

Oncology Nutrition DPG Symposium Orlando 2014

Diabetes/Cancer Link

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Objectives

1. Case Study



Objectives

1. Case Study



2. 4 Questions

Objectives

1. Case Study



2. 4 Questions

3. Diabetes and Pancreatic Cancer

Objectives

1. Case Study



2. 4 Questions

3. Diabetes and Pancreatic Cancer

Case Presentation

Chief Complaint: Polyuria

History of Present Illness:

- 52 y/o female
- Hypertension
- Active triathlete/BMI 21
- Excessive thirst and polyuria

Case Presentation

Chief Complaint: Polyuria

Labs:

8.8	14.5	262
	48.2	

140	107	26	423
4.6	32	0.9	

C-Peptide 0.7

She has new diabetes and is not making insulin

Case Presentation

Started on Metformin and referred to diabetes educator

Question

Why does a healthy, thin, 52 y/o female suddenly develop c-peptide negative diabetes?

Case Presentation

9 months later...

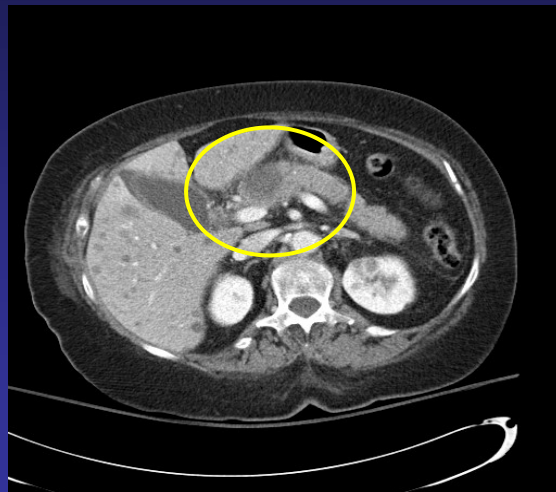
Diabetes has been under excellent control

BMI has remained the same

Patient develops painless jaundice with pruritis, dark urine and scleral icterus

Case Presentation

CT Scan



Case Presentation

What happened to this patient?

Could the new diagnosis of pancreatic cancer be related to the diabetes diagnosis?

Could this have been prevented?

Objectives

1. Case Study

2. 4 Questions



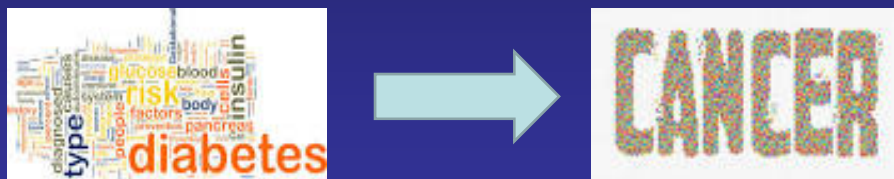
3. Diabetes and Pancreatic Cancer

4 Questions

- Is there an association between diabetes and cancer?
- What are the risk factors common to both cancer and diabetes?
- What are the biologic links between diabetes and cancer risk?
- Does the treatment of diabetes cause cancer?

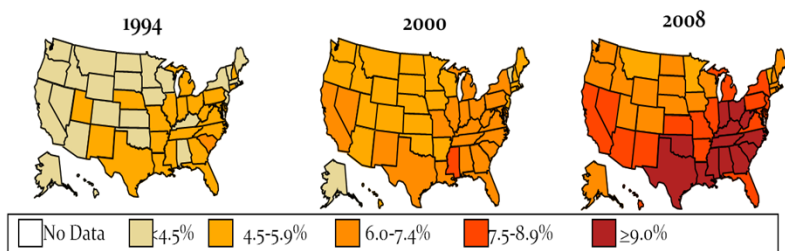
Question 1

Is there an association between diabetes and cancer?



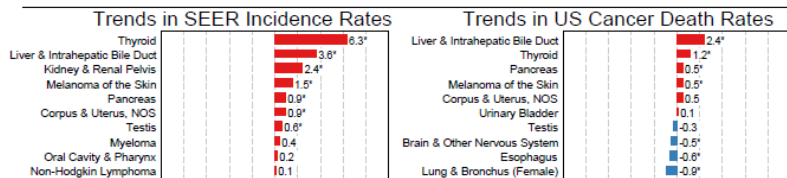
The Rise of Diabetes

Diabetes

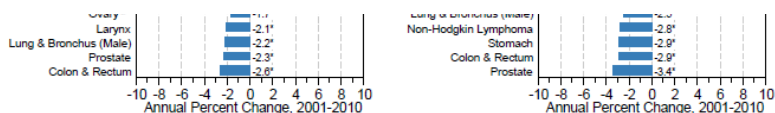


The Rise of Cancer?

Trends in SEER Incidence and US Death Rates by Primary Cancer Site 2001-2010



Is there an association between diabetes and cancer?

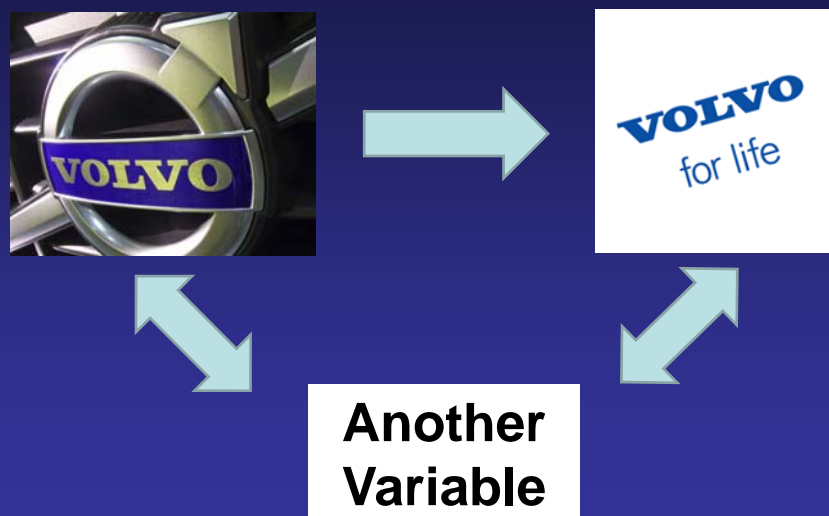


CONFOUNDING!!!

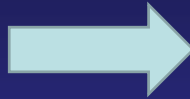
Definition: An extraneous variable in a statistical model that correlates (directly or inversely) with both the dependent variable and the independent variable.



CONFOUNDING!!!



CONFOUNDING!!!

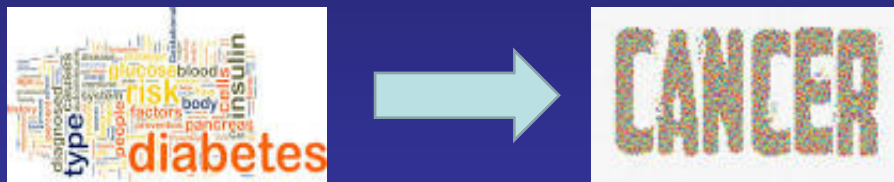


CONFOUNDING!!!



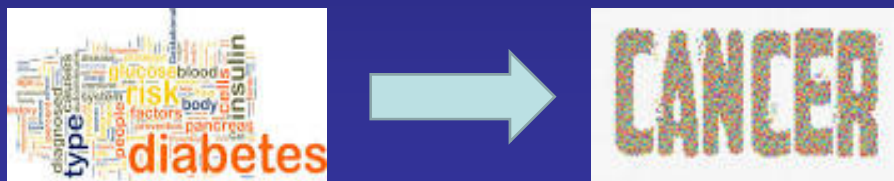
Question 1

Is there an association between diabetes and cancer?



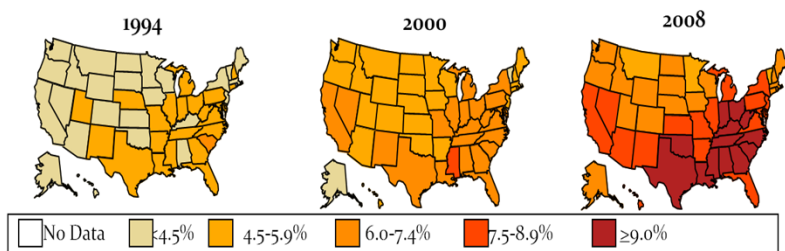
Diabetes and Cancer

- Is the association direct – hyperglycemia?
- Does diabetes alter underlying biologic factors?
- Indirect association due to common risk factors such as obesity?



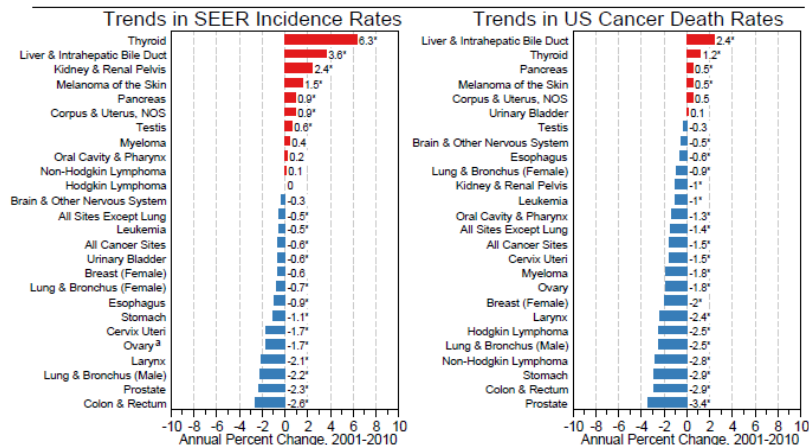
The Rise of Diabetes

Diabetes



The Rise of Cancer?

Trends in SEER Incidence and US Death Rates by Primary Cancer Site 2001-2010



Obesity the Cause?

Table 1. Body mass index and risk of several cancer types

Type of Cancer	Men RR (95% CI)*	Women RR (95% CI)*	Reference
Endometrial	–	2.89 (2.62-3.18)	Reeves (2007) (ref. 10) [†]
	–	1.59 (1.50-1.68)	Renehan (2008) (ref. 11) [‡]
Esophageal adenocarcinoma	1.52 (1.33-1.74)	1.51 (1.31-1.74)	Renehan (2008) (ref. 11) [‡]
Postmenopausal breast	–	1.40 (1.31-1.49)	Reeves (2007) (ref. 10) [†]
	–	1.12 (1.08-1.16)	Renehan (2008) (ref. 11) [‡]
Colon	1.30 (1.25-1.35)	1.12 (1.07-1.18)	Larsson (2007) (ref. 12) [‡]
	1.53 (1.33-1.75)	1.09 (0.93-1.28)	Moghaddam (2007) (ref. 13) [§]
	1.24 (1.20-1.28)	1.09 (1.05-1.13)	Renehan (2008) (ref. 11) [‡]
Rectal	1.12 (1.09-1.16)	1.03 (0.99-1.08)	Larsson (2007) (ref. 12) [‡]
	1.27 (1.17-1.37)	1.02 (0.85-1.22)	Moghaddam (2007) (ref. 13) [§]
	1.09 (1.06-1.12)	1.02 (1.00-1.05)	Renehan (2008) (ref. 11) [‡]
Thyroid	1.33 (1.04-1.70)	1.14 (1.06-1.23)	Renehan (2008) (ref. 11) [‡]
Renal	1.24 (1.15-1.34)	1.34 (1.25-1.43)	Renehan (2008) (ref. 11) [‡]
Pancreatic	1.16 (1.05-1.28)	1.10 (1.02-1.09)	Larsson (2007) (ref. 14) [‡]
	1.07 (0.93-1.23)	1.12 (1.02-1.22)	Renehan (2008) (ref. 11) [‡]
Ovarian	–	1.14 (1.03-1.27)	Reeves (2007) (ref. 10) [†]
	–	1.03 (0.99-1.08)	Renehan (2008) (ref. 11) [‡]
Multiple myeloma	1.11 (1.05-1.18)	1.11 (1.07-1.15)	Renehan (2008) (ref. 11) [‡]
Gallbladder	1.09 (0.99-1.21)	1.59 (1.02-2.47)	Renehan (2008) (ref. 11) [‡]
Leukemia	1.08 (1.02-1.14)	1.17 (1.04-1.32)	Renehan (2008) (ref. 11) [‡]
Non-Hodgkin lymphoma	1.06 (1.03-1.09)	1.07 (1.00-1.14)	Renehan (2008) (ref. 11) [‡]
Prostate high-grade	1.25 (1.06-1.49)	–	–
Prostate low-grade	0.85 (0.77-0.93)	–	Hsing (2007) (ref. 15) [‡]

*Relative risk (RR) and 95% confidence interval (CI).

[†]Estimated trends in the RR associated with every 10 kg/m² increase in Body Mass Index (BMI).

[‡]RR associated with every 5 kg/m² increase in BMI.

[§]RR with BMI ≥ 30 kg/m² compared to BMI < 25 kg/m².

Cancer Epidemiol Biomarkers Prev 2009;18(10). October 2009

Question 1

Is there an association between diabetes and cancer?

Yes...but it is unclear if this association is causative

Question 2

What are the risk factors common to both cancer and diabetes?

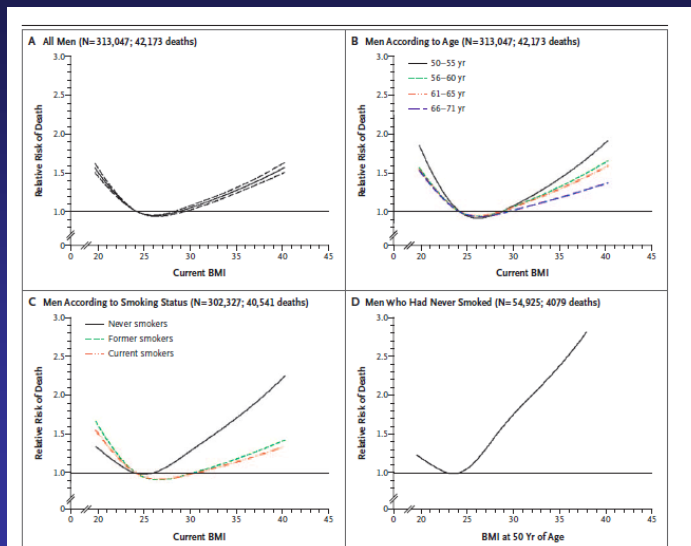
Modifiable Risk Factors



Common Risk Factors



The Rise of Cancer?



Adams et al. NEJM 2006

Question 2

What are the risk factors common to both cancer and diabetes?

Diet, obesity, smoking, alcohol, exercise...but is this relevant?

Question 3

What are the possible biologic links between diabetes and cancer?

Possible Mechanisms

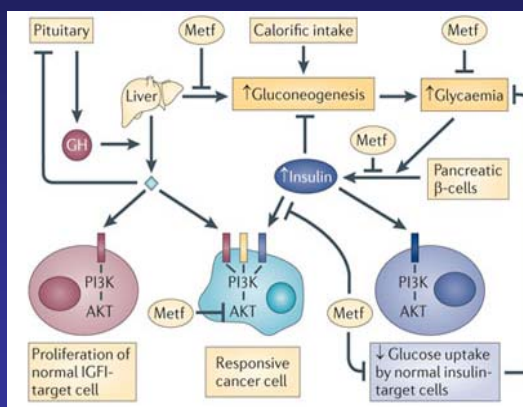
1. Hyperinsulinemia → Insulin/IGF Axis
2. Hyperglycemia → Glycolysis Theory
3. Inflammation → Inflammatory Cytokines

The IGF Axis

1. Hyperinsulinemia → Insulin/IGF Axis

Most cancer cells express insulin and Insulin-like Growth Factor receptors

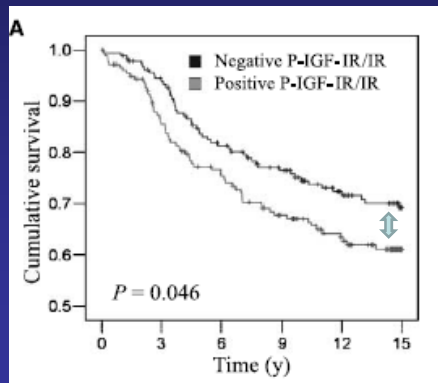
IGF receptors can stimulate insulin-mediated mitogenesis



Pollak. Nature Reviews Cancer 2012

The IGF Axis

1. Hyperinsulinemia → Insulin/IGF Axis
Breast Cancer

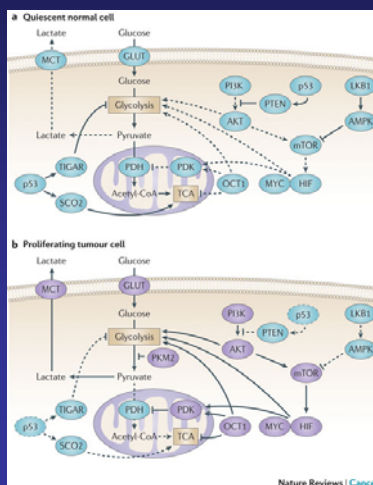


Law et al. Cancer Res 2008

Hyperglycemia

2. Hyperglycemia → Glycolysis

Many cancers depend on glycolysis for energy and untreated hyperglycemia may facilitate neoplastic proliferation



Nature Reviews | Cancer

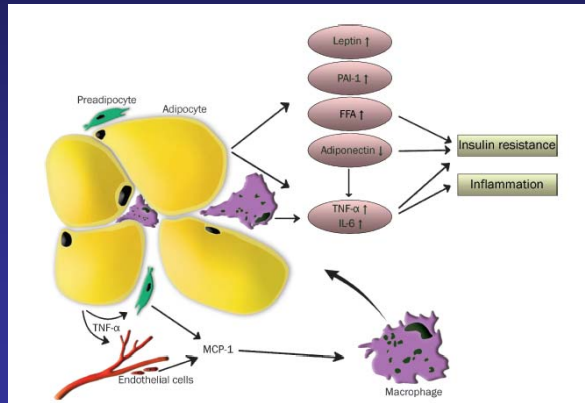
Inflammation

3. Inflammation



Inflammatory Cytokines

Enhanced production of free fatty acids, IL-6, MCP, PAI-I may drive uncontrolled cellular proliferation



Van Kruijsdijk et al. Cancer Epidemiol Biomarkers Prev. 2009

Question 3

What are the possible biologic links between diabetes and cancer?

Hyperinsulinemia, hyperglycemia and inflammation may play a biologically plausible role

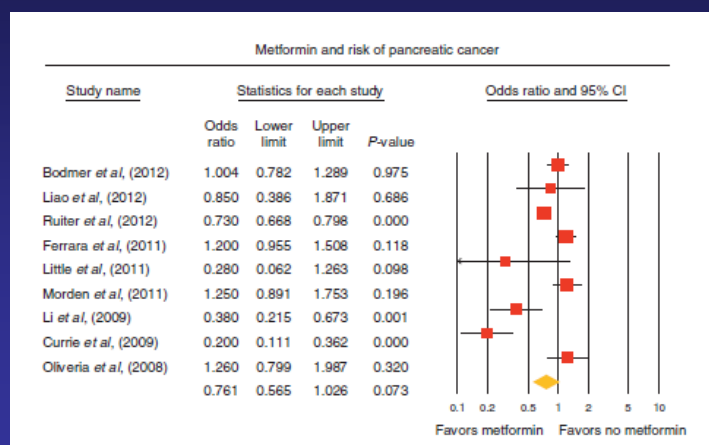
Question 4

Does the treatment of diabetes cause cancer?

Let's look at the relationship between medications and pancreatic cancer

Metformin

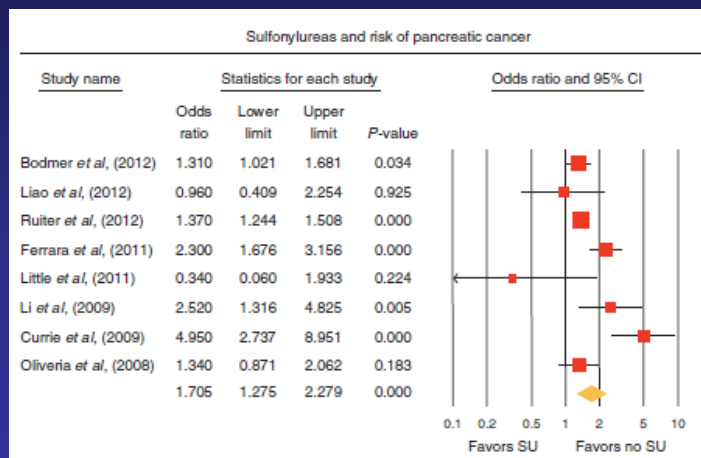
Does the treatment of diabetes cause cancer?



Singh *et al.* Am J Gastroenterology. 2013

Sulfonylureas

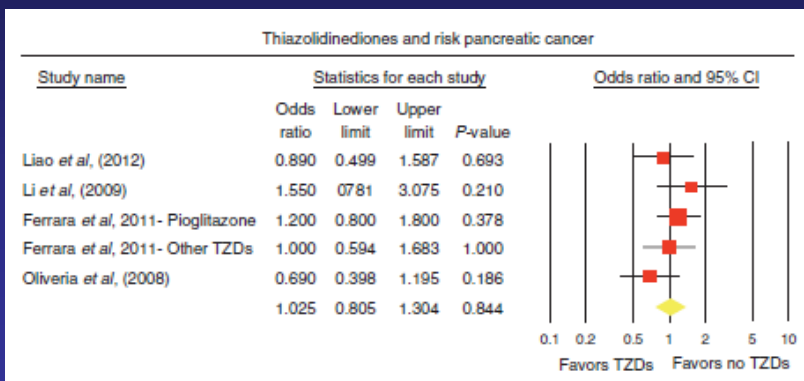
Does the treatment of diabetes cause cancer?



Singh *et al.* Am J Gastroenterology. 2013

Thiazolidinediones

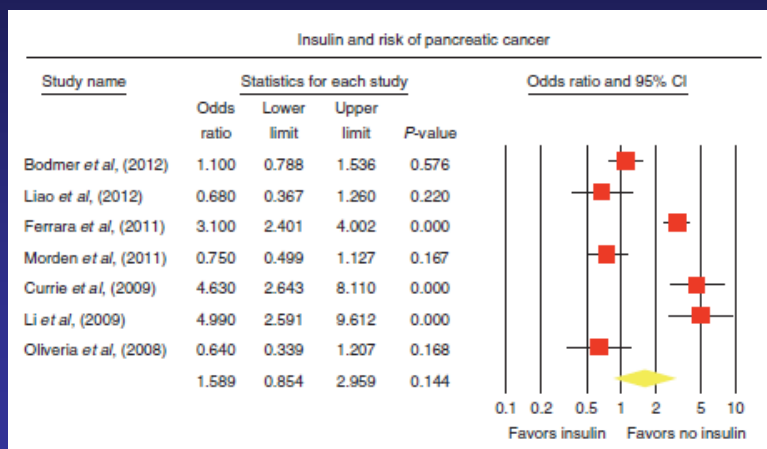
Does the treatment of diabetes cause cancer?



Singh *et al.* Am J Gastroenterology. 2013

Insulin

Does the treatment of diabetes cause cancer?



Singh *et al.* Am J Gastroenterology. 2013

Question 4

Does the treatment of diabetes cause cancer?

There does not appear to be an association between diabetes treatment and cancer

Objectives

1. Case Study

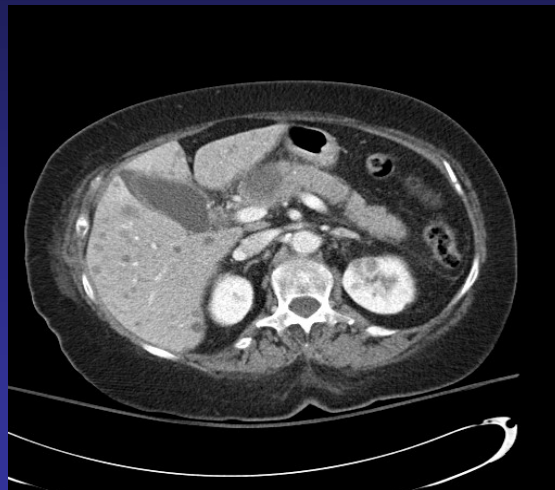


2. 4 Questions

3. Diabetes and Pancreatic Cancer

Case Presentation

52 y/o female with newly diagnosed pancreatic cancer



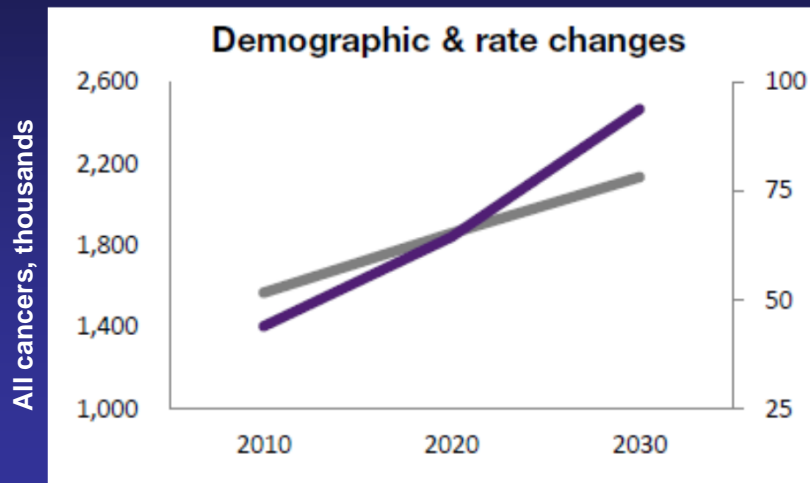
Case Presentation

How is diabetes related to this patient's pancreatic cancer?



Diabetes and Pancreatic Cancer

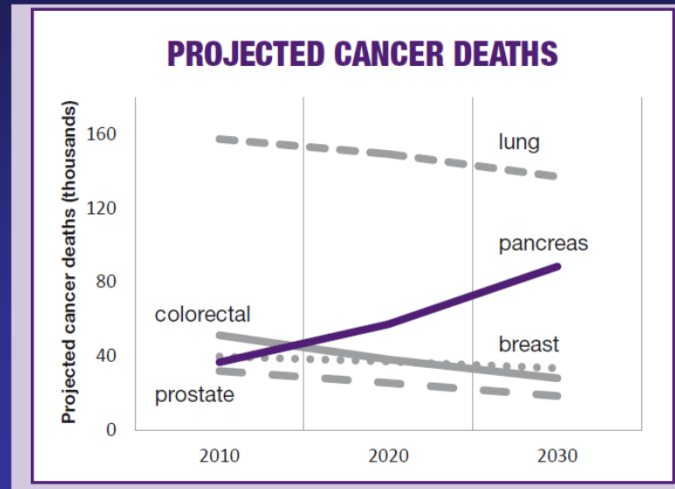
How much of a problem is pancreatic cancer?



www.pancan.com

Diabetes and Pancreatic Cancer

How much of a problem is pancreatic cancer?



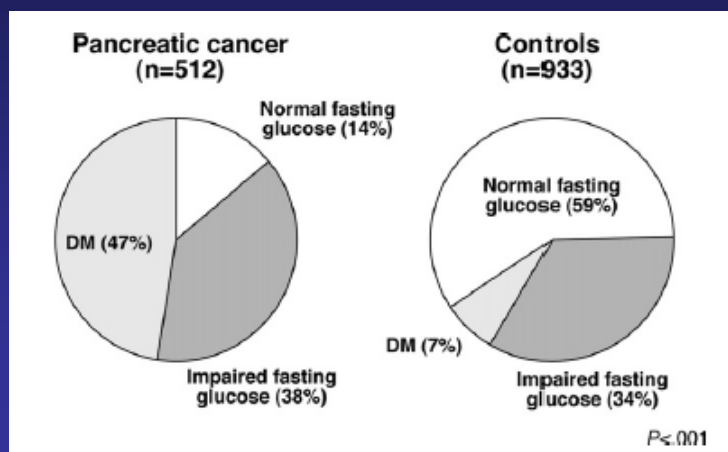
Diabetes and Pancreatic Cancer

Pancreatic Cancer is a Big Problem

Pancreatic Incidence = Pancreatic Mortality

Diabetes and Pancreatic Cancer

How often do patients with pancreatic cancer develop diabetes?

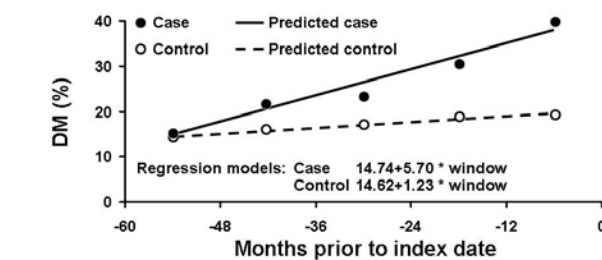


Pannala et al. Gastroenterology 2008

Diabetes and Pancreatic Cancer

How often do patients with pancreatic cancer develop diabetes?

Figure 1: Observed and Predicted Prevalence of DM at 12-Month Intervals Prior to Index



Time	-48 to -60	-36 to -48	-24 to -36	-12 to -24	+1 to -12
Window	0	1	2	3	4
Cases (no.)	157	160	165	168	685
Controls (no.)	891	1,027	1,071	1,172	1,162
P	0.76	0.06	0.04	0.001	<0.0001

Chari et al. Gastroenterology 2005

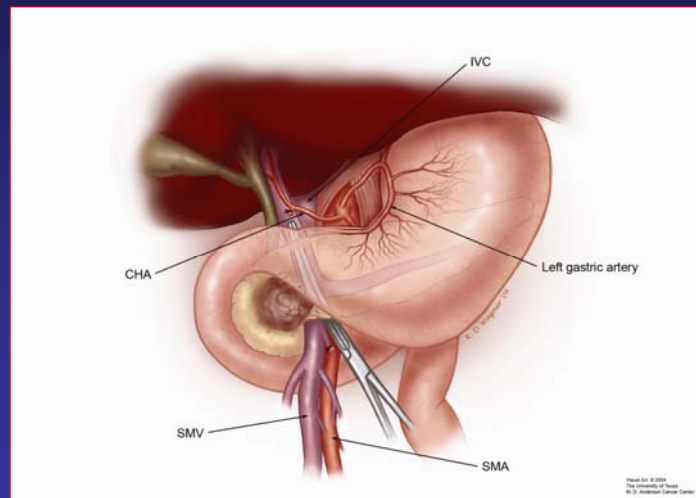
Diabetes and Pancreatic Cancer

Pancreatic Cancer is associated with diabetes

60-70% of patients with pancreatic cancer develop diabetes in the year before their diagnosis

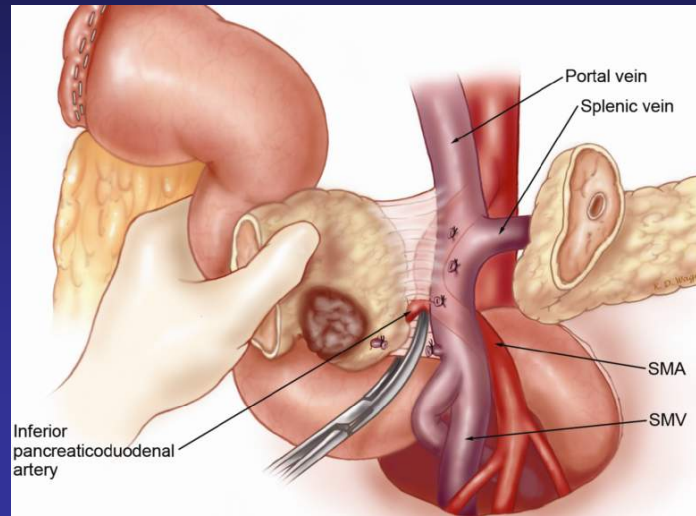
Diabetes and Pancreatic Cancer

Does pancreatic cancer cause diabetes?



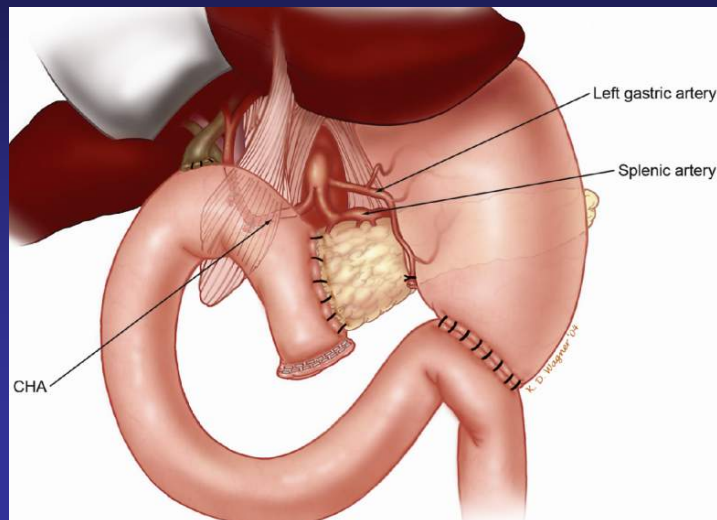
Diabetes and Pancreatic Cancer

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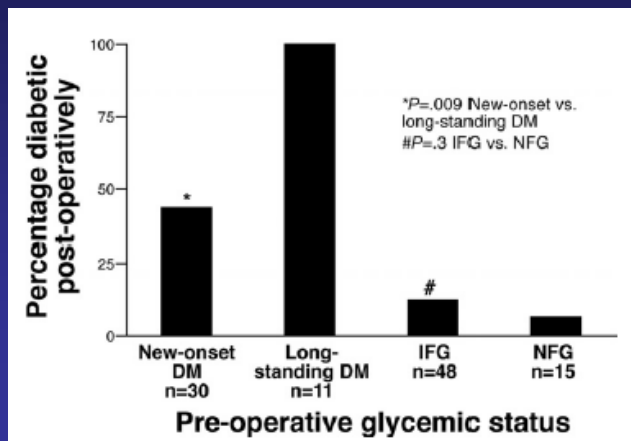
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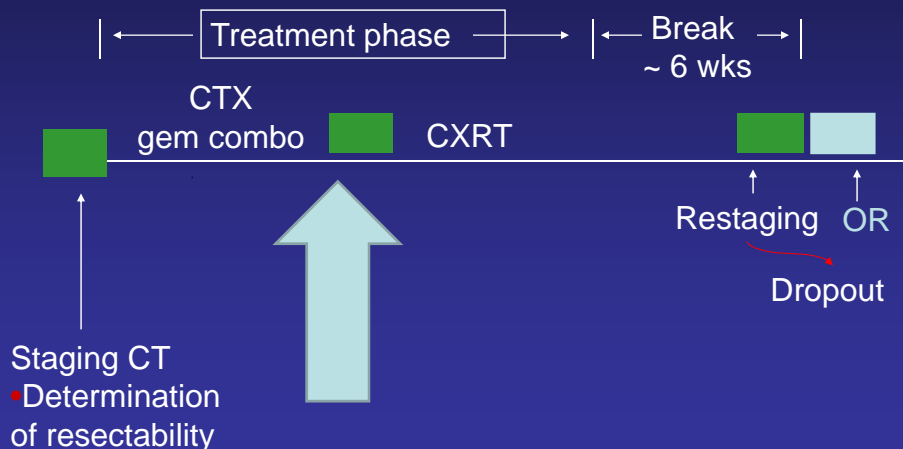
Diabetes and Pancreatic Cancer

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Diabetes and Pancreatic Cancer

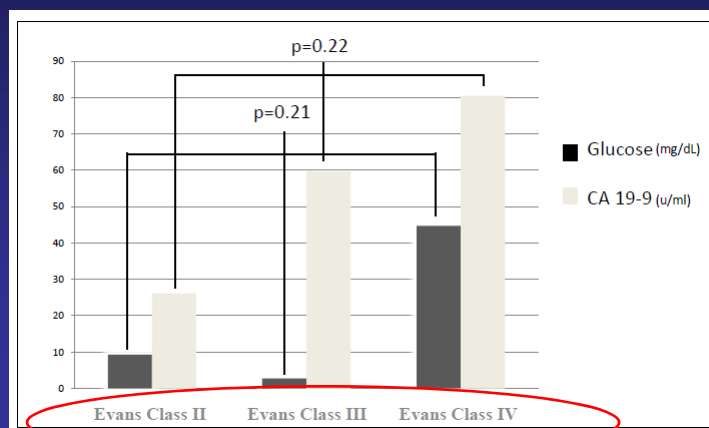
Does pancreatic cancer cause diabetes?



Diabetes and Pancreatic Cancer

Does pancreatic cancer cause diabetes?

Change in blood glucose control during neoadjuvant therapy



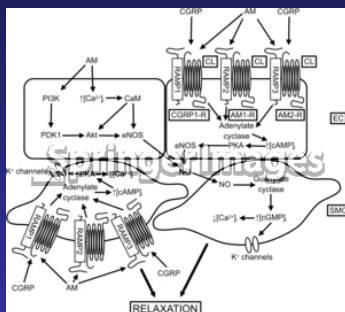
Diabetes and Pancreatic Cancer

Pancreatic cancer appears to cause diabetes

Diabetes resolves after surgery and as the tumor regresses during neoadjuvant therapy, the diabetes improves

Diabetes and Pancreatic Cancer

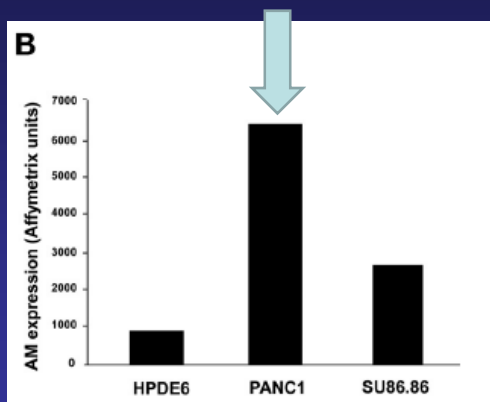
What is it about the cancer that causes diabetes?



Adrenomedullin is up-regulated in patients with pancreatic cancer and causes insulinresistance in cells and mice.

Diabetes and Pancreatic Cancer

What is it about the cancer that causes diabetes?



Adrenomedullin

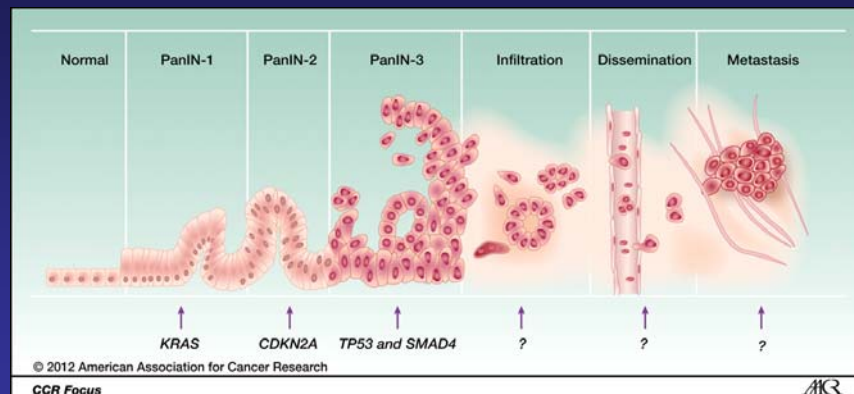
Diabetes and Pancreatic Cancer

So why do we care?

- 90% of patients with pancreatic cancer have metastasized at time of diagnosis
- There is no screening test for pancreatic cancer
- Could diabetes and adrenomedullin be used as screening tests?

Diabetes and Pancreatic Cancer

Screening for Pancreatic Cancer



Diabetes and Pancreatic Cancer

Screening for Pancreatic Cancer

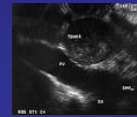
New Onset Diabetes
Mellitus > 50 years old



Elevated Adrenomedullin
and CA 19-9



Endoscopic Ultrasound



Early Detection



Diabetes and Pancreatic Cancer

The diabetes and pancreatic cancer relationship may allow for the development of an effective screening test for this disease

Not only can diabetes contribute to cancer, it can also be caused by cancer

Objectives

1. Case Study



Objectives

1. Case Study

2. 4 Questions



Objectives

1. Case Study



2. 4 Questions

3. Diabetes and Pancreatic Cancer

Thank You

“Man cannot discover new oceans unless he has the courage to lose sight of the shore”

*- Andre Gide
1947 Nobel prize for literature*

