs. 6.2 +/- 11.6, P = 0.02). Pancreatic juice mutation concentrations distinguished patients with pancreatic cancer or high-grade dysplasia in their resection specimen from all other subjects with **72.2% sensitivity and 89.4% specificity** [area under the curve (AUC) = 0.872]. Mutant TP53/SMAD4 concentrations could distinguish patients with pancreatic cancer or high-grade dysplasia in their resection specimen from all other subjects with 61.1% sensitivity and 95.7% specificity (AUC = 0.819). Among 31 high-risk individuals under surveillance, 2 of the 3 individuals with most abnormal pancreatic juice mutation profiles also had the most abnormalities on pancreatic imaging.Conclusions: Pancreatic juice mutation analysis using digital NGS has potential diagnostic utility in the evaluation of patients undergoing pancreatic surveillance.

4. Surveillance intervals

Yu, Wolfgang, Goggins, et al. Gut 2015[60]

Time to progression of pancreatic ductal adenocarcinoma from low-to-high tumour stages

OBJECTIVE: Although pancreatic ductal adenocarcinoma is considered a rapidly progressive disease, mathematical models estimate that it takes many years for an initiating pancreatic cancer cell to grow into an advanced stage cancer. In order to estimate the time it takes for a pancreatic cancer to progress through different tumor, node, metastasis (TNM) stages, **we compared the mean age of patients with pancreatic cancers of different sizes and stages.**

DESIGN: Patient age, tumour size, stage and demographic information were analysed for **13,131 patients** with pancreatic ductal adenocarcinoma entered into the National Cancer Institute's Surveillance, Epidemiology and End Results (**SEER) database**. Multiple linear regression models for age were generated, adjusting for patient ethnicity,

gender, tumour location and neoplastic grades.
RESULTS: **African-American ethnicity and male gender were associated with an earlier age at diagnosis**. Patients **with stage I cancers** (mean age 64.8 years) were on average **1.3 adjusted years younger** at diagnosis **than those with stage IV cancers** (p=0.001). Among patients without distant metastases, those with T1 stage cancers were on average 1.06 and 1.19 adjusted years younger, respectively, than patients with T3 or T4 cancers (p=0.03 for both). Among patients with stage IIB cancers, those with T1/T2 cancers were 0.79 adjusted years younger than those with T3 cancers (p=0.06). There was no significant difference in the mean adjusted age of patients with stage IA versus stage IB cancers. CONCLUSIONS: **These results are consistent with the hypothesis that once pancreatic ductal adenocarcinomas become detectable clinically progression from low-stage to advanced-stage disease is rapid.**

Bartsch et al. Gut 2016[24]
Refinement of screening for familial pancreatic cancer
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.**

Konings et al. Pancreas 2016.[13]
Prevalence and Progression of Pancreatic Cystic Precursor Lesions Differ Between Groups at High Risk of Developing Pancreatic Cancer
OBJECTIVES: The aim of this study was to compare the prevalence of cystic pancreatic lesions and their natural behavior in 2 distinct high-risk groups for developing pancreatic ductal adenocarcinoma (PDAC): (1) carriers of a mutation that predisposes to PDAC and (2) individuals without a known gene mutation but with a family history of PDAC (familial pancreatic cancer [FPC]). METHODS: Pancreatic surveillance by annual magnetic resonance imaging and endoscopic ultrasound was performed in individuals with an estimated lifetime risk of developing PDAC of 10% or greater**. Progression of a lesion was defined as growth 4 mm or greater or the development of worrisome features.** RESULTS: We included 186 individuals: 98 mutation carriers and 88 FPC individuals (mean follow-up, 51 months). **Individuals with FPC were significantly more likely than mutation carriers to have a pancreatic cyst 10 mm or greater** (16% vs 5%, P = 0.045). **Pancreatic cysts detected in mutation carriers, however, were significantly more likely to progress than those in FPC individuals** (16% vs 2%, P = 0.050). CONCLUSIONS: This study provides evidence that the prevalence and growth characteristics of pancreatic cysts differ between distinct high-risk groups: individuals with FPC have a higher prevalence of pancreatic cysts 10 mm or greater, whereas cysts in mutation carriers are more likely to progress. These observations may help to develop more optimally tailored surveillance strategies in specific high-risk populations.

Potjer et al. Clin Cancer Res 2012.[12]
Variation in precursor lesions of pancreatic cancer among high-risk groups
PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) surveillance programs are currently offered to high-risk individuals aiming to detect precursor lesions or PDAC at an early stage. We assessed differences in frequency and behavior of precursor lesions and PDAC between two high-risk groups. EXPERIMENTAL DESIGN: Individuals

with a p16-Leiden germline mutation (N = 116; median age 54 years) and individuals from familial pancreatic cancer (FPC) families (N = 125; median age 47 years) were offered annual surveillance by MRI and magnetic resonance cholangiopancreatography (MRCP) with or without endoscopic ultrasound (EUS) for a median surveillance period of 34 months (0-127 months) or 36 months (0-110 months), respectively. Detailed information was collected on pancreatic cystic lesions detected on MRCP and precursor lesions in surgical specimens of patients who underwent pancreatic surgery. RESULTS: **Cystic lesions were more common in the FPC cohort (42% vs. 16% in p16-Leiden cohort),** whereas **PDAC was more common in the p16-Leiden cohort** (7% vs. 0.8% in FPC cohort). Intraductal papillary mucinous neoplasm (IPMN) was a common finding in surgical specimens of FPC-individuals, and was only found in two patients of the p16-Leiden cohort. **In the p16-Leiden cohort, a substantial proportion of cystic lesions showed growth or malignant transformation during follow-up, whereas in FPC individuals most cystic lesions remain stable**. CONCLUSION: In p16-Leiden mutation carriers, cystic lesions have a higher malignant potential than in FPC-individuals. On the basis of these findings, a more intensive surveillance program may be considered in this high-risk group.

Ibrahim et al. Cancer Prev Res. 2018[17]

High Growth Rate of Pancreatic Ductal Adenocarcinoma in CDKN2A-p16-Leiden Mutation Carriers

CDKN2A-p16-Leiden mutation carriers have a 20% to 25% risk of developing pancreatic ductal adenocarcinoma (PDAC). Better understanding of the natural course of PDAC might allow the surveillance protocol to be improved. The aims of the study were to evaluate the role of cystic precursor lesions in the development of PDAC and to assess the growth rate. In 2000, a surveillance program was initiated, consisting of annual MRI in carriers of a CDKN2A-p16-Leiden mutation. The study cohort included 204 (42% male) patients. Cystic precursor lesions were found in 52 (25%) of 204 mutation carriers. **Five (9.7%) of 52 mutation carriers with cystic lesions and 8 (7.0%) of 114 mutation carriers without cystic lesions developed PDAC (P = 0.56). Three of 6 patients with a cystic lesion of >/=10 mm developed PDAC**. The median size of all incident PDAC detected between 9 and 12 months since the previous normal MRI was 15 mm, suggesting an annual growth rate of about 15 mm/year. In conclusion, our findings show that patients with and without a cystic lesions have a similar risk of PDAC. However, cystic precursor lesions between 10 and 20 mm increase the risk of PDAC substantially. **In view of the large size of the screen-detected tumors, a shorter interval of screening might be recommended for all patients**.

5. Patient selection for surgery and post-operative surveillance

Ibrahim et al. Fam Cancer 2017.[61]

Dilemmas in the management of screen-detected lesions in patients at high risk for pancreatic cancer

In 3-5 % of all cases of pancreatic ductal adenocarcinoma (PDAC), hereditary factors influence etiology. While surveillance of high-risk individuals may improve the prognosis**, this study describes two very different outcomes in patients with screen-detected lesions.** In 2000, a surveillance program of carriers of a CDKN2A/p16-Leiden-mutation consisting of annual MRI was initiated. Patients with a suspected pancreatic lesion undergo CT-scan and Endoscopic Ultrasound, and surgery is offered when a lesion is confirmed. In 2015, two patients with a screen-detected solid lesion were identified. In both patients, lesions were visible on MRI and CT scan, while the EUS was unremarkable. Surgical resection of the head of the pancreas resulted in nearly fatal complications in the first patient. This patient was shown to have a benign lesion. In contrast, timely identification of an early cancer in the second patient was accompanied by an uneventful postoperative course. **These cases underline the risks inherent to a PDAC prevention program. All patients should be fully informed about the possible outcomes before joining a surveillance program.**

Takeda at al. J Gastrointest Surg 2017[62]

Asymptomatic Pancreatic Cancer: Does Incidental Detection Impact Long-Term Outcomes?

METHODS: This retrospective study included 569 consecutive patients with PDAC treated in our institution (250 underwent surgical resection and 319 had unresectable PDAC). The patients' demographics, tumor locations, pathologic stages, treatment, and overall survival (OS) were compared between the asymptomatic and symptomatic patients.

RESULTS: In total, 163 (29%) patients presented without subjective symptoms. These patients had an earlier stage of PDAC on presentation ($p < 0.001$), higher resectability rate (64 vs. 36%, $p < 0.001$), and higher 5-year OS rate (18 vs. 7%, $p < 0.001$) than patients with symptoms. Among the patients who underwent resection, asymptomatic patients did not have a significantly higher chance of complete resection (88 vs. 78%, $p = 0.06$) or 5-year OS rate

(23 vs. 22%, p = 0.09). However, symptomatic patients more often required complex operations such as concomitant vascular resection and reconstruction (57 vs. 29%, p < 0.001).
CONCLUSIONS: **Asymptomatic PDAC is associated with better long-term outcomes than symptomatic PDAC** because of the earlier stage at presentation and higher chance of resectability. Our findings **highlight the potential implication of screening programs for early detection of PDAC in selected high-risk populations**.

Konings et al. Unpublished results of the retrospective CAPS registry
Detection and treatment of pancreatic cancer and high-grade precursor lesions in high-risk individuals undergoing surveillance: Results from the international caps consortium registry
In this current study, we focused on HRI participating in a surveillance program who underwent a pancreatic resection or were diagnosed with inoperable PDAC. **The aim of this study was to determine the prevalence and overall mortality of PDAC and high-grade dysplastic precursor lesions (HGD) in these HRI.** Methods A multicenter retrospective cohort-study was conducted through the International CAPS Consortium Registry. Data were collected from **10 prospective PDAC surveillance programs in 4 countries** (United States, The Netherlands, Italy, Israel) on HRI in whom pancreatic lesions were detected and confirmed by pathologic diagnosis. For this study, all invasive PDAC and HGD (branch-duct (BD)-IPMN with HGD, PanIN3, and main-duct (MD)-IPMN) were analyzed. Univariate and multivariate analyses were used to compare patients with and without proven PDAC/HGD to assess potential predictive indicators, including family history, genetic background, BMI, race, smoking, alcohol use, history of diabetes, and history of pancreatitis. Results Seventy-six HRI were included (74% from familial PDAC, 26% mutation carriers; mean age 66 (range 42-90), 49% women). Seventyone individuals had undergone surgery (2 patients had irresectable disease, 69 had resections: 34 distal resection, 18 pancreaticoduodenectomy only, 6 pancreaticoduodenectomy followed by completion pancreatectomy, 2 central pancreatectomy, and 9 total pancreatectomy). Additionally, 5 individuals were diagnosed with inoperable PDAC. PDAC and HGD were detected in 42% of FPC relatives and 58% of mutation carriers (P=0.24**). Thirty-three of the 71 operated cases (47%) had PDAC or HGD:** 17 PDAC, 4 MD-IPMN, 6 HGD BD-IPMN, and 6 PanIN3. **Additionally, 7 pancreatic neuroendocrine tumors (NET) were detected, including 1 with nodal metastasis**. **Eight of the 22 (36%) PDAC cases were diagnosed at baseline screening**, the remaining 14 (64%) were detected on follow-up (11 resectable and 3 advanced). **Only female gender (OR 3.3, P=0.01) was significantly associated with PDAC/ HGD**. Eight of the 17 (47%) asymptomatic PDAC and 15/16 (94%) of HGD cases detected during surveillance were alive at last follow-up (mean 22 months). Conclusion **Fifty-seven percent of HRI who underwent surgery had clinically relevant pancreatic neoplasms** (24% PDAC, 23% HGD, and 10% NET) that were detected and treated within a surveillance program. More research, including large worldwide prospective studies, is needed to better understand the risk factors for individuals at high risk of developing PDAC and to improve selection of patients for surgery.

Potjer et al. Letter to the editor in response to CAPS consensus guidelines 2013, Gut 2015[63]
Limited resection of pancreatic cancer in high-risk patients can result in a second primary
See full text PDF in OneDrive.

Peters et al. Pancreatology 2018[64]
Progression to pancreatic ductal adenocarcinoma from pancreatic intraepithelial neoplasia: Results of a simulation model
OBJECTIVES: To gain insight into the natural history and carcinogenesis pathway of Pancreatic Intraepithelial Neoplasia (PanIN) lesions by building a calibrated simulation model of PanIN progression to pancreatic ductal adenocarcinoma (PDAC) METHODS: We revised a previously validated simulation model of solid PDAC, calibrating the model to fit data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program and published literature on PanIN prevalence by age. We estimated the likelihood of progression from PanIN states (1, 2, and 3) to PDAC and the time between PanIN onset and PDAC (dwell time). We evaluated a hypothetical intervention to test for and treat PanIN 3 lesions to estimate the potential benefits from PanIN detection. RESULTS: We estimated the lifetime probability of progressing from PanIN 1 to PDAC to be 1.5% (men), 1.3% (women). Progression from **PanIN 1 to PDAC took 33.6 years and 35.3 years, respectively, and from PanIN 3 to PDAC took 11.3 years and 12.3 years.** A hypothetical test for PanIN 3 detection and treatment could provide a maximum, average life expectancy gain of 40 days. CONCLUSIONS: Our modeling analysis estimates PanINs have a relatively indolent course to PDAC, supporting the feasibility of potential future early detection strategies.

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

6. Psychology

Konings et al. Fam Cancer 2016[65]

Factors associated with cancer worries in individuals participating in annual pancreatic cancer surveillance

Previously, we reported that repeated participation in annual surveillance imposes low psychological burden. However, selected individuals showed intermediate to high levels of cancer worry. The aim of this study was to evaluate possible factors associated with these cancer worries. Methods High-risk individuals (estimated lifetime risk of PDAC ≥ 10%), participating in an annual prospective multicenter Dutch EUS-MRI based PDAC surveillance program, were invited to complete an **annual questionnaire** to assess their cancer worries with the **Cancer Worry Scale (CWS).** The questionnaire was sent after counseling by the clinical geneticist (T0), after intake for participation but prior to the first MRI and EUS (T1), and thereafter annually after MRI and EUS (T2 and further). Univariate and multivariate analyses were performed to identify sociodemographic and clinical factors associated with cancer worries in the second year of participation (T3). Results A total of 118 out of 166 (71%) individuals returned at least a T0, T1 or T2, as well as a T3 questionnaire. The mean age of respondents was 52 years with a **mean follow-up of 49 months**. The **mean CWS-score was 12.8** (range 8-26). Both univariate and multivariate analysis showed one baseline factor to be associated with cancer worries in the second year of follow-up: **having a family member affected by PDAC <50 years of age** (β=1.38,P=0.04). **Not associated were** age, carriership of a gene mutation associated with PDAC, a personal history of any type of cancer, having children, educational level, smoking behavior, alcohol consumption, and the number of PDAC-cases in the family. **The detection of a cystic lesion or the recommendation of a shortened surveillance interval, did not alter the CWS-score significantly** in the year of that event in comparison to the year prior and after the event. Conclusion **Having a family member affected by pancreatic cancer <50 years of age is a factor significantly associated with cancer worries in the second year of PDAC surveillance. Recognizing this factor can help clinicians to timely identify individuals who might likely benefit from psychosocial support to prevent psychological distress**.

Konings et al. Psychooncology 2015[66]

Repeated pancreatic surveillance in high risk individuals for pancreatic cancer: The psychological burden

This is a multicenter prospective study. High-risk individuals who undergo annual pancreatic surveillance with magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) were invited to complete **questionnaires to assess motivations for participating in surveillance, experiences with participation, perceived PC risk, topics of concern, and psychological distress.** Questionnaires were sent after intake for participation (T1), after the first MRI and EUS (T2), and after the MRI and EUS 1 (T3), 2 (T4), and 3 years (T5) after first surveillance. In total, 140 out of 152 individuals returned one or more of the questionnaires **(response 92%)**; 477 questionnaires were analyzed. The most frequently reported motivation for participating in surveillance was **the possible early detection of (a precursor stage of) cancer (95-100%).** Only **a minority of respondents experienced MRI and EUS as uncomfortable (10% and 11%, respectively),** and respondents **dreaded their next EUS investigation less as surveillance progressed**. Respondents' **cancer worries decreased significantly over time**, and both their **anxiety and depression scores remained stable and low over the 3-year period of follow-up**.|The psychological burden of pancreatic surveillance **is low at all assessments**. Therefore, from a psychological point of view, participation of high-risk individuals in an annual pancreatic surveillance program is **feasible**.

Cazacu et al. Endosc Ultrasound 2018[67]

Psychological impact of pancreatic cancer screening by EUS or magnetic resonance imaging in high-risk individuals: A systematic review

The aim of this systematic review was to investigate the current knowledge regarding the psychological impact of participation in routine screening for PC. Methods: A systematic literature search was carried out in January 2018 in three major databases which are as follows: PubMed, Scopus, and Web of Science. Cross-sectional and prospective studies evaluating the psychological aspects of screening in high-risk individuals were included in the study. For each study, the following data were recorded: name of first author, year of publication, study design, study population, aims, screening protocol, outcomes and instruments, main results, and summary of findings. Results: **Six cohort studies and one cross-sectional study that addressed the psychological aspects of PC screening were included in the analysis**. Overall, studies have shown that high-risk individuals have **positive psychological outcomes from participating in PC screening programs**. Conclusions: Although screening might not always be reassuring, it may improve individuals' quality of life, and this should be an important aspect when considering PC screening.

Goggins M, *et al. Gut* 2019; 69:7–17. doi: 10.1136/gutjnl-2019-319352

Franke et al. Hered Cancer Clin Pract 2018[68]

German National Case Collection for familial pancreatic Cancer (FaPaCa) - acceptance and psychological aspects of a pancreatic cancer screening program

Background: Pancreatic cancer screening is recommended to individuals at risk (IAR) of familial pancreatic cancer (FPC) families, but little is known about the acceptance of such screening programs. Thus, the acceptance and psychological aspects of a controlled FPC screening program was evaluated. Methods: IAR of FPC families underwent comprehensive counseling by a geneticist and pancreatologist prior to the proposed screening. **Participating IAR, IAR who discontinued screening and IAR who never participated in the screening program were invited to complete questionnaires to assess the motivation for participating in surveillance, cancer worries, structural distress and experiences with participation**. Questionnaires were completed anonymously to receive most accurate answers. Results: Of 286 IAR to whom pancreatic ductal adenocarcinoma (PDAC) screening was recommended, 139 (48.6%) IAR regularly participated (group 1), 49 (17.1%) IAR (group 2) discontinued screening after median 1 (1-10) screening visits and 98 (34.2%) IAR (group 3) never underwent screening. The overall response rate of questionnaires was 67% (189/286) with rates of 100% (139 of 139 IAR), 49% (29 of 49 IAR) and 23.4% (23 of 98 IAR) for groups 1, 2 and 3, respectively. At least 93% of IAR felt adequately informed about the screening program after initial counseling. However, only 38.8% received knowledge of or the recommendation for PDAC screening by physicians**. The reported cancer-related distress and the fear of investigations were highest in group 1, but acceptably low in all three groups.** The main reasons to discontinue or not to participate in screening were the time efforts and travel costs (groups 2 and 3 48,7%). Conclusion: Less than 50% of IAR regularly participate in a proposed PDAC screening program, although the associated psychological burden is quite low. Physicians should be educated about high risk PDAC groups and screening recommendations. **Time and travel efforts must be reduced to encourage more IAR to participate in a recommended screening.**

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

7. Cohort studies – ongoing programmes – Overview of programmes

Study	City (Country)	N	High-risk group (n)	Imaging modalities (if abnormal surveillance)	Follow-up	Diag-nostic yield (%)*	Definition of diagnostic yield±
Kimmey 2002§	Seattle (United States)	46	FPC (46)	EUS (ERCP)	0-5y	26	Dysplasia
Canto 2004	Baltimore (United States)	38	FPC (37), PJS (1)	EUS (EUS-FNA, ERCP, MDCT)	11-51m	5.3	PDAC, IPMN
Canto 2006	Baltimore (United States)	78	FPC (72), PJS (6)	EUS (EUS-FNA, ERCP, MDCT)	3-12m	10.3	PDAC, IPMN, PanIN1-3
Kluijt 2009	Amsterdam (The Netherlands)	3	CDKN2A (3)	EUS, MRI	NA	100	PDAC, SB-IPMN
Poley 2009	Rotterdam (The Netherlands)	44	FPC (21), CDKN2A (13), PJS (2), HP (3), BRCA1 (3), BRCA2 (2), p53 (1)	EUS (MRI, CT)	NA	23	PDAC, IPMN
Verna 2010	New York (United States)	51	FPC (44), BRCA1/2 (7)	EUS, MRI/MRCP (EUS-FNA, ERCP)	NA	11.7	PDAC, IPMN, PanIN-2
Ludwig 2011	New York (United States)	109	FPC (102), BRCA1/2 (7)	MRCP (EUS-FNA)	NA	7.3	PDAC, IPMN, PanIN2-3
Schneider 2011¥	Marburg (Germany)	72	FPC, BRCA2, PALB2, CDKN2A (NR)	EUS, MRI/MRCP-S (EUS-FNA)	Median 44m	15.2	PDAC, IPMN PanIN1-3
Vasen 2011	Leiden (The Netherlands)	79	CDKN2A (79)	MRI/MRCP	0-10y	15.2	PDAC, IPMN
Al-Sukhni 2012	Toronto (Canada)	262	FPC (159), BRCA2 (68), BRCA1 (5), CDKN2A (11), PJS (7), HP (2), FDR of multiple primary cancers (10)	MRI/MRCP (EUS, MRI, CT, ERCP)	0-8y	7.3	PDAC, SB-IPMN, NET
Canto 2012	Baltimore (United States)	216	FPC (195), BRCA2 (19), PJS (2),	EUS, MRI/MRCP-S, CT (EUS-FNA)	NA	42.6	Dilated MPD, cystic lesion, solid lesion
Potjer 2013	Leiden (The Netherlands) Marburg (Germany)	241	FPC (116), CDKN2A (116), PALB2 (6), BRCA2 (3)	EUS, MRI/MRCP	0-127m	32.8	PDAC, cystic lesion
Sud 2014	Milwaukee (United States)	16µ	FPC (19), BRCA1/2 (7), PJS (2), CDKN2A (1), LS (1)	EUS (EUS-FNA)	0-3y	18.8	PDAC, IPMN
Del Chiaro 2015	Stockholm (Sweden)	40	FPC (32), CDKN2A (4), BRCA2 (3), BRCA1 (1)	MRI/MRCP-S (EUS-FNA)	Mean 13m	40	PDAC, IPMN
Mocci 2015	Madrid (Spain)	38α	FPC (NR), BRCA1/2 (NR), early onset PC (5)	EUS, CT (MRI, EUS-FNA)	0-2y	10.5	Cystic lesion
Bartsch 2016	Marburg (Germany) Madrid (Spain) Leiden (The Netherlands)	253	236 (FPC), BRCA2(8), BRCA1 (3), PALB2 (6)	EUS, MRI/MRCP-S	1-152m	5.9	PC, PanIN1-3, IPMN, NET
Joergensen 2016	Odense (Denmark)	71	FPC (40), HP (31)	EUS	Mean 60m	2.8β	PDAC
Vasen 2016	Leiden (The Netherlands) Marburg (Germany) Madrid (Spain)	411	FPC (214), CDKN2A (178) BRCA1/2/PALB2 (19)	EUS, MRI/MRCP (EUS-FNA, CT)	0-169m	4.4	PDAC, IPMN, PanIN3
Chang 2017	Taipei (Taiwan)	119	FPC (54), BRCA1/2 (1), PRSS1 (24), SPINK1 (7)	MRI/MRCP (EUS-FNA)	1-12y	19.3	Solid mass lesion
Barnes 2017	Milwaukee (United States)	75€	FPC (33), BRCA1 (6), BRCA2 (18), PALB2 (3), ATM (8), CDKN2A (4), PJS (1), Lynch (2)	MRI (EUS-FNA)	NA	43	Cystic lesion
DaVee 2018	Houston (United States)	86	BRCA2 (50), BRCA1 (14), STK11 (5), MSH2 (3), ATM (1), APC (1)	EUS, MRI, CT	NA, Retrospective	12.8	Cystic lesion

Goggins M, *et al. Gut* 2019; 69:7–17. doi: 10.1136/gutjnl-2019-319352

Gangi 2018	Tampa (United States)	58	BRCA2 (9), PJS (1), 48 (FPC)	EUS, MRI (EUS-FNA)	0-5y	41	Abnormal finding
Lachter 2018	Haifa (Israel)	123	?	EUS	0-10y	2.4	Potential life-saving surgery
Paiella 2018	Verona (Italy)	187	FPC (165), BRCA1 (5), BRCA2 (5), CDKN2A (3), PJS (5) PRSS1 (4)	MRI/MRCP, EUS	Baseline	2.6	PDAC
Sheel 2018	Liverpool (United Kingdom)	321	?	CT, EUS, MRI	0-5y	0.3	PDAC
* Based on per-patient analysis; ± Serous cystadenomas were excluded; § Continuation of Brentnall 1999 and Rulyak 2001 ¥ Continuation of Langer 2009; µ 30 patients were included, 16 underwent EUS; α 41 patients were included, 38 underwent EUS; β Both lesions were found amongst the FPC population; € 75 patients were included, 65 underwent MRI;							

Abstracts of cohort publications

Vasen et al. Gastroenterology 2011.[69]

Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation

BACKGROUND & AIMS: Surveillance of high-risk groups for pancreatic cancer might increase early detection and treatment outcomes. Individuals with germline mutations in p16-Leiden have a lifetime risk of 15% to 20% of developing pancreatic cancer. We assessed the feasibility of detecting pancreatic cancer at an early stage and investigated the outcomes of patients with neoplastic lesions. METHODS: Individuals with germline mutations in p16-Leiden (N = 79; 31 male; mean age, 56 years; range, 39-72 years) were offered annual surveillance by magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP). Those found to have neoplastic lesions were offered options for surgery or intensive follow-up. Individuals found to have possible neoplastic lesions were examined again by MRI/MRCP within 2 to 4 months. RESULTS: After a median follow-up period of 4 years (range, 0-10 years), pancreatic cancer was diagnosed in 7 patients (9%). The mean age at diagnosis was 59 years (range, 49-72 years). Three of the tumors were present at the first examination, and 4 were detected after a negative result in the initial examination. All 7 patients had a resectable lesion; 5 underwent surgery, 3 had an R0 resection, and 2 had lymph node metastases. Possible precursor lesions (ie, duct ectasias, based on MRCP) were found in 9 individuals (11%). CONCLUSIONS: MRI/MRCP detects small, solid pancreatic tumors and small duct ectasias. Although surveillance increases the rate of resectability, carriers of a p16-Leiden mutation develop aggressive tumors.

Al-Sukhni et al. J Gastrointest Surg 2011.[70]

Screening for pancreatic cancer in a high-risk cohort: an eight-year experience

BACKGROUND: Pancreatic adenocarcinoma is the fourth leading cause of cancer death. METHODS: A prospective cohort study was undertaken between 2003 and 2011 at a tertiary care centre in Toronto, Canada. Two hundred and sixty-two subjects were enrolled based on an elevated estimated lifetime risk for pancreatic cancer due to known genetic mutations and/or cancer family history. Subjects underwent annual magnetic resonance imaging, followed by additional investigations if abnormal findings were detected. Evidence of malignancy or suspicious macroscopic abnormalities prompted referral for surgical intervention. RESULTS: Average length of follow-up was 4.2 years, during which 84/262 (32%) subjects demonstrated pancreatic abnormalities. Three participants developed pancreatic adenocarcinoma (one 1.5-cm tumor was resected but recurred, while the other two subjects developed metastatic cancer), and a fourth participant developed a pancreatic neuroendocrine tumor that was resected. Fifteen subjects had radiologic evidence of branch-duct intraductal papillary mucinous neoplasms, of which two underwent surgical resection. Sixty-five subjects had simple pancreatic cysts that have remained stable. CONCLUSION: Magnetic resonance imaging can detect small pancreatic tumors and cystic lesions, but further improvement in sensitivity is needed. An understanding of the natural history of pre-invasive lesions in members of high-risk families is necessary for developing a more effective screening program.

Canto et al. Gastroenterology 2012.[23]

Frequent detection of pancreatic lesions in asymptomatic high-risk individuals

BACKGROUND & AIMS: The risk of pancreatic cancer is increased in patients with a strong family history of pancreatic cancer or a predisposing germline mutation. Screening can detect curable, noninvasive pancreatic neoplasms, but the optimal imaging approach is not known. We determined the baseline prevalence and characteristics of pancreatic abnormalities using 3 imaging tests to screen asymptomatic, high-risk individuals (HRIs). METHODS: We screened 225 asymptomatic adult HRIs at 5 academic US medical centers once, using computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). We compared results in a blinded, independent fashion. RESULTS: Ninety-two of 216 HRIs (42%) were found to have at least 1 pancreatic mass (84 cystic, 3 solid) or a dilated pancreatic duct (n = 5) by any of the imaging modalities. Fifty-one of the 84 HRIs with a cyst (60.7%) had multiple lesions, typically small (mean, 0.55 cm; range, 2-39 mm), in multiple locations. The prevalence of pancreatic lesions increased with age; they were detected in 14% of subjects younger than 50 years old, 34% of subjects 50-59 years old, and 53% of subjects 60-69 years old (P < .0001). CT, MRI, and EUS detected a pancreatic abnormality in 11%, 33.3%, and 42.6% of the HRIs, respectively. Among these abnormalities, proven or suspected neoplasms were identified in 85 HRIs (82 intraductal papillary mucinous neoplasms and 3 pancreatic endocrine tumors). Three of 5 HRIs who underwent pancreatic resection had high-grade dysplasia in less than 3 cm intraductal papillary mucinous neoplasms and in multiple intraepithelial neoplasias. CONCLUSIONS: Screening of asymptomatic HRIs frequently detects small pancreatic cysts, including curable, noninvasive high-grade neoplasms. EUS and MRI detect pancreatic lesions better than CT.

Potjer et al. Clin Cancer Res 2012.[12]

Variation in precursor lesions of pancreatic cancer among high-risk groups

PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) surveillance programs are currently offered to high-risk individuals aiming to detect precursor lesions or PDAC at an early stage. We assessed differences in frequency and behavior of precursor lesions and PDAC between two high-risk groups. EXPERIMENTAL DESIGN: Individuals with a p16-Leiden germline mutation (N = 116; median age 54 years) and individuals from familial pancreatic cancer (FPC) families (N = 125; median age 47 years) were offered annual surveillance by MRI and magnetic resonance cholangiopancreatography (MRCP) with or without endoscopic ultrasound (EUS) for a median surveillance period of 34 months (0-127 months) or 36 months (0-110 months), respectively. Detailed information was collected on pancreatic cystic lesions detected on MRCP and precursor lesions in surgical specimens of patients who underwent pancreatic surgery. RESULTS: Cystic lesions were more common in the FPC cohort (42% vs. 16% in p16-Leiden cohort), whereas PDAC was more common in the p16-Leiden cohort (7% vs. 0.8% in FPC cohort). Intraductal papillary mucinous neoplasm (IPMN) was a common finding in surgical specimens of FPC-individuals, and was only found in two patients of the p16-Leiden cohort. In the p16-Leiden cohort, a substantial proportion of cystic lesions showed growth or malignant transformation during follow-up, whereas in FPC individuals most cystic lesions remain stable. CONCLUSION: In p16-Leiden mutation carriers, cystic lesions have a higher malignant potential than in FPC-individuals. On the basis of these findings, a more intensive surveillance program may be considered in this high-risk group.

Sud et al. Pancreas 2014.[71]

Promising outcomes of screening for pancreatic cancer by genetic testing and endoscopic ultrasound.

OBJECTIVE: This study aimed to determine if screening patients based on certain cancer syndromes or family history criteria can lead to early detection of pancreatic cancer. METHODS: This was a cohort study from 2008 to 2011 at a large tertiary referral center. A total of 30 patients met high-risk criteria after genetic counseling and were referred to a gastroenterologist for possible endoscopic ultrasound (EUS). RESULTS: Of the 30 patients, 16 underwent EUS. Subsequently, 3 patients had fine needle aspiration. Two patients had pancreatic adenocarcinoma, and 1 patient had an intraductal papillary mucinous neoplasm with low-grade dysplasia. The 2 patients with pancreatic adenocarcinoma both had breast cancer and BRCA2 mutations. The patient with the intraductal papillary mucinous neoplasm had Peutz-Jeghers syndrome. All 3 patients underwent surgery and have remained cancer free. CONCLUSIONS: Genetic risk assessment with EUS +/- fine needle aspiration in high-risk patients may lead to earlier detection of pancreatic cancer and potentially improve overall morbidity and mortality. Greater emphasis should be placed on screening patients for hereditary cancer syndromes that increase the risk of pancreatic cancer.

Del Chiaro et al. JAMA surgery 2015.[72]

Short-term Results of a Magnetic Resonance Imaging-Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer

IMPORTANCE: Pancreatic cancer is the fourth leading cause of cancer-related death in Western countries. In approximately 10% of all patients with pancreatic cancer, it is possible to define a positive family history for pancreatic cancer or for one of the other related genetic syndromes. A screening program for individuals at risk is recommended; however, surveillance modalities have not been defined yet. OBJECTIVE: To analyze the short-term results of a prospective clinical surveillance program for individuals at risk for pancreatic cancer using a noninvasive magnetic resonance imaging (MRI)-based screening protocol. DESIGN, SETTING AND PARTICIPANTS: A prospective observational study of all patients with a genetic risk for developing pancreatic cancer who were referred to Karolinska University Hospital between January 1, 2010, and January 31, 2013, using an MRI-based surveillance program. All patients were investigated for the most common genetic mutations associated with pancreatic cancer. EXPOSURE: A noninvasive MRI-based screening protocol. MAIN OUTCOMES AND MEASURES: The ability of MRI to identify potential precancerous or early cancers in individuals at risk for pancreatic cancer. RESULTS: Forty patients (24 women and 16 men) were enrolled. The mean age was 49.9 years. The mean length of follow-up was 12.9 months. The numbers of relatives affected by pancreatic cancer were 5 in 2 patients (5%), 4 in 5 patients (12.5%), 3 in 17 patients (42.5%), 2 in 14 patients (35%), and 1 in 2 patients (5%). In 4 patients (10%), a p16 mutation was found; in 3, a BRCA2 mutation (7.5%); and in 1, a BRCA1 mutation (2.5%). In 16 patients (40%), MRI revealed a pancreatic lesion: intraductal papillary mucinous neoplasia (14 patients, 35%) and pancreatic ductal adenocarcinoma (2 patients, 5%). One patient had a synchronous intraductal papillary mucinous neoplasia and pancreatic ductal adenocarcinoma. Five patients (12.5%) required surgery (3 for pancreatic ductal adenocarcinoma and 2 for intraductal papillary mucinous neoplasia), while the remaining 35 are under continued surveillance. CONCLUSIONS AND RELEVANCE: During a median follow-up of approximately 1 year, pancreatic lesions were detected in 40% of the patients, of whom 5 underwent surgery. Although the study time was relatively short, the surveillance program in individuals at risk seems to be effective.

Mocci et al. Eur J Cancer 2015.

PanGen-Fam: Spanish registry of hereditary pancreatic cancer

PURPOSE: To describe the organisation of the registry and the preliminary results in terms of characteristics of high-risk pancreatic ductal adenocarcinoma (PDAC) families recruited to date and findings of the screening programme. To compare early onset sporadic cases (50 years), sporadic cases (>50 years) and cases with family history of cancer, for PDAC possible risk factors. METHODS/PATIENTS: Families with hereditary cancer syndromes predisposing to PDAC were recruited from two main sources: Spanish hospitals participating in PanGenEU, a pan-European multicentre case-control study, and their genetic counseling unit. Individuals at high-risk of PDAC were enrolled into a screening programme, consisting of Endoscopic ultrasound, computerised tomography, magnetic resonance imaging. Genetic testing of candidate genes was offered according to each patient's risk. RESULTS: Among 577 consecutive PDAC cases, recruited via PanGenEU, 36 (6%) had 2 first-degree relative with PDAC: Familial pancreatic cancer (FPC). So far PanGen-Fam has recruited 42 high-risk PDAC families; 25 (60%) had FPC. Five index cases with cancer were positive for BRCA2 and one for BRCA1 germline mutations. In the second year of prospective PDAC screening, one neuroendocrine tumour and a high-grade dysplasia lesion suspicious of carcinoma were diagnosed among 41 high-risk individuals. Furthermore EUS detected chronic-pancreatitis-like parenchymal changes in 15 patients. CONCLUDING STATEMENT: The identification and recruitment of PDAC high-risk families into the PanGen-Fam registry provides an opportunity to detect early onset cancer and precursor pancreatic cancer lesions at a potentially curative stage and to increase the knowledge of the natural history of the disease.

Bartsch et al. Gut 2016[24]

Refinement of screening for familial pancreatic cancer

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.

Joergensen et al. Pancreatology 2016.[73]

Is screening for pancreatic cancer in high-risk groups cost-effective? - Experience from a Danish national screening program

OBJECTIVE: Pancreatic cancer (PC) is the fourth leading cause of cancer death worldwide, symptoms are few and diffuse, and when the diagnosis has been made only 10-15% would benefit from resection. Surgery is the only potentially curable treatment for pancreatic cancer, and the prognosis seems to improve with early detection. A hereditary component has been identified in 1-10% of the PC cases. To comply with this, screening for PC in high-risk groups with a genetic disposition for PC has been recommended in research settings. DESIGN: Between January 2006 and February 2014 31 patients with Hereditary pancreatitis or with a disposition of HP and 40 first-degree relatives of patients with Familial Pancreatic Cancer (FPC) were screened for development of Pancreatic Ductal Adenocarcinoma (PDAC) with yearly endoscopic ultrasound. The cost-effectiveness of screening in comparison with no-screening was assessed by the incremental cost-utility ratio (ICER). RESULTS: By screening the FPC group we identified 2 patients with PDAC who were treated by total pancreatectomy. One patient is still alive, while the other died after 7 months due to cardiac surgery complications. Stratified analysis of patients with HP and FPC provided ICERs of 47,156 US$ vs. 35,493 US$ per life-year and 58,647 US$ vs. 47,867 US$ per QALY. Including only PDAC related death changed the ICER to 31,722 US$ per life-year and 42,128 US$ per QALY. The ICER for patients with FPC was estimated at 28,834 US$ per life-year and 38,785 US$ per QALY. CONCLUSIONS: With a threshold value of 50,000 US$ per QALY this screening program appears to constitute a cost-effective intervention although screening of HP patients appears to be less cost-effective than FPC patients.

Vasen et al. J Clin Oncol 2016.[74]

Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers

PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis. Hereditary factors play a role in the development of PDAC in 3% to 5% of all patients. Surveillance of high-risk groups, may facilitate detection of PDAC at an early stage. The aim of this study was to assess whether surveillance aids detection of early-stage PDAC or precursor lesions (PRLs) and improves the prognosis. PATIENTS AND METHODS: Screening outcomes were collected from three European centers that conduct prospective screening in high-risk groups including families with clustering of PDAC (familial pancreatic cancer [FPC]) or families with a gene defect that predisposes to PDAC. The surveillance program consisted of annual magnetic resonance imaging, magnetic resonance cholangiopancreatography, and/or endoscopic ultrasound. RESULTS: Four hundred eleven asymptomatic individuals participated in the surveillance programs, including 178 CDKN2A mutation carriers, 214 individuals with FPC, and 19 BRCA1/2 or PALB2 mutation carriers. PDAC was detected in 13 (7.3%) of 178 CDKN2A mutation carriers. The resection rate was 75%, and the 5-year survival rate was 24%. Two CDKN2A mutation carriers (1%) underwent surgical resection for low-risk PRL. Two individuals (0.9%) in the FPC cohort had a pancreatic tumor, including one advanced PDAC and one early grade 2 neuroendocrine tumor. Thirteen individuals with FPC (6.1%) underwent surgical resection for a suspected PRL, but only four (1.9%) had high-risk lesions (ie, high-grade intraductal papillary mucinous neoplasms or grade 3 pancreatic intraepithelial neoplasms). One BRCA2 mutation carrier was found to have PDAC, and another BRCA2 mutation carrier and a PALB2 mutation carrier underwent surgery and were found to have low-risk PRL. No serious complications occurred as consequence of the program. CONCLUSION: Surveillance of CDNK2A mutation carriers is relatively

successful, detecting most PDACs at a resectable stage. The benefit of surveillance in families with FPC is less evident.

Chang et al. Am J Cancer Res 2017.[75]

Pancreatic cancer screening in different risk individuals with family history of pancreatic cancer-a prospective cohort study in Taiwan.

Pancreatic cancer (PC) is usually diagnosed at advanced stage. Our aim was to investigate the risk of malignant and premalignant pancreatic lesions in individuals with family history of PC. Individuals at risk of PC were enrolled prospectively in a screening program in Taiwan. All risk individuals received genetic testing of cationic trypsinogen (PRSS1) gene and the serine protease inhibitor Kazal type 1 (SPINK1) gene. They were stratified into three risk groups (high, moderate, and low) based on the family history and genetic testing. Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatogram (MRCP) were performed in all screened individuals. A total of three hundred and three risk individuals in 165 families were enrolled with the mean age of 51.1 years, 38.3% of whom were male. A total of 24 of 303 (7.9%) screened individuals had the PRSS1 mutation, and 7/234 (0.3%) had the SPINK1 mutation. Nineteen (6.3%) risk individuals had pancreatic pathology including seven with pancreatic cancer, and four with pancreatic mucinous neoplasms. The earliest age of onset of PC in affected members was an independent factor associated with risk of developing PC in all risk groups. DM was associated with much-increased risk of developing PC in low and moderate risk groups (OR45.8. 95% CI. 13.82-151.64, P=0.001). Combined family history of non-PC malignancy in the family in the low-risk individual was associated with abnormal findings on MRI (OR8.4, 95% CI 3.29-21.88, P < 0.0001). There was no any complication of screening. In summary, pancreatic cancer screening may benefit in risk individuals with family history of pancreatic cancer in our population. The diagnostic yield is similar to prior studies. MRCP as initial screening modality is safe and effective. Future study will be needed to tailor PC screening strategy in different risk populations.

Barnes et al. Fam Cancer 2017.[76]

Development of a high risk pancreatic screening clinic using 3.0 T MRI

Selective screening for pancreatic cancer (PC) has been proposed. We describe the establishment of a comprehensive multidisciplinary screening program using 3.0 T MRI. Criteria for screening included the presence of PC in: >/= 2 first degree relatives (FDR), 1 FDR and 1 s degree relative (SDR), >/= 3 any degree relatives (ADR), or any known hereditary cancer syndrome with increased PC risk. Imaging with 3.0 T MRI was performed routinely and endoscopic ultrasound was used selectively. Screening was completed in 75 patients (pts). Hereditary cancer syndromes were present in 42 (56%) of the 75 pts: BRCA2 (18), ATM (8), BRCA1 (6), CDKN2A (4), PALB2 (3), Lynch (2), and Peutz-Jeghers (1). A family history of PC was present in >/= 2 FDR in 12 (16%) pts, 1 FDR and 1 SDR in 5 (7) pts, and >/= 3 ADR in 16 (21%) pts. Of the 65 pts who received screening MRI, 28 (43%) pts had pancreatic cystic lesions identified, including 1 (1%) patient in whom a cholangiocarcinoma was diagnosed as well. No patient underwent surgical resection. Using a 3.0 T MRI to screen patients at high risk for developing PC identified radiographic abnormalities in 43% of patients, which were stable on subsequent surveillance. Specific guidelines for the frequency of surveillance and indications for surgery remain areas of active investigation as the global experience with high risk screening continues to mature.

DaVee et al. Gastrointestinal endoscopy 2018.[77]

Pancreatic cancer screening in high-risk individuals with germline genetic mutations

BACKGROUND AND AIMS: Pancreatic cancer (PC) is a deadly disease that is most commonly diagnosed at an incurable stage. Different high-risk genetic variants and cancer syndromes increase the lifetime risk of developing PC. This study aims to assess the yield of initial PC screening in patients with high-risk germline mutations. METHODS: Asymptomatic adults underwent PC screening by EUS, magnetic resonance imaging, or CT during a 10-year period and were retrospectively identified. High-risk individuals were defined as carrying germline mutations in BRCA1, BRCA2, p53 (Li-Fraumeni), STK11 (Peutz-Jeghers), MSH2 (Lynch), ATM (ataxia-telangiectasia), or APC (familial adenomatous polyposis). Patients without germline mutations were excluded. RESULTS: In total, 86 patients met the study criteria. The median age was 48.5 years (interquartile range, 40-58), 79.1% (68) were women, and 43.0% (37) had a family history of PC. The genetic mutations were BRCA2 (50, 58.1%), BRCA1 (14, 16.3%), p53 (12, 14.0%), STK11 (5, 5.8%), MSH2 (3, 3.5%), ATM (1, 1.2%), and APC (1, 1.2%). Screening detected a pancreatic abnormality (PA) in 26.7% (23/86), including cysts (11, 47.8%),

hyperechoic strands and foci (10, 43.5%), and mild pancreatic duct dilation (2, 8.7%). Patients older than 60 years were more likely to have a PA detected (P = .043). EUS detected more PAs than magnetic resonance imaging or CT. No cases of PC were diagnosed by screening or during follow-up (median, 29.8 months; interquartile range, 21.7-43.5). CONCLUSIONS: Unless indicated otherwise by family or personal history, PC screening under the age of 50 is low yield. Linear EUS may be the preferred modality for initial PC screening.

Canto et al. Gastroenterology 2018.[78]

Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance

Screening of individuals who have a high risk of pancreatic ductal adenocarcinoma (PDAC), because of genetic factors, frequently leads to identification of pancreatic lesions. We investigated the incidence of PDAC and risk factors for neoplastic progression in individuals at high risk for PDAC enrolled in a long-term screening study. METHODS: We analyzed data from 354 individuals at high risk for PDAC (based on genetic factors of family history), enrolled in Cancer of the Pancreas Screening cohort studies at tertiary care academic centers from 1998 through 2014 (median follow-up time, 5.6 years). All subjects were evaluated at study entry (baseline) by endoscopic ultrasonography and underwent surveillance with endoscopic ultrasonography, magnetic resonance imaging, and/or computed tomography. The primary endpoint was the cumulative incidence of PDAC, pancreatic intraepithelial neoplasia grade 3, or intraductal papillary mucinous neoplasm with high-grade dysplasia (HGD) after baseline. We performed multivariate Cox regression and Kaplan-Meier analyses. RESULTS: During the follow-up period, pancreatic lesions with worrisome features (solid mass, multiple cysts, cyst size > 3 cm, thickened/enhancing walls, mural nodule, dilated main pancreatic duct > 5 mm, or abrupt change in duct caliber) or rapid cyst growth (>4 mm/year) were detected in 68 patients (19%). Overall, 24 of 354 patients (7%) had neoplastic progression (14 PDACs and 10 HGDs) over a 16-year period; the rate of progression was 1.6%/year, and 93% had detectable lesions with worrisome features before diagnosis of the PDAC or HGD. Nine of the 10 PDACs detected during routine surveillance were resectable; a significantly higher proportion of patients with resectable PDACs survived 3 years (85%) compared with the 4 subjects with symptomatic, unresectable PDACs (25%), which developed outside surveillance (log rank P < .0001). Neoplastic progression occurred at a median age of 67 years; the median time from baseline screening until PDAC diagnosis was 4.8 years (interquartile range, 1.6-6.9 years). CONCLUSIONS: In a long-term (16-year) follow-up study of individuals at high-risk for PDAC, we found most PDACs detected during surveillance (9/10) to be resectable, and 85% of these patients survived for 3 years. We identified radiologic features associated with neoplastic progression.

Gangi et al. Pancreas 2018 [79]

Endoscopic Ultrasound-Based Pancreatic Cancer Screening of High-Risk Individuals: A Prospective Observational Trial

OBJECTIVES: Pancreatic cancer (PC), a common cause of cancer death, is rarely diagnosed at an early stage. Early detection of PC may improve outcomes in affected patients. This study evaluated the utility of screening of high-risk individuals (HRIs) using an **endoscopic ultrasound (EUS)-only approach** to detect early malignant changes. METHODS: A prospective PC screening program for HRIs was opened in 2007. **Fifty-eight** patients have enrolled to date. Patients with normal EUS examinations underwent repeat EUS annually for 5 years. Patients with abnormal EUS underwent **fine-needle aspiration (FNA) if a mass/cyst 1 cm or longer was found.** Those with cysts/mass shorter than 1 cm or benign FNA underwent repeat EUS in 3 months. If unchanged, patients were followed with magnetic resonance imaging. RESULTS: Thirty-nine patients (67%) had initial normal EUS examinations, and **16 patients completed the 5-year trial.** Five patients who initially had a normal EUS developed cysts on subsequent examinations. Of the 24 subjects (41%) with abnormal findings, 3 underwent FNA: 2 consistent with intraductal papillary mucinous neoplasm, 1 with benign cytology. The 21 remaining patients had 1 subcentimeter cyst or more followed by magnetic resonance imaging. No PCs have been detected. CONCLUSIONS: Precancerous cysts are frequently detected with EUS in HRI. Whether screening impacts survival in HRIs remains unclear and requires further evaluation in larger multicenter trials.

Lachter et al. Rambam Maimonides Med J.[80]

Screening to Detect Precursor Lesions of Pancreatic Adenocarcinoma in High-risk Individuals: A Single-center Experience

RESEARCH AIM: Pancreatic cancer screening guidelines, based on consensus opinions, have been applied in various tertiary centers around the world; however, evidence for effectiveness is lacking. At Rambam Health Care

Campus, we have established a cohort of high-risk individuals, **and we report our local 10-year experience results of screening for pancreatic cancer.** METHODS: Between 2008 and 2018, a cohort of **123** asymptomatic high-risk individuals came **for annual/biannual EUS screening** for pancreatic cancer. Retrospective and prospectively collected data were obtained, analyzed, and compared on the basis of several variables. These variables include age at beginning of screening, gender, smoking, obesity, diabetes, and presence of tumor markers, as well as the patients' personal and family history of cancers. Findings on each EUS are described. RESULTS: **Three patients out of 123 underwent potentially life-saving surgery** as a result of this screening program. All of these three had only one first-degree relative (FDR) with pancreatic cancer at the time of their first screenings, but two eventually had a second FDR with PC. Findings from 296 EUS exams regarding smoking, obesity, and other risk factors are presented. Minor, possibly trivial, EUS findings are found to be common. Detection of precursor pancreatic lesions is feasible with EUS screenings. CONCLUSIONS: Adherence was an important limiting factor in screening. Better stratification of patients according to specific risk factors, including thorough genetics and family history, may direct when and how to initiate screening. International collaborations, such as the International Cancer of Pancreas Screening (CAPS) Consortium, of which Rambam is a collaborating partner, are needed to collate evidence for impact of screening to prevent pancreatic cancer morbidity and mortality, and are essential to achieve proof of concept. Different countries with varying health-care systems and budgets can find variance of appropriateness of screening procedures.

Paiella et al. Am J Gastroenterol. 2018[81]

Results of First-round of Surveillance in Individuals at High-risk of Pancreatic Cancer from the AISP (Italian Association for the Study of the Pancreas) Registry

We report the results of **the first screening round** of the Italian multicenter program supported by the Italian Association for the study of the Pancreas (AISP). METHODS: The multicenter surveillance program included asymptomatic HRIs with familial (FPC) or genetic frailty (GS: BRCA1/2, p16/CDKN2A, STK11/LKB1or PRSS1, mutated genes) predisposition to PC. The surveillance program included at least an annual **magnetic resonance cholangio pancreatography (MRCP**). Endoscopic ultrasound (EUS) was proposed to patients who refused or could not be submitted to MRCP. RESULTS: **One-hundreds eighty-seven** HRIs underwent a first-round screening examination with MRCP (174; 93.1%) or EUS (13; 6.9%) from September 2015 to March 2018.The mean age was 51 years (range 21-80).One-hundreds sixty-five (88.2%) FPC and 22 (11.8%) GF HRIs were included. MRCP detected 28 (14.9%) presumed branch-duct intraductal papillary mucinous neoplasms (IPMN), 1 invasive carcinoma/IPMN and one low-grade mixed-type IPMN, respectively. EUS detected 4 PC (2.1%): 1 was resected, 1 was found locally advanced intraoperatively, and 2 were metastatic. Age > 50 (OR 3.3, 95%CI 1.4-8), smoking habit (OR 2.8, 95%CI 1.1-7.5), and having > 2 relatives with PC (OR 2.7, 95%CI 1.1-6.4) were independently associated with detection of pre-malignant and malignant lesions. **The diagnostic yield for MRCP/EUS was 24% for cystic lesions.** The overall rate of surgery was 2.6% with nil mortality. DISCUSSION: **The rate of malignancies found in this cohort was high (2.6%).** According to the International Cancer of the Pancreas Screening Consortium the screening goal achievement was high (1%).

Sheel et al. Am J Gastroenterol 2018.[82]

Identification of Cystic Lesions by Secondary Screening of Familial Pancreatic Cancer (FPC) Kindreds Is Not Associated with the Stratified Risk of Cancer

OBJECTIVES: Intraductal papillary mucinous neoplasms (IPMNs) are associated with risk of pancreatic ductal adenocarcinoma (PDAC). It is unclear if an IPMN in individuals at high risk of PDAC should be considered as a positive screening result or as an incidental finding. Stratified familial pancreatic cancer (FPC) populations were used to determine if IPMN risk is linked to familial risk of PDAC. METHODS: This is a cohort study of **321** individuals from 258 kindreds suspected of being FPC and undergoing secondary screening for PDAC through the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC). Computerised tomography, endoscopic ultrasound of the pancreas and magnetic resonance imaging were used. The risk of being a carrier of a dominant mutation predisposing to pancreatic cancer was stratified into three even categories (**low, medium and high**) based on: Mendelian probability, the number of PDAC cases and the number of people at risk in a kindred. RESULTS: There was a median (interquartile range (IQR**)) follow-up of 2 (0-5) years** and a median (IQR) number of investigations per participant of 4 (2-6). **One PDAC, two low-grade neuroendocrine tumours and 41 cystic lesions were identified**, including 23 IPMN (22 branch-duct (BD)). The PDAC case occurred in the top 10% of risk, and the **BD-IPMN cases were evenly distributed amongst risk categories: low (6/107), medium (10/107) and high (6/107)** (P = 0.63). CONCLUSIONS: The risk of finding BD-IPMN was independent of genetic predisposition and so they should be managed according to guidelines for incidental finding of IPMN.

CAPS Consortium - Literature overview 2011-2018, updated 20 January 2019

Systematic reviews and meta-analyses of cohort studies

Lu et al. World Journal of Gastroenterology 2015[45]

Screening for pancreatic cancer in familial high-risk individuals: A systematic review

AIM: To analyze the benefits and harms of pancreatic cancer screening in familial high-risk individuals (HRIs).
METHODS: Studies were identified by searching PubMed, EBSCO, ClinicalTrials.gov and the Cochrane database from database inception to June 2014. We also obtained papers from the reference lists of pertinent studies and systematic reviews. However, anticipating only a few of these studies, we also included observational studies with or without control groups. We also included studies concerning the anxiety associated with pancreatic cancer risk and other psychological changes in familial HRIs.
RESULTS: Sixteen studies on pancreatic cancer screening were included. Five studies included control groups, nine were observational studies without control groups, and the other two studies investigated the worry associated with pancreatic cancer risk. **We found that pancreatic cancer screening resulted in a high curative resection rate** (60% vs 25%, P = 0.011), **longer median survival time** (14.5 mo vs 4 mo, P < 0.001), and **higher 3-year survival rate** (20% vs 15.0%, P = 0.624). We also found that **familial HRIs had a higher diagnostic rate of pancreatic tumors than controls** (34% vs 7.2%, P < 0.001). In patients who underwent regular physical examinations, more stage I pancreatic cancers were observed (19% vs 2.6%, P = 0.001). In addition, **endoscopic ultrasonography, which was the main means of detection, diagnosed 64.3% of pancreatic cancers**. In **comparison, endoscopic retrograde cannulation of the pancreas, magnetic resonance imaging, and computed tomography diagnosed 28.6%, 42.9%, and 21.4%, respectively.** For mass lesions, instant surgery was recommended because of the beneficial effects of post-operative chemotherapy. However, in patients with intraductal papillary mucinous neoplasms, we did not find a significant difference in outcome between surgery and follow-up without treatment. Moreover, pancreatic cancer screening in familial HRIs had a greater perceived risk of pancreatic cancer (P < 0.0001), higher levels of anxiety regarding pancreatic cancer (P < 0.0001), and increased economic burden.

Paiella et al. Pancreatology 2018

We performed a **systematic review and meta-analysis** of currently available data coming from screening/surveillance programs to evaluate the **proportion of screening goal achievement (SGA), overall surgery and unnecessary surgery.**
METHODS: SGA was defined as any diagnosis of resectable PC, PanIN3, or high-grade dysplasia IPMN. Unnecessary surgery was defined as any other final pathology.
RESULTS: In a meta-analysis of 16 studies reporting on 1551 FPC-HRI cases, 30 subjects (1.82%), received a diagnosis of PC, PanIN3 or HGD-IPMNs. The pooled proportion of **SGA was 1.4%** (95% CI 0.8-2, p<0.001, I^2=0%). The **pooled proportion of overall surgery was 6%** (95% CI 4.1-7.9, p<0.001, I^2=60.91%).**The pooled proportion of unnecessary surgery was 68.1%** (95% CI 59.5-76.7, p<0.001, I^2=4.05%); 105 subjects (6.3%) received surgery, and the overall number of diagnoses from non-malignant specimens was 156 (1.5 lesion/subject).
CONCLUSIONS: The weighted proportion of SGA of screening/surveillance programs published thus far is excellent. However, the probability of receiving surgery during the screening/surveillance program is non-negligible, and unnecessary surgery is a potential negative outcome.

Corral et al. Clin Gastroenterol Hepatol. 2019

Diagnostic Yield From Screening Asymptomatic Individuals at High Risk for Pancreatic Cancer: A Meta-analysis of Cohort Studies

We performed a **meta-analysis of prospective cohort studies to determine the diagnostic yield** and outcomes of abdominal imaging screening for asymptomatic individuals at high risk. METHODS: Through a systematic review of multiple electronic databases and conference proceedings through July 2017, we identified prospective cohort studies (>20 patients) of asymptomatic adults determined to be at high-risk of pancreatic cancer (lifetime risk >5%, including specific genetic-associated conditions) who were screened by endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) to detect pancreatic lesions. Our primary outcome was identification of high-risk pancreatic lesions (high-grade pancreatic intraepithelial neoplasia, high-grade dysplasia, or adenocarcinoma) at initial screening, and overall incidence during follow up. Summary estimates were reported as incidence rates per 100 patient-years. RESULTS: We identified 19 studies comprising 7085 individuals at high risk for pancreatic cancer; of these, 1660 patients were evaluated by EUS and/or MRI. Fifty-nine high-risk lesions were identified (43 adenocarcinomas: 28 during the initial exam and 15 during follow-up surveillance) and 257 patients

underwent pancreatic surgery. Based on our meta-analysis, the **overall diagnostic yield screening for high-risk pancreatic lesions was 0.74 (95% CI, 0.33-1.14),** with moderate heterogeneity among studies. The **number needed to screen to identify 1 patient with a high-risk lesion was 135 (95% CI, 88-303).** The diagnostic yield was similar for patients with different genetic features that increased risk, and whether patients were screened by EUS or MRI. CONCLUSIONS: Based on meta-analysis, 135 patients at high-risk for pancreatic cancer must be screened to identify 1 patient with a high-risk pancreatic lesion. Further studies are needed to determine whether screening reduces mortality and is cost effectiveness for individuals at high-risk of pancreatic cancer.

Signoretti et al. United European Gastroenterol J. 2018[83]

Results of surveillance in individuals at high-risk of pancreatic cancer: A systematic review and meta-analysis

Objective: We conducted a systematic review and meta-analysis of PDAC surveillance studies in HRIs. Methods: Prevalence of solid/cystic pancreatic lesions and of lesions considered a successful target of surveillance (proven resectable PDAC and high-grade precursors) was pooled across studies. The rate of lesions diagnosed by endoscopic ultrasonography (EUS)/magnetic resonance imaging (MRI) and across different HRI groups was calculated. Results: **Sixteen studies incorporating 1588 HRIs were included**. The pooled prevalence of **pancreatic solid and cystic lesions was 5.8% and 20.2%,** respectively. The pooled prevalence of patients with lesions considered a **successful target of surveillance was 3.3%,** being similar to EUS or MRI and varying across subgroups, being 3% in FPC, 4% in hereditary pancreatitis, 5% in familial melanoma, 6.3% in hereditary breast/ovarian cancer, and 12.2% in Peutz-Jeghers syndrome. The pooled estimated rate of lesions considered a successful target of surveillance during follow-up was 5/1000 person-years. Conclusion**: Surveillance programs identify successful target lesions in 3.3% of HRIs with a similar yield of EUS and MRI and an annual risk of 0.5%.** A higher rate of target lesions was reported in HRIs with specific DNA mutations.

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