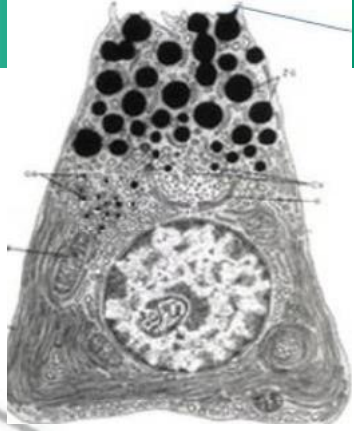
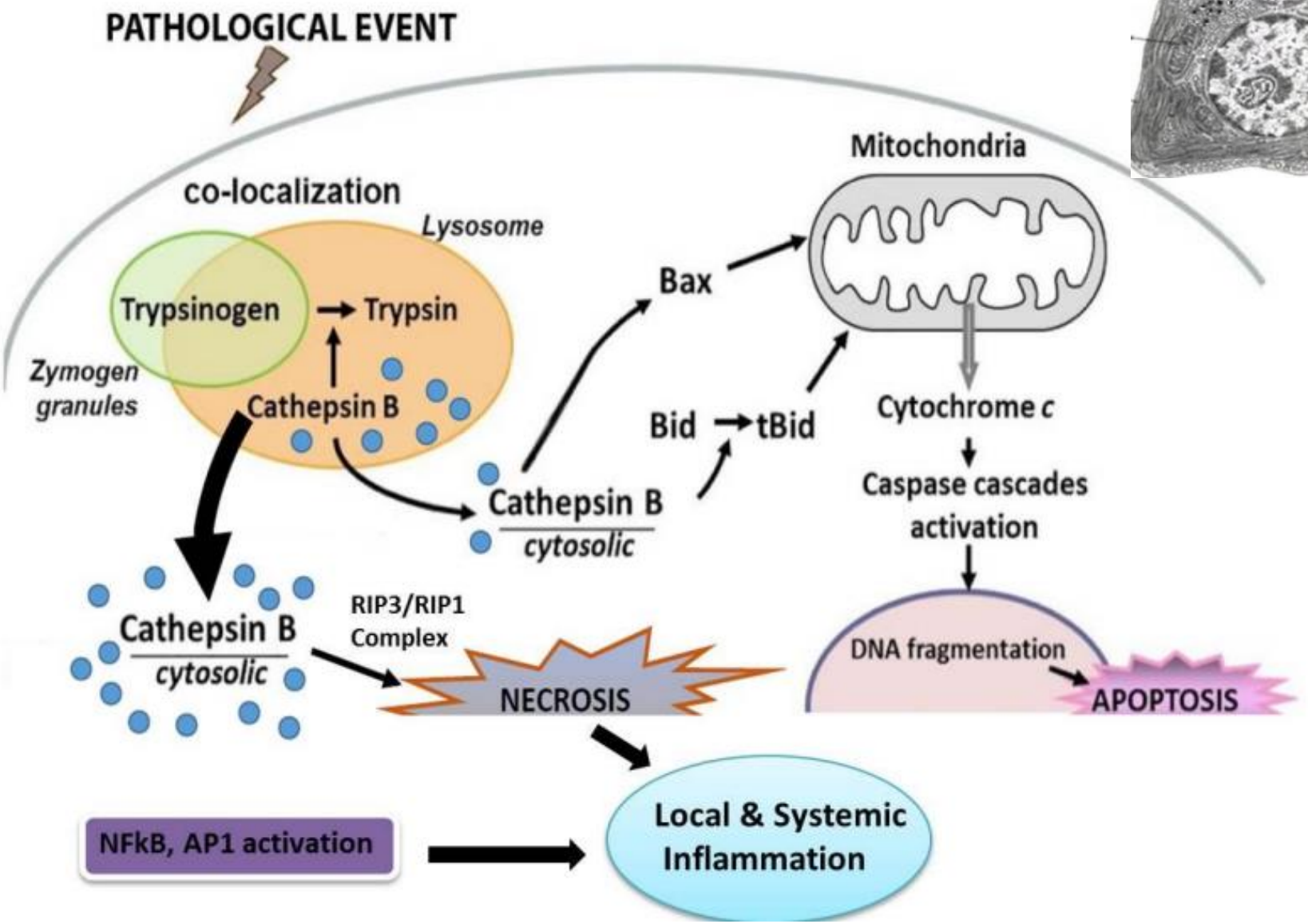
INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

Hereditary Pancreatitis and Pancreas-Cancer…….

Reiner Wiest M.D



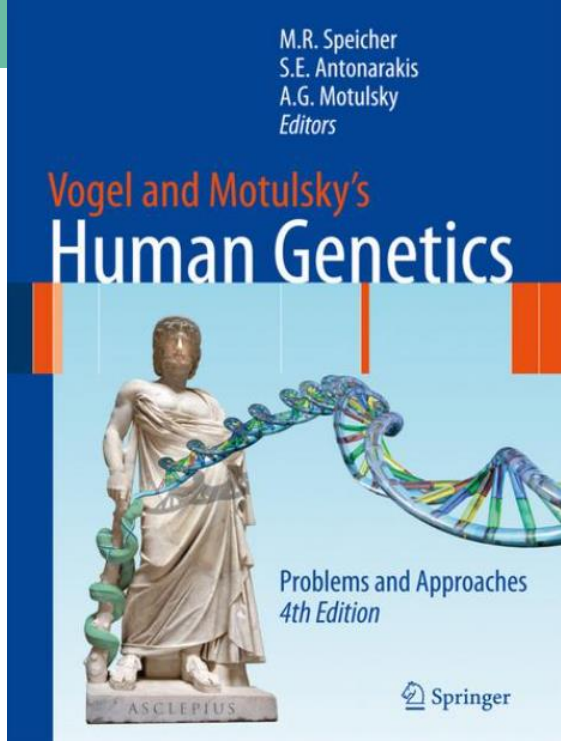

PATHOLOGICAL EVENT
co-localization
Lysosome
Trypsinogen
Trypsin
Zymogen granules
Cathepsin B
Mitochondria
Bax
Bid
tBid
Cytochrome c
Caspase cascades activation
Cathepsin B
cytosolic
Cathepsin B
cytosolic
RIP3/RIP1 Complex
NECROSIS
DNA fragmentation
APOPTOSIS
NFkB, AP1 activation
Local & Systemic Inflammation

Etiology based classification for recurrent acute/chronic pancreatitis

TIGARO-Classification:

T: Toxic-metabolic (alcohol, smoking….)
I: Idiopathic
G: ***Genetic***
A: Autoimmune
R: Recurrent or severe acute
O: Obstructive

Key Points in Genetics: Basic Knowledge



- Pathogenic genetic variants act by:
  - Altering protein **expression**
  - Altering protein **location**
  - Altering protein **function**
    - Loss of function
    - Gain of function
    - Change of function

- Pathogenic genetic variants cause disease by:
  - Altering normal **development** (congenital)
  - Altering **function** (congenital or acquired)
  - **Altering responses to stress or injury (acquired)**

What is the most common pathophysiology/ mechanism by which genetic variants /mutations cause pancreatitis ?

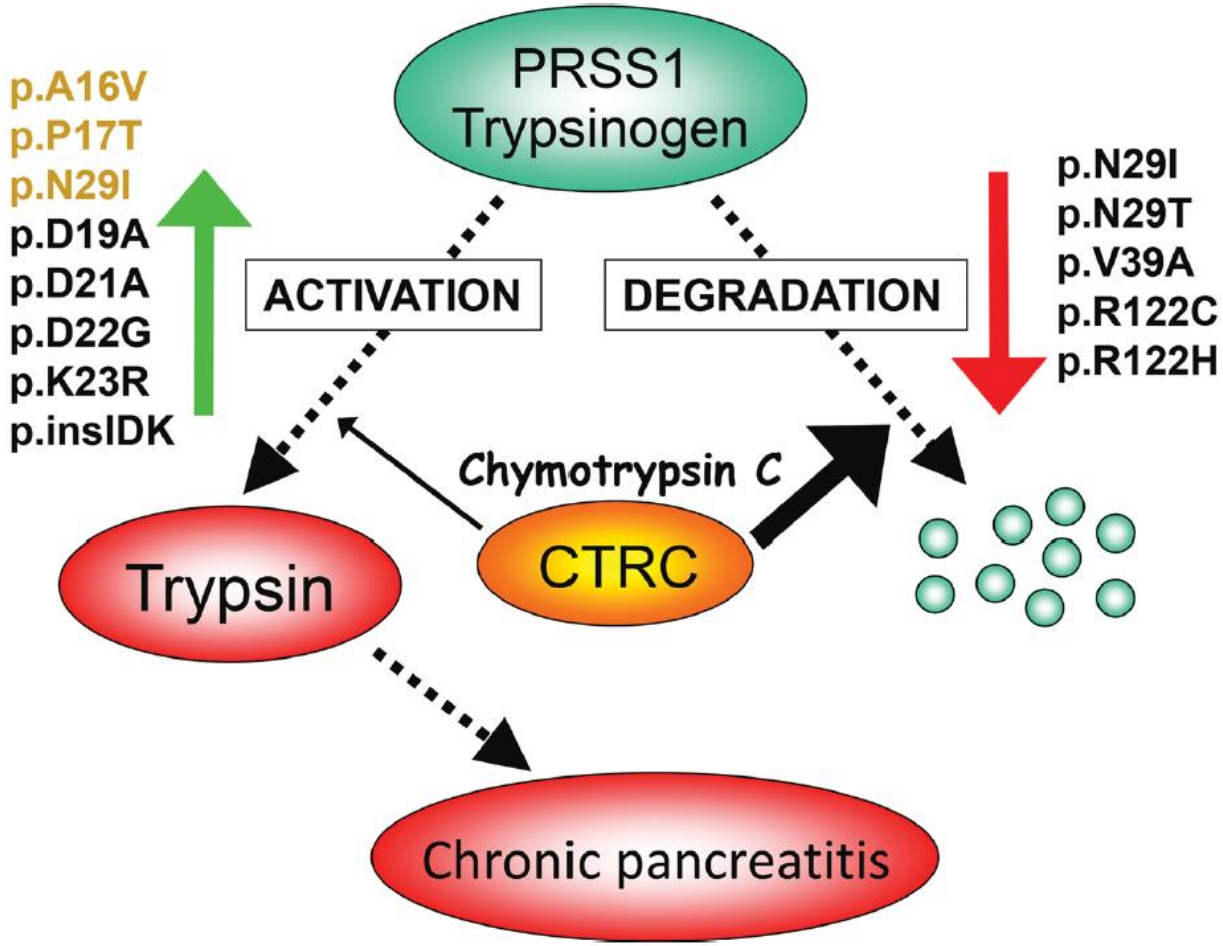
Autoactivation of Trypsinogen

common biochemical term for the reaction:
trypsin activates trypsinogen in a self-amplifying manner

regulated through
proteolytic cleavages by

e.g. Chymotrypsin

Mechanismof PRSS1-related hereditary pancreatitis



Sahin-Toth M Pancreas 2022

Definition of hereditary pancreatitis ?

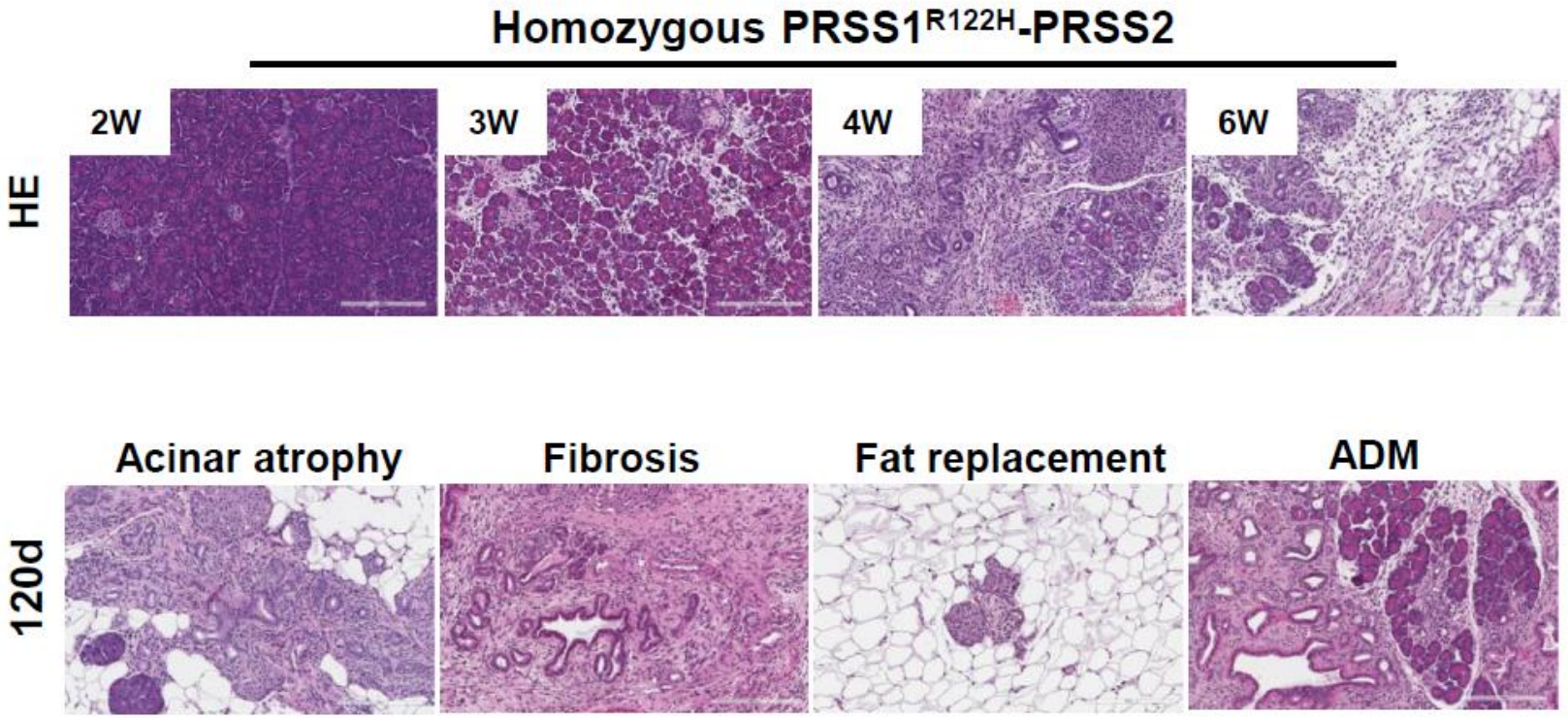
- **Presence of chronic pancreatitis in two first – degree or three second degree relatives in two or more generations, without precipitating factors and with a negative work-up for known causes**

- **Detecting a causative gene mutation**

Which genes- when mutated affect risk for HP ?

- **PRSS-cationic trypsinogen gene**
- **SPINK1: Serin-Protease-Inhibitor-Kazal-Typ 1= SPINK**
- **CTRC: Chymotrypsinogen-C**
- **CFTR: cystic fibrosis transmembrane conductance regulator**
- **Calcium-sensing receptor Gene**
- **Claudin-2 (CLDN2)**
- **Carboxypeptidase A1 (CPA1)**
- **….**

«Humanized mouse model for PRSS1-HP»



Wang et al. Gastroenterology 2022

Clinics and Research in Hepatology and Gastroenterology (2021) 45, 101497

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

More than 50 variants
Divers clinical effect
Review on management

REVIEW

Clinical interpretation of *PRSS1* variants in patients with pancreatitis

Emmanuelle Girodon[a], Vinciane Rebours[b], Jian Min Chen[c], Adrien Pagin[d], Philippe Levy[b], Claude Ferec[c], Thierry Bienvenu[a,*]

Nucleotide-Change
Amino acid-Change
Allele frequency general population
Allele frequency pancreatitis

OR carrier pancreatitis
Functional effect

Table 5 Genetic and environmental recommendations according to the class of *PRSS1* variants.

Variant class	*PRSS1* analysis in affected individuals	*PRSS1* analysis in unaffected related individuals	Other pancreatitis-related genes testing	Dietetic recommandations	Surveillance to pancreatic cancer

exon 3	c.310C > G	p.L104V	NI	NE	ND	Deleterious	Benign	[73]	Yes
exon 3	c.403A > G	p.T135A	2/280096	NE	ND	Tolerated	Benign	[19]	Yes
exon 3	c.417C > T	p.C139=	108/282894	NE	ND	NE	NE	[19]	Yes
exon 3	c.443C > T	p.A148V	98/271810	NE	ND	Tolerated	Benign	[19]	Yes
exon 4	c.486T > G	p.D162N	NI	NE	ND	Tolerated	Benign	[76]	Yes
exon 4	c.487G > A	p.A163T	12/282894	NE	ND	Deleterious	Benign	[78]	Yes

What you know about SPINK1 ?

SPINK1 is an acute phase protein and specific trypsin inhibitor

Few SPINK1-mutations directly associated with HP: autosomal-recessive

One SPINK1-mutation (c.27delC) inherited autosomal dominant

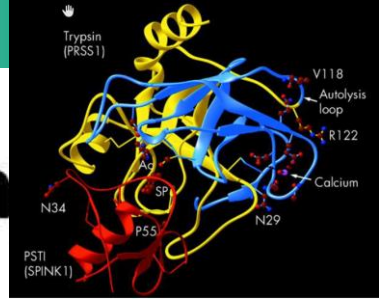
Majority inherited in heterocygous form

Phenotypic expression of pancreatitis requires interactions with

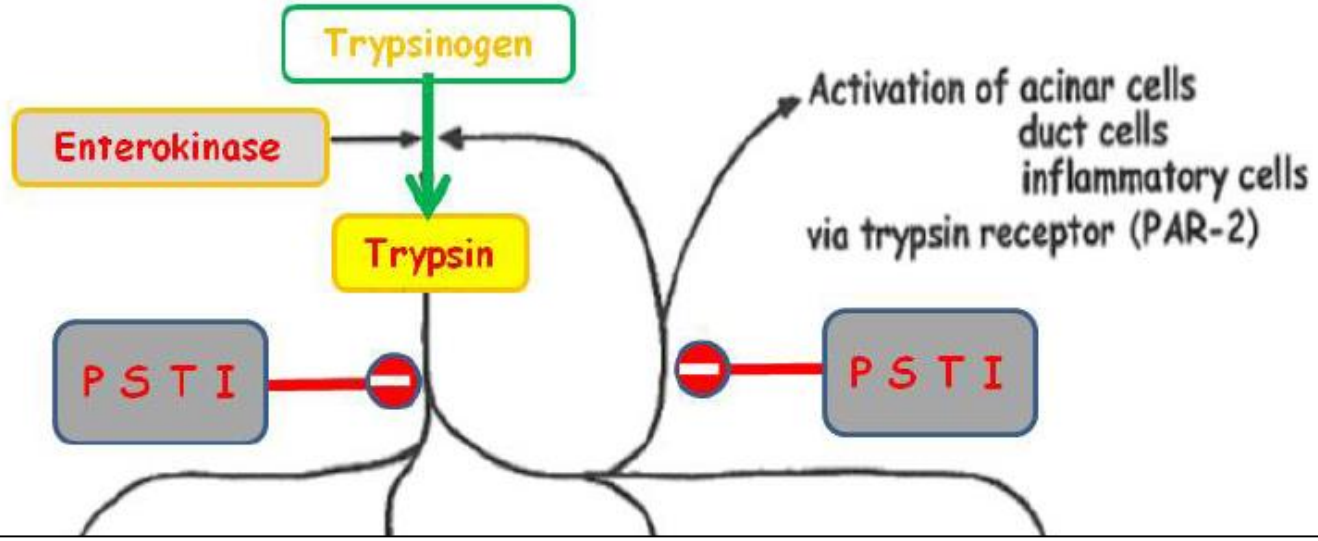
Other genetic mutations and/or environmental factors

= *disease-modifying mutations*

Mutations in SPINK1 in HP



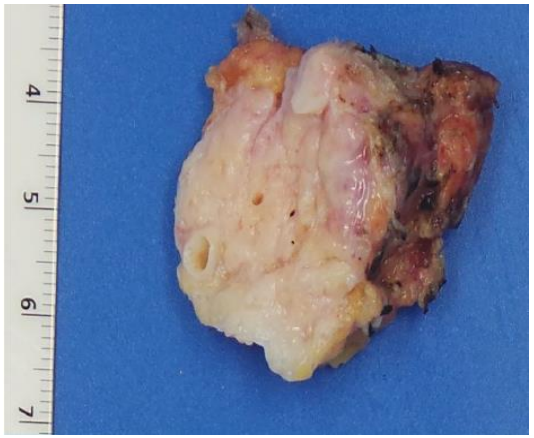
- **PSTI** Pancreatic Secretory Trypsin-Inhibitor
  - Serin-Protease-Inhibitor, Kazal-Typ 1: **SPINK1**



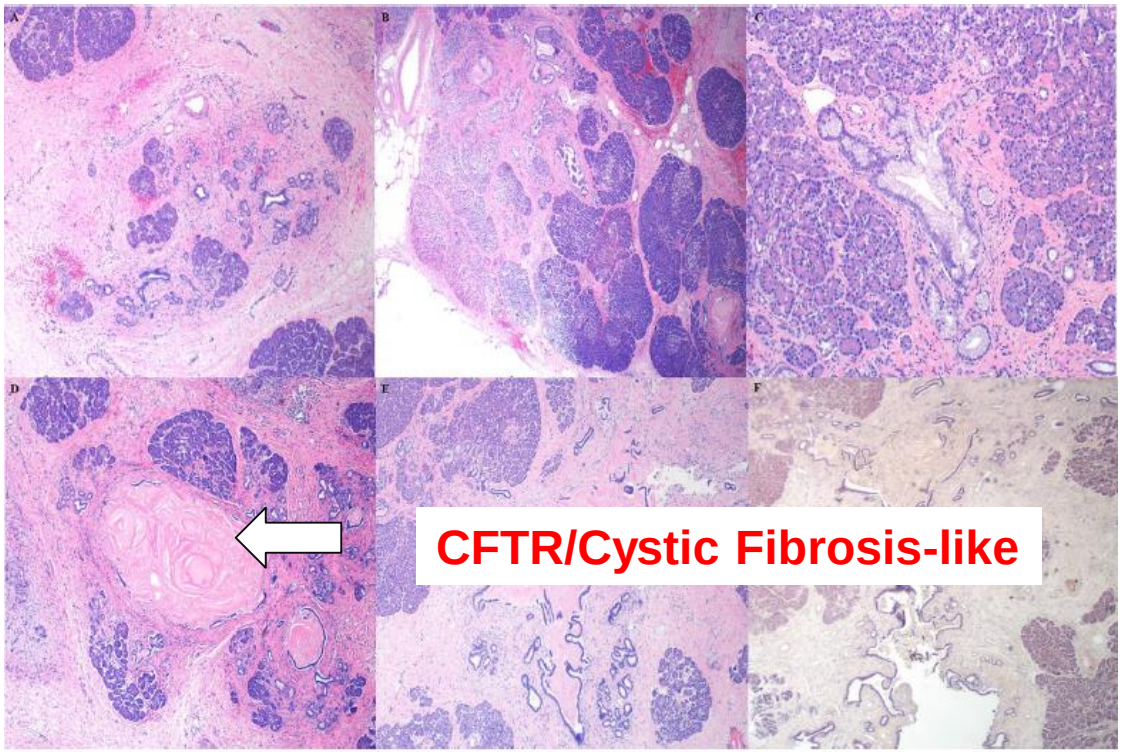
In pancreas: inhibits up to 20% of trypsinogen
e.g. mutation: L14R in 2 european large families:
rapid intracellular degradation of the mutant protein= abolished secretion of SPINK1

Histopathology of SPINK1-variant HP

24y fem repetitive APs
Since 17 y hospitalizations
Exo/endocrine insufficiency
Complete Pancreatectomy +
Autologous islet-transplant
SPINK1 c101A>G mutation
other genetic testing normal



Atrophic lobules, perilobular fibrosis



PanIN 1A neoplasia, ducts plugged secretions

Felicelli et al. Int J Surg Pathology 2021

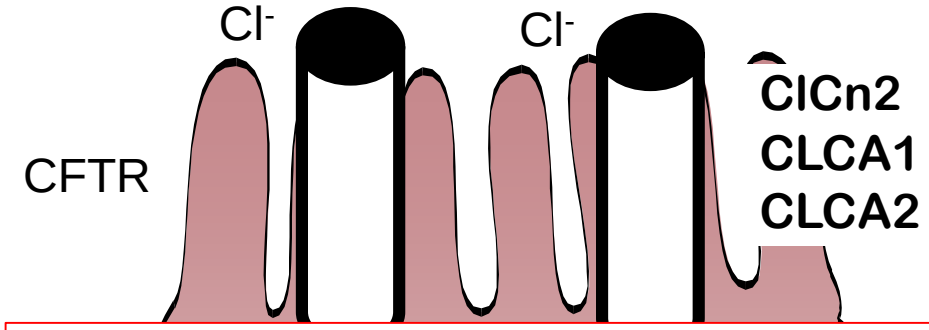
Cystic Fibrosis and Pancreas/-itis

Over one thousand mutations
have currently been identified in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene associated with CF disease

CF phenotyp very very heterogenous
Even between siblings with the same mutation!
= environmental factors important
but usually, often (> 90%) in symptomatic CF pancreas involved

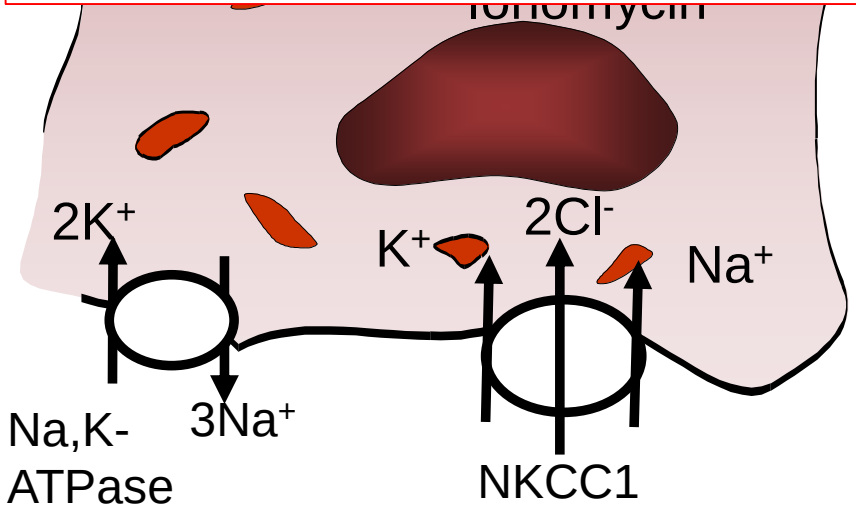
Rowntree R et al. Ann Hum Genetics 2013

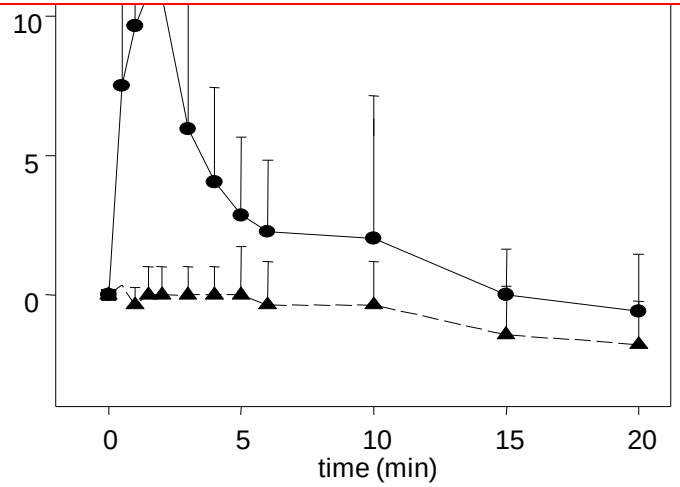
Pathophysiology cystic fibrosis ?



- Mutation des CFTR Chlorid-Kanals
- damit Störung der Sekretion von Chlorid-Ionen und Bildung eines zähen Sekrets
- Prävalenz 1:2500, heterozygot: 1:25

CFTR in pancreas = primary molecule in bicarbonate conductance



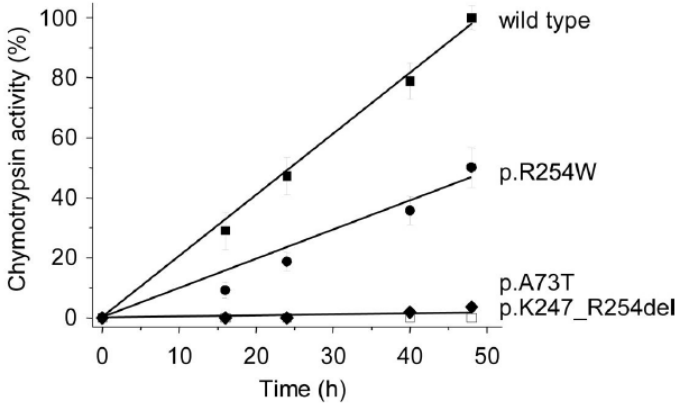


CFTR and clinical presentation

- **Cystic Fibrosis (of the pancreas)**
  - Clinical syndrome(s)
    - **Classic CF**: pancreatic insufficiency, abnormal sweat chloride, progressive lung disease, meconium ileus, male infertility (CBAVD), liver disease.
    - **Atypical CF**: like CF but milder symptoms
    - **CFTR-Related Disorders**: (CFTR-RD)
      - Recurrent acute & chronic pancreatitis (CFTR + SPINK1)*
      - Pancreatitis, male infertility, chronic sinusitis (CFTR-BD**)
  - Genotype: $CFTR^{x}/CFTR^{X}$ (x = $CFTR^{sev}$, $CFTR^{mv}$ or $CFTR^{BD}$)***
  - Diagnosis: Clinical features, + Sweat chloride or nasal potential difference + abnormal *CFTR* genotype.
  - Consider referral to a CF Center to make the diagnosis.

* *CFTR/SPINK1* genotypes represents a complex disorder
** BD, bicarbonate conductance defective.
*** functional effects on CFTR function, sev=severe, mv=mild variable

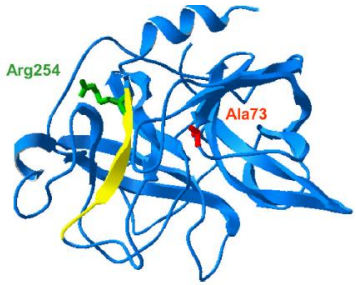
Chymotrypsinogen-C: CTRC ?



- **relatively rare (1-3% of HP)**
- **degrades Trypsin**
- **mutations with loss of function**

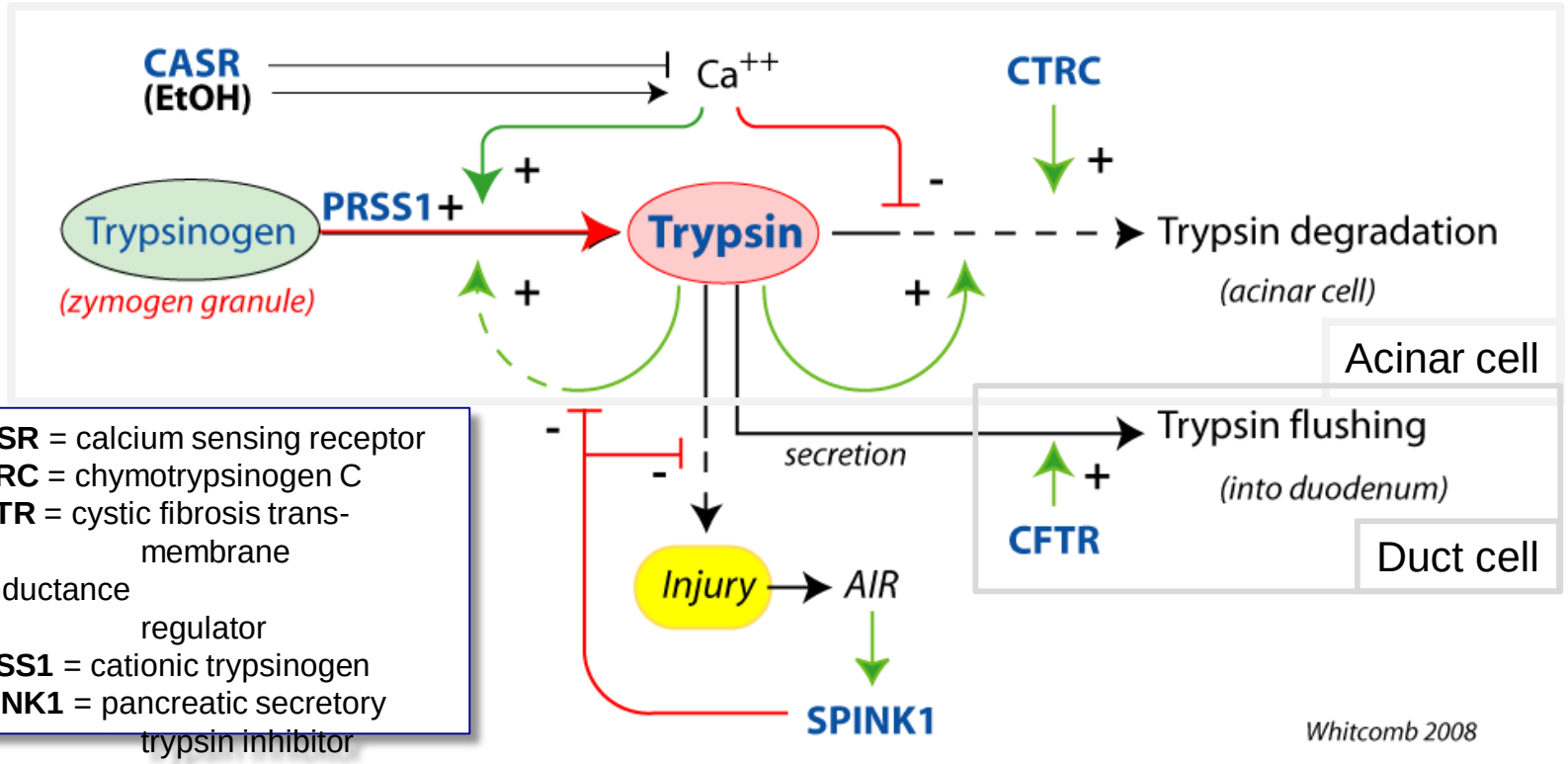
  (reduced CTRC-secretion or catalytic defect within CTRC-protein)

  ->increased Trypsin-action (since no degradation)
- **confer increased risk for pancreatitis in interaction with**
- **SPINK1, CFTR-mutations and/or environmental factors**
- **increased risk by 4-8 fold for pancreatitis**



Rosenthal J et al. Nature Genetics 2008; Klein AP Nature Reviews 2021

Genetic Variants Related to Trypsin



CASR = calcium sensing receptor
CTRC = chymotrypsinogen C
CFTR = cystic fibrosis trans-membrane conductance regulator
PRSS1 = cationic trypsinogen
SPINK1 = pancreatic secretory trypsin inhibitor

AIR = Acute inflammatory response (acute phase protein expression)

- Genes linked to **CP susceptibility** all regulate intra-pancreatic **trypsin** activity.
- Both the acinar cells and duct cells are linked with pancreatitis-causing variations

Whitcomb DC. *Annu Rev Med*. 2010;61:413-24.

In children genetic etiology of pancreatitis is found how frequent ?

In previously diagnosed

- **Idiopathic acute** **33%**
- **Recurrent acute** **45%**
- **Chronic pancreatitis** **55%**

HP is (one of) **the main causes of pancreatitis in children**

Genetic testing ? When – Whom to consider ?

Before performing molecular analysis- genetic counseling

Consider genetic testing for HP when

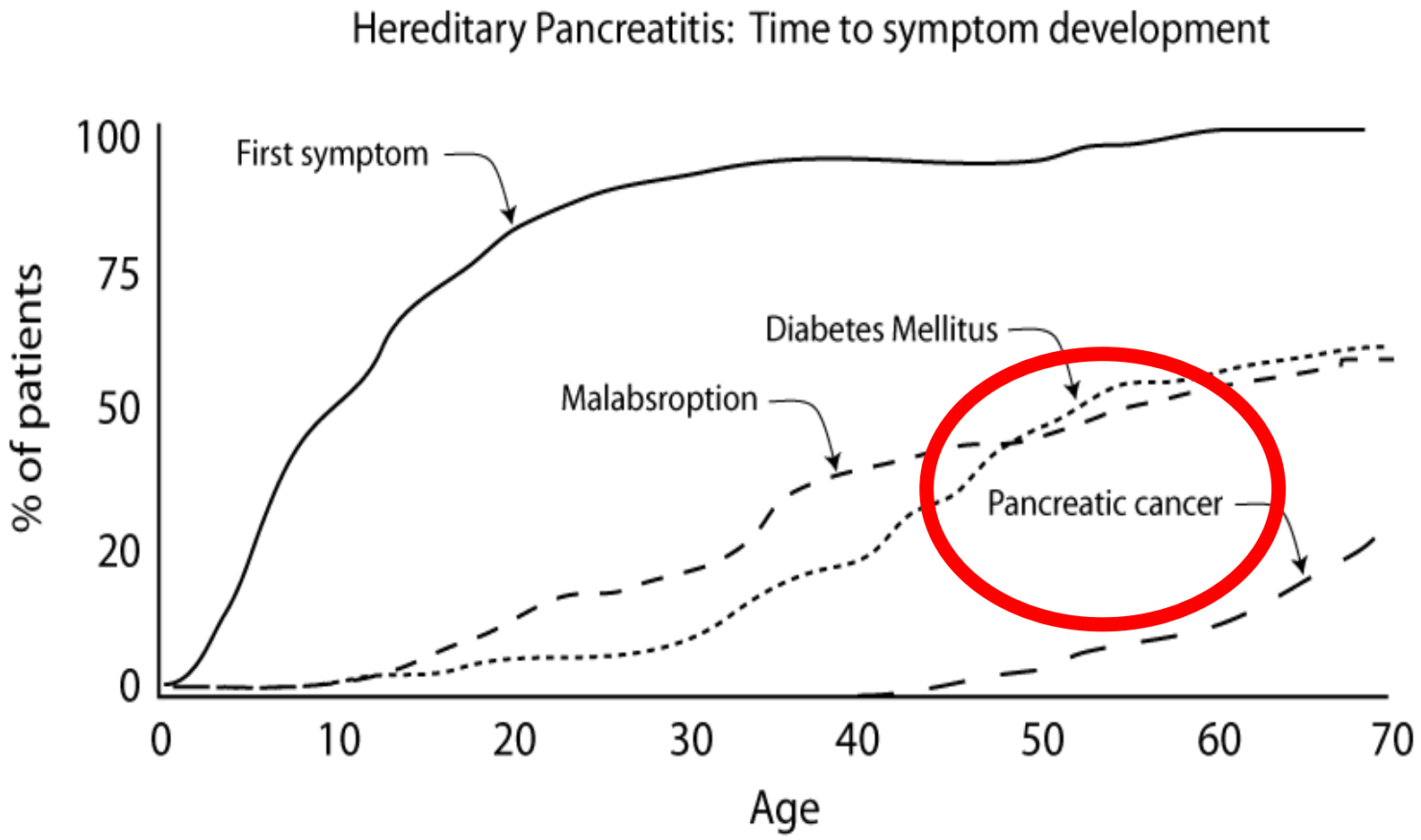
- **Family history of idiopathic CP, recurrent pancreatitis or**
- **Childhood pancreatitis (or < 25 years in age with recurrent acute pancreatitis or CP) without explanation after extensive work-up**
- **Relatives with known mutations associated with HP**

Special clinical relevance of hereditary pancreatitis…

Cumulative risk of

- **Exocrine insufficiency** — **60%**
- **Diabetes** — **68%**
- **Pancreatic cancer** — **To be anounced**

Natural History of hereditary pancreatitis



Howes et al. Clin Gastroenterol Hepatol. 2004;2(3):252-61

Epidemiology Pancreas-Adenocarcinoma

Numbers doubled in last decades worldwide

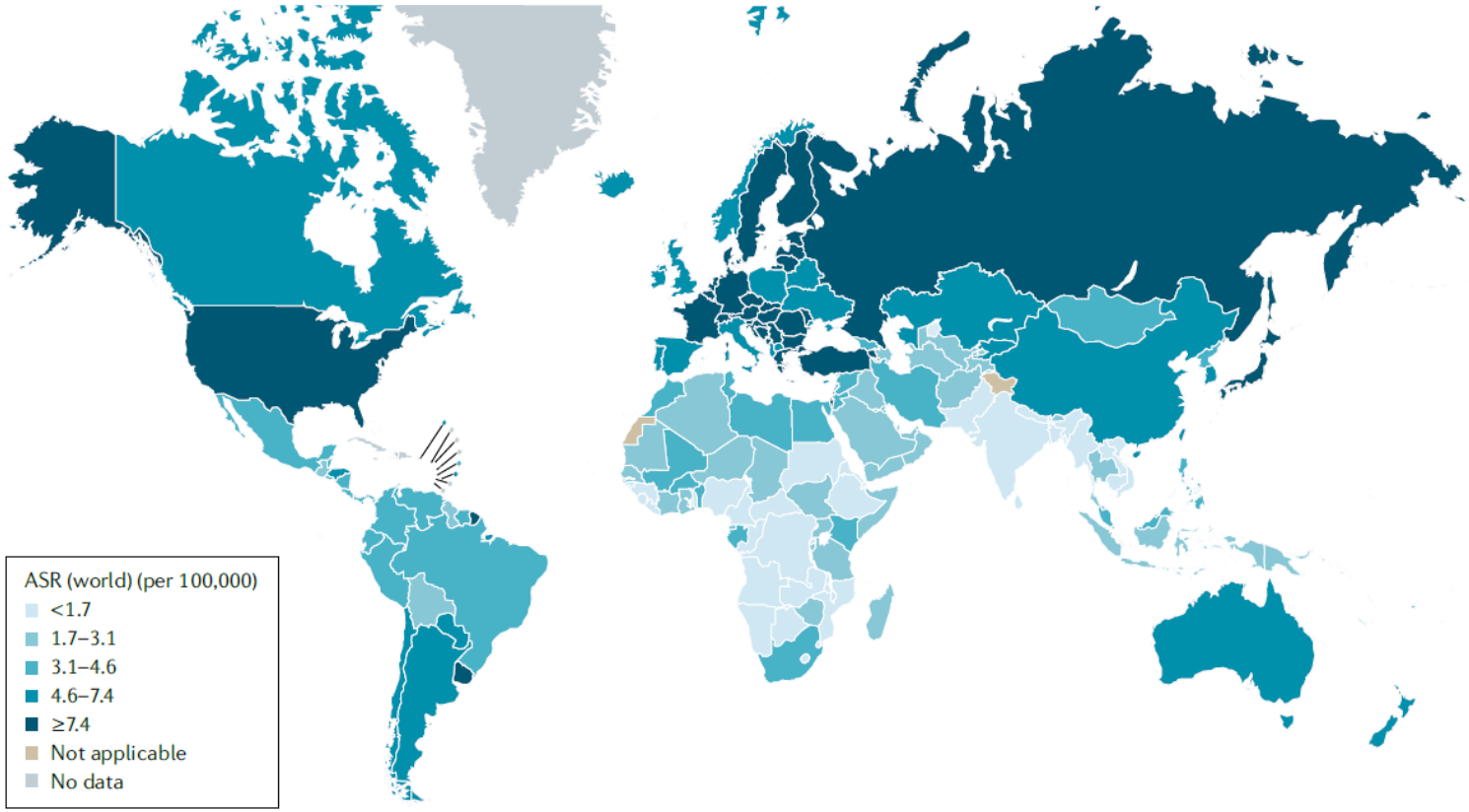
1990: 196.000 to 2017: 441.000

Risk of death from pancreatic cancer age dependent

<2/100.000 person-years in 35-39y age

>90/100.000 person-years in > 80y age

Age-standardized incidence-rate globally



What does high-risk for pancreatic cancer mean ?
Is defined = screening worthwile

> 5% life time risk for developing (pancreas) cancer

or

> 5-times increased risk overall

Canto et al. Gut 2013 CAPS-consortium

Positive family history for = high risk for pancreatic cancer is when ?

PA-Cancer in at least one first degree relative and either

- **2 relatives on same side or**
- **2 relatives who are first degree related to each other**

Risk of first degree relative with positive family history or so called «familial» PDAC
=

individuals with at least two close family members with pancreatic cancer

7-fold increased risk for PDAC as compared to general population

Brune et al. JNCI 2010

proportion of pancreatic cancers due to inherited genetic factors (heritability) has been estimated to be 20–36%

Chen F et al. Cancer Biomarker 2019

Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion

Elena M. Stoffel, MD[1]; Shannon E. McKernin[2]; Randall Brand, MD[3]; Marcia Canto, MD[4]; Michael Goggins, MD[4]; Cassadie Moravek[5]; Arun Nagarajan, MD[6]; Gloria M. Petersen, PhD[7]; Diane M. Simeone, MD[8]; Matthew Yurgelun, MD[9]; and Alok A. Khorana, MD[6]

90% of families

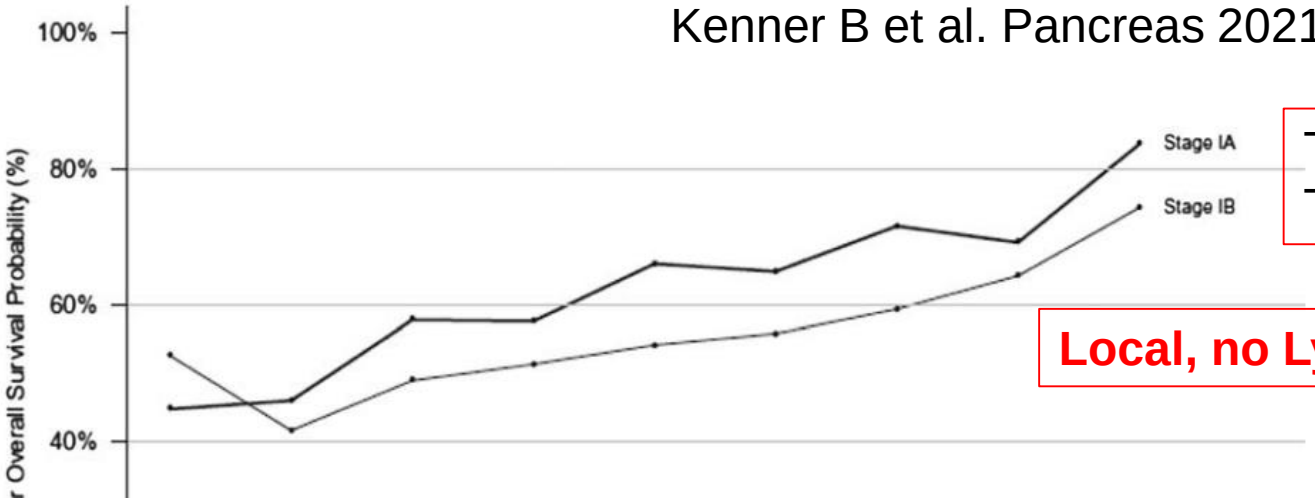
meeting criteria for familial pancreatic cancer

genetic testing does not detect a pathogenic mutation

= additional shared epigenetic, genetic, or environmental factors contribute to pancreatic cancer risk

J Clin Oncology 2018

Goal: Early Diagnosis of Pancreas-Cancer – Benefit achievable – Prognosis depending on stage



Kenner B et al. Pancreas 2021

T1: < 2 cm
T2: < 4 cm

Local, no Lymph node

Once symptoms develop percent of cases inoperable ?

80%

Who should undergo surveillance for pancreatic cancer development ?

- **All patients with Peutz-Jeghers (germline LKB1/STK11 mutation)**
- **All carriers germline CDKN2A mutation**
- **Carriers of germline BRCA2, BRCA1, PLAB2, MLH1, MSH2 or MSH6**
- **Individuals who have at least one FDR with PDAC**

(and in turn a FDR+ PDAC)

Inherited Susceptability Genes for High-Risk-Individuals for Pancreatic-Cancer

Explains only < 10%% of all Pancreas-Cancer
Explains only about 20% of all presumed heritability

BRCA2	Z=7
PALB2	<0.5
BRCA1	
ATM	
STK11	
P16/CDKN2A	<1–2.5
PRSS1	<1
MLH1, MSH2, MSH6, PMS2	1

Peutz-Jeghers:
remarkably high risk of any cancer
(40% by 40 y, 76% by age 70 y
lifetime risk of pancreatic cancer up to 32%

Lynch-syndrome:
3.68% (95% CI 1.45–5.88%) risk
of pancreatic cancer by age 70 years
=8.6- fold
higher than in the general population

Klein AP Nature Review 2021

BRCA2 and BRCA1-associated risk for PDAC ?

Up to 7% of all PDCA are BRCA 1 or -2 positive`!

	BRCA2	BRCA1
Relative Risk (RR)	**5.9%** (95 CI: 3.9-6.3%)	**1.9%** (95 CI 1-2.8%)
-> cumulative life-time risk up to age 80	5.2%	4.9%
Standardized Incidence Ratio (SIR)	**7.2%** (95 CI 1.5-13.0)	**3.7%** (95 CI 2-5.6%)
-> cumulative life-time risk up to age 80	**7.4%**	**3.8%**

Only 1 of 3 pts. with BRCA1/2-associated PDAC has pos. family history

Surveillance for pancreatic cancer at which age ?

Positive family history – without germline mutation known/found:

-then start at age 50 (or 55) or

-10 years younger than youngest affected relative

Mutation carrieres: depends on mutation, namely

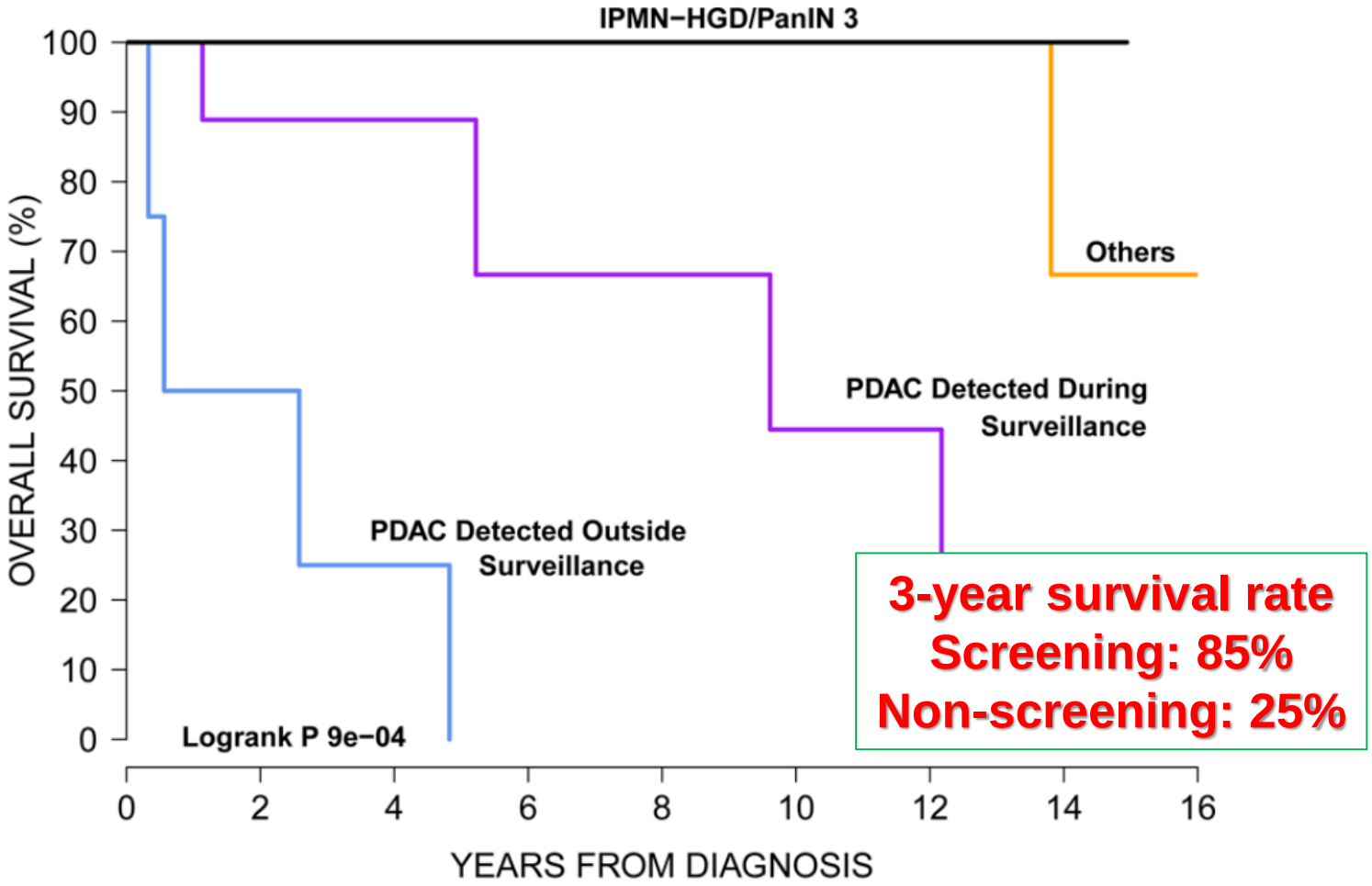
CDKN2A or Petz Jegher Syndrome start at age 40

BRAC2, ATM, PALB2, BRCA1, MLH1/MSH2:

-start age 45 (or 50) or

-10 years younger than youngest affected relative

To screen or not to screen in High-Risk Individuals ?



Canto et al. Gastroenterology 2018

How to perform surveillance for pancreatic cancer ?

At baseline:

MR/MRCP + EUS + fasting glucose (and/or HbA1c)

Follow-up:

alternate MR/MRCP and EUS, routinely fasting glucose (and/or HbA1c)

On indication:

Serum CA19-9 (if imaging shows concerning features)

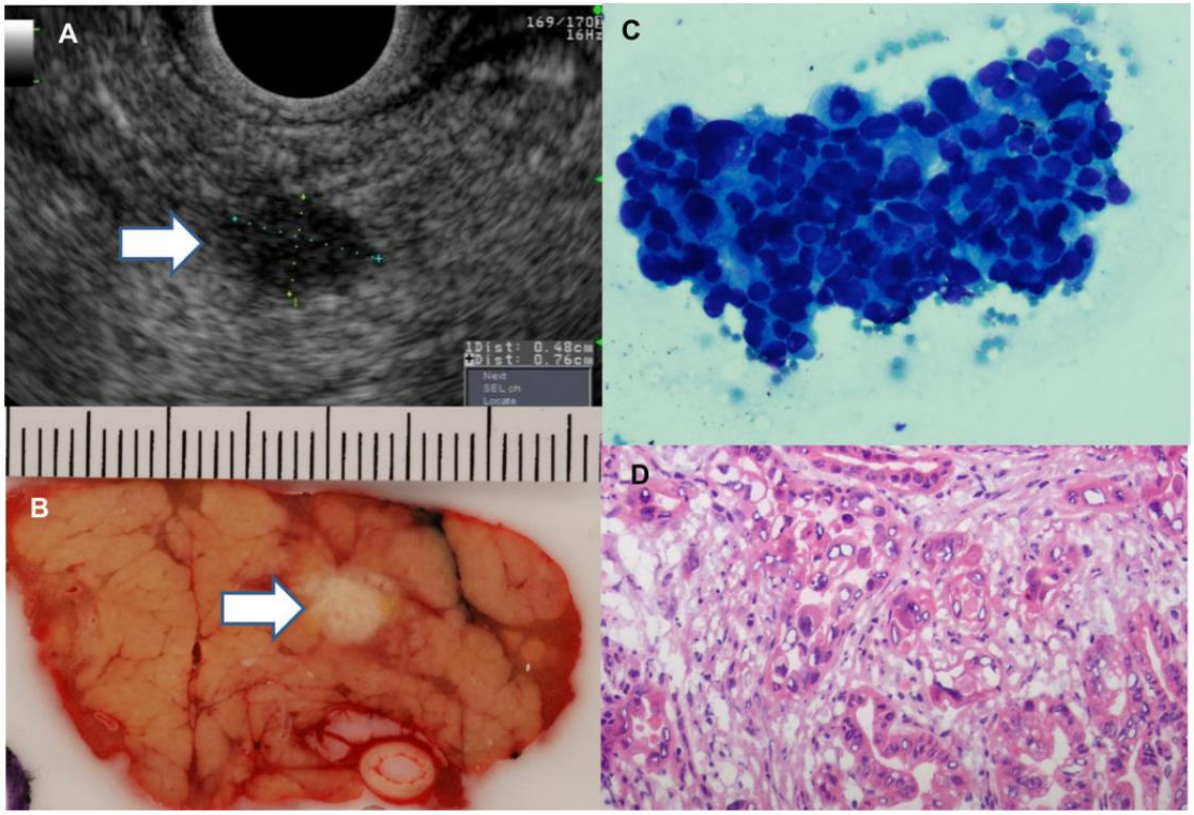
EUS-FNA

solid lesion (> 5mm), cystic lesion + worrisome features, MPD strictures

CT

solid lesion (regardless of size) or MPD stricture of unknown etiology

Early detection PDAC in asymptomatic pts at risk !!



8 mm PDAC after 10 y surveillance

detected by

EUS

Grant et al. Gastroenterology 2015

Factors that increase risk for PDAC add-on to genetic suscepatbility ?

- **Age**
- **Diabetes**
- **Cigarette smoking**
- **Alcohol**
- **Obesity, or**
- **History chronic pancreatitis**

Alcohol and acute pancreatitis ?

Bier

ALCOHOL

- No threshold below which no pancreatitis is caused or triggered
- Dose: Risk of pancreatitis increases with dose
- 5% of «heavy drinker» (> 80g/d for > 10 y) develop chronic pancreatitis

Amann RW et al. Pancreas 1997

Alcohol and risk for PDAC

Dosing Alcohol	Relative Risk (increase)
1 drink > 30 g/d	**1.22** (95% CI 1.03-1.45)
> 3 drinks/d	**1.45** (95% CI 1.17-1.8)
Heavy **> 9 drinks/d**	**1.77** (95% CI 1.1-2.95)

Yadav et al. Gastroenterology 2013; Klein AP Nature Review 2021

Diabetes mellitus and risk for PDAC

= consequence of pancreatic cancer
= risk factor for development of pancreatic cancer
longstanding DM (> 3 y) increases risk by 1.4-2.5 fold

New-onset diabetes highest risk:
up to 1% of those within 3 years diagnosed with PDCA (general population without diabetes < 0.1%)

Increasing prevalence of diabetes worldwide
> 400 Mio affected currently = driver
increasing prevalence of PDAC

Chiari et al. Gastro 2005

Smoking and risk for PDAC

Almost doubles the risk for PDAC in general population

One/the most modifiable (stoppable) risk factor for Pa-Cancer!

Up to 25% of PDAC are thought to be caused by cigarette smoking

In HP: age of onset of pancreatic cancer about 20 years younger

C2 + Nikotin and Pancreatitis

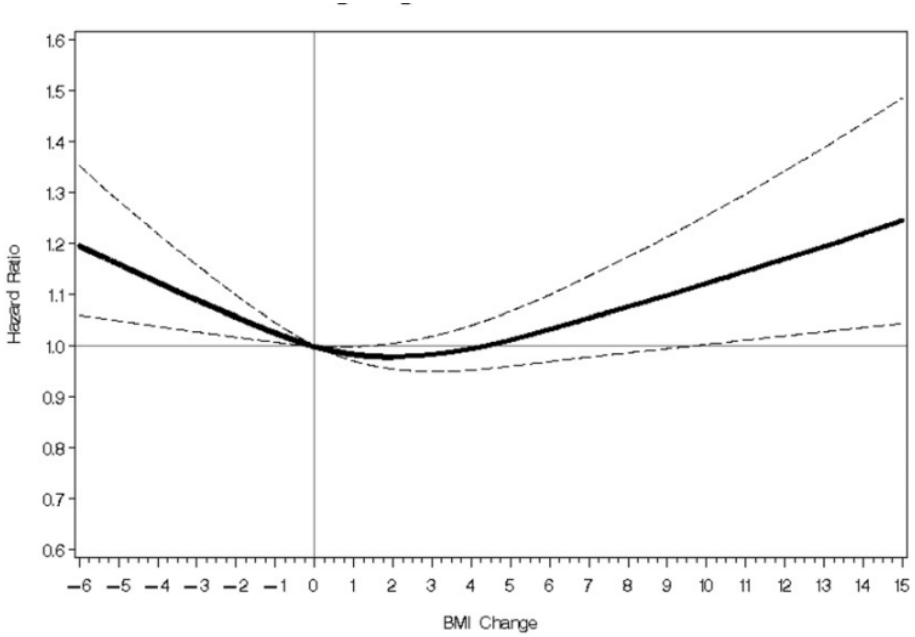
	Alcohol consumption (g/month)			
	<400		≥400	
	RR† (95% CI)	p Value	RR (95% CI	
Smoking status*				
Never	1 (Ref)			
Former	1.30 (0.88 to 1.90			0.02
Current	1.63 (1.0		.19)	<0.01
Pack-years of				
N			1 (Ref)	
	.06)	0.20	1.97 (0.91 to 4.24)	0.08
	(0.81 to 2.55)	0.21	3.96 (1.87 to 8.39)	<0.01
<20	1.69 (0.99 to 2.90)	0.06	2.13 (0.84 to 5.40)	0.11
≥20	1.94 (1.18 to 3.19)	<0.01	4.12 (1.98 to 8.60)	<0.01

After two decades of smoking cessation risk of non-gallstone-related acute pancreatitis is reduced to a level comparable to that of never smokers

Obesity – independent risk factor for PDAC

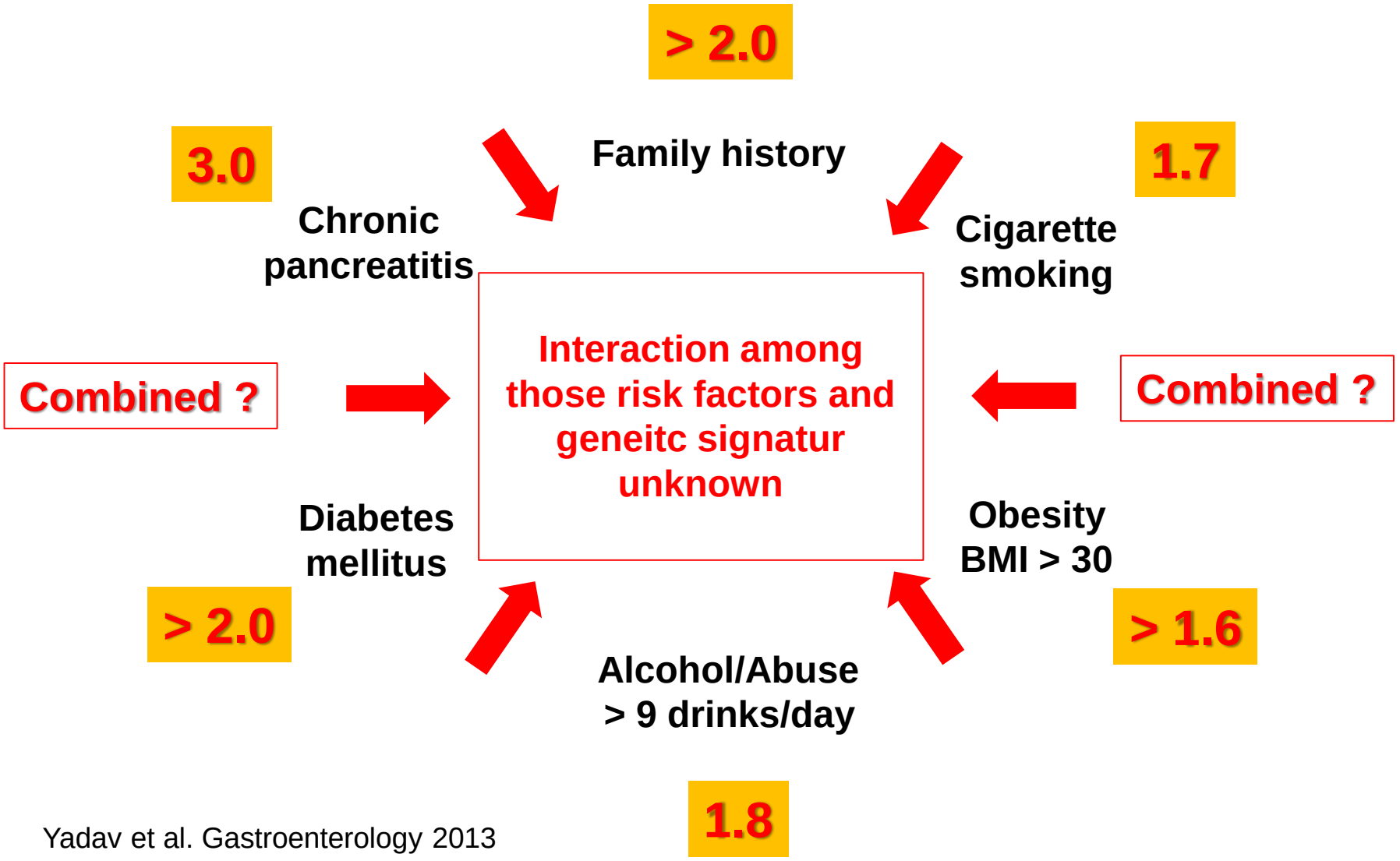
Incidence obesity from 1975 till today: 3-times

BMI-change after age 50 (adjusted age, smoking)



Stolzenberg-Solomon Am J Clin Nutr 2013;

Comorbidities increasing risk for PDAC



Yadav et al. Gastroenterology 2013

Is there anything protective factor ? Preventing PDAC ?

Allergy

Hay fever/Atopy

25% lower risk for PDAC

Hypothesis:

Active immune system = increased anti-tumor activity?

Olson, S. H. et al. Allergies and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Case- Control Consortium. *Am. J. Epidemiol.* **178**, 691–700 (2013).

Are there therapeutic consequences of genetic mutiatons/risk-profile in pancreatic cancer ?

***BRCA2*- deficient or *PALB2*- deficient cancers**
-> increased sensitivity to PARP inhibitors or mitomycin C

Microsatellite instability- high pancreatic cancers
-> accessible for anti- PD1 immunotherapy

Klein AP Nature Review 2021

What should you eat to treat your pancreas well ?

ORIGINAL ARTICLE

Vegetables, fruit and risk of non-gallstone-related acute pancreatitis: a population-based prospective cohort study

Viktor Oskarsson,[1] Omid Sadr-Azodi,[1,2] Nicola Orsini,[1] Åke Andrén-Sandberg,[2] Alicja Wolk[1]

Gut 2017

Thank you for your attention