



## Genetics of Pancreatic Cancer

March 11, 2015

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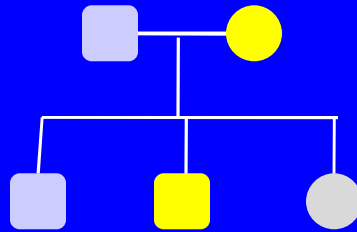
## Inherited Pancreatic Cancer: Causes and Management



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University of Washington

About 10% of patients with PC  
will have a positive family  
history of the disease

## Family history gives clues



## Hopkins Registry of 362 families

- Risk of Pancreatic cancer:  
4% (familial) vs 0.6% (non-familial)
- Risk of Non-pancreatic cancer:  
27% (familial) vs 12% (non-familial)
- breast, colon, lung

## Familial Risk—Break down the 4%

- Dependent on the gene involved
- Not all gene carriers get cancer
- Penetrance of the gene

## Penetrance

- Just because you have a gene mutation—will you really get the disease?
- Low penetrance: probably won't get the disease
- High penetrance: likely to get the disease

## Some families inherit only PC

Some families inherit PC and other cancers as well

## Spectrum of cancers

- Breast—often developing >age 50
- Lung
- Colon
- Gastric
- Osteosarcoma
- Prostate
- Ovarian

## Syndromes with Pancreatic Cancer and Colon Cancer

- Lynch Syndrome
- Familial Adenomatous Polyposis (FAP) 5x

## Syndromes with Pancreatic Cancer and Breast Cancer

- Peutz-Jeghers                      lifetime risk 36%
- BRCA1 & 2                        10x (5%)

## Pancreatic Cancer Plus

- Familial Atypical Mole Melanoma (FAMM) 13-20x (19%)
- Hereditary pancreatitis 53x (40%)
- Cystic Fibrosis 32x (25%)

Probably >80% of Familial Pancreatic Cancer is due to genes yet to be identified

## Environmental/Behavioral Factors

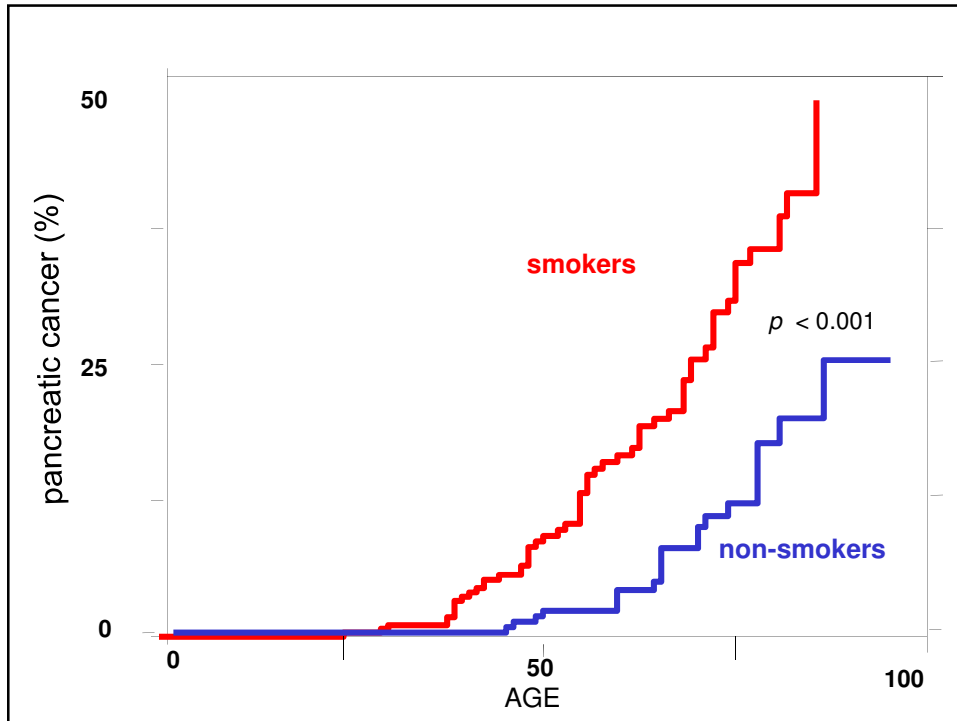
## Gene-Environment Interactions

251 members of 28 families

- Smoking
- diabetes
- gender
- number of affected family members

*Rulyak et al.*





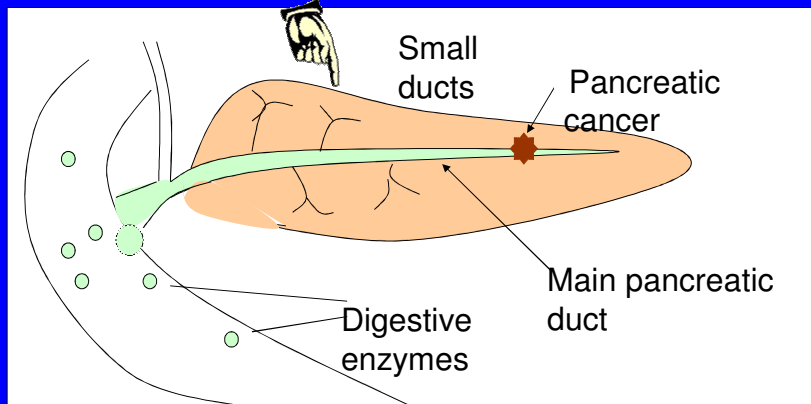
## Occupation

- 3 dry cleaners in 251 family members
- Anticipated 0.5 dry cleaners
- Early data

## SURVEILLANCE

### Why is pancreatic cancer so hard to diagnose?

- Most patients have no symptoms
- The pancreas can not be felt on physical exam
- No good tests to find early cancer and pre-cancer.



Pancreatic cancer forms in the small and mid-size ducts first.

## Surveillance of high risk families

- 2 or more family members with PC; or 1 family member <50
- one first degree relative
- data derived from 100 patients from 75 different families

## Precursors of Pancreatic Cancer

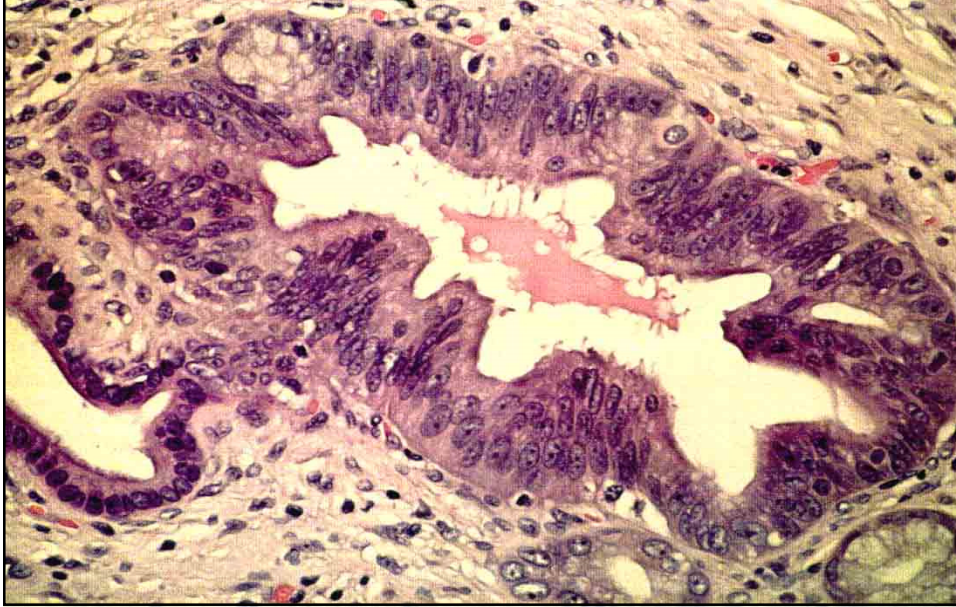
### Precursor lesion to pancreatic cancer

Pancreatic intraductal neoplasia (PanIN)

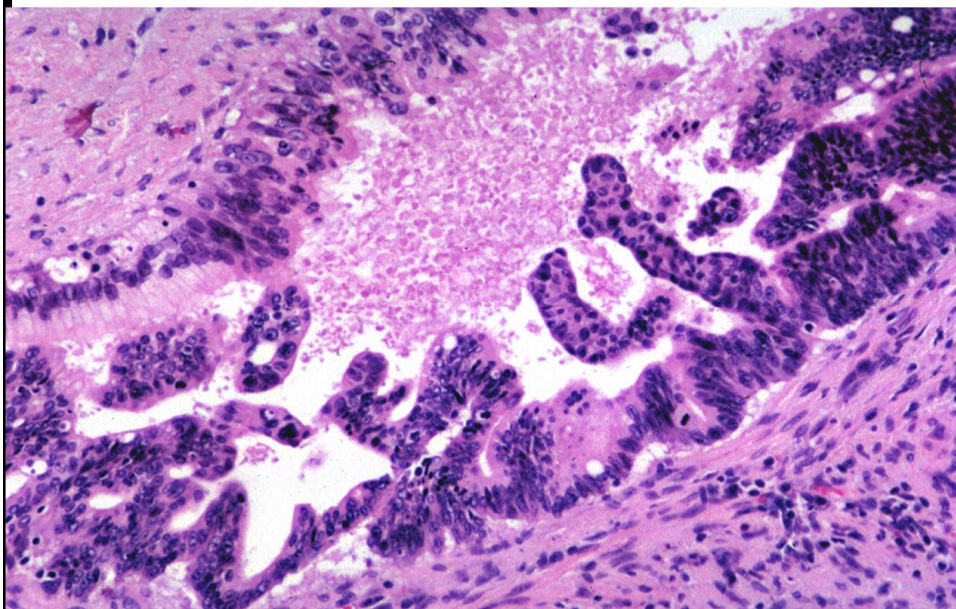
Shares histologic & molecular features of cancer

Not invasive

## Pancreatic Dysplasia: PanIN II



## PanIN III: Carcinoma in-situ



## Management of patients who have positive family history

### Who is at risk?

- 2 or more affected relatives, one of whom is a first degree relative
- one *first degree* relative at *early age* (50's or younger)
- Some individuals with known gene mutations

## Prophylactic Pancreatectomy

Not all gene  
carriers get  
cancer

Morbidity and  
mortality

Decades may  
precede cancer



## The task at hand

Identify patients

....**after** they have started down the  
neoplastic pathway

.....**before** the neoplasia becomes invasive

## Family History

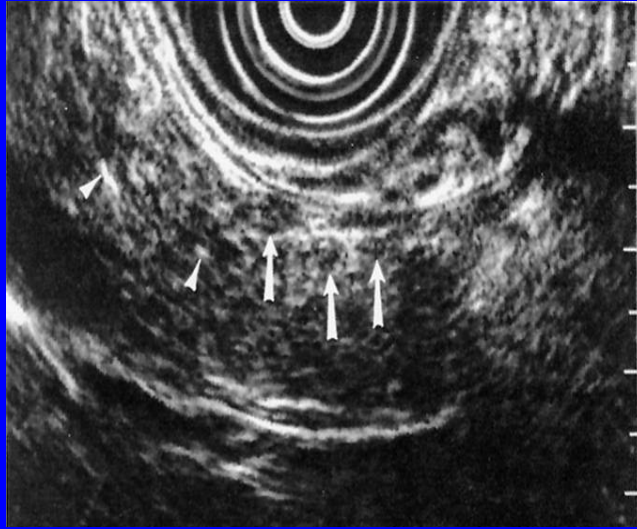
- presenting symptoms
- duration of symptoms
- *ages of affected family members*

## Endoscopic Surveillance

- Endoscopic Ultrasound
- ERCP
- Centers with experience

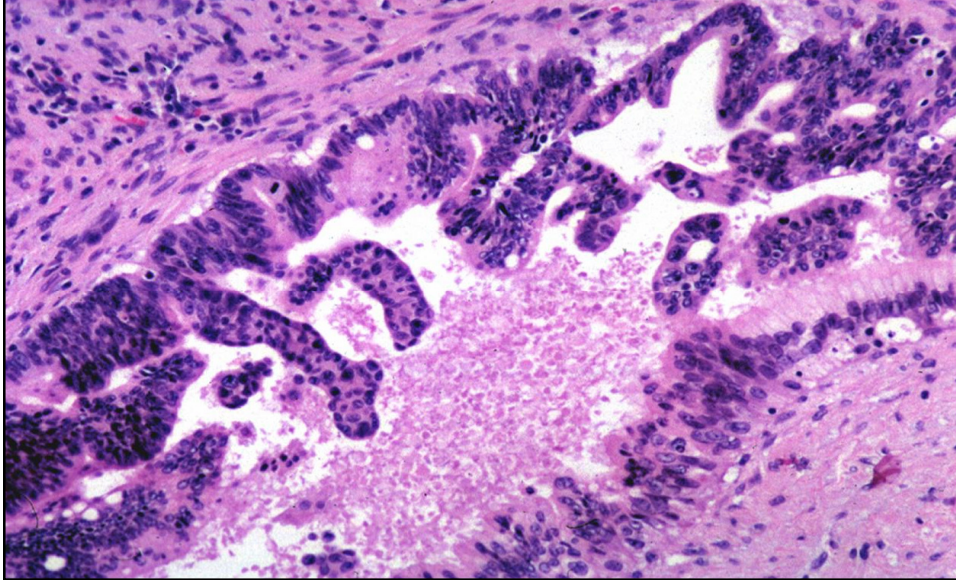


## Endoscopic Ultrasound Findings



If EUS and ERCP are abnormal  
consider getting a piece of the  
pancreas histologic diagnosis

## PanIN III: Carcinoma in-situ

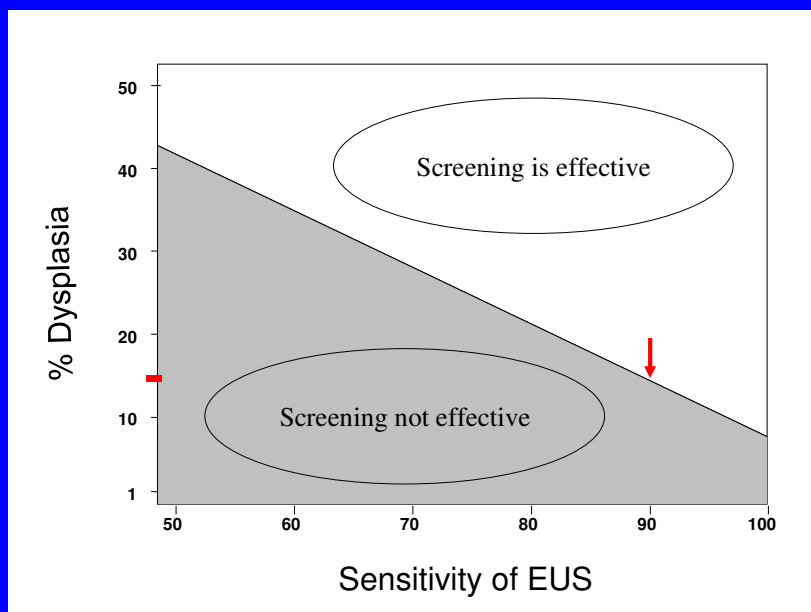


### If Carcinoma in-situ is present

- Discuss risks and benefits of total pancreatectomy
- There is no right or wrong answer
- Patients who have surgery will be diabetics

## Endoscopic Screening: Cost-Effective?

- Cost-effectiveness ratio= \$17,000  
(mammography 22K; pap smear 250K; CRC 6-92k)
- Procedure costs have limited impact
- Screening after age 70 is not cost effective



## Summary

≥10% of PC may be due to genetics

Most FPC is probably from unknown genes

Penetrance plays a key role

Families that inherit PC may get other cancers

## Summary

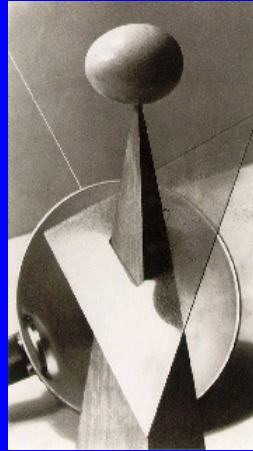
Gene/environment interactions influence penetrance and age at onset

Endoscopic surveillance appears to be promising; more biomarkers are needed

Screening is cost-effective as long as prevalence of dysplasia is 16%

# Familial Pancreatic Cancer

- Mike Saunders
- Irl Hirsch
- Mary Bronner
- Steve Rulyak
- Dave Byrd
- Josephine Maurer
- Mike Kimmey
- Joo Ha Hwang





## Thank you for your participation.

If you have questions, please contact our Patient and Liaison Services  
(PALS) program at  
(877) 272-6226 or e-mail [pals@pancan.org](mailto:pals@pancan.org).

[www.pancan.org](http://www.pancan.org) or [wagehope.org](http://wagehope.org)

