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Pancreatic Cancer

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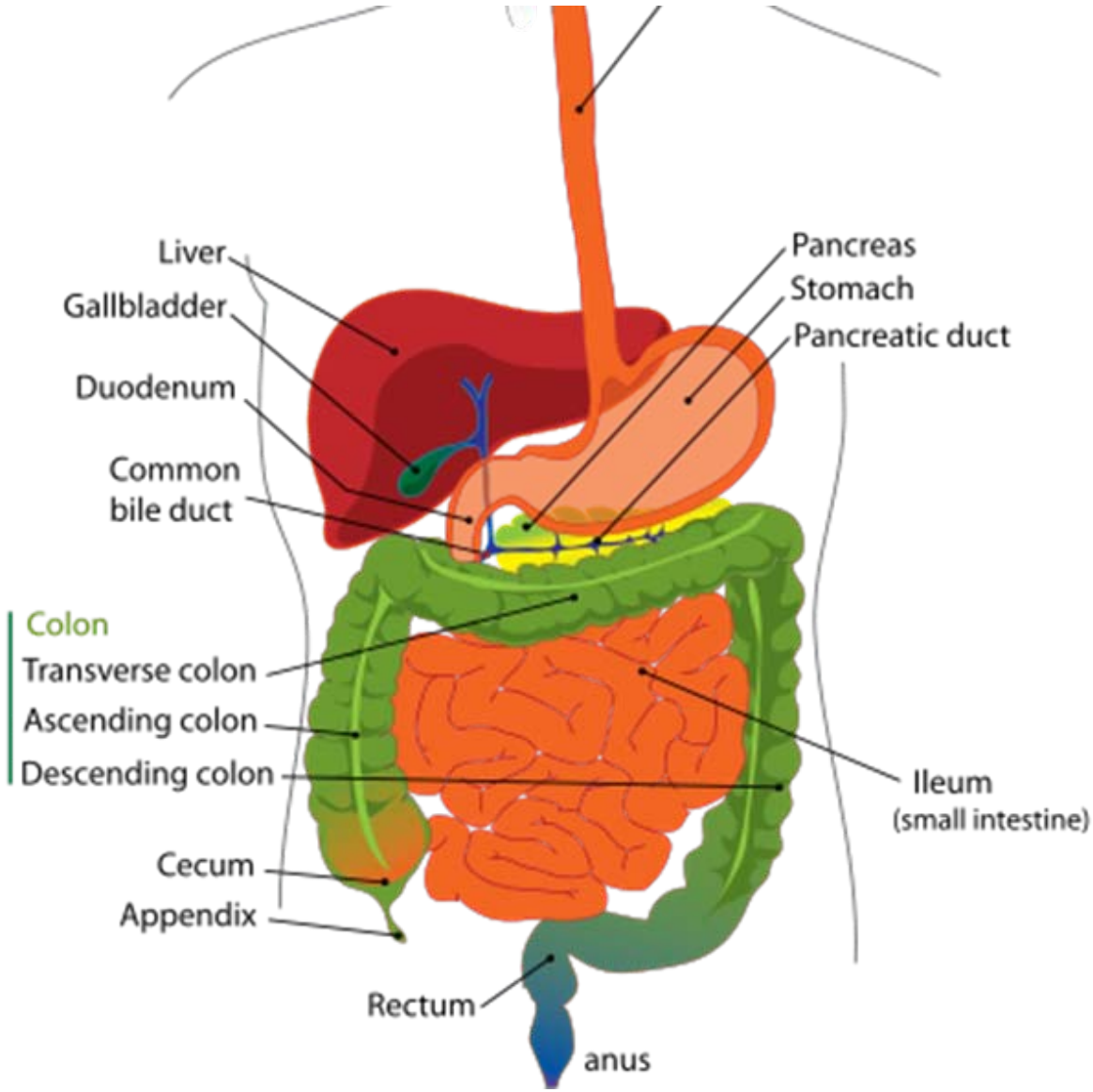
Outline

- What is the pancreas?
- What is pancreatic cancer?
- How do we diagnose pancreatic cancer?
- How do we treat pancreatic cancer?
- What are the known risk factors?
- What is the prognosis?
- How can we beat pancreatic cancer? (precursors, genetics, screening)

What is the Pancreas?



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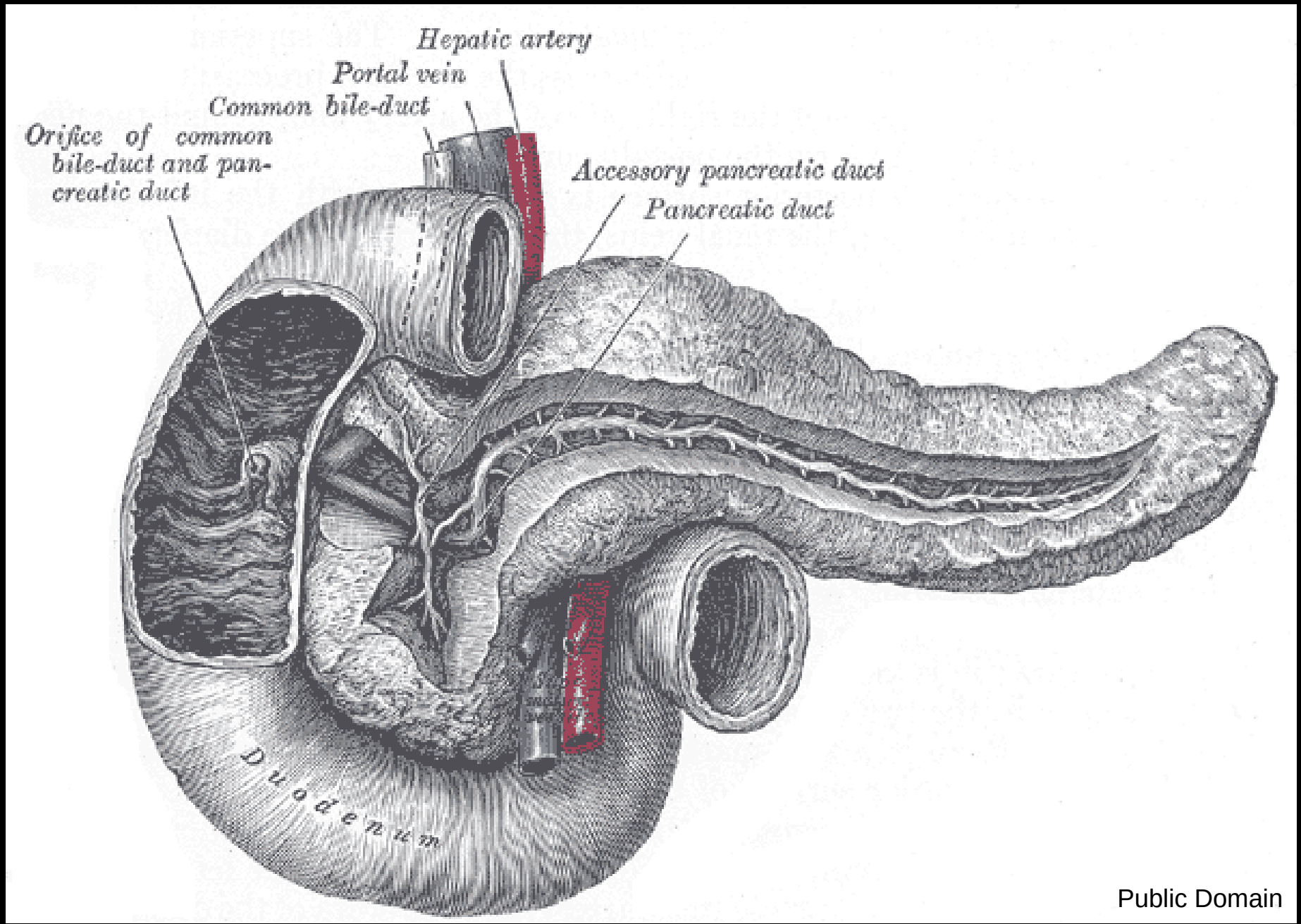

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How do we Diagnose Pancreatic Cancer?

- Computed Tomography
- Endoscopic Retrograde Cholangio Pancreatography
- Endoscopic ultrasound (EUS)
- Biopsy – The gold standard for diagnosis

The Biopsy is the Gold Standard for Diagnosis

- Perineural invasion
- Lymphatic invasion
- Venous invasion

How do we Treat Pancreatic Cancer?

- Pancreatoduodenectomy (Whipple Resection)
- Chemoradiation Therapy
  - 5-Flurouracil
  - Gemcitabine (Gemzar)

What are the Risk Factors for Pancreatic Cancer?

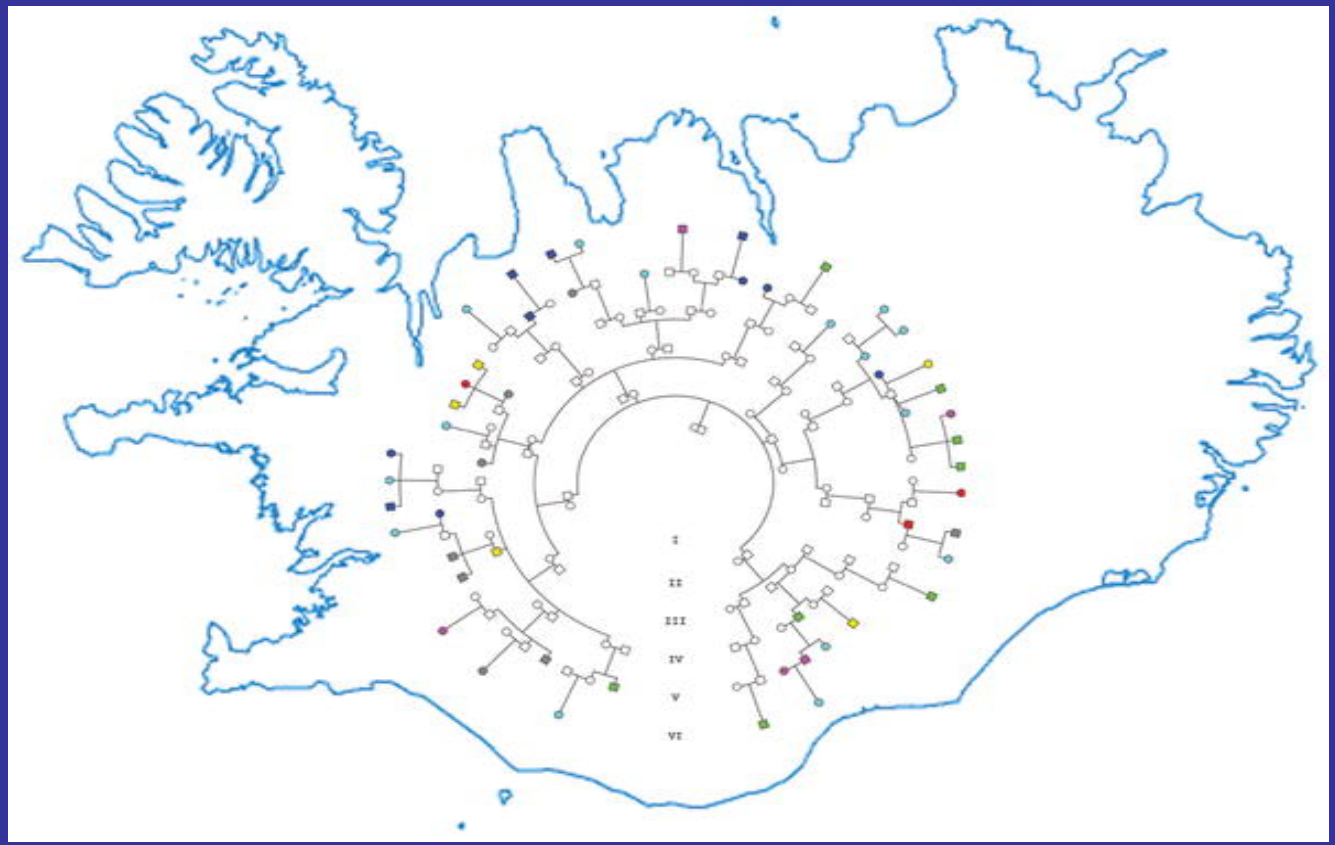
- **Cigarette smoking:** For example, smoking during college has been associated with a 2-3 fold increased risk of pancreatic cancer.
- **Age:** The risk of developing pancreatic cancer increases with age. Over 80% of the cases develop between the ages of 60 and 80.
- **Race:** Studies in the United States have shown that pancreatic cancer is more common in the African-American population than it is in the white population. Some of this increased risk may be due to socioeconomic factors and to cigarette smoking.
- **Gender:** Cancer of the pancreas is more common in men than in women. Men are more likely to smoke than women.

Risk Factors

- Religious Background: Pancreatic cancer is proportionally more common in Jews than the rest of the population. This may be because of a particular inherited mutation in the breast cancer gene (BRCA2) which runs in some Jewish families.
- Chronic pancreatitis: Long-term inflammation of the pancreas (pancreatitis) has been linked to cancer of the pancreas.
- Diabetes: Diabetes is both a symptom of pancreatic cancer, and long-standing adult-onset diabetes also increases the risk of pancreatic cancer.
- Obesity: Obesity significantly increases the risk of pancreatic cancer
- Diet: Diets high in meats, cholesterol fried foods and nitrosamines may increase risk, while diets high in fruits and vegetables reduce risk. Folate may be protective
- Genetics: A number of genetic syndromes increase risk (BRCA2, FAMMM, Peutz-Jeghers) as does a strong family history of pancreatic cancer

Family History

Cancer as a Complex Phenotype: Pattern of Cancer Distribution within and beyond the Nuclear Family



L. Amundadottir et al. Cancer as a Complex Phenotype: Pattern of Cancer Distribution within and beyond the Nuclear Family. PLoS Medicine 2004;1(3):e65

Methods

- Iceland Cancer Registry- All cancer cases diagnosed in Iceland after January 1, 1955
- 95% of the cancers were histologically confirmed
- Genealogic database- (deCODE)- 687,500 individuals
- The names of all 288,000 Icelanders currently alive and a large proportion of all Icelanders who have ever lived

Cancer Site	ICD10	Number Affected	RR [90% Confidence Interval]						Combined p V
			1° Relatives	2° Relatives	3° Relatives	4° Relatives	5° Relatives	Mates	1°–5° Relatives
Breast	C50	3,812	**2.02 [1.88,2.15]**	**1.36 [1.27,1.43]**	**1.21 [1.15,1.25]**	**1.13 [1.08,1.16]**	**1.05 [1.01,1.06]**	2.02 [0.83,5.68]	<**0.00001**[a]
Prostate	C61	3,380	**1.89 [1.75,2.01]**	**1.36 [1.26,1.45]**	**1.19 [1.13,1.24]**	**1.10 [1.05,1.13]**	**1.10 [1.07,1.12]**	na[b]	<**0.00001**[a]
Lung	C34	2,904	**2.00 [1.83,2.16]**	**1.39 [1.26,1.50]**	**1.10 [1.03,1.16]**	1.02 [0.97,1.07]	**1.04 [1.01,1.08]**	**1.68 [1.35,2.06]**	<**0.00001**[a]
Stomach	C16	2,890	**1.90 [1.74,2.05]**	**1.38 [1.25,1.48]**	**1.23 [1.16,1.29]**	**1.15 [1.09,1.19]**	**1.09 [1.04,1.11]**	**1.72 [1.33,2.18]**	<**0.00001**[a]
Colon	C18	2,224	**1.92 [1.71,2.14]**	**1.26 [1.12,1.40]**	**1.16 [1.07,1.24]**	1.05 [0.98,1.10]	**1.06 [1.01,1.09]**	**1.46 [1.03,2.08]**	<**0.00001**[a]
Bladder	C67	1,384	**1.68 [1.39,2.05]**	1.19 [0.98,1.43]	**1.26 [1.13,1.41]**	1.08 [0.99,1.19]	1.03 [0.97,1.10]	0.41 [0.09,1.23]	<**0.00001**[a]
Kidney	C64	1,227	**2.30 [1.89,2.80]**	**1.31 [1.06,1.57]**	**1.32 [1.15,1.48]**	**1.15 [1.03,1.26]**	1.03 [0.95,1.09]	1.20 [0.52,2.30]	<**0.00001**[a]
Thyroid	C73	957	**3.02 [2.33,3.85]**	**1.64 [1.29,2.02]**	**1.30 [1.07,1.51]**	1.08 [0.93,1.21]	1.11 [1.00,1.19]	1.12 [0.23,3.93]	<**0.00001**[a]
Pancreas	C25	930	**2.33 [1.83,2.96]**	1.28 [0.97,1.66]	1.09 [0.90,1.29]	1.06 [0.93,1.21]	0.99 [0.91,1.08]	1.29 [0.53,4.08]	**0.00001**[a]
Ovary	C56	906	**2.01 [1.48,2.70]**	**1.62 [1.27,2.05]**	**1.24 [1.03,1.47]**	**1.18 [1.03,1.33]**	0.92 [0.83,1.01]	na[b]	<**0.00001**[a]
Non-melanoma skin	C44	781	1.46 [0.97,2.07]	0.96 [0.64,1.35]	**1.44 [1.18,1.71]**	1.04 [0.87,1.20]	1.12 [1.00,1.23]	2.16 [0.85,5.73]	**0.00727**
Rectum	C20	767	**1.68 [1.17,2.42]**	**1.63 [1.22,2.15]**	**1.31 [1.08,1.61]**	0.90 [0.76,1.06]	1.00 [0.90,1.12]	1.63 [0.52,4.83]	**0.00051**[a]
Endometrium	C54	753	**1.86 [1.31,2.62]**	1.26 [0.90,1.74]	**1.57 [1.30,1.89]**	1.05 [0.89,1.24]	1.12 [1.00,1.24]	na[b]	<**0.00001**[a]
Cervix uteri	C53	724	**1.74 [1.12,2.73]**	**1.71 [1.24,2.26]**	1.10 [0.86,1.40]	1.16 [0.98,1.36]	0.99 [0.88,1.12]	na[b]	**0.00053**[a]
Brain	C71	663	1.41 [0.74,2.40]	1.10 [0.69,1.62]	0.83 [0.59,1.10]	**1.31 [1.09,1.54]**	0.99 [0.85,1.11]	1.22 [0.20,4.45]	0.16029
Melanoma skin	C43	618	**1.86 [1.06,3.35]**	**1.61 [1.08,2.31]**	1.23 [0.90,1.58]	1.00 [0.78,1.19]	0.92 [0.77,1.04]	1.52 [0.19,4.90]	**0.02082**
Esophagus	C15	535	**2.09 [1.30,3.31]**	**1.62 [1.07,2.38]**	1.04 [0.74,1.41]	1.14 [0.91,1.40]	1.07 [0.92,1.23]	2.40 [0.66,5.94]	**0.0015**[a]

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National Familial Pancreas Tumor Registry at Johns Hopkins

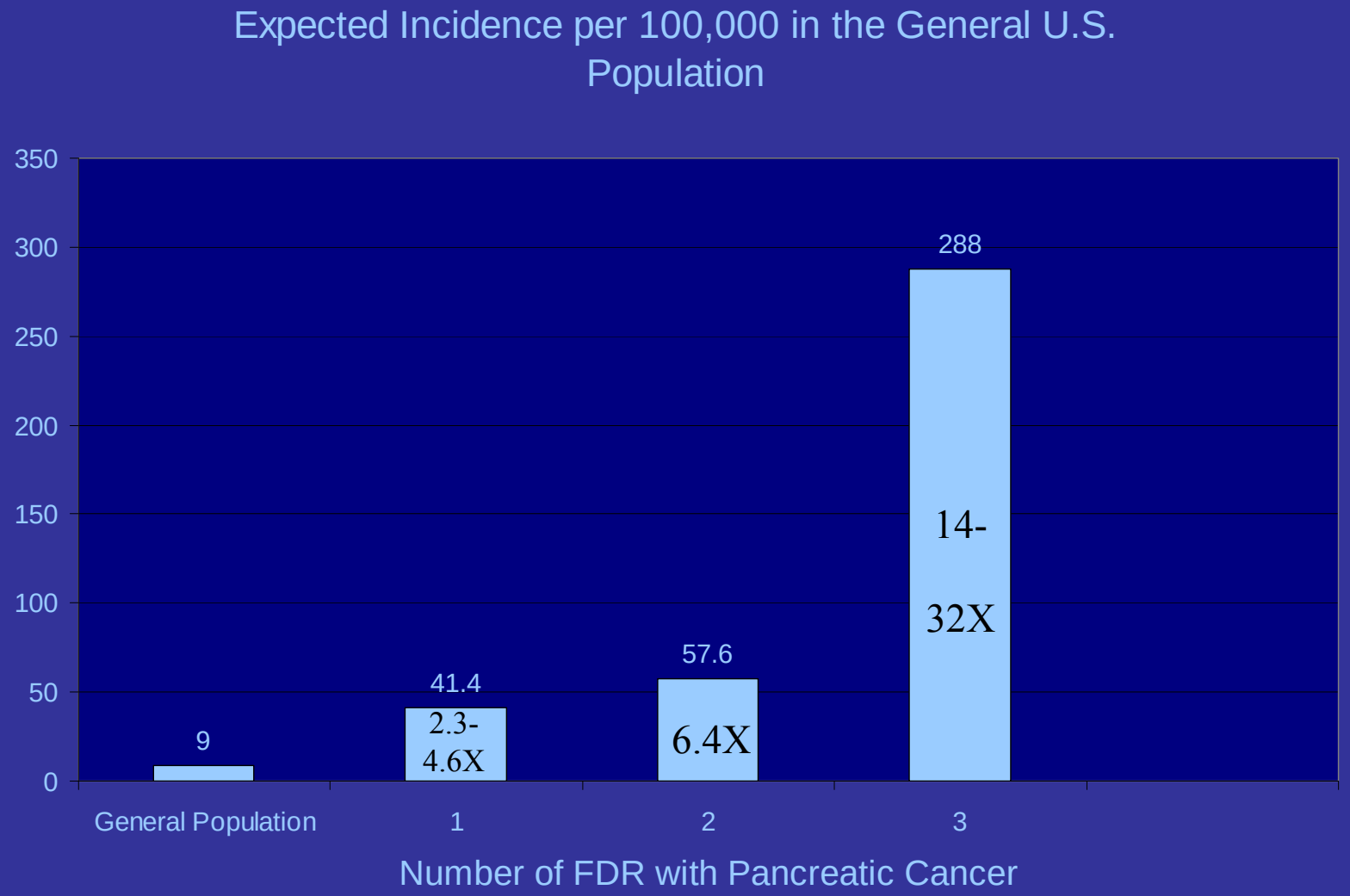
- Established 1994, Alison Klein, Director
- Emily Palmisano and Marian Raben
- 2403 Families enrolled (7/15/2007):
  - 1537 Non-Familial Kindreds
  - 866 Familial Kindreds (>= 2 FDR with PC)

# Affected Members	# of Families
2	565
3	203
4	68
≥5	30

Prospective Pancreatic Cancers

- 56 incident pancreatic cancers have developed in NFPTR kindreds
- 52 in blood relatives, only four in spouses
- 8 of the 56 were resectable, and most of the resections revealed lymph node metastases
- One early cancer was detected serendipitously during imaging for a kidney stone
- Prospective pancreatic cancers help establish the existence of familial pancreatic cancer and can serve as a surrogate for gene status

Klein et al, Clin Cancer Res 7:738-744, 2001



Data Source: Klein AP, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Research.* 2004;64(7):2634-8

Is it the environment or a gene?

Segregation Analysis

A statistical methodology aimed at determining if a major gene could cause the observed familial aggregation of a trait. Segregation analysis can also provide a model for how this gene is inherited (AD vs. AR, frequency, penetrance)

Segregation Analysis

- **Segregation analysis of 287 families ascertained through an index case diagnosed with pancreatic cancer at JHMI**
- **Able to reject non-genetic transmission models ($p<0.0001$)**
- **Most parsimonious models included autosomal dominant inheritance of a rare allele**
- **~0.6% of the population estimated to carry this allele**

A. Klein, Genetic Epi, 2002, 23:133-149

Risk of Pancreas Cancer

Individual	Risk	Age 50	Age 70
No History	RR=1	.05%	0.5%
BRCA2	3.5-10x	0.5%	5%
p16	20-34x	1%	10-17%
Familial PC	32x	1.6%	16%
Trypsinogen	50-80x	2.5%	25-40%
Peutz-Jeghers	132x	6.6%	30-60%

BRCA2

BRCA2 and Familial Breast Cancer

- Carriers of the 6174 del T *BRCA2* mutation have ~10x increased risk of developing pancreatic cancer
- ~17% of patients with 3 relatives with pancreatic cancer have a germline *BRCA2* mutations
- ~12% of patients with 2 relatives with pancreatic cancer have a germline *BRCA2* mutations
- ~7% of patients with “sporadic” pancreatic cancer have germline *BRCA2* mutations

Cancer Res 1996;56:5360

Cancer Res 2002, 62:3789-3793

Nat Genet 1997;16:17

J Natl Cancer Inst. 2003;95:214-21.

Familial Atypical Multiple Mole Melanoma Syndrome

p16 and FAMMM

- **The Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome is characterized by multiple nevi, multiple atypical nevi and multiple melanomas**
- **FAMMM can be caused by germline mutations in the *p16* gene**
- **Patients with FAMMM have a 20-34 fold increased risk of developing pancreatic cancer**

NEJM 1995; 333:970

Peutz-Jeghers Syndrome

- 132 fold increased risk of pancreatic cancer

Risk of Pancreas Cancer

Individual	Risk	Age 50	Age 70
No History	RR=1	.05%	0.5%
HNPCC	?	?	<5%
BRCA2	3.5-10x	0.5%	5%
Familial PC (3)	32x	1.6%	16%
FAMMM	20-34x	1-2%	10-17%
Pancreatitis	50-80x	2.5%	25-40%
Peutz-Jeghers	75-132x	3.6%	36% (age 60)

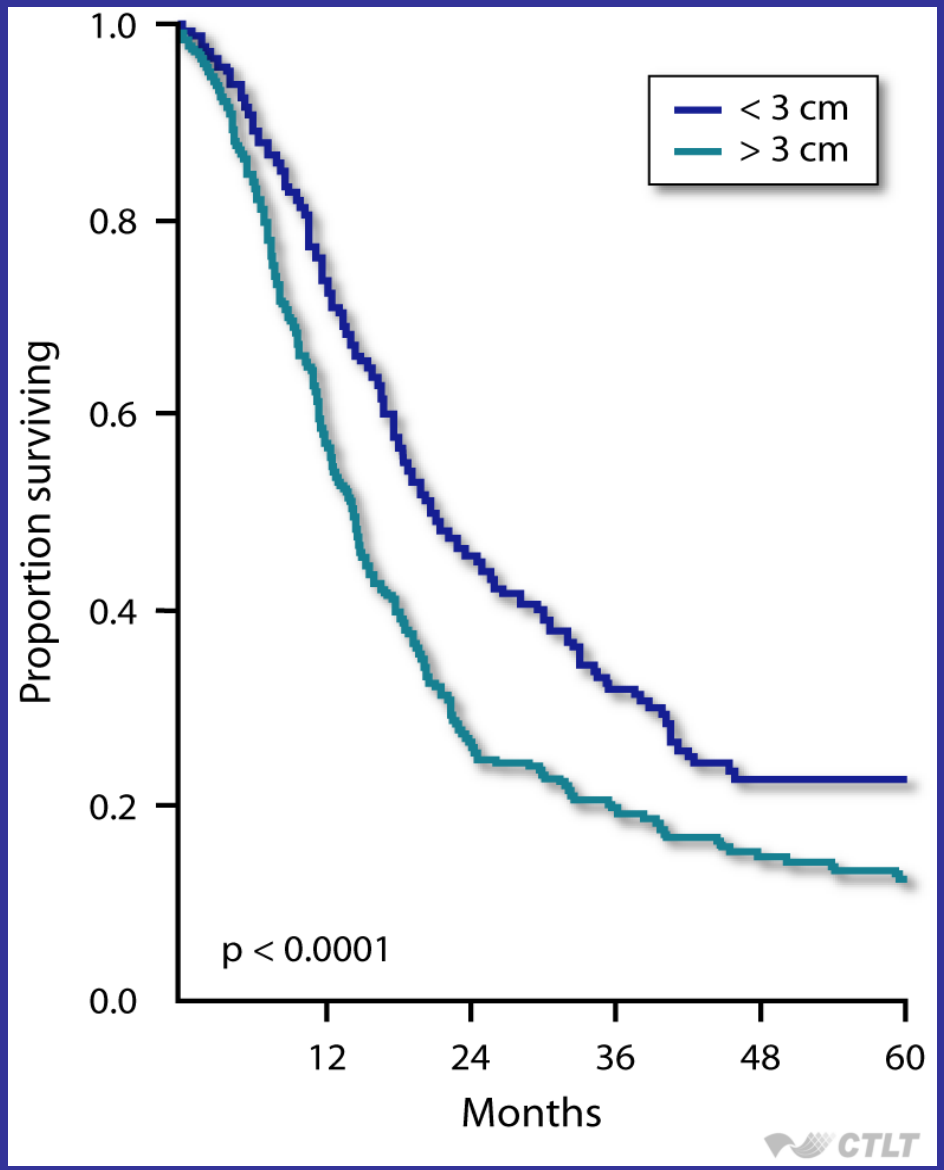
“It’s hard to make predictions, especially about the future.”

– Yogi Berra

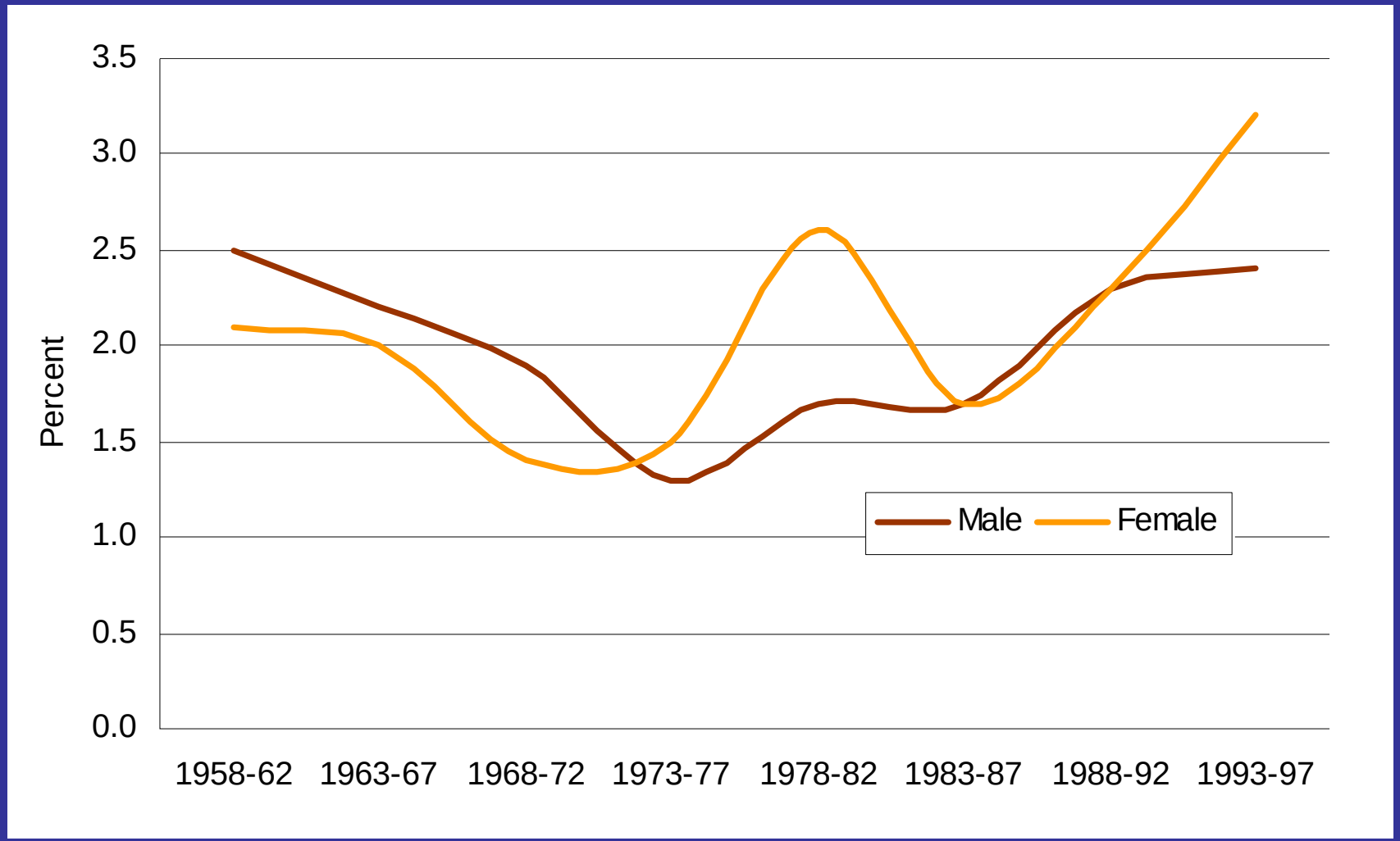
These known genetic syndromes account for only 10-20% of familial pancreatic cancer

What is the Prognosis for Patients with Pancreatic Cancer?

Surgically Resected Patients



Cancer in Norway 1958-97. Five-year relative pancreatic cancer survival in percent by period of diagnosis, sex, and stage



Data Source: Cancer Registry of Norway. http://www.kreftregisteret.no

How Can we Beat Pancreatic Cancer?

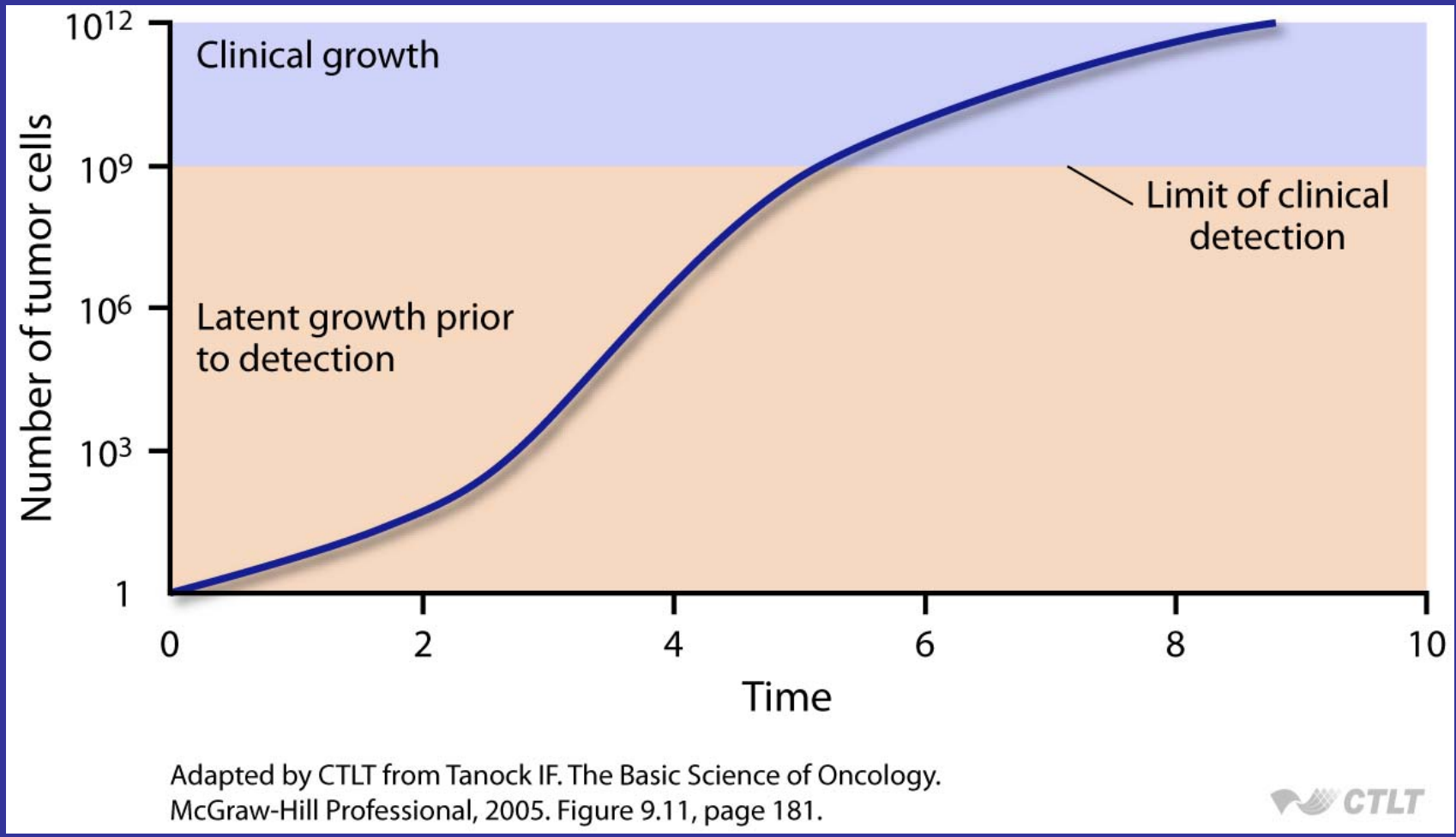
1. By Understanding the Precursors to Invasive Pancreatic Cancer

What are the precursors to invasive pancreatic cancer?

- Intraductal Papillary Mucinous Neoplasms (IPMN)
- Pancreatic Intraepithelial Neoplasia (PanIN)

Intraductal Papillary Mucinous Neoplasms and Pancreatic Intraepithelial Neoplasia

Pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms are curable neoplasms and, if left untreated, some will progress to infiltrating carcinoma



Adapted by CTLT from Tanock IF. The Basic Science of Oncology. McGraw-Hill Professional, 2005. Figure 9.11, page 181.

CTLT

2. By Understanding the Genetics of Invasive Pancreatic Cancer

Genetic profile of pancreatic cancer

Gene	*% rate of genetic alteration*
p16	98
K-ras(90%) (+ 5% BRAF)	95
p53	70
DPC4/SMAD4	55
BRCA2 (FANC C and G)	7-10
Mismatch repair genes	4
STK11 (Peutz-Jeghers)	5
AKT2, AIB1, c-MYC, c-MYB	Amplified

Pancreatic Cancer is a genetic disease

3. Screening- how can we find Precursor lesions/early cancers?

There are no Effective Screening Tests for Pancreatic Cancer

Sensitivity and Specifity Needed to Detect a Disease with an Incidence of 9 per 100,000 per year

Pancreas cancer is a disease of inherited and acquired mutations