

Genetics of Pancreatic Cancer

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Genetics of Pancreatic Cancer



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#2 Cause of Cancer Death by 2020



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Inherited Syndromes Predisposing to Pancreatic Cancer

	Mutation	Relative Risk
Breast cancer	BRCA1, BRCA2, PALB2	2-10 increased
FAMMM	CDKN2A/P16	15-65
Peutz-Jeghers Syndrome	STK11	130
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	8
Hereditary pancreatitis	PRSS1	69
Familial Polyposis	APC	5
Ataxia Telangectasia	ATM	increased

Age of Onset



Incidence of Pancreatic Cancer by Number of Affected First Degree Relatives

10-15% of patients with pancreatic cancer have a familial aggregation or an inherited predisposition

Number of FDRs	Standardized Incidence Ratio	Incidence (per 100,000 in the US Population)
General U.S. (reference)	-	9
1	4.5 x	41
2	6.4 x	58
3 or more	32.0 x	288

Klein AP et al. Cancer Research 2004; 64; 2634-2638

Familial Pancreatic Cancer

- Families with at least two first-degree relatives diagnosed with pancreatic cancer
- 2 or more FDR with pancreatic cancer
- ▶ 1 FDR with pancreas cancer, \leq 50 years old
- 2 or more second degree relatives with pancreatic cancer, one at an early age

Human Cell Formation



Two Kinds of Gene Mutations

- ► Somatic Mutations → Sporadic Cancer
- ► Germ Line Mutations → Inherited Syndrome

Somatic Mutations (Sporadic Disease)



Calvert & Frucht, Ann Int Med, 2002;137:603-613

Germline Mutation (Inherited Disease)



Smoking...

is the major known risk factor for this cancer

- associated with ~ 30% of all cases
- results in accelerated tumor progression
- Smokers have YOUNGER onset
- Dose-dependent

Incidence Ratios for Pancreatic Cancer by Cigarette Smoking Status for Those with At Least One First-Degree Relative (FDR) with Pancreatic Cancer

	Standardized Incidence Ratio (95% Confidence Intervals)
Smokers	19.2 (7.7 – 39.5)
Non Smokers	6.25 (1.70 – 16.0)

Other risk factors...

Risk factor	Increased PDAC risk
Current cigarette use	1.7-2.2
Current pipe or cigar use	1.5
> 3 alcoholic drinks per day	1.2-1.4
Chronic pancreatitis	13.3
BMI > 40 kg/m^2 , male	1.5
BMI > 40 kg/m^2 , female	2.8
Diabetes mellitus, type 1	2.0
Diabetes mellitus, type 2	1.8
Cholecystectomy	1.2
Gastrectomy	1.5
Helicobacter pylori infection	1.4
Becker AE, Hernandez YG, Frucht H, Lucas AL. 2014	15

Can we prevent patients from developing pancreatic cancer?

(Or catch it at a treatable stage?)

Pancreatic Intraepithelial Neoplasia (PanIN)

- Small intraductal lesions formed by abnormal proliferation of ducts
- Pan-IN demonstrate varying degrees of dysplasia
 PanIN-1, PanIN-2, and PanIN-3
- Some pancreatic cancers arise from PanIN, but not all PanIN become cancers
- Unable to visualize clearly on imaging

Maitra et al. Mod Path 2003. Terhune et al. CEBP 1998.

Pancreatic Intraepithelial Neoplasia



Hruban et al. Clinical Cancer Research. 2000.

Mucinous Cystic Neoplasms & Intraductal Papillary Mucinous Neoplasms

Mucinous Cystic Neoplasm (MCN)

- Ovarian stroma, possibly arising from ovarian rests within pancreas
- Invasive carcinoma 6-36%

Intraductal Papillary Mucinous Neoplasm (IPMN)

- Branch duct vs main duct
 - Different risk of malignancy
 - Branch Duct: ~25%
 - Main Duct: ~70%

Tanaka et al. Pancreatology 2006

What about clinical genetic testing for asymptomatic individuals?





Incorporating Genetic Testing for Pancreatic Cancer into Clinical Practice

Three-generation pedigree

- Personal and family history
- Genetic counselors

Limited use previously for pancreatic cancer

Exception: BRCA1/2 gene mutations

Since 2013

- Technology advances
- ▶ \$\$
- Patent issues
- VUS vs pathologic mutation https://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf

- Summary of Consensus Statements for High Risk Individuals – Who to Screen?
- > 3 or more affected blood relatives, with at least one affected FDR
- > 2 affected family members, with at least one affected FDR
- All Peutz-Jeghers
- P16 carriers with one affected FDR
- BRCA2 carriers with one affected FDR
- BRCA2 carriers with 2 affected family members
- PALB2 carriers with 1 affected FDR
- Mismatch repair gene mutations (Lynch syndrome) with one affected FDR

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Summary of Consensus Statements for HRIs – How to Screen?

- Initial screening should include:
 - EUS (87.3%), MRI/MRCP (73.5%), CT (26.5%), abd US (14.3%), ERCP (2%)
- When previous screening did not detect an abnormality that met criteria for shortening of the interval or surgical resection, follow-up screening should include:
 - EUS (79.6%), MRI/MRCP (69.4%), CT (22.4%), abd US (4.1%), ERCP (2%)



Summary of Consensus Statements for HRIs – Targets of Screening?

- Resectable carcinoma is a potential target for early detection and treatment
- Detection and treatment of multifocal PanIN-3 should be considered a success of a screening/surveillance program
- Detection and treatment of IPMNs with high-grade dysplasia should be considered a success of a screening/surveillance program
- Detection and treatment of invasive cancer T1N0M0 should be considered a success of a screening/surveillance program

Canto et al. Gut 2013.

Cancer Screening Definitions

Screening

• Testing healthy, asymptomatic people in the general population

Surveillance

• Testing healthy, asymptomatic people in a high-risk population

Diagnostic Testing

· Testing when people have symptoms

Pancreas Cancer Testing Options

Endoscopic Ultrasound (EUS)

- Requires sedation
- Invasive procedure
- Ability to biopsy abnormalities

Magnetic Resonance Imaging (MRI)

- Non-invasive
- Unable to biopsy
- Patient tolerance

PATIENT PRESENTATION - 1

- Sex: Male
- Age: 61
- Ashkenazi Jewish: Yes
- Cigarette Use: Discontinued (minimal use in past)
- Alcohol Use: Occasional
- Diabetes Mellitus: No
- Pancreatitis: No
- Cancer Hx: None
- Past Medical Hx: None

- Physical Exam
 - Normal
- Laboratory Exam
 - Normal, except CA 19-9





RECOMMENDATIONS

- EUS
- MRI
- Genetic testing

Endoscopic Ultrasound





GENETIC TESTING



SURGICAL INTERVENTION

Total pancreatectomy

PATHOLOGY RESULTS

 Pancreatic adenocarcinoma with adjacent IPMN and multifocal PanIN2



PATIENT CASE #2

PATIENT PRESENTATION - 2

- Sex: Male
- Age: 73
- Ashkenazi Jewish: Yes
- Cigarette Use: 2nd hand smoke
- Alcohol Use: Occasional
- Diabetes Mellitus: Yes
- Pancreatitis: No
- Cancer History: None
- Past Medical History: hypertension, cholesterol, ulcerative colitis

- Physical Exam
 - Normal
- Laboratory Exam
 - Normal



RECOMMENDATIONS

- EUS
- MRI
- Genetic testing

Endoscopic Ultrasound



CEA was 121.47 NG/ML and cytology from the FNA revealed rare atypical glandular cells with dysplastic changes

Magnetic Resonance Imaging



Cystic lesion in the pancreatic neck/body and is oblong shaped, measuring 3.4 x 1.3 x 1.1 cm $^{\scriptscriptstyle \rm 46}$

SURGICAL INTERVENTION

Distal pancreatectomy

PATHOLOGY RESULTS

- Two **intraductal papillary mucinous neoplasms** (IPMNs), predominantly involving branch ducts.
- The IPMN is lined by gastric foveolar type epithelium with up to **severe dysplasia**.
- No invasive carcinoma seen.



PATIENT CASE #3

Patient #3 INITIAL CONSULT

- Sex: Male
- Age: 65
- Ashkenazi Jewish: Yes
- Cigarette Use: Discontinued (smoked for 36 years; 1.5 ppd)
- Alcohol Use: 2-3 vodka/week
- Diabetes Mellitus: Yes (64 years old)
- Pancreatitis: No
- Cancer Hx: None
- Past Medical Hx:
 - GERD (35 years old)
 - Colon polyps (64 years old)
 - Barrett's Esophagus (64 years old)

• Physical Exam Normal

FAMILY HISTORY



RECOMMENDATIONS

- Genetic testing
 - Test sister first



RECOMMENDATIONS

- Laboratories (normal)
- EUS (secretin protocol)
- MRI (secretin protocol)

MRI and EUS = Cystic changes Irregular Ducts







SURGICAL INTERVENTION (Sister)

Prophylactic TAH-BSO

PATHOLOGY RESULTS (Sister)

Ovarian adenocarcinoma

Summary

- Several genetic syndromes contribute to the risk of pancreatic cancer
- Smoking is the largest identifiable and modifiable risk factor
- Pre-cancerous lesions can be identified before the development of pancreatic cancer
- Genetic counseling and testing is an important part of pancreatic cancer screening, prevention and management
- More work is required to understand the genetics of pancreatic cancer

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Thank you for your participation.

If you have questions, please contact Patient Central at (877) 272-6226 or e-mail patientcentral@pancan.org.

www.pancan.org

