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A Cost Analysis of a Pancreatic Cancer Screening Protocol in High-Risk Populations

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Abstract

Background—Pancreatic cancer is the 4th leading cause of cancer death in the U.S. A screening protocol is needed to catch early stage, resectable disease. This study suggests a protocol for high-risk individuals and assesses the cost in the context of the Affordable Care Act.

Methods—Medicare and national average pricing were used for cost analysis of a protocol using MRI/MRCP biannually in high-risk groups.

Results: '—Costs per year of life added' based on Medicare and national average costs, respectively, are: $638.62 and $2542.37 for Peutz-Jehgers Syndrome, $945.33 and $3763.44 for Hereditary Pancreatitis, $1141.77 and $4545.45 for Familial Pancreatic Cancer and *p16-Leiden* mutations, and $356.42 and $1418.92 for new-onset diabetes over age 50 with weight loss or smoking.

Conclusion—A screening program using MRI/MRCP is affordable in high-risk populations. The U.S. Preventive Services Task Force must reevaluate its pancreatic cancer screening guidelines to make screening more cost-effective for the individual.

Keywords

Pancreatic Cancer; Screening; Idiopathic; Genetic Predisposition; Cost Analysis; High-risk

Introduction

Pancreatic cancer (PC) was the 10th most common cancer in the US in 2013 but the 4th leading cause of cancer death.[1] It maintains a dismal prognosis, owing to a lack of effective treatment and a usual late stage at diagnosis. A screening program for asymptomatic high-

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risk individuals (HRIs) is needed, in order to detect early stage PC or precursor lesions, such as intraductal papillary mucinous neoplasms (IPMN) and pancreatic intraepithelial neoplasias (PanIN). Cost estimates of such a screening protocol can be calculated, based on current average pricing for screening modalities.

Current United States Preventive Services Task Force (USPSTF) guidelines give asymptomatic screening for PC a D rating.[2] Under the Affordable Care Act (ACA), this leaves the patient with the expense, making compliance much less likely.[3] A screening protocol must be adopted for those at high risk for PC, and USPSTF guidelines must be updated in order to reflect these advancements.

Methods

Literature search

A literature search was conducted using Pubmed via EndNote with the search terms "pancreatic cancer," "screening," "MRI," "magnetic resonance imaging," "MRCP," "cost," "cancer," "Affordable Care Act," "US Preventive Services," "policy," "prevention," and "preventive services."

Studies regarding imaging were restricted to English language, human studies, and publish dates from 2006–2013, in order to include only recent data (n=43). They were further restricted to those that focused on screening HRIs for PC using presumed validated methods (n=15). Studies were required to have >20 subjects, to maintain large sample size, and subjects had to be asymptomatic for PC. This is because PC symptoms usually do no appear until unresectable stages of disease. Additionally, because the aim of this paper is to recommend the efficacy of MRI/MRCP and not present a systematic review of all imaging techniques, only studies that employed MRI/MRCP as a screening method were retained (n=12). After removal of overlaps, 6 studies remained. Three used MRI in conjunction with other screening modalities, but only 2 provided the results of each modality, separately. This yielded 5 studies with data relating to efficacy of MRI/MRCP, alone. Eight reviews were kept for reference.

Articles pertaining to cost were restricted to English language, human studies, and publish dates from 2006–2013 (n=22) and were further restricted to only those that centrally focused on cost of screening for PC (n=4). Articles regarding the ACA were restricted to English language, human studies, with publish dates from 2010 to 2013, as the ACA was passed in 2010 (n=27). They were further restricted to articles that focused on PC specifically, or cancer in general, leaving 13 articles.

Creation of screening protocol (Table 1)

Based on a recently conducted risk analysis, a screening protocol was developed for individuals with the greatest known risk for developing PC, including those with genetic risk factors (5–10% of PC sufferers) and those with idiopathic risk factors (90–95% of PC sufferers).[4] Genetic risk factors that confer the greatest risk for PC include Familial Pancreatic Cancer (FPC)(>2 first-degree relatives with PC), Peutz-Jehgers Syndrome (PJS),

Hereditary Pancreatitis (HP), and *p16-Leiden* mutations. The greatest risk factor for idiopathic PC is new-onset diabetes over the age of 50 with weight loss or smoking history.

Screening age in FPC kindreds was chosen to be age 50, at the latest, or 10 years younger than the earliest PC diagnosis in an affected blood relative.[5] Screening ages for the other risk factors were chosen as approximately 10 years younger than reported mean ages of diagnosis.[6–10] Screening in the diabetic high-risk group was chosen to begin at time of diabetes diagnosis and terminate after 3 years, as findings indicate that PC-associated diabetes precedes PC diagnosis by 36 months or fewer.[4,11,12]

MRI/MRCP was chosen as the best imaging modality based on the reviewed literature. Screening frequency was chosen to be 6 months, with follow-up MRI/MRCP and Ca19-9 performed within 3 months of abnormal findings. These parameters were chosen due to the aggressive nature of the disease.[13]

Cost data collection

Pricing data for imaging techniques were obtained from the "Medicare Physician Fee Schedule" search tool, located on the Centers for Medicare and Medicaid Services website, and included both the professional and technical fees.[14] Additional data were obtained from Norton Healthcare billing services in Louisville, KY, and the medical cost comparison website *New Choice Health*, which averages pricing data across the U.S. but does not specify the details of what is included in those prices.[15] Pricing data for anesthesia fees came from Norton Healthcare anesthesia billing services.

Population and PC statistics

Life expectancy information was taken from the CDC's most recent available data.[16] PC statistics were taken from the most recent Surveillance Epidemiology and End Results (SEER) data.[17]

Cost analysis calculations

Cost analyses were conducted based on pricing and life expectancy data. Calculations were made using Microsoft® Excel® for Mac 2011. The specific formulas used were:

a. Total cost of screening, per risk factor: annual cost of MRI/MRCP (twice per year) multiplied by the total number of screening years (20 years for inherited risk factors, 3 years for diabetes).

b. Average survival after PC diagnosis: SEER median age of PC death minus SEER median age of PC diagnosis. This equaled 2 years.

c. Average age of PC death: median/mean age of PC diagnosis (individualized for each risk factor) plus average survival after PC diagnosis (2 years). Average age at diagnosis in the diabetic population was taken to be that of the general population.

d. Potential years of life added: life expectancy at age 65 minus average age of PC death (as calculated above).

e. Cost per year of life added: total cost of screening divided by years of life added.

Results

Cost comparison of imaging modalities

Current pricing for the most common PC imaging techniques can be found in Table 2.[14,15] In terms of raw cost, CT of the abdomen is the least expensive procedure, ranging from $325.60 to $3394.00. Medicare fees show EUS as having an intermediate cost, at $601.23. However, EUS has the highest out-of-pocket cost, at $5370.00. In reality, EUS will have a wide range of pricing, based on the necessity of sedation and the potential for recovery time fees, particularly if FNA is added. MRI/MRCP of the abdomen has the highest Medicare cost, with an average of $659.37. However, out-of-pocket cost remains intermediate, at $4656.00, and national average cost for MRI is only slightly above the national average for CT, at $2625.00.

Cost analysis of screening protocol with MRI/MRCP

Using MRI/MRCP prices in conjunction with statistical data from the CDC and SEER (Table 3),[16,17] the costs of a screening program were estimated (Table 4). Based on Medicare data, the total costs for the PJS, HP, *p16-Leiden*, and FPC populations would be the same, at $26,374.80. This is because for each of these populations, screening would total 20 years – beginning 10 years before the mean age of PC diagnosis and ending 10 years after the mean age of PC diagnosis. However, cost per year of life added differs amongst these groups, with the least expensive being $638.62 per year in the PJS population. This is to be expected, as individuals with PJS are diagnosed at younger ages, therefore, screening will add the greatest number of years to their lives. Following this trend, the HP population has intermediate costs, at $945.33 per year of life added. Finally, the *p16-Leiden* and FPC population see the greatest costs, at $1141.77 per year of life added. The least expensive screening program, overall, would be in those with new-onset diabetes over the age of 50 with a history of smoking or with weight loss, as they would require only 3 years of screening. Total cost for this group, would be $3956.22, or $356.42 per year of life added.

Based on national average data, total costs for the PJS, HP, *p16-Leiden,* and FPC populations would be $105,000.00. Cost per year of life would be $2542.37, $3763.44, $4545.45, and $4545.45, respectively. Total cost for the new-onset diabetes risk group would be $15,750.00, with a cost of $1418.92 per year of life added.

Discussion

PC is a rapidly fatal disease, with a 5-year survival rate of only 6%.[17] This outlines the need for a screening program to detect lesions at a resectable stage, which offers the only hope for survival. A complete discussion of a screening protocol should not only include efficacy of the screening modality, but should also include likelihood of compliance, which invariably relates to cost. Discussions of screening protocols for PC have not included this aspect in great detail, particularly in regard to costs under the ACA. This study aims to not only estimate the total costs of a PC screening program, but also discuss the direct costs to individuals, which will possibly be the greatest determinant of compliance.

Several imaging techniques have been studied for efficacy in PC screening, including CT, EUS, and MRI/MRCP. We chose MRI/MRCP as the preferred imaging tool for a PC screening protocol, based on its proven efficacy and its relative low cost. Five studies have examined the efficacy of MRI/MRCP as a screening tool for PC (Table 5).[5,18–21] Each study used either MRI, MRCP, or both as a screening technique, and each had subject criteria based on genetic risk factors for PC. The most comprehensive of these was conducted by Al-Sukhni et al., which included the largest sample size (262), the greatest reported mean length of follow-up (4.2 years), and the most comprehensive criteria for screening based on elevated risk, as opposed to one or two known PC risk factors (mean risk = 18-fold).[18] Subjects underwent a non-contrasted MRI with MRCP every 12 months. Upon abnormal findings, contrasted MRI, EUS, multiphase contrast-enhanced CT scans, and/or ERCP were conducted as follow-up within 3–6 months. This study yielded 3 findings of adenocarcinoma, 15 BD-IPMNs, 2 PanIN 1–2 lesions, 22 main duct dilations, 65 simple pancreatic cysts, 1 neuroendocrine tumor, and 7 extrapancreatic neoplasms. All 3 of the adenocarcinomas were discovered on follow-up imaging, 2 of which had initial findings of main duct dilation with increasing diameter on follow-up imaging that ultimately led to adenocarcinoma. This underscores the aggressive nature of the disease and the need for frequent follow-up. As such we have suggested a 6-month screening interval for our protocol, with a 3-month maximum follow-up upon abnormal findings. Immediate follow-up with definitive diagnostic evaluation is suggested if progressive abnormalities are found, with surgery performed only when indicated.

MRI/MRCP, in addition to proven efficacy, has a relatively low cost. While CT is actually the least expensive imaging modality, it is not an ideal tool due to repeated radiation exposure and an inability to detect small resectable precursor or early stage lesions.[5,13,21] Likewise, EUS was not chosen as the ideal tool, as the need for sedation and recovery time make costs widely variable. Additionally, EUS is operator-dependent, leading to great inter-observer variability and a potential for misdiagnosis and complications.[13] This is especially true in non-academic centers, where EUS-trained physicians are scarce. MRI/MRCP represents the best tool for PC screening because of its ability to detect small lesions, its low complication rate, and its general acceptance amongst patients.[19–21]

Based on MRI/MRCP pricing data, the least expensive screening program would be in those with new-onset diabetes over the age of 50 with a history of smoking or recent weight loss. This group represents those with the greatest risk of developing idiopathic PC, which makes up 90–95% of PC diagnosis. There is evidence that up to 64% of those with idiopathic PC present with new-onset diabetes up to 36 months before traditional PC symptoms present. Screening in this group would not only be the least expensive, at the individual level, it would also have the ability to capture a large percentage of those with resectable, early stage PC.[4]

While total costs of a screening protocol deserve great consideration, cost to the individual is also of importance, as it has a direct correlation to patient compliance. Under the ACA, insurance companies are required to provide complete coverage, also known as first-dollar coverage, for preventive services receiving an A or B rating by the USPSTF.[3] Asymptomatic screening for PC currently has a D rating, leaving the patient with some or all of the cost.

This cost-sharing will decrease the use of any screening protocol aimed at PC prevention.[22,23] Since a major goal of the ACA is to increase the use of preventive services, the USPSTF must update its PC screening guidelines to reflect recent knowledge and advances in risk stratification and PC screening.

USPSTF guidelines for PC were last updated in 2004 and state that there is no evidence that screening for PC reduces mortality. They conclude that the harms of PC screening outweigh the benefits due to the low prevalence of PC, the low accuracy and invasive nature of screening and diagnostic tests, and the low efficacy of treatment. Additionally, the statement acknowledges those with HP as the only group with an increased risk for PC.[2]

These statements do not reflect current knowledge. Recently, the International Cancer of the Pancreas Screening Consortium described that the overall goal of any PC screening program is ultimately to reduce PC mortality. However, the low prevalence of PC makes it difficult to conduct the large, randomized, controlled trials necessary to prove that PC screening accomplishes this goal. Therefore, surrogate definitions of success have been established for PC screening in the place of reduced PC mortality and are defined as the ability to resect early invasive cancer and high-grade precursor neoplasms (IPMN with high-grade dysplasia, multifocal PanIN-3 lesions). This is because it is known and accepted that early detection and resection of lesions offers the *only* potential for reduced PC morality.[13]

Screening with MRI in several high-risk groups has proven efficacy at detecting such lesions, as evidenced by the 5 studies reviewed in this article.[5,18–21] Additionally, MRI is noninvasive and safe, particularly for the frequent screening that is required in those at high-risk for PC. While treatment outcomes for PC do remain poor, this further emphasizes the need for PC screening, as it offers the only hope of detecting precursor lesions and small tumors at a resectable stage.

Finally, the USPSTF's statement on high-risk groups is outdated. Several groups, including those with HP, *p16-Leiden* mutations, PJS, FPC, and new-onset diabetes over age 50 with a history of smoking or weight loss represent known groups with a high risk for PC (8-fold to 132-fold risk).[4] When compared to the levels of risk that warrant screening for other types of cancer, screening in these groups should certainly be warranted, as well (breast cancer screening for women over age 40 –12.29% risk; colon cancer screening beginning age 50 – 4.82% risk).[17]

The USPSTF uses scientific evidence as its only tool in forming recommendations. Traditionally, these findings have been used as a scientific guide toward decision-making in an evidence-based medical system, which is not dictated solely by clinical trials and science.[24,25] In the past, the USPSTF has used a "firewall" argument, asserting that its guidelines should not be used as rigid rules for decision-making in patient care, rather, they should be used in the context of each individual.[24,26] The ACA removes this "firewall," however, in utilizing solely the USPSTF guidelines as those that dictate first-dollar coverage. As such, the USPSTF should recognize the newfound gravity of their recommendations, and at the very least, should work toward a continually updated set of recommendations, with the

most recent evidence dictating current standards in a constantly advancing field. The need for this is evident in the D recommendation given for PC screening.

The limitations of this study include the fact that pricing for diagnostic imaging varies widely, so calculating costs based on Medicare and national average data will yield only estimates of true costs. Additionally, this study calculates cost per year of life added on an individual basis, which assumes that 100% of individuals screened will eventually develop PC. While the inclusion of only those at a very high risk of developing PC attempts to mitigate this factor, it remains that not all individuals screened will go on to develop PC. This limits our ability to calculate cost at the level of the system, such as total cost per year of life added or cost per cure.

However, we recognize that such comprehensive figures are important components of a cost analysis. We do know that screening in the new-onset diabetes group could be quite high, as approximately 1 million people over age 50 are newly diagnosed with diabetes per year.[27] Quick calculations show a total cost of roughly $1.3 billion per year based on Medicare pricing, or $5.25 billion per year based on national average pricing. Cost-benefit analyses become particularly important with such high figures in question. Unfortunately, accurate cost-benefit analyses remain very complicated and rely heavily on factors that are yet unknown, such as true increased survival benefit and cost of follow-up evaluation and treatment for both neoplastic and nonneoplastic lesions. As such, overall cost-benefit analysis is beyond the scope of this study and will need to be determined separately. If cost of screening in the diabetes risk group is found to be beyond acceptable cost standards, once all cost and benefit factors are considered, it is possible further risk stratification within this group could lower costs while still allowing those at the highest risk to undergo screening.

Finally, the mechanism of the development of precursor lesions to malignant neoplasms is not well-understood. This introduces a potential for overtreatment. While further information is needed in this area, sufficient knowledge does exist for physicians to make sound, beneficent treatment decisions once precursor or non-precursor lesions are detected. In other words, it is the belief of this study that sufficient evidence exists to warrant a screening protocol in HRIs, and that the benefits of screening in HRIs, only, does outweigh the risks associated with a screening protocol.

Conclusion

Several studies have proven the efficacy of screening individuals at a high risk for PC using MRI/MRCP. Based on these findings, as well as recent advances in risk stratification, it is now time to adopt a screening protocol for HRIs. This study reveals a relatively low cost of such a screening protocol, particularly in terms of cost per year of life added. The USPSTF affords an A or B rating when evidence shows that the benefits of a preventive service outweigh the harms.[24] Recent knowledge should lead the USPSTF to conclude that the benefits (detection of precursor lesions or early stage resectable PC) of screening HRIs for PC using MRI/MRCP outweigh the harms (risk of overtreatment). As such, PC screening in HRIs should now meet the requirement for an A or B rating, allowing those at the highest risk to access the preventive services they require. This will ensure that a relatively low-cost

screening program will be no-cost to the individual, leading to greater compliance and greater ability to catch early stage PC.

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Highlights

- A pancreatic cancer screening protocol is needed to catch resectable disease.
- A screening protocol was chosen for high-risk groups using MRI.
- Medicare and national average pricing were used for cost analysis.
- Screening is affordable and should be initiated in high-risk populations.
- USPSTF must rethink ratings to make screening affordable for individuals.

Summary

Pancreatic cancer is the 4th leading cause of cancer death in the U.S. A screening protocol is needed to catch early stage, resectable disease. A screening program using MRI/MRCP is affordable in high-risk populations. The U.S. Preventive Services Task Force must reevaluate its pancreatic cancer screening guidelines to make screening more cost-effective for the individual.

Table 1

Screening protocol parameters based on risk factor

Risk Factor	Increased Risk	Mean age at PC dx	Age at which screening should begin	Total years of screening
Peutz-Jehgers Syndrome	132x	40.8	30	20
Hereditary Pancreatitis	87x	54.2	45	20
p16-Leiden mutation	48x	59	50	20
Familial PC (>2 first-degree relatives with PC)	32x	NA	50, or 10 years before youngest PC dx in blood relative	20
New-onset diabetes > age 50, with hx weight loss or smoking	8x	71[a]	Time of diabetes dx	3

[a]SEER median age of PC diagnosis in general population

PC pancreatic cancer, hx history, dx diagnosis

Table 2

Diagnostic imaging costs

Procedure	CPT Code	National Average Medicare Physician Fee (Professional + Technical Fee) (Facility/Non-Facility Price)(Range)	National Average Cost (Range)	Norton Out-of-Pocket Fee (Professional + Technical Fee)
MRI Abdomen (with and without contrast)	74183	$587.92 ($421.47 – $773.69)	**$2625.00** ($1600.00 – $6600.00)	$3869.00
MRCP	76376	$60.22 ($42.73 – $79.37)	NA	$500.00
	76377	$82.68 ($63.98 – $103.26)	NA	$1074.00
Average MRCP Cost		$71.45	NA	$787.00
MRI + MRCP		**$659.37**	NA	**$4656.00**
CT Abdomen (with and without contrast)	74170	**$325.60** ($234.78 – $426.51)	**$2175.00** ($1600.00 – $8200.00)	**$3394.00**
Endoscopic Ultrasound (EUS)	43259	$307.23 ($254.21 – $393.91)	NA	$3900.00
with 1 hour anesthesia	00740	**$601.23**	NA	**$5370.00**
with 1 hour anesthesia + CRNA	00740	NA	NA	$6840.00

Table 3

CDC/SEER population and pancreatic cancer statistics

	Both	Males	Females
Median age at PC dx	71	69	74
Median age at PC death	73	70	75
Life expectancy at birth	78.7	76.2	81
Life expectancy at 65	84.1	82.7	85.3

PC pancreatic cancer, dx diagnosis

Table 4

Cost analysis of pancreatic cancer screening protocol

	Based on Medicare Costs for MRI Abdomen + MRCP			Based on National Average Cost for MRI Abdomen		
	Both	**Males**	**Females**	**Both**	**Males**	**Females**
Annual Cost of MRI/MRCP, 2x/yr	$1,318.74	$1,318.74	$1,318.74	$5,250.00	$5,250.00	$5,250.00
Peutz-Jehgers Syndrome - Begin Screening at 30						
Total cost of screening (20 years)	$26,374.80	$26,374.80	$26,374.80	$105,000.00	$105,000.00	$105,000.00
Potential years of life added	41.3	39.9	42.5	41.3	39.9	42.5
Cost per Year of Life Added (Based on LE at 65)	**$638.62**	**$661.02**	**$620.58**	**$2,542.37**	**$2,631.58**	**$2,470.59**
Hereditary Pancreatitis - Begin Screening at 45						
Total cost of screening (20 years)	$26,374.80	$26,374.80	$26,374.80	$105,000.00	$105,000.00	$105,000.00
Potential years of life added	27.9	26.5	29.1	27.9	26.5	29.1
Cost per Year of Life Added (Based on LE at 65)	**$945.33**	**$995.28**	**$906.35**	**$3,763.44**	**$3,962.26**	**$3,608.25**
Familial PC,*p-16 Leiden carriers*- Begin Screening at 50						
Total cost of screening (20 years)	$26,374.80	$26,374.80	$26,374.80	$105,000.00	$105,000.00	$105,000.00
Potential years of life added	23.1	21.7	24.3	23.1	21.7	24.3
Cost per Year of Life Added (Based on LE at 65)	**$1,141.77**	**$1,215.43**	**$1,085.38**	**$4,545.45**	**$4,838.71**	**$4,320.99**
New-onset diabetes over age 50, with weight loss or smoking history - Screen for 3 years after diabetes dx						
Total cost of screening (3 years)	$3,956.22	$3,956.22	$3,956.22	$15,750.00	$15,750.00	$15,750.00
Potential years of life added	11.1	12.7	10.3	11.1	12.7	10.3
Cost per Year of Life Added (Based on LE at 65)	**$356.42**	**$311.51**	**$384.10**	**$1,418.92**	**$1,240.16**	**$1,529.13**

Table 5

Review of previous studies examining MRI/MRCP

Study	Imaging	n	Subject Criteria	Findings
Al-Sukhni 2012[18]	MRI/MRCP (without contrast)	262	FDR or SDR of a PC patient in a FPC family, FDR of individuals with PC + other primary cancers, p16, STK11, or BRCA mutation carriers, or PJS or Hereditary Pancreatitis patients	3 adenocarcinomas, 15 BD-IPMNs, 2 PanIN 1–2 lesions, 22 main duct dilations, 1 neuorendocrine tumor, 7 extrapancreatic lesions
Ludwig 2011[19]	MRCP	109 (98 had MRCP)	1+ FDR with PC before age 50 years, 2+ relatives with PC (one of whom is a FDR), 3+ SDR with PC, or BRCA mutation carrier with 1+ relatives with PC	1 adenocarcinoma, 3 MD-IPMNs, 2 BD-IPMNs, 1 PanIN2, 1 PanIN3, 1 SCA w/PanIN1 cells
Vasen 2011[20]	MRI/MRCP	79	p16-Leiden mutation carriers	7 adenocarcinomas, 9 duct ectasias
Verna 2010[21]	EUS and/or MRI/MRCP + Ca19-9/OGTT	23 (# HRIs who got MRI/MRCP)	≥3 FDR, SDR, or third-degree relatives with PC, ≥2 FDRs with PC, 1 FDR and 1 SDR with PC with 1 at <55 years old, or Genetic syndrome with PC	2 adenocarcinomas, 1 ‘other cyst,’1 ‘isolated PD irregularity, at least 1 extrapancreatic neoplasm
Canto 2012[5]	MRI/MRCP	216	PJS patients, FBOC patients with ≥1 affected FDR or SDR with PC, or Relatives of patients with FPC with ≥1 affected FDR	1 solid mass, 72 cystic masses, 5 main duct dilations, 29 branch duct dilations

[a]Data in this table are taken from the screening of high-risk pts with MRI/MRCP, not the entire study

FDR first-degree relative, SDR second-degree relative, PC pancreatic cancer, FPC familial pancreatic cancer, PJS Peutz-Jehgers Syndrome, BD-IPMNs branch duct intraductal papillary mucinous neoplasms, Pan-IN pancreatic intraepithelial, MD-IPMNs main duct intraductal papillary mucinous neoplasms, SCA Serous cystadenoma, OGTT Oral glucose tolerance test, HRIs high-risk individuals, PD pancreatic duct, FBOC Familial breast and ovarian cancer