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Pancreas Cancer Prevention: Can We Make a Difference?

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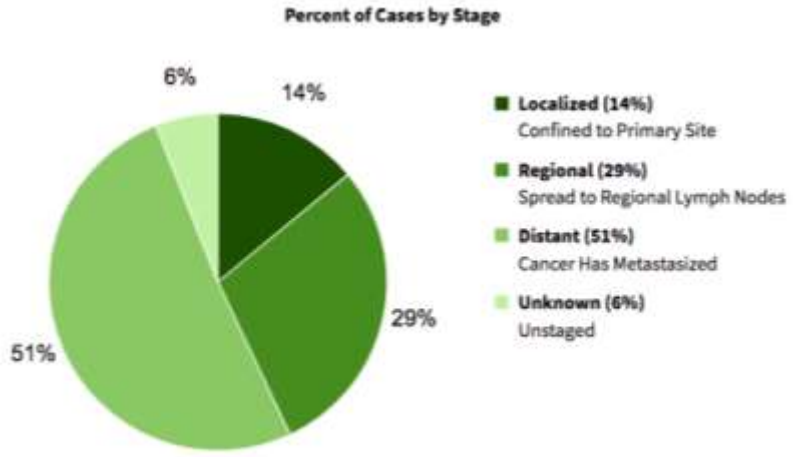
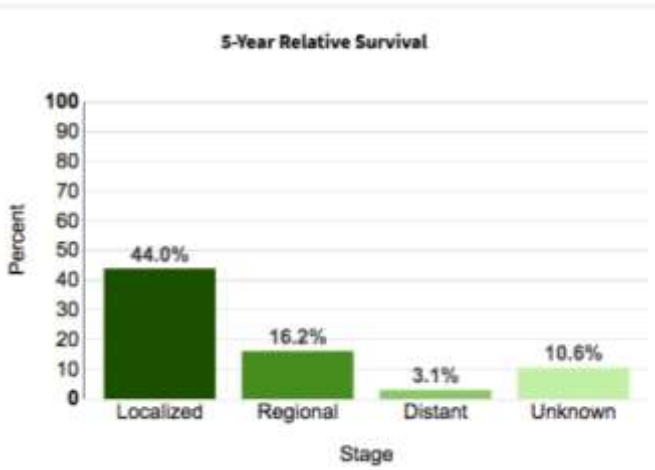
No relevant disclosures

Epidemiology of Pancreatic Cancer

- Age-adjusted rate of new cases: 13.5 per 100,000 persons per year
- Median age diagnosis 70
- Lifetime risk of developing PC: 1.7%
- 5 year survival 12.8% (data 2014-2020, up from 6.0% 2003-2009)





SEER 22, 2017-2021

Risk Factors for Pancreatic Cancer

Non-Inherited

- Non-modifiable
  - Age
  - Gender
  - Ethnicity
- Modifiable
  - Tobacco
  - Alcohol
  - Diabetes
  - Obesity
  - Chronic pancreatitis
  - Physical inactivity
  - Helicobacter pylori
  - Occupational exposures
  - Periodontal disease

Inherited

- Hereditary pancreatitis
- Inherited cancer syndromes
  - Breast and ovarian cancer
  - Peutz-Jeghers
  - FAMMM syndrome
  - Lynch syndrome
  - Familial pancreatic cancer
- Non-O blood group

Tobacco

- RR at least 1.5-2
- Increase with amount of cigarettes consumed
- Decreases with smoking cessation
  - After 10-20 years, risk returns to level of non-smokers
- Risk may exist with smokeless tobacco as well

- Estimated that 25% pancreatic cancer deaths in US are attributable to tobacco

Fuchs 1996; Bosetti 2012

Alcohol

- No significant correlation with mild to moderate alcohol use
- Dose dependent
- Heavy alcohol use
  - >6 drinks/day – OR 1.5
  - >3 drinks/day – OR 1.2
- Heavy liquor increases risk compared to beer or wine
- Binge drinking pattern increases risk

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Wang 2016, Midha 2016, Gupta 2010

Diabetes

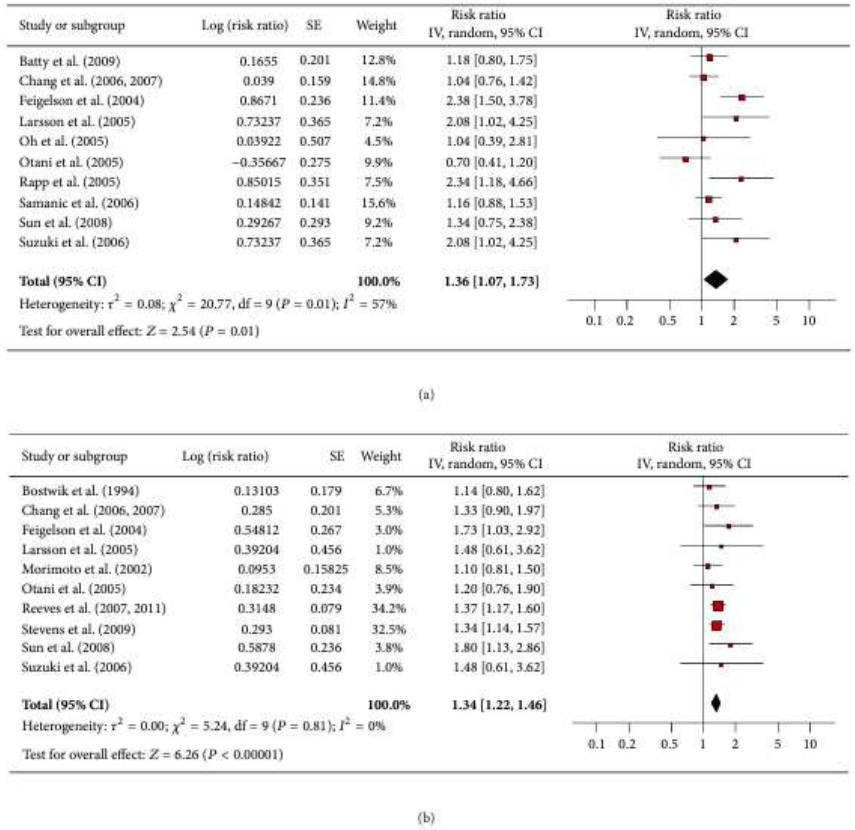
- Pooled OR ~2

- Cause or effect?
  - Case control study in PC showed DM more prevalent in cases than controls (47 vs 7%) and more likely diagnosed in past 2 years (74 vs 53%)
  - But studies following pts prospectively also showed increased PC in pts with DM than in those without

Pannala 2008; Gapstur 2000; Stolzenberg-Solomon 2005

Obesity

- RR 1.3 for both men and women
  - meta-analysis 9-10 studies
- Increases with BMI
  - BMI 25-30: 13% increased risk PC
  - BMI 30-35: 19% increased risk PC
  - In women, waist circumference significantly associated with increased risk PC



Study or subgroup	Log (risk ratio)	SE	Weight	Risk ratio IV, random, 95% CI
Batty et al. (2009)	0.1655	0.201	12.8%	1.18 [0.80, 1.75]
Chang et al. (2006, 2007)	0.039	0.159	14.8%	1.04 [0.76, 1.42]
Feigelson et al. (2004)	0.8671	0.236	11.4%	2.38 [1.50, 3.78]
Larsson et al. (2005)	0.73237	0.365	7.2%	2.08 [1.02, 4.25]
Oh et al. (2005)	0.03922	0.507	4.5%	1.04 [0.39, 2.81]
Otani et al. (2005)	−0.35667	0.275	9.9%	0.70 [0.41, 1.20]
Rapp et al. (2005)	0.85015	0.351	7.5%	2.34 [1.18, 4.66]
Samanic et al. (2006)	0.14842	0.141	15.6%	1.16 [0.88, 1.53]
Sun et al. (2008)	0.29267	0.293	9.2%	1.34 [0.75, 2.38]
Suzuki et al. (2006)	0.73237	0.365	7.2%	2.08 [1.02, 4.25]
Total (95% CI)			**100.0%**	**1.36 [1.07, 1.73]**

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 20.77$, df = 9 ($P = 0.01$); $I^2 = 57\%$

Test for overall effect: $Z = 2.54$ ($P = 0.01$)

Risk ratio IV, random, 95% CI

0.1 0.2 0.5 1 2 5 10

(a)

Study or subgroup	Log (risk ratio)	SE	Weight	Risk ratio IV, random, 95% CI
Bostwik et al. (1994)	0.13103	0.179	6.7%	1.14 [0.80, 1.62]
Chang et al. (2006, 2007)	0.285	0.201	5.3%	1.33 [0.90, 1.97]
Feigelson et al. (2004)	0.54812	0.267	3.0%	1.73 [1.03, 2.92]
Larsson et al. (2005)	0.39204	0.456	1.0%	1.48 [0.61, 3.62]
Morimoto et al. (2002)	0.0953	0.15825	8.5%	1.10 [0.81, 1.50]
Otani et al. (2005)	0.18232	0.234	3.9%	1.20 [0.76, 1.90]
Reeves et al. (2007, 2011)	0.3148	0.079	34.2%	1.37 [1.17, 1.60]
Stevens et al. (2009)	0.293	0.081	32.5%	1.34 [1.14, 1.57]
Sun et al. (2008)	0.5878	0.236	3.8%	1.80 [1.13, 2.86]
Suzuki et al. (2006)	0.39204	0.456	1.0%	1.48 [0.61, 3.62]
Total (95% CI)			**100.0%**	**1.34 [1.22, 1.46]**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.24$, df = 9 ($P = 0.81$); $I^2 = 0\%$

Test for overall effect: $Z = 6.26$ ($P < 0.00001$)

Risk ratio IV, random, 95% CI

0.1 0.2 0.5 1 2 5 10

(b)

Figure 10: (a) Obesity and pancreatic cancer in men. (b) Obesity and pancreatic cancer in women.

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Dobbins 2013, Arslan 2010

Protective Factors

- Statin
  - Case control study
    - Ever use statin reduced risk OR 0.66
      - In men OR 0.5
    - >10 year use statin OR 0.51

- ASA
  - Meta-analysis - OR 0.77
  - Systematic review of 12 observational studies – OR 0.82

Walker 2015, Zhang 2015, Sun 2019

Inherited Risk Factors

- 5-10% of patients with pancreatic cancer have a first degree relative (FDR) with PC
- Risk for PC increased with family history of PC
- Risk may be higher in those with family history of young-onset PC (less than age 50)

Inherited Risk Factors

Table 1. Risk for Pancreatic Cancer Related to Genetic Mutation

Genes	Common name	Risk of pancreatic cancer
STK11/LKB1	Peutz–Jeghers syndrome	RR, 132 (95% CI, 44–261)
PRSS1	Hereditary pancreatitis	SIR, 53 (95% CI, 23–105)
CDKN2A	Familial atypical multiple mole/melanoma syndrome	RR, 13–39
MLH1, MSH2, MSH6	Lynch syndrome	RR, 8.6–11
TP53	Li-Fraumeni syndrome	RR, 7.3 (95% CI, 2–19)
ATM	NA	RR, 3.92 (95% CI, 0.44–14.2)
BRCA1	Hereditary breast and ovarian cancer	RR, 2.26 (95% CI, 1.26–4.06)
BRCA2, PALB2		RR, 3.5–6.2 (95% CI 1.87–6.58)
Familial pancreas cancer in 1 or 2 first-degree relatives	Familial pancreas cancer	RR, 4–9.3

From Davee et al,[9] adapted with permission.
NA, not applicable; RR, relative risk; SIR, standardized incidence ratio.

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Aslanian 2020

Hereditary Pancreatitis

- estimated lifetime risk of PC of 40%

- autosomal dominant
- recurrent attacks acute pancreatitis, beginning in childhood, develop chronic pancreatitis at a young age
- hereditary pancreatitis associated with mutations in *PRSS1*:
  - cationic trypsinogen gene -> prevent inactivation of trypsin -> pancreatic autodigestion
  - more than 25 different mutations described

- mutations of *PST1/SPINK1*:
  - pancreatic secretory trypsin inhibitor aka serine protease inhibitor Kazal type 1
  - associated with chronic pancreatitis in children, tropical pancreatitis, alcoholic chronic pancreatitis

Lowenfels 1997

Peutz-Jeghers

- STK11

- Pigmented mucocutaneous macules
- Multiple hamartomatous gastrointestinal polyps

- Lifetime risk PC up to 36%

Giardiello 1987; Giardiello 2000

Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)

- CDK2NA
- Characterized by multiple nevi, cutaneous and ocular malignant melanomas, pancreatic cancer

- Variant FAMMM-pancreatic carcinoma syndrome – specific p16 mutation, with risk of PC up to 17%

Lynch Syndrome

- Autosomal dominant mismatch repair gene defect
- MLH1, MSH2, MSH5, PMS2

Table 3. Age-Specific Cumulative Risk of Pancreatic Cancer[a]

Age, y	Cumulative Risk: Population, %[b]	Cumulative Risk: Families With MMR Gene Mutation, % (95% CI)	Hazard Ratio (95% CI)	
20	0	0		
30	0	0.03	30.5 (14.2-65.7)[c]	
40	0.01	0.23		8.6 (4.7-15.7)[e]
50	0.04	1.31 (0.31-2.32)		
60	0.18	1.98	5.1 (2.2-11.8)[d]	
70	0.52	3.68 (1.45-5.88)		

Kastrinos 2009

Hereditary Breast and Ovarian Cancer

- BRCA1
  - 2.3x increased risk
- BRCA2
  - 3.5-5.9x increased risk
  - Found in 12-17% pts with FPC
- PALB2 (partner and localizer of BRCA2)
  - Found in 1-3% pts with FPC
  - Increased risk of breast and pancreatic cancer

- Among Ashkenazi Jews with PC, 2-10% have BRCA mutation, even in absence of FH with typical BRCA-assoc cancers

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Thompson 2002; Hahn 2003; Couch 2007; van Asperen

Familial Pancreatic Cancer

- Multiple 1st and 2nd degree relatives with PC in absence of known genetic susceptibility syndrome
- Usually defined as 2 FDRs
  - ≥ 2 FDRs: 6x risk
  - ≥ 3 FDRs: 32x risk

Klein 2004

Guidelines for Screening High Risk Individuals

- ACG 2015
- CAPS 2019
- AGA 2020
- ASGE 2022
- NCCN 2024

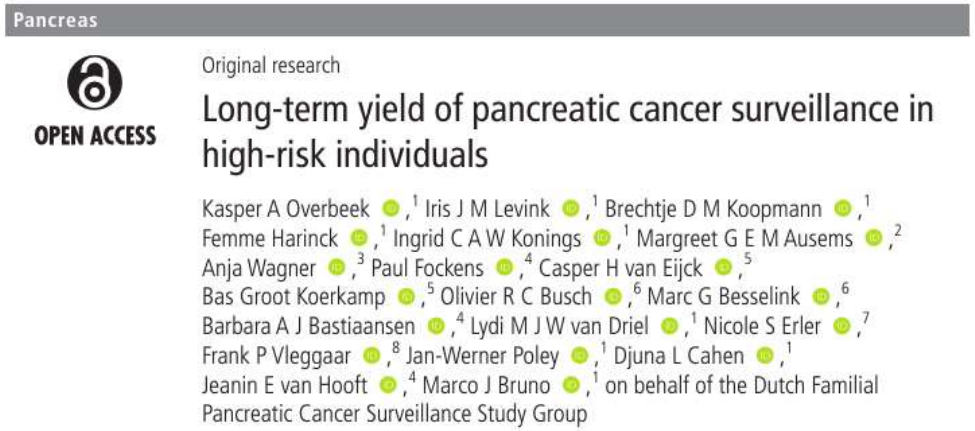
- US Preventive Service Task Force 2019 – recommends against screening for pancreatic cancer in asymptomatic individuals

CAPS 2019

Table 3 Summary of the main recommendations of the 2019 International Cancer of the Pancreas Surveillance (CAPS) Consortium

Who?	
► All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* gene mutation) ► All carriers of a germline *CDKN2A* mutation ► Carriers of a germline *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6* gene mutation with at least one affected first-degree blood relative ► Individuals who have at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)	
When (at what age)?	
► Age to initiate surveillance depends on an individual's gene mutation status and family history	
Familial pancreatic cancer kindred (without a known germline mutation)	Start at age 50 or 55* or 10 years younger than the youngest affected blood relative
Mutation carriers: For *CDKN2A*†, Peutz-Jegher syndrome, start at age 40; *BRCA2*,*ATM*, *PALB2 BRCA1*, *MLH1/MSH2* start at age 45 or 50 or 10 years younger than youngest affected blood relative	
► There is no consensus on the age to end surveillance	
How?	
At baseline	► MRI/MRCP+EUS + fasting blood glucose and/or HbA1c
During follow-up	► Alternate MRI/MRCP and EUS (no consensus if and how to alternate) ► Routinely test fasting blood glucose and/or HbA1c

Outcomes of Screening High Risk Individuals



Pancreas

OPEN ACCESS

Original research

Long-term yield of pancreatic cancer surveillance in high-risk individuals

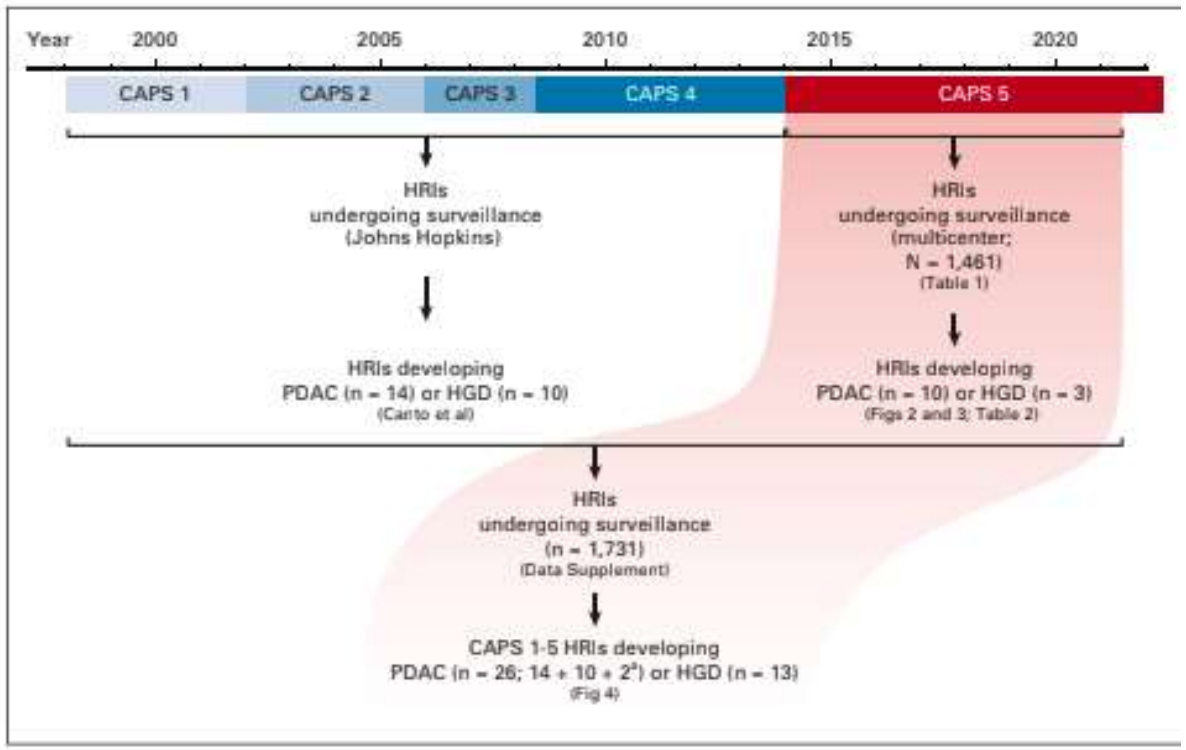
Kasper A Overbeek ,[1] Iris J M Levink ,[1] Brechtje D M Koopmann ,[1] Femme Harinck ,[1] Ingrid C A W Konings ,[1] Margreet G E M Ausems ,[2] Anja Wagner ,[3] Paul Fockens ,[4] Casper H van Eijck ,[5] Bas Groot Koerkamp ,[5] Olivier R C Busch ,[6] Marc G Besselink ,[6] Barbara A J Bastiaansen ,[4] Lydi M J W van Driel ,[1] Nicole S Erler ,[7] Frank P Vleggaar ,[8] Jan-Werner Poley ,[1] Djuna L Cahen ,[1] Jeanin E van Hooft ,[4] Marco J Bruno ,[1] on behalf of the Dutch Familial Pancreatic Cancer Surveillance Study Group

- 366 individuals
  - 201 FPC mutation negative
  - 165 gene mutation carriers
    - 58% CDKN2A
- Average 63 month follow-up
- 10 PDAC
  - 4 presented symptomatic metastatic cancers
  - 50% screening PDAC underwent surgery
  - Survival 18 months
- PDAC incidence
  - 9.3% among gene mutation carriers
  - 0% among FPC

Outcomes of Screening High Risk Individuals

The Multicenter Cancer of Pancreas Screening Study: Impact on Stage and Survival

Mohamad Dbouk, MD[1]; Bryson W. Katona, MD[2]; Randall E. Brand, MD[3]; Amitabh Chak, MD, PhD[4]; Sapna Syngal, MD[5,6]; James J. Farrell, MD[7]; Fay Kastrinos, MD[8]; Elena M. Stoffel, MD[9]; Amanda L. Blackford, MS[10]; Anil K. Rustgi, MD, PhD[7]; Beth Dudley, MS[3]; Linda S. Lee, MD[5,6]; Ankit Chhoda, MD[7]; Richard Kwon, MD[9]; Gregory G. Ginsberg, MD[2]; Alison P. Klein, PhD, MHS[1,10,11,12]; Ihab Kamel, MD[10,13]; Ralph H. Hruban, MD[1,10]; Jin He, MD, PhD[10,14]; Eun Ji Shin, MD, PhD[11]; Anne Marie Lennon, MB, PhD[10,11,13,14]; Marcia Irene Canto, MD, MHS[10,11]; and Michael Goggins, MB, MD[1,10,11]



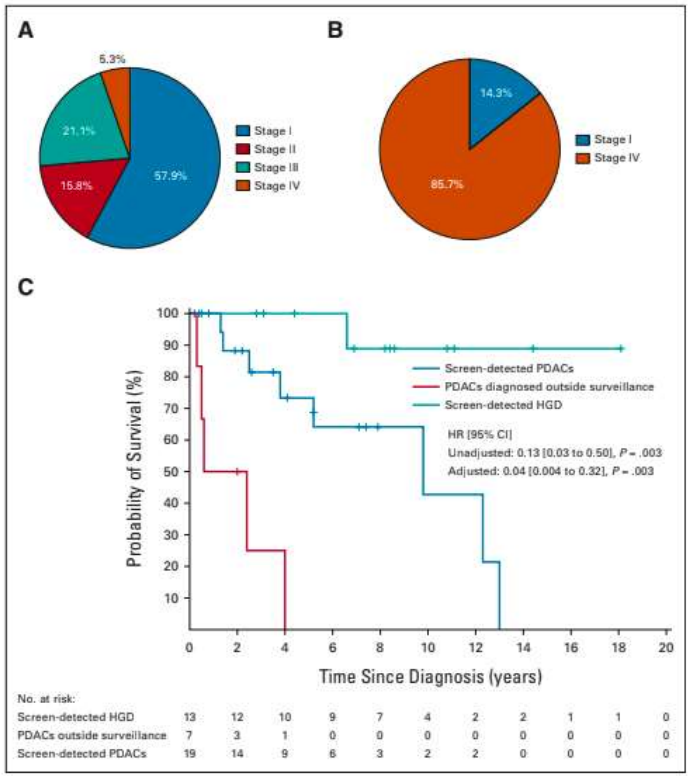


FIG 4. Screen-detected pancreatic cancers in the combined Cancer of Pancreas Screening 1-5 cohorts. (A) Graph showing eighth edition American Joint Committee on Cancer stage distribution of the screen-detected PDACs (n = 19) and (B) PDACs detected outside surveillance (n = 7). (C) Kaplan-Meier curves showing survival of all screen-detected PDACs, PDACs diagnosed outside surveillance, and screen-detected HGD. HGD, high-grade dysplasia; HR, hazard ratio; PDAC, pancreatic ductal adenocarcinoma.

Dbouk 2022

Pancreas Cancer Prevention: Can We Make a Difference?

- All patients
  - Counsel tobacco cessation
  - Advise alcohol in moderation
  - Encourage control of obesity and diabetes
- Take a careful family history for cancer and personal and family history for pancreatitis
  - Refer for genetic counseling and testing if appropriate
  - Refer to a high risk screening program and research protocols if appropriate