Early detection of pancreatic cancer in high-risk individuals

Klatte, D.C.F.

General introduction and thesis outline

GENERAL INTRODUCTION

Adapted from: Derk C.F. Klatte, Michael B. Wallace, Matthias Löhr, Marco J. Bruno, and Monique E. van Leerdam. Hereditary Pancreatic Cancer. Best Pract Res Clin Gastroenterol. 2022 Jun-Aug;58-59:101783.

PANCREATIC CANCER

Pancreatic cancer incidence and mortality are rising rapidly. Globally, the number of cases has more than doubled between 1990 to 2017 and pancreatic cancer is soon expected to be the second leading cause of cancer-related mortality.[1] As only a minority of approximately 16% of patients have a resectable tumor at time of presentation[2], there is an urgent need for detection and treatment of early lesions to improve outcomes. Currently, the implementation of widespread general population-based screening is not feasible due to the low overall incidence (5.7 per 100.000 person-years) and absence of accurate screening tests.[3, 4] However, it is estimated that up to 10% of cases occur in individuals with a strong family history or carriers of a germline mutation[5], referred to as high-risk individuals, for whom pancreatic cancer surveillance in expert centers is recommended.[6-8]

HIGH-RISK INDIVIDUALS

The average lifetime risk of pancreatic cancer in the general population is approximately 1.5%.[9] There is consensus that individuals with a lifetime risk of pancreatic cancer greater than 5%, or a 5-fold increased relative risk, are considered high-risk individuals.[10] These individuals can be categorized into familial pancreatic cancer (FPC) or those with hereditary cancer syndromes, each with varying population prevalence and pancreatic cancer risk (**Table 1**).

Familial pancreatic cancer

FPC is defined as a family clustering of pancreatic cancer with at least two first-degree relatives without a known hereditary cancer syndrome (*nonsyndromic* FPC). The risk of pancreatic cancer increases with the number of affected family members.[11] Early onset of pancreatic cancer in the family is also associated with a higher individual risk.[11, 12]

Hereditary pancreatic cancer

Approximately 50 forms of hereditary cancer syndromes have been identified in humans.[13] A number of these have been associated with development of pancreatic cancer. The "two-hit" hypothesis proposed by Knudson is an intriguing concept that has been demonstrated in several autosomal dominant inherited cancers. [14] According to this hypothesis, the first genetic hit occurs due to a germline mutation of one allele, while the second hit involves a somatic deletion of the other allele, resulting to a condition known as loss-of-heterozygosity. This process leads to the inactivation of tumor suppressor genes, paving the way for the development of cancer. The applicability of this theory to different hereditary cancer syndromes underscores its significance in understanding the genetic basis of cancer predisposition, including in cases of pancreatic cancer.[15] Cancer predisposition syndromes with the greatest risk of developing pancreatic cancer include Peutz-Jeghers syndrome (*STK11/LKB1* gene), hereditary pancreatitis (*PRSS1/SPINK1* gene) and familial atypical multiple melanoma (FAMMM) syndrome, also known as hereditary melanoma (*CDKN2A* gene).[16-25]

Table 1. Epidemiology of germline mutations, associated cancer syndromes and risk of pancreatic cancer

Gene(s)	Cancer syndrome	Inheritance pattern	Prevalence general population	Associated cancers	Relative risk for PC	Lifetime risk for PC	Ref.
APC	Familial Adenomatous Polyposis (FAP)	Autosomal dominant	1/10,000	Gastrointestinal, brain, thyroid, hepatic	4.5		[58, 59]
ATM	Ataxia-telangiectasia (AT)	Autosomal recessive	1/40,000-1/100,000	Lymphoma, acute leukemia, breast	6.5	9.5%	[60, 61]
BRCA1	Hereditary Breast and Ovarian syndrome (HBOC)	Autosomal dominant	1/300-1/500	Breast, ovarian, prostate	2.3-3.0	2.2%-3.0%	[62-64]
BRCA2					3.5-10.0	3.0%-7.0%	
CDKN2A/p16	Hereditary melanoma, Familial Atypical Multiple Melanoma Mole (FAMMM) syndrome	Autosomal dominant	<1/1,000	Melanoma and non-melanoma skin, oropharynx, respiratory, respiratory	13-47.8	19%	[25, 65, 66]
STK11/LKB1	Peutz-Jeghers syndrome (PJS)	Autosomal dominant	1/50,000-1/200,000	Colorectal, breast, small bowel, gastric	132	11%-36%	[16, 17, 19]
MLH1/MSH2/MSH6	Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	Autosomal dominant	1/279-1/2,000	Gastrointestinal, endometrial, urological	8.6	3.68%	[67-69]
PALB2	-	Autosomal dominant	1/500	Breast, ovarian	2.4	4%	[70, 71]
TP53	Li-Fraumeni syndrome	Autosomal dominant	1/3,000-1/5,000	Breast, sarcoma, leukemia, adrenocortical, brain	7.3	-	[72, 73]
PRSS1/SPINK1	Hereditary pancreatitis	Autosomal dominant (*PRSS1*)	<1/100,000	-	69	7.2%-53.3%	[21-23]

Recommendations for genetic testing

Genetic testing for hereditary cancer syndromes is useful in identifying individuals at high risk of pancreatic cancer or other related cancers, who could benefit from cancer surveillance.[26] However, because of the large variety of cancer syndromes associated with pancreatic cancer, identification of individuals who are candidates for genetic testing is complex. Family history, in combination with a patient's personal cancer history, is key to identifying those individuals who have an inherited predisposition to malignancy. A three-generation pedigree is the gold standard for autosomal inherited disorders, which should include tumor types and ages at diagnosis. Family history of cancer in first- and second-degree relatives is most important. Factors that increase the likelihood of a hereditary component are an early age of cancer onset, multiple affected relatives within the same family, and multiple primary tumors, especially in specific organs that are associated with a particular cancer syndrome such as the breast and ovaries in context of a *BRCA1/2* germline mutation or the colon in Lynch syndrome. When obtaining family history, clinicians should be aware of any information regarding ethnicity that may be relevant to specific cancer syndromes of interest. Traditionally, guidelines have recommended genetic testing for suspected hereditary cancer syndromes, however more recent guidelines from the United States advocate for genetic testing of all individuals diagnosed with pancreatic cancer, regardless of family history.[27]

PANCREATIC CANCER SURVEILLANCE

Whom to offer surveillance

Several guidelines have been published with recommendations for pancreatic cancer surveillance of high-risk individuals.[6, 10, 26] All guidelines recommend that carriers of germline mutations in *CDKN2A* and *STK11/LKB1* – who are at highest risk of developing pancreatic cancer – are offered pancreatic surveillance regardless of family history of pancreatic cancer, starting at age 40 years, or 10 years younger than the youngest affected blood relative (**Table 2**). For carriers of germline mutations in *ATM*, *BRCA1/2, PALB2*, *MLH1/MSH2/MSH6*, surveillance is recommended in the presence of one or more first-degree relative with pancreatic cancer. In individuals with a familial clustering of pancreatic cancer, without a known germline mutation (FPC), international guidelines recommend surveillance in those with at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer, starting at age 50 or 10 years younger than the youngest affected blood relative. However, recent data from a large pancreatic cancer surveillance study in the Netherlands showed that the diagnostic yield of FPC was non-existent.[28] Therefore, whether surveillance is beneficial in these individuals remains to be proven.

Table 2. Summary of pancreatic surveillance recommendations for high-risk individuals from the International Cancer of the Pancreas Screening (CAPS) Consortium and the American Gastroenterological Association (AGA)

	CAPS 2019[6]		AGA 2020[26]	
High-risk group	**Family criteria**	**Starting age***	**Family criteria**	**Starting age***
FPC	≥1 FDR who in turn also has ≥1 FDR	50 or 55†	≥2 affected relatives	50
APC	-	-	-	-
ATM	≥1 FDR	45 or 50	≥1 FDR	50
BRCA1	≥1 FDR	45 or 50	≥1 FDR	50
BRCA2	≥1 FDR	45 or 50	≥1 FDR	50
CDKN2A/p16	Regardless of family history	40	Regardless of family history	40
STK11/LKB1	Regardless of family history	40	Regardless of family history	35
MLH1/MSH2/MSH6	≥1 FDR	45 or 50	≥1 FDR	50
PALB2	≥1 FDR	45 or 50	≥1 FDR	50
TP53	-	-	-	-
PRSS1/SPINK1	-	40 or 20 years after the first pancreatitis attack	Regardless of family history	40

Abbreviations: FDR, first-degree relative. FPC, familial pancreatic cancer.
*Or 10 years younger than the initial age of onset in the family.
†Consensus as to when to start surveillance was not reached for FPC.

How to perform surveillance

Currently, pancreatic cancer surveillance is performed using imaging with magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), or a combination of both.[6, 26, 29] While EUS appears to be more sensitive in detecting small solid lesions, MRI is superior in detecting and characterizing cystic lesions.[30] Therefore, it is recommended that both modalities are used complementary rather than interchangeable.[6] EUS offers the advantage of performing tissue sampling through fine-needle aspiration or biopsy, but it also comes with potential interobserver variability and risks associated with the procedure and sedation.[31, 32] Computed tomography is useful for staging and assessing resectability but has limitations in detecting small lesions and carries radiation exposure, which is undesirable for long-term surveillance. Reliable biomarkers for surveillance are currently not yet available. Although CA19-9 has proven useful for monitoring treatment response and detecting disease recurrence[33], its performance in detecting early-stage disease has been shown to be inadequate, and false-positive results are common.[34] As a result, surveillance remains currently limited to MRI and EUS. In the case of a normal pancreas or non-concerning abnormalities, follow-up imaging should be performed after 12 months. If worrisome features are found that do not warrant immediate surgery, the surveillance interval should be shortened to 6 months for intermediate (e.g., cystic lesions ≥ 3 cm) and within 3 months for high-risk lesions (e.g., solid lesion < 5 mm). Further characterization by EUS-guided tissue sampling is recommended for indeterminate or high-risk lesions. In cases with high suspicion of malignancy (e.g., solid lesions ≥ 10 mm or cystic lesions with

an enhancing solid component), surgical resection should be performed.[6, 26] Overall, surveillance and management decisions should be made by dedicated multidisciplinary teams in expert centers.

Targets for surveillance

Small, early-stage tumors and high-grade precursors are considered ideal target lesions for pancreatic surveillance. These lesions are usually resectable and have by far the most favorable prognosis. [35, 36] Therefore, the goal of surveillance is to detect and treat stage I pancreatic cancer that is confined to the pancreas, resected with negative margins, and pancreatic cancer precursor lesions with high-grade dysplasia. The most relevant precursor lesions are pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCN).

The majority of PDAC are thought to arise from PanINs and therefore considered the most important precursor lesions for pancreatic malignancy. PanINs are defined as microscopic (<5 mm) papillary or flat, noninvasive epithelial lesions in the pancreatic duct.[37] They are characterized by columnar-to-cuboidal cells with variable amounts of mucin and varying degrees of cytological and architectural atypia. PanINs are part of a multistep tumor progression model, in which genetic events are observed in *KRAS*, *CDKN2A*, *TP53* and *SMAD4* are observed during progression from low-grade to high-grade dysplasia (**Figure 1**). [38] Low-grade PanIN previously encompassed three older definitions: PanIN-1A (flat), PanIN-1B (papillary), and PanIN-2, representing low- and intermediate-grade lesions, respectively. Thus, the term high-grade dysplasia is now used only for most advanced dysplasia, characterized by severe cytologic and architectural atypia.[39] Although PanIN are microscopic lesions and are typically diagnosed on histopathologic evaluation, they may be surrounded by multifocal lobular atrophy, which may serve as an indirect marker of neoplasia on imaging.[40] PanIN lesions are common in the pancreas. A histopathologic review of resected pancreata without PDAC identified PanIN in 26% of patients, including 8% with high-grade dysplasia. In contrast, high-grade PanIN was found in 40% of patients with PDAC.[41] Only a very small proportion of low-grade PanIN is expected to progress to PDAC, therefore only resection of high-grade PanIN is considered a success of surveillance.

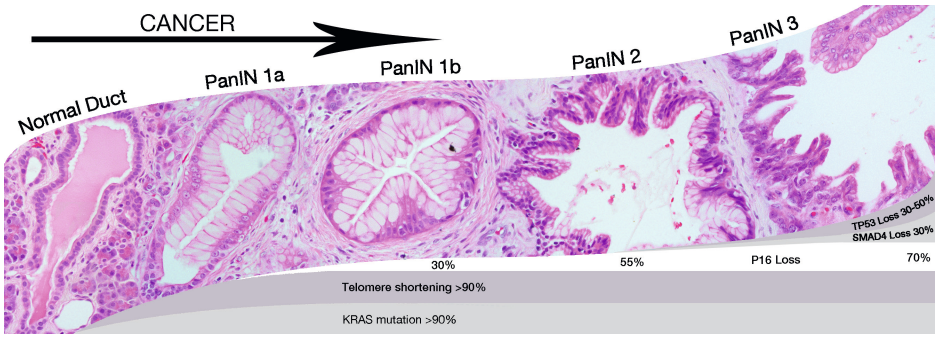

Figure 1. Progression model for pancreatic cancer. The PanIN progression model shown here shows that accumulation of genetic and epigenetic alterations drives neoplastic progression in these precursor lesions from low-grade dysplasia (PanIN-1 and PanIN-2) to high-grade dysplasia (PanIN-3) to eventually invasive cancer. Progressive telomere shortening creates genetic instability that facilitates tumor development. Reprinted with permission from *Hackeng et al. Diagn Pathol. 2016.*[38]

IPMN are grossly visible (>5 mm), noninvasive, epithelial neoplasms that are composed of mucin-producing columnar cells. They are usually found in the pancreatic head, but can be found throughout the entire length of the pancreas. Similar to PanIN, IPMN can harbor different grades of dysplasia, including low-grade, high-grade and invasive carcinoma. Morphologically, IPMNs can be classified as originating from the main pancreatic duct (MD-IPMN), one of the side branches (SB-IPMN), but can also involve both the main duct and side branches (mixed type; MT-IPMN). MD-IPMN have a much higher risk of progression to malignancy (61.6%), compared to SB-IPMN (25.5%).[42] Up to 40% of BD-IPMN are multifocal, but this has not been shown to increase the risk of malignancy.[43] IPMN can become symptomatic and cause pancreatitis-like symptoms, such as abdominal pain, jaundice and weight loss. Several international, European and American guidelines have been developed regarding the prediction of malignancy, surveillance, and management of IPMNs. Factors that require immediate surgery ("high-risk stigmata") include obstructive jaundice, an enhancing mural nodule ≥5 mm, and main pancreatic duct dilatation ≥ 10 mm. "Worrisome features" – which are relative indications for surgery – are cysts ≥3 cm, an enhancing mural nodule <5 mm, thickened/enhancing cyst walls, a main duct size of 5-9 mm, an abrupt change in pancreatic duct caliber with distal atrophy, lymphadenopathy, an elevated serum CA19-9, and a cyst growth rate > 5 mm in 2 years.[44]

MCNs are typically large mucin-producing cysts found predominantly in women. Most MCNs are found in the body or tail of the pancreas, and unlike IPMN usually do not communicate with the pancreatic duct. Malignant transformation of MCNs is comparable with the multistep tumor progression model as observed in PanIN.[45] Up to 34% of all resected MCNs are malignant, however in asymptomatic lesions < 40 mm with no worrisome features, the rate of malignant progression is less than 0.10%.[46, 47] Therefore, European guidelines advocate surveillance for small MCNs.[48] Larger cysts (≥40 mm) or those with worrisome features such as mural nodules or enhancing walls should be considered for surgery due to the high malignant potential.[49]

Although pancreatic cancer is notorious for its high metastatic potential, it is estimated that it takes many years for precursor lesions to progress to a malignant clone.[50] This is encouraging from an early detection perspective as it would in potential provide a large window for surveillance programs to detect malignant precursor lesions and early stage cancer.

Outcomes of surveillance

Over the past two decades, multiple centers have reported their findings from surveillance programs in various high-risk populations, yielding mixed results.[24, 28, 36, 51-53] More recent evaluations have shown promise in detecting early-stage cancer with improved survival rates, mostly in carriers of germline mutations.[24, 36] However, the benefit of surveillance for FPC remains questionable, with a low success rate in detecting target lesions and a higher risk of unnecessary surgical procedures.[28, 54] The variation in outcomes from these programs emphasize that continuous evaluation is essential. A key limitation in assessing the survival benefit of pancreatic surveillance programs is the use of observational data in which lead time represents a potential source of bias. Lead-time bias arises when cancer is detected by screening earlier than that it would have been diagnosed based on symptoms, without affecting the disease course, leading to an apparent increase in survival time. Only randomized controlled trials can completely control for this source of bias. It is however unlikely

that such a trial will be conducted, because this would require a large number of participants and a long follow-up duration to accurately assess differences in survival. Moreover, there are ethical concerns in withholding high-risk individuals from surveillance in a trial setting. Besides, individuals will be unlikely to participate when informed about potential risks and benefits. As effects of lead-time are most prominent in short term survival, long-term (> 10-year) follow-up studies are most likely to give a reliable appraisal of a true survival benefit of surveillance participation.

Harms of surveillance

Individuals undergoing surveillance programs should be informed about the potential harms of screening before starting the program. Some risks are directly related to some of the limitations of imaging-based surveillance, including the lacking discriminative capabilities to distinguish low-grade from high-grade precursor lesions, and incidental findings, which may result in surgical resection of benign lesions.[55] Overtreatment is particularly troublesome as pancreatic resection is associated with considerable perioperative morbidity, exocrine and endocrine dysfunction Moreover, there is a risk treatment of malignancies diagnosed at an advanced stage, where the potential for survival benefit is limited or absent. Another important consideration is the psychological impact on individuals with hereditary cancer syndromes, who may experience increased distress and a lower quality of life compared to the general population.[56] However, current literature does not clearly indicate that surveillance participation itself significantly increases cancer-specific anxiety or general distress, as cancer worries may even decrease over time.[57]

SUMMARY

Approximately 10% of PDAC cases are observed in high-risk individuals with a strong family history or germline mutations. Pancreatic surveillance is recommended for these individuals, and genetic testing plays a critical role in identifying those who may benefit from such screening. Combining family history with a patient's personal cancer history is essential in identifying individuals with an inherited predisposition to malignancy. There is a wide variation in the lifetime risk of PDAC between different cancer syndromes and the number of affected relatives in FPC, which determines the starting age and family criteria for participation in surveillance. Surveillance aims to detect early-stage pancreatic cancer and high-grade precursor lesions, of which the two most relevant are PanIN and IPMN. Although PanINs are considered the most important precursors, they are microscopic lesions and therefore extremely difficult to detect with conventional imaging. Surveillance should be performed by multidisciplinary teams in expert centers, with most programs using MRI and/or EUS. Several studies have demonstrated a potential survival benefit of surveillance, although this benefit is less certain in FPC. Potential harms of surveillance include the risk of false-positive findings and overtreatment, detection and treatment of lesions at advanced stages, with a minimal survival benefit, and psychological distress.

THESIS OUTLINE AND AIMS

The overall aim of the studies conducted in this thesis is to improve surveillance of individuals at high risk of developing pancreatic cancer, with a specific focus on carriers of a germline *CDKN2A* mutation. In Part I, we evaluate the effectiveness of pancreatic cancer surveillance by reporting on the long-term yield and outcomes of pancreatic surveillance conducted in germline *CDKN2A* mutation carriers (**Chapter 2**) and comparing these outcomes with a control group while correcting for potential lead-time bias (**Chapter 3**). The second part focuses on various aspects to improve pancreatic cancer surveillance programs. In **Chapter 4** we explore the psychosocial aspects associated with carriership of a germline *CDKN2A* mutation. Next, **Chapter 5** describes the study of longitudinal changes in serum protein *N*-glycans as a biomarker for early detection. In **Chapter 6** we assess whether risk stratification can help to identify which individuals with a germline *CDKN2A* mutation participating in surveillance are at highest risk of developing pancreatic cancer. The final part of this thesis examines and evaluates strategies to identify high-risk individuals who may be eligible for participation in surveillance. **Chapter 7** describes the identification of individuals at high risk for pancreatic cancer using a tool that focuses on family history and development of new-onset diabetes. The use and outcomes of multigene panel testing in patients with PDAC to identify a hereditary predisposition are evaluated in **Chapter 8**. In **Chapter 9**, we investigate the prediagnostic changes occuring in body composition and metabolic markers prior to diagnosis of PDAC in a large cohort of patients. Finally, in **Chapter 10**, the main findings of this thesis and future perspectives are summarized and discussed.

REFERENCES

1. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
2. Kardosh A, Lichtensztajn DY, Gubens MA, et al. Long-Term Survivors of Pancreatic Cancer: A California Population-Based Study. Pancreas 2018;47:958-966.
3. Pourshams A, Sepanlou SG, Ikuta KS, et al. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology & Hepatology 2019;4:934-947.
4. Owens DK, Davidson KW, Krist AH, et al. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. Jama 2019;322:438-444.
5. Whitcomb DC, Shelton CA, Brand RE. Genetics and Genetic Testing in Pancreatic Cancer. Gastroenterology 2015;149:1252-1264.e4.
6. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut 2020;69:7-17.
7. Syngal S, Brand RE, Church JM, et al. ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes. American Journal of Gastroenterology 2015;110:223-262.
8. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:439-457.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
10. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62:339-47.
11. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004;64:2634-8.
12. Brune KA, Lau B, Palmisano E, et al. Importance of age of onset in pancreatic cancer kindreds. Journal of the National Cancer Institute 2010;102:119-126.
13. Kopelovich L, Shea-Herbert B. Heritable one-hit events defining cancer prevention? Cell cycle (Georgetown, Tex.) 2013;12:2553-2557.
14. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A 1971;68:820-3.
15. Lowery MA, Wong W, Jordan EJ, et al. Prospective Evaluation of Germline Alterations in Patients With Exocrine Pancreatic Neoplasms. JNCI: Journal of the National Cancer Institute 2018;110:1067-1074.
16. van Lier MGF, Wagner A, Mathus-Vliegen EMH, et al. High Cancer Risk in Peutz–Jeghers Syndrome: A Systematic Review and Surveillance Recommendations. Official journal of the American College of Gastroenterology | ACG 2010;105:1258-1264.
17. Korsse SE, Harinck F, van Lier MGF, et al. Pancreatic cancer risk in Peutz-Jeghers syndrome patients: a large cohort study and implications for surveillance. Journal of Medical Genetics 2013;50:59-64.
18. van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol 2010;105:1258-64; author reply 1265.
19. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447-53.
20. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol 2010;24:349-58.

21. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 1997;89:442-6.
22. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2004;2:252-61.
23. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. Gut 2009;58:97-103.
24. Vasen H, Ibrahim I, Ponce CG, et al. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers. Journal of Clinical Oncology 2016;34:2010-2019.
25. de Snoo FA, Bishop DT, Bergman W, et al. Increased risk of cancer other than melanoma in *CDKN2A* founder mutation (p16-Leiden)-positive melanoma families. Clin Cancer Res 2008;14:7151-7.
26. Aslanian HR, Lee JH, Canto MI. AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review. Gastroenterology 2020;159:358-362.
27. Daly MB, Pilarski R, Yurgelun MB, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020. J Natl Compr Canc Netw 2020;18:380-391.
28. Overbeek KA, Levink IJM, Koopmann BDM, et al. Long-term yield of pancreatic cancer surveillance in high-risk individuals. Gut 2021:gutjnl-2020-323611.
29. Corral JE, Mareth KF, Riegert-Johnson DL, et al. Diagnostic Yield From Screening Asymptomatic Individuals at High Risk for Pancreatic Cancer: A Meta-analysis of Cohort Studies. Clin Gastroenterol Hepatol 2019;17:41-53.
30. Harinck F, Konings ICAW, Kluijt I, et al. A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. Gut 2016;65:1505-1513.
31. Topazian M, Enders F, Kimmey M, et al. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. Gastrointestinal Endoscopy 2007;66:62-67.
32. Amornyotin S. Sedation-related complications in gastrointestinal endoscopy. World journal of gastrointestinal endoscopy 2013;5:527-533.
33. Luo G, Jin K, Deng S, et al. Roles of CA19-9 in pancreatic cancer: Biomarker, predictor and promoter. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer 2021;1875:188409.
34. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J Gastrointest Oncol 2012;3:105-19.
35. Blackford AL, Canto MI, Klein AP, et al. Recent Trends in the Incidence and Survival of Stage 1A Pancreatic Cancer: A Surveillance, Epidemiology, and End Results Analysis. J Natl Cancer Inst 2020;112:1162-1169.
36. Canto MI, Almario JA, Schulick RD, et al. Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance. Gastroenterology 2018;155:740-751.e2.
37. Teng X. Intraepithelial Neoplasia of Pancreas, Biliary Tract and Gallbladder. In: Lai M, ed. Intraepithelial Neoplasia. Berlin, Heidelberg: Springer Berlin Heidelberg, 2009:112-169.
38. Hackeng WM, Hruban RH, Offerhaus GJ, et al. Surgical and molecular pathology of pancreatic neoplasms. Diagn Pathol 2016;11:47.
39. Hruban RH, Takaori K, Klimstra DS, et al. An Illustrated Consensus on the Classification of Pancreatic Intraepithelial Neoplasia and Intraductal Papillary Mucinous Neoplasms. The American Journal of Surgical Pathology 2004;28:977-987.
40. Brune K, Abe T, Canto M, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. The American journal of surgical pathology 2006;30:1067-1076.

41. Andea A, Sarkar F, Adsay VN. Clinicopathological Correlates of Pancreatic Intraepithelial Neoplasia: A Comparative Analysis of 82 Cases With and 152 Cases Without Pancreatic Ductal Adenocarcinoma. Modern Pathology 2003;16:996-1006.
42. Tanaka M, Fernández-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012;12:183-97.
43. Levink I, Bruno MJ, Cahen DL. Management of Intraductal Papillary Mucinous Neoplasms: Controversies in Guidelines and Future Perspectives. Current treatment options in gastroenterology 2018;16:316-332.
44. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17:738-753.
45. Noë M, Niknafs N, Fischer CG, et al. Genomic characterization of malignant progression in neoplastic pancreatic cysts. Nature Communications 2020;11:4085.
46. Crippa S, Fernández–del Castillo C, Salvia R, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. Clinical Gastroenterology and Hepatology 2010;8:213-219. e4.
47. Nilsson LN, Keane MG, Shamali A, et al. Nature and management of pancreatic mucinous cystic neoplasm (MCN): A systematic review of the literature. Pancreatology 2016;16:1028-1036.
48. European Study Group on Cystic Tumours of the P. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018;67:789-804.
49. Marchegiani G, Andrianello S, Crippa S, et al. Actual malignancy risk of either operated or non-operated presumed mucinous cystic neoplasms of the pancreas under surveillance. Br J Surg 2021;108:1097-1104.
50. Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 2010;467:1114-1117.
51. Al-Sukhni W, Borgida A, Rothenmund H, et al. Screening for Pancreatic Cancer in a High-Risk Cohort: An Eight-Year Experience. J Gastrointest Surg 2012;16:771-783.
52. Del Chiaro M, Verbeke CS, Kartalis N, et al. Short-term Results of a Magnetic Resonance Imaging-Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer. JAMA Surg 2015;150:512-8.
53. Ludwig E, Olson SH, Bayuga S, et al. Feasibility and Yield of Screening in Relatives From Familial Pancreatic Cancer Families. Am J Gastroenterol 2011;106:946-954.
54. Signoretti M, Bruno MJ, Zerboni G, et al. Results of surveillance in individuals at high-risk of pancreatic cancer: A systematic review and meta-analysis. United European Gastroenterology Journal 2018;6:489-499.
55. de Mestier L, Muller M, Cros J, et al. Appropriateness of pancreatic resection in high-risk individuals for familial pancreatic ductal adenocarcinoma: a patient-level meta-analysis and proposition of the Beaujon score. United European Gastroenterology Journal 2019;7:358-368.
56. Van Lier M, Mathus-Vliegen E, Van Leerdam M, et al. Quality of life and psychological distress in patients with Peutz–Jeghers syndrome. Clinical Genetics 2010;78:219-226.
57. Konings ICAW, Sidharta GN, Harinck F, et al. Repeated participation in pancreatic cancer surveillance by high-risk individuals imposes low psychological burden. Psycho-Oncology 2016;25:971-978.
58. Vasen HF, Möslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57:704-13.
59. Groen EJ, Roos A, Muntinghe FL, et al. Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol 2008;15:2439-50.
60. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, et al. Ataxia telangiectasia: a review. Orphanet J Rare Dis 2016;11:159.
61. Hsu FC, Roberts NJ, Childs E, et al. Risk of Pancreatic Cancer Among Individuals With Pathogenic Variants in the ATM Gene. JAMA Oncol 2021.

62. Nelson HD, Fu R, Goddard K, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Rockville (MD): Agency for Healthcare Research and Quality (US), 2013.
63. Wong W, Raufi AG, Safyan RA, et al. BRCA Mutations in Pancreas Cancer: Spectrum, Current Management, Challenges and Future Prospects. Cancer Manag Res 2020;12:2731-2742.
64. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005;42:711-9.
65. Helgadottir H, Ghiorzo P, van Doorn R, et al. Efficacy of novel immunotherapy regimens in patients with metastatic melanoma with germline *CDKN2A* mutations. J Med Genet 2020;57:316-321.
66. Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. Jama 2018;319:2401-2409.
67. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of Pancreatic Cancer in Families With Lynch Syndrome. JAMA 2009;302:1790-1795.
68. Watson P, Vasen HFA, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008;123:444-449.
69. van Leerdam ME, Roos VH, van Hooft JE, et al. Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2019;51:1082-1093.
70. Yang X, Leslie G, Doroszuk A, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. Journal of Clinical Oncology 2020;38:674-685.
71. Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. New England Journal of Medicine 2021;384:440-451.
72. de Andrade KC, Frone MN, Wegman-Ostrosky T, et al. Variable population prevalence estimates of germline TP53 variants: A gnomAD-based analysis. Hum Mutat 2019;40:97-105.
73. Ruijs MWG, Verhoef S, Rookus MA, et al. TP53 germline mutation testing in 180 families suspected of Li–Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. Journal of Medical Genetics 2010;47:421-428.