Diabetes, diabetes treatment and cancer risk: the epidemiology

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CANCER RESEARCH UK

Duality of interest declaration

I report the following potential duality/dualities of interest in the field covered by my lecture:

- *Advisory Board Panels*
- *Speaker Honoraria*
- *Research Support*

Funded by: Novo Nordisk; Sanofi Pasteur MSD

Andrew G Renehan

Session structure

- Part 1: Epidemiology — Renehan
- Part 2: X10 story & updates — Russell-Jones
- Part 3: IGF-I cancer biology — Renehan
- Part 3: clinical implications — Renehan

Iran: Night Raids Terrorize Civilians

Security Forces Wreck Homes, Destroy Property to Stop Protest Chants; News Access Curtailed

JUNE 26, 2009

(New York) - Iran's paramilitary Basij are carrying out brutal nighttime raids, destroying property in private homes and beating civilians in an attempt to stop nightly protest chants, Human Rights Watch said today. Human Rights Watch also said the Iranian authorities are confiscating satellite dishes from private homes to prevent citizens from seeing foreign news.

OTHER MATERIAL:

Stark footage of what appear to be Basiji night raids

Human Rights Watch reporting on Iran

"While most of the world's attenti... focused on the beat... Ir...

BBC NEWS CHANNEL

Page last updated at 11:01 GMT, Friday, 26 June

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Printable

Singer Michael Jackso...

Michael Jackson had been due to play 50 concert dates in the UK this summer

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« States Should Plan for H1N1 Vaccinations as Numbers Rise More

Health Blog

WSJ's blog on health and the business of health.

JUNE 26, 2009, 6:09 PM ET

Study: Sanofi's Lantus Insulin Has Possible Cancer Link

Article | Comments (19)

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By Shirley S. Wang

New data published today suggest that there is a "possible link" between French drug maker Sanofi-Aventis's Lantus insulin for diabetes and a higher risk of cancer, according to Diabetologia, the journal in which the data were published.

European Association for the Study of Diabetes, which ... also made an "urgent call for more ... It said the concern was specific to artificial insulin like

The 'big' four

Table 3 | Studies of insulin analogues and incident cancer risk

Study	Insulin analog and comparator (number of patients)	Total no. of all cancers (mean FU)	All-cancer risk*	Sub-group analyses	Cancer subtotals (analog)	Sub-group risks
Observational studies						
Hemkens *et al.* (2009)[150]	Glargine (n=23,855) and human insulin (n=95,804)	5,009 (1.63 years)	1.18 (1.08–1.28)	Daily dose: 10 IU Daily dose: 30 IU Daily dose: 50 IU	NR NR NR	1.09 (1.00–1.19) 1.19 (1.10–1.30) 1.31 (1.20–1.42)
Currie *et al.* (2009)[149]	Glargine (n=2,286) and human insulin (n=5,748)	2,106 (2.9 years)	0.81 (0.59–1.11)	Breast	305 (10)	0.86 (0.42–1.75)
Jonasson *et al.* (2009)[151]	Glargine (n=5,970) and other insulins (n=88,555)	2,348 (NR)	1.06 (0.90–1.25)	Breast Prostate Gastrointestinal	208 (25) 464 (32) 454 (24)	1.97 (1.29–3.00) 1.26 (0.88–1.80) 0.91 (0.61–1.38)
Colhoun *et al.* (2009)[148]	Glargine (n=477)‡ and other insulins (n=36,254)‡	715 (34,441 person-years)	1.73 (0.98–3.05)	Breast Prostate Colorectal Lung	92 (6) 48 (1) 109 (3) 149 (4)	3.65 (1.05–12.68) 1.16 (0.16–8.50) 1.43 (0.45–4.57) 1.43 (0.53–3.88)

Clayton, Banerjee, Murray, Renehan Nat Rev Endocrinol 2010

(some) Limitations & critics

- Classification of patients into treatment groups based on follow-up information
- Insulin dose calculated as the mean during follow-up, then included in survival analysis as if it were a baseline covariate
- Short follow-up
- Absence of key confounders (e.g. BMI, smoking)
- Reference group classifications/problems
- Small numbers for individual cancer types

Editorials

Comment

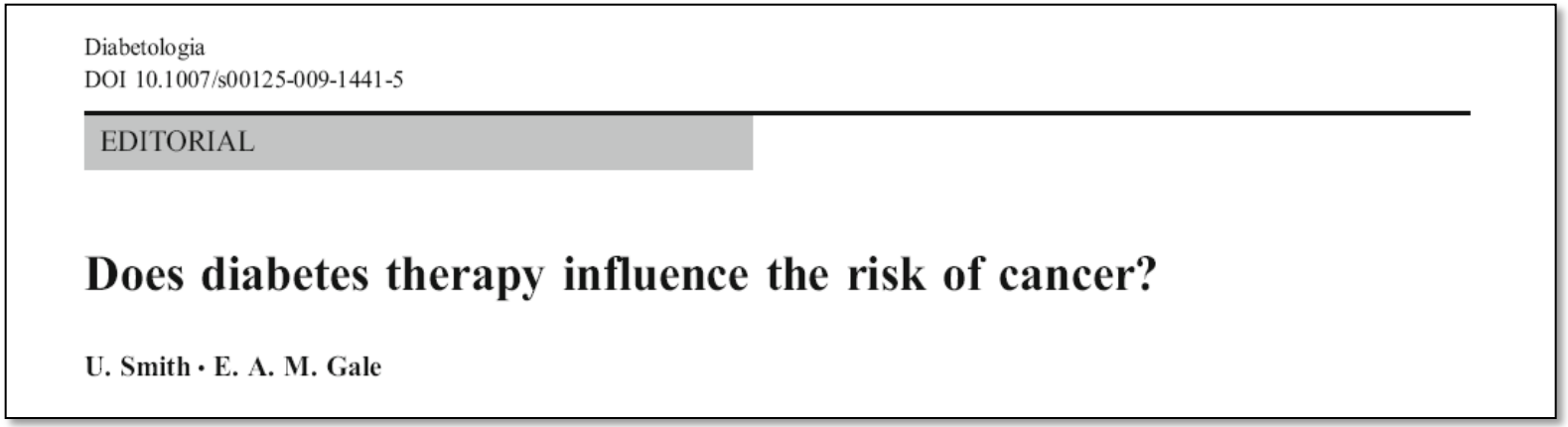
Pocock, Smeeth. *Lancet* 2009; DOI 10.1016/S0140-6736(09)61307-6

Insulin glargine and malignancy: an unwarranted alarm

Insulin glargine is a recombinant insulin analogue that has become widely used, largely because of a lower risk of hypoglycaemia and prolonged stable action. Synthetic

any time-to-event (survival) analysis is that allocation to treatment groups and other covariates (such as drug dose) must be determined before follow-up starts. Unfortunately,

Published Online
July 20, 2009
DOI:10.1016/S0140-6736(09)61307-6



Diabetologia
DOI 10.1007/s00125-009-1441-5

EDITORIAL

Does diabetes therapy influence the risk of cancer?

U. Smith · E. A. M. Gale

A case to be answered

Not a surprise to the cancer community

- Obesity is a common shared risk factor
- Diabetes $\Rightarrow \uparrow$risk of incidence & mortality
- Glucose environment - ? relevant
- Metformin may be cancer protective
  (multi-actions in cancer)
- Insulin analogues have a ‘IGF-I look’

Obesity & cancer

BMI, cancer risk and men

- Search to Dec 2007 ⇒ analysis of Asia-Pacific populations
- Standardisation of inclusion criteria & analyses
- Inclusion of less common malignancies
- Sex-specific summary estimates

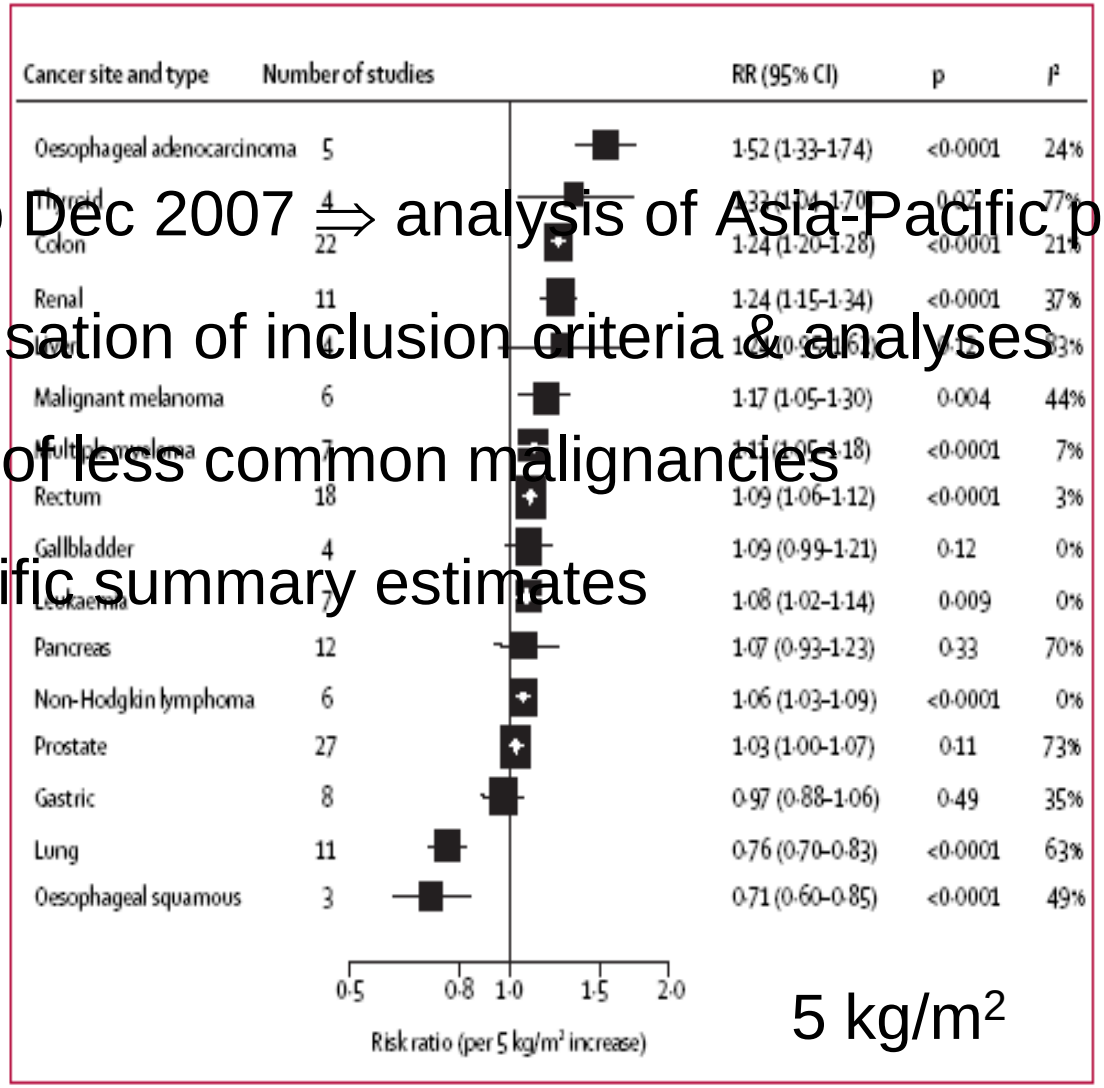


Figure 3: Summary risk estimates by cancer sites in men

Renehan et al. Lancet 371: 569-578, 2008

BMI, cancer risk and women

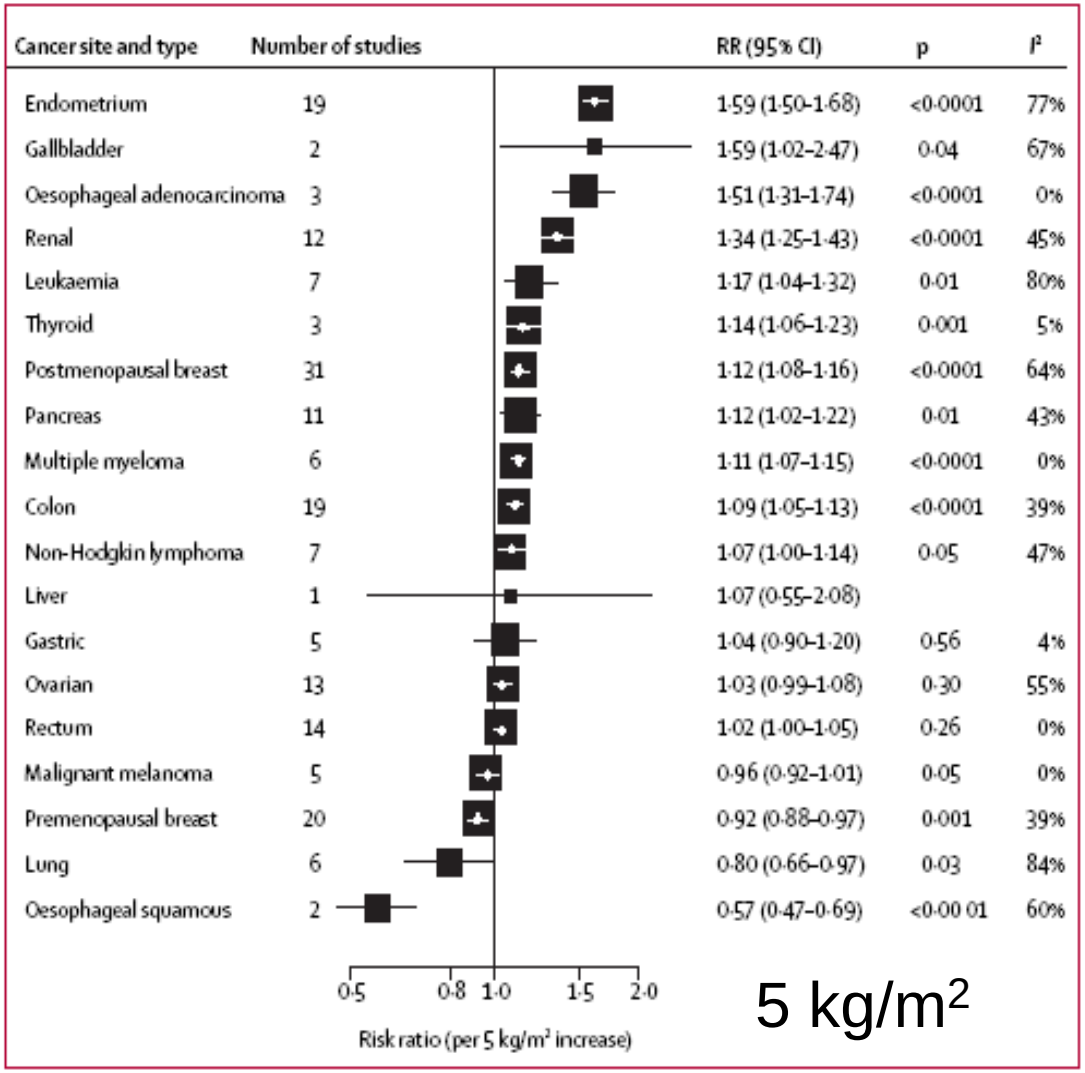


Figure 4: Summary risk estimates by cancer sites in women

Renehan et al. Lancet 371: 569-578, 2008

BMI & cancer: sex-specific associations

	Studies		Cases		Risk ratio in men*	Risk ratio in women*	p value†
	Men	Women	Men	Women			
Colon cancer							
All studies	22	19	22 440	20 975	1·24 (1·21–1·28)	1·09 (1·05–1·14)	<0·0001
Studies with both sexes	13	13	17 495	19 256	1·24 (1·18–1·31)	1·08 (1·02–1·34)	0·001
All but one study[46]	21	18	8635	4337	1·26 (1·21–1·30)	1·10 (1·06–1·15)	<0·0001
Rectal cancer							
All studies	18	14	14 894	9052	1·09 (1·06–1·12)	1·02 (0·99–1·04)	0·001
Studies with both sexes	11	11	11 035	8644	1·08 (1·05–1·11)	1·01 (0·98–1·04)	0·003
All but one study[46]	17	13	5712	1560	1·09 (1·05–1·15)	1·05 (0·99–1·12)	0·32

*Risk ratio per 5 kg/m² increase in BMI (95% CI). †Meta-regression analysis with univariable model of sex. ‡Meta-regression analysis with multivariable models including the method of BMI determination (measured or self-reported)–the extent of cancer-site specific risk factor adjustment–and geographic region. We analysed only cancer sites with more than 10 studies that included both sexes.

Table 2: Comparisons of risk ratios in men and women

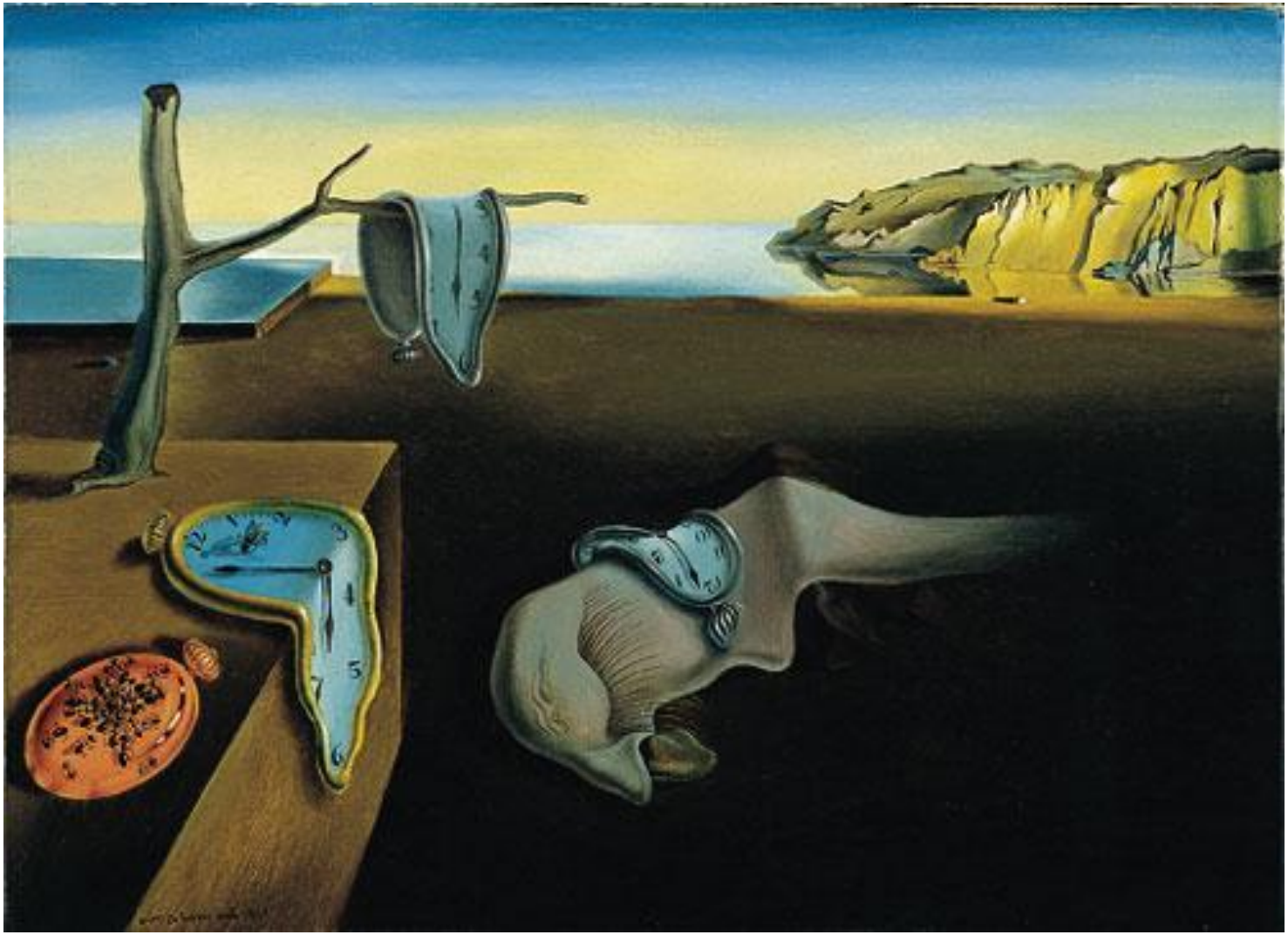
Renehan et al. Lancet 371: 569-578, 2008

Central obesity & cancer risk

Metabolic syndrome (syndrome X)

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance

Diabetes – cancer incidence & mortality



Diabetes and incident cancer risk

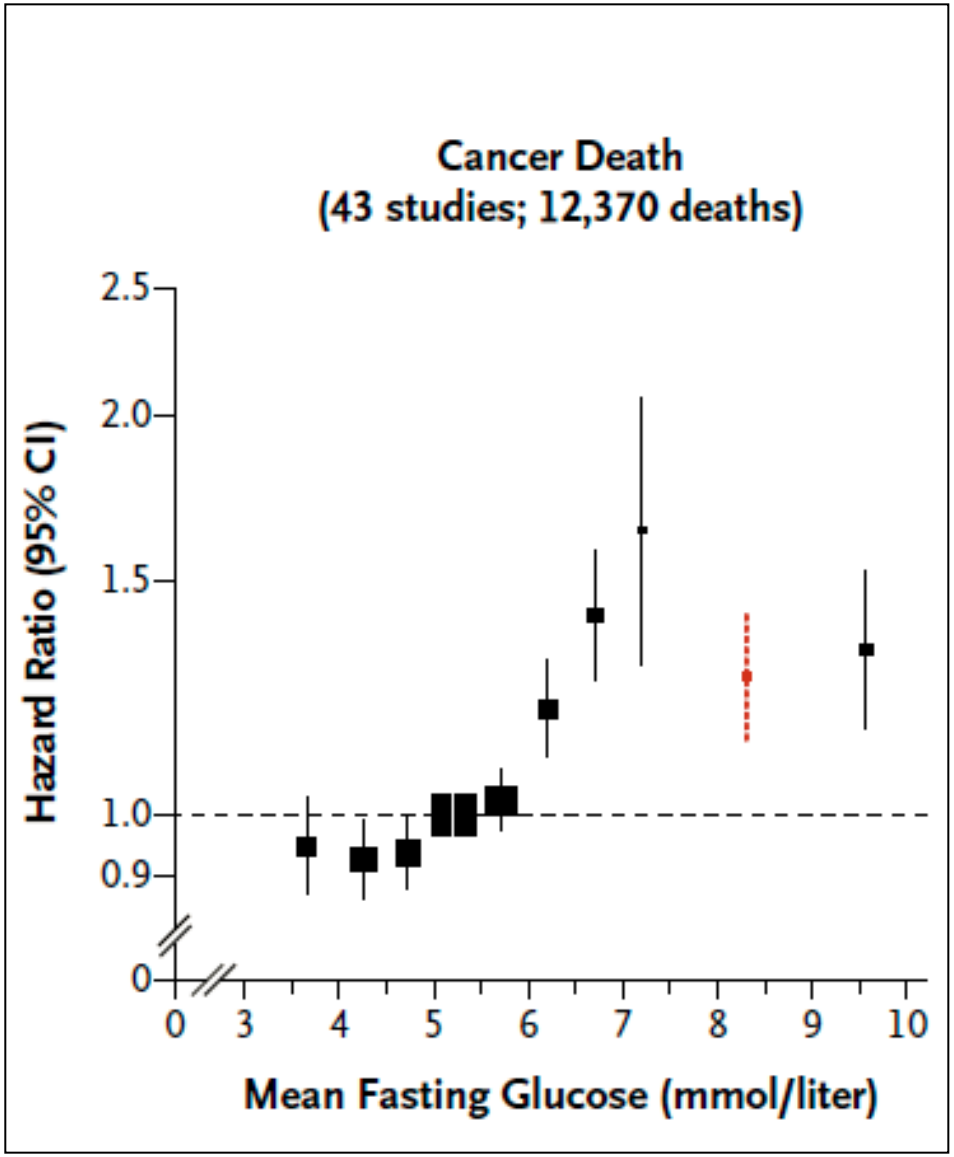
Cancer type	Meta-analysis	Number of cohorts/ number of case-control studies*	Number of cancers	Risk ratio (95% CI)
Breast (all)	Larsson et al, 2007[6]	15/5	30 407	1·20 (1·12–1·28)
Premenopausal	Larsson et al, 2007[6]	Not stated	Not stated	0·91 (0·62–1·34)
Postmenopausal	Larsson et al, 2007[6]	Not stated	Not stated	1·16 (1·09–1·24)
Colorectal	Larsson et al, 2005[7]	9/6	26 306	1·30 (1·20–1·40
Endometrial	Friberg et al, 2007[8]	3/13	7596	2·10 (1·93–3·24)
Liver	El-Serag et al, 2006[9]	13/13	Not stated	2·50 (1·93–3·24)
Pancreas	Huxley et al, 2005[10]	19/17	9220	1·82 (1·71–1·94)
Non-Hodgkin lymphoma	Mitri et al, 2008[11]	5/11	Not stated	1·19 (1·07–1·32)
Bladder	Larsson et al, 2006[12]	3/7	Not stated	1·24 (1·08–1·42)
Prostate	Kasper et al, 2006[13]	12/7	20 373	0·84 (0·76–0·93)

Data are fully adjusted estimates. *Different meta-analyses had substantial heterogeneity in how studies were included. Cohorts included population cohorts and diabetes cohorts; case-control studies ranged from hospital-based to population-based. Diabetes inclusion was heterogeneous: most meta-analyses included studies of patients with type 1 and 2 diabetes (variably defined).

Table: **Summary of meta-analyses linking diabetes with cancer risk**

Renehan, Smith, Kirkman Lancet 2010, 375:2201-02.

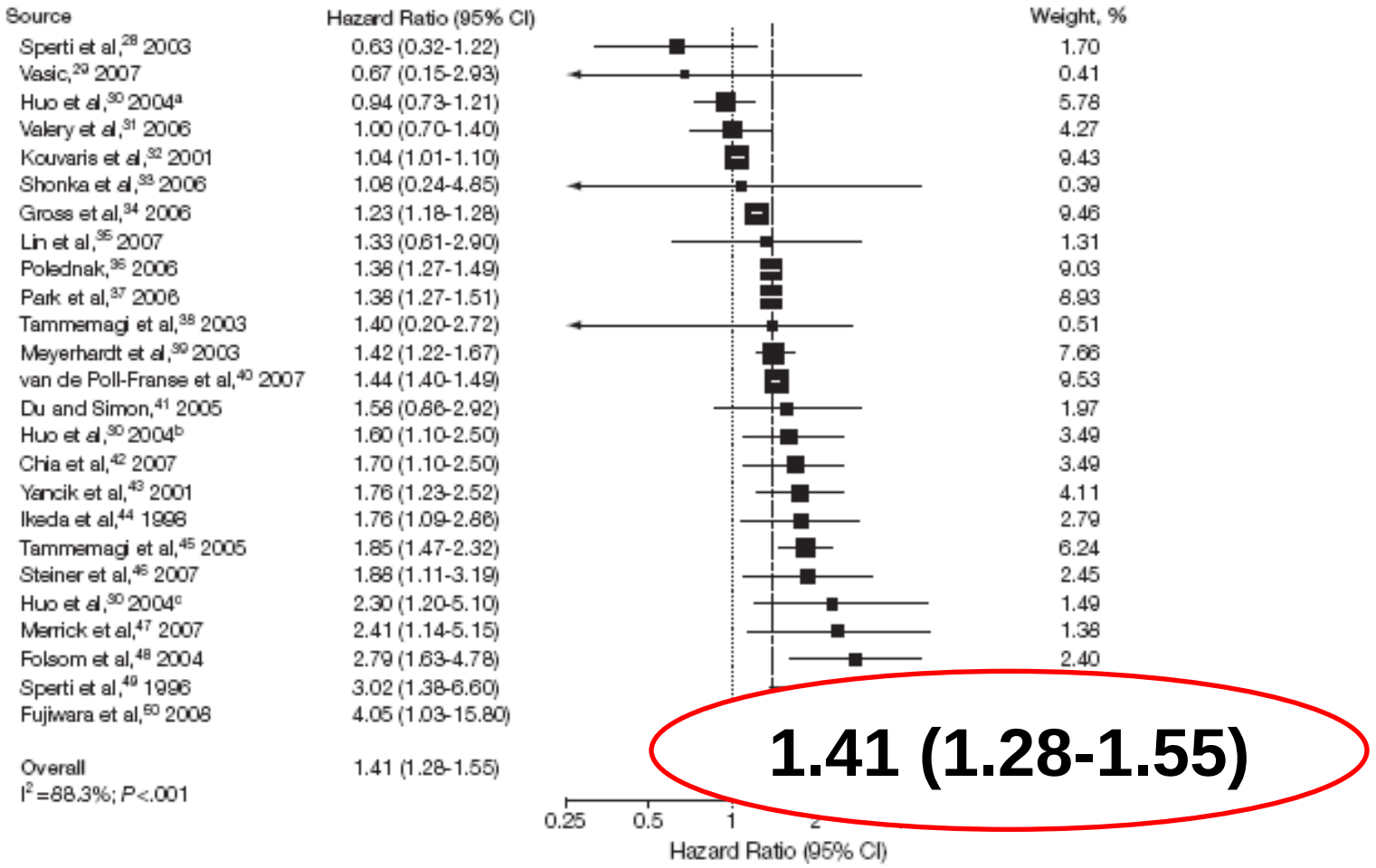
Cancer mortality in type 2 diabetic patients



Emerging Risk Factors Collaboration NEJM 2011

Cancer in type 2 diabetes & mortality

Figure 2. Meta-analysis and Pooled Hazard Ratio of Long-term, All-Cause Mortality in 23 Studies Comparing Cancer Patients With and Without Preexisting Diabetes Mellitus



1.41 (1.28-1.55)

Barone et al. JAMA 2008

Evaluating lifestyle/co-morbidity & cancer outcome

- Cancer screening
- Delayed diagnosis
- Selection for initial treatment
- Complications of initial treatment
- Peri-treatment mortality
- Selection for adjuvant therapy
- Competing risks for death
- Interactions with therapies

Cancer screening in diabetic patients

ORIGINAL INVESTIGATION

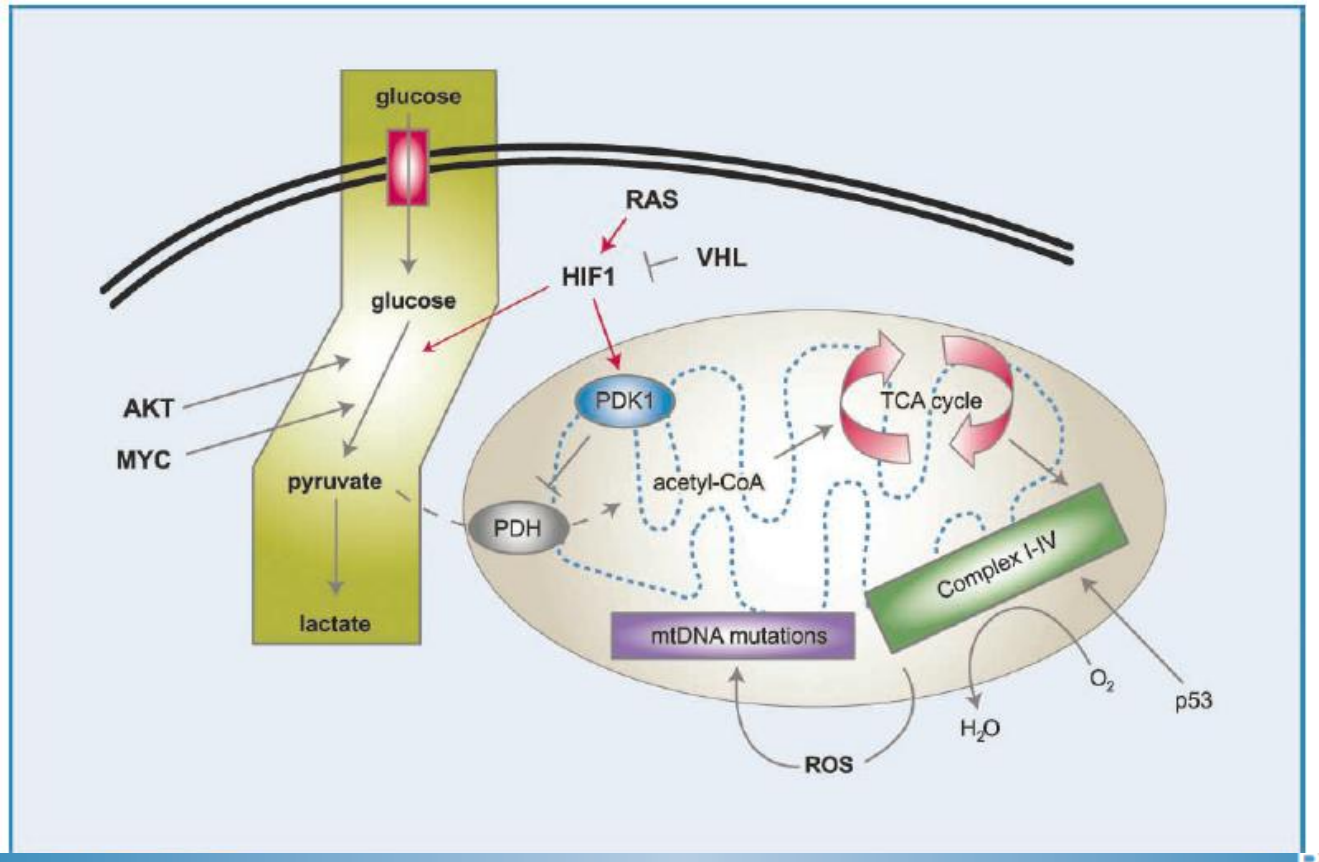
Reduced Screening Mammography Among Women With Diabetes

Lorraine L. Lipscombe, MD; Janet E. Hux, MD, MSc; Gillian L. Booth, MD, MSc

Arch Intern Med. 2005;165:2090-2095

Glucose environment & cancer

Cancer 'sweet-tooth' hypothesis



Review

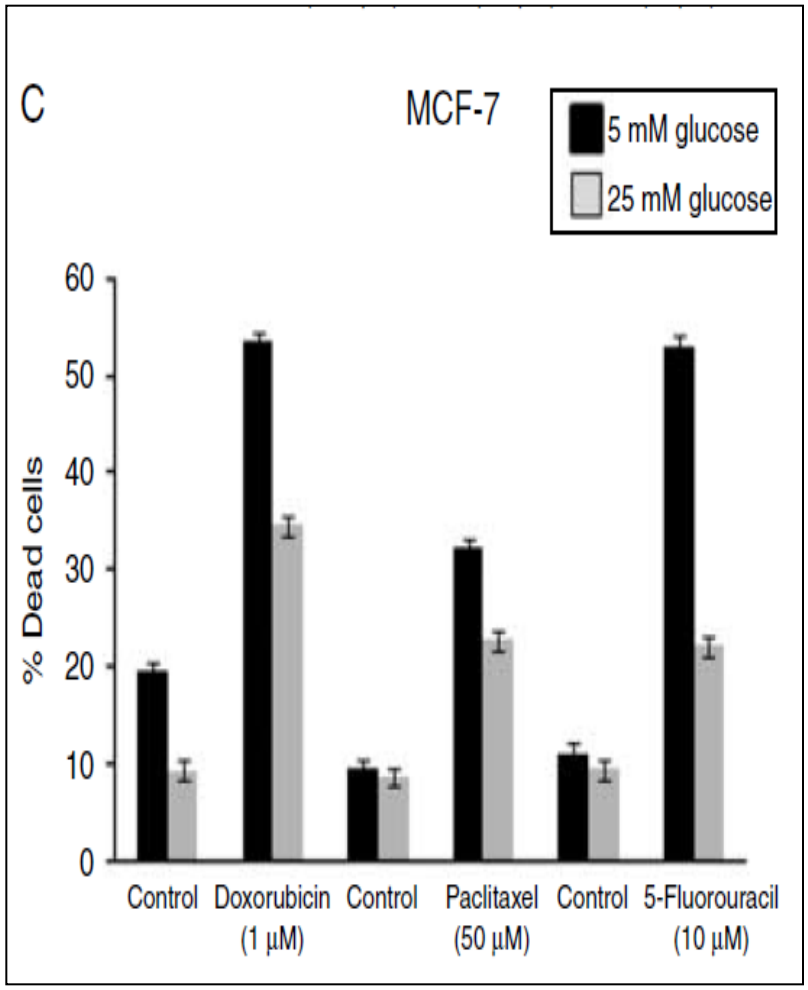
Cancer's Molecular Sweet Tooth and the Warburg Effect

Jung-whan Kim[1] and Chi V. Dang[1,2]

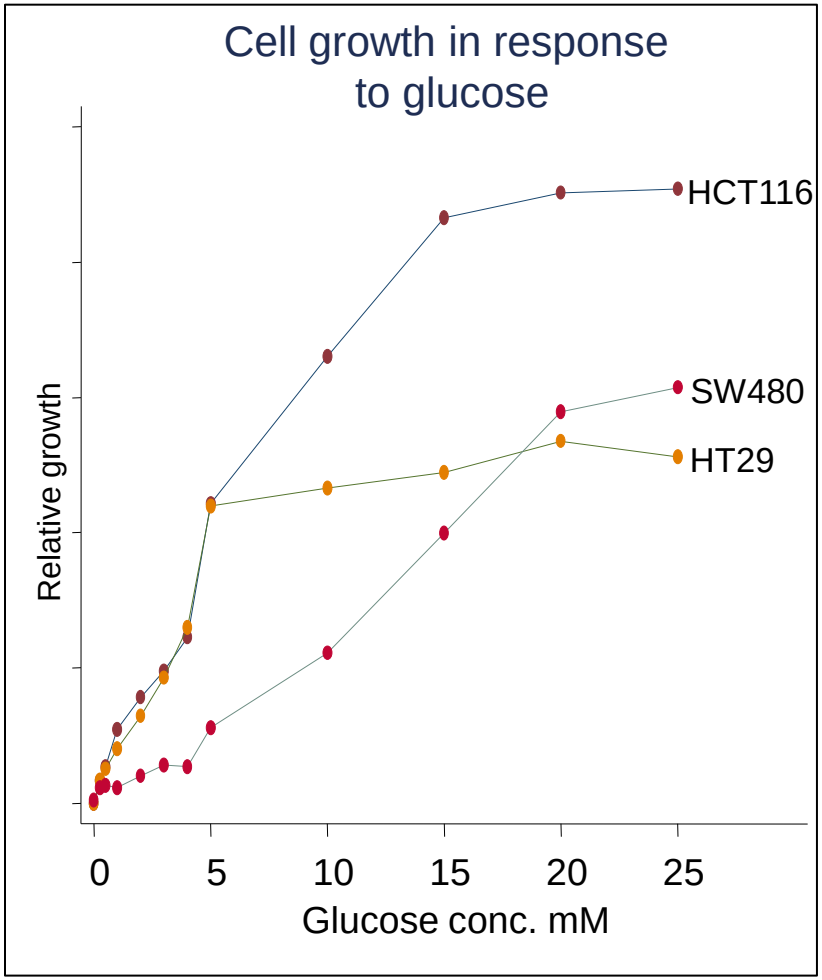
[1]Division of Hematology, Department of Medicine, [2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins University School of Medicine, Baltimore, Maryland

Cancer Res 2006

Glucose & cancer cell biology



Zeng .... Perks Endo-rel-cancers 2010 17: 539-551.



Unpublished Renehan laboratory

Glucose control & cancer risk

Table. Incident Cancers in Large Randomized Trials of Glucose Lowering[a]

Trial	No. in Treatment Group	Follow-up, y	Intensive Treatment, % per Year	Control, % per Year	RRR (95% CI)
UKPDS					
All intensive[b]	2729	10	0.44	0.44	0.98 (0.64-1.52)
Insulin[b]	911	10	0.46	0.48	0.94 (0.55-1.62)
Glyburide	615	10	0.44	0.48	0.91 (0.49-1.67)
Metformin	342	10.7	0.35	0.49	0.71 (0.29-1.76)
VADT[b]	892	5.6	0.48	0.42	1.15 (0.65-2.05)
ACCORD[b]	5128	3.5	1.3	1.2	1.08 (0.90-1.30)
ADVANCE[b]	5571	5	0.43	0.43	1.00 (0.78-1.29)

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax + Diamicron Modified Release Controlled Evaluation; CI, confidence interval; RRR, relative risk reduction; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

[a] Numbers and rates of cancer-related death are shown for all trials except ADVANCE, which shows the numbers and rates of cancer hospitalizations.

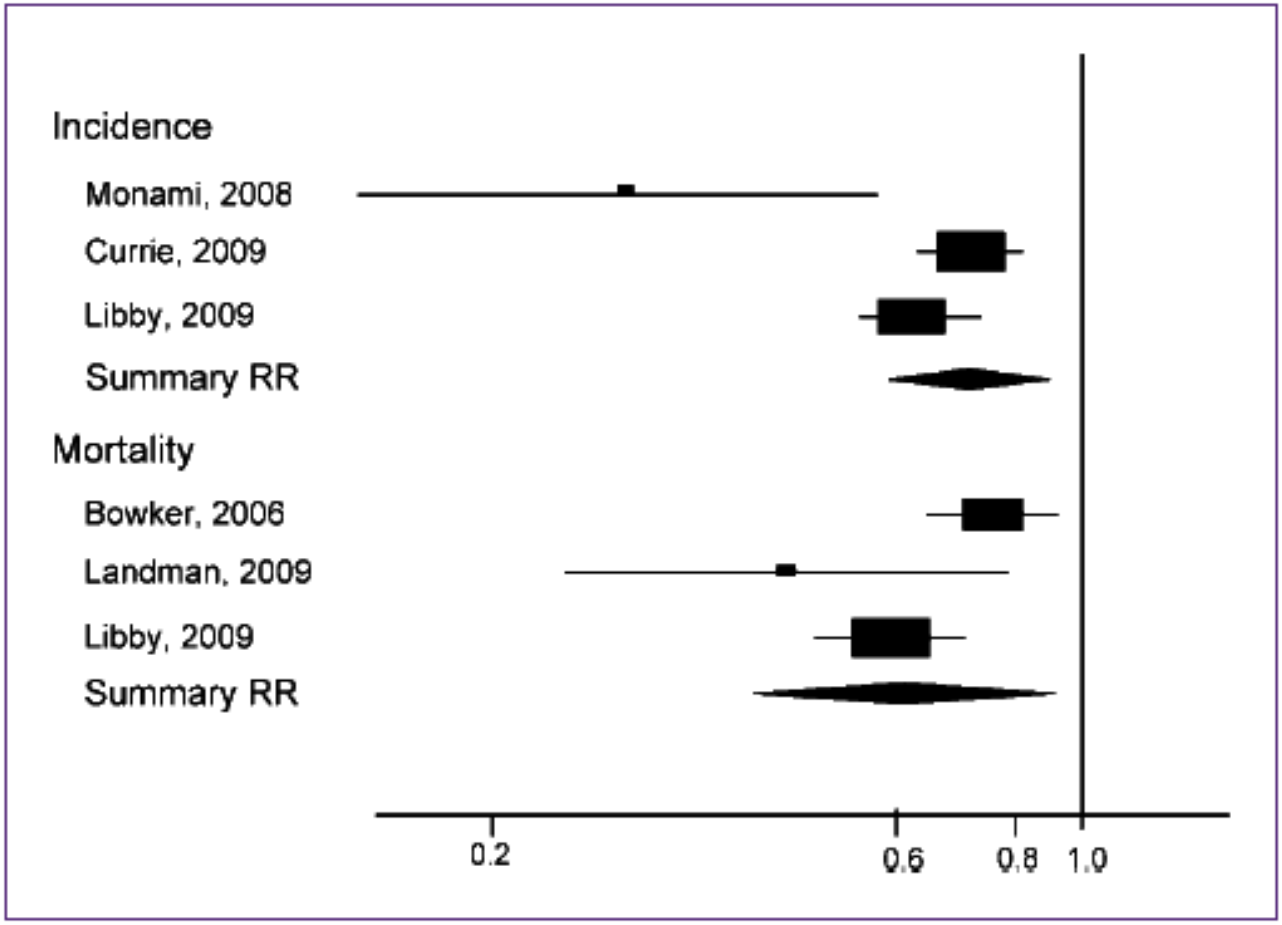
[b] More insulin was used in the intensive treatment groups in these comparisons.

Gerstein JAMA 2010

Metformin & cancer

French lilac (Galega officinalis)

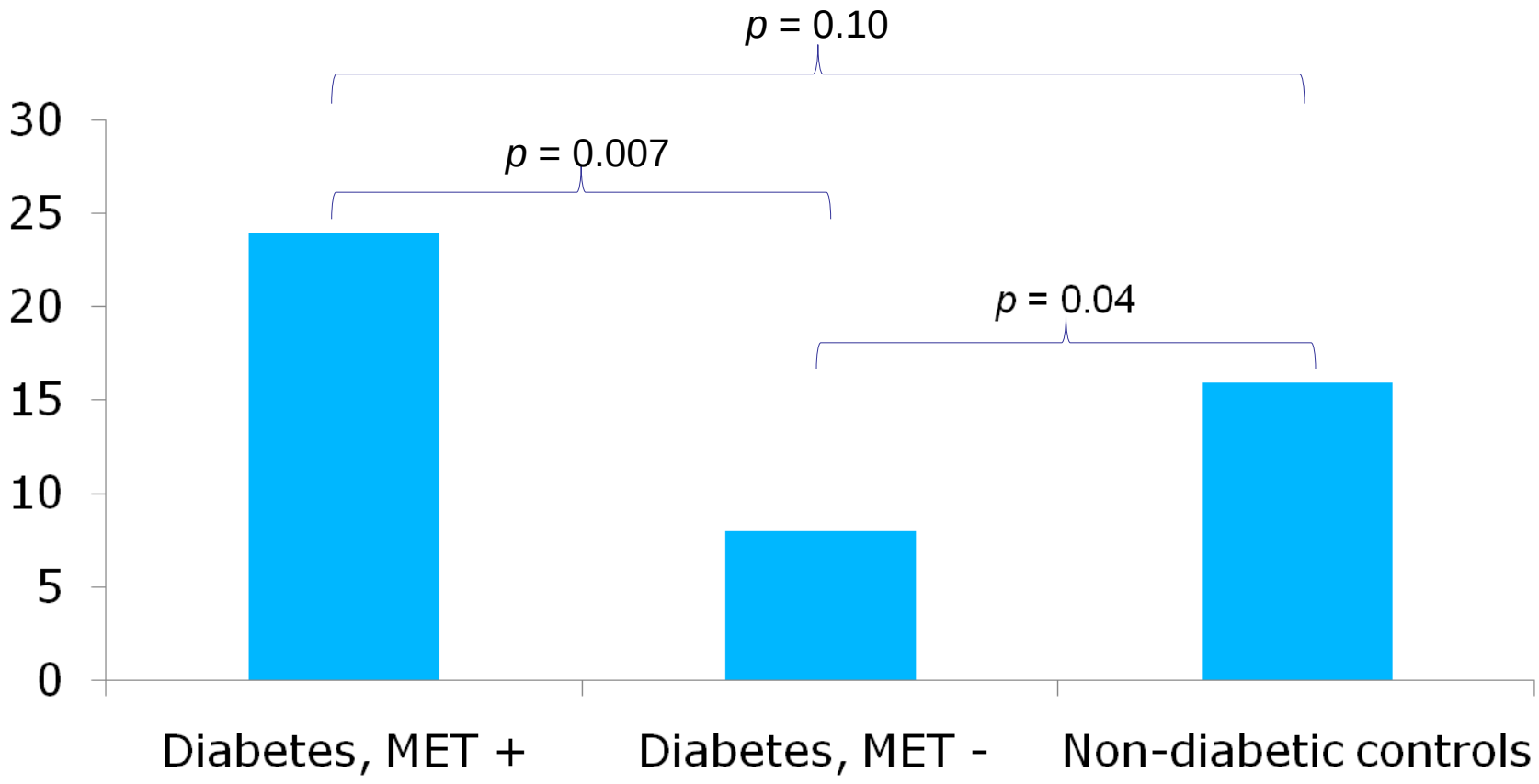
Metformin: cancer incidence & mortality



DeCensi et al Cancer Prev Res 2010

Metformin & cancer treatment

Effect of metformin on pathologic complete response to neoadjuvant chemotherapy, early-stage breast Ca



Jiralerspong et al. J Clin Oncol 2009

Metformin actions & cancer

- Activation of LKB1/AMPK pathway
- Induction of cell cycle arrest/ apoptosis
- Inhibition of protein synthesis
- Reduction in circulating insulin levels (but not IGF-I)
- Inhibition of the unfolded protein response (UPR)
- Activation of the immune system
- Inhibition of cancer stem cells

Candidate mechanisms

Biological mechanisms

- Insulin and insulin-like growth factors (IGFs)
- Sex steroids and sex-steroid binding globulin
- Adipokines (e.g. adiponectin and leptin)
- Nuclear factor κB system/inflammatory cytokines
- Altered immune response

Shared genetic susceptibility

Obesity-related hypoxia & angiogenesis

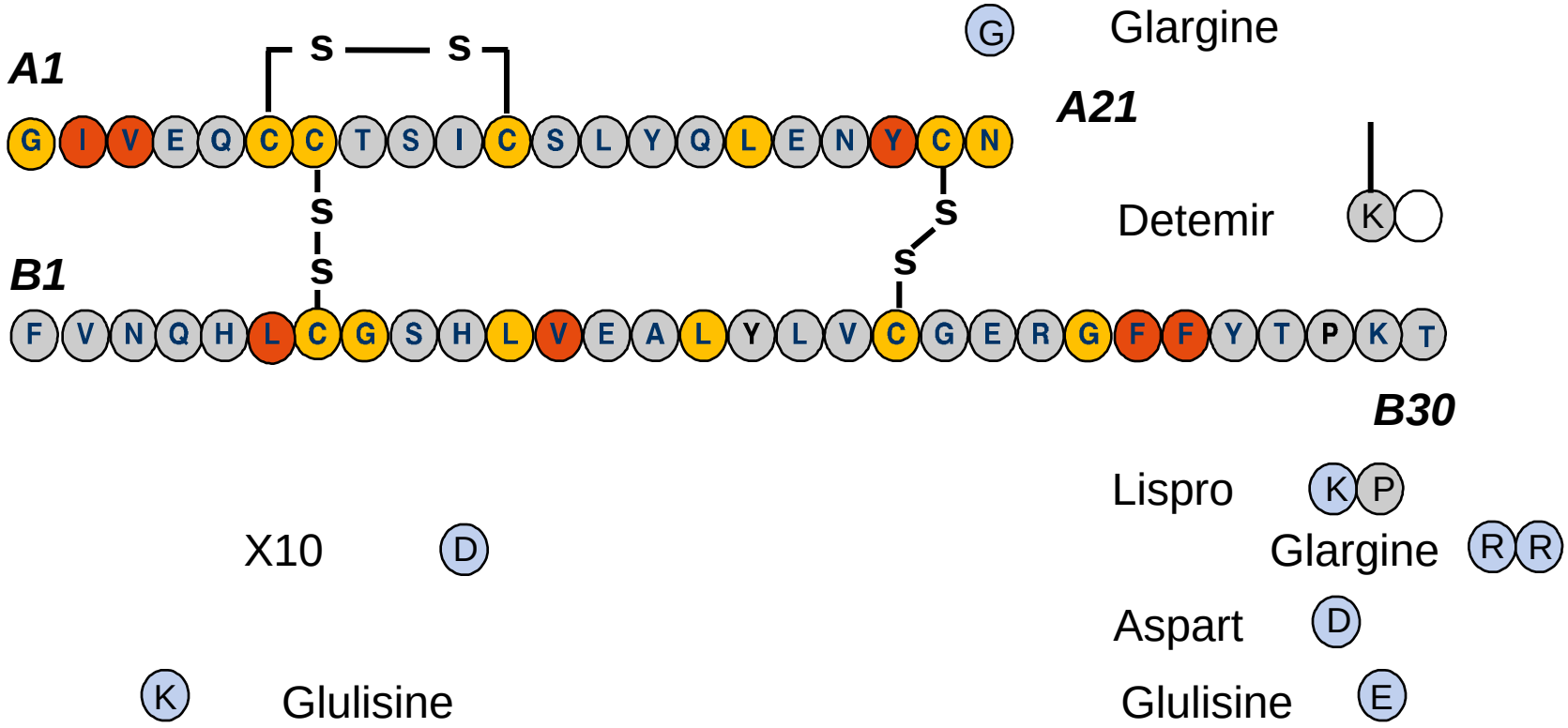
Migrating adipose stromal cells

Mechanical mechanisms

- Hypertension and renal cancer
- Acid reflux and oesophageal adenocarcinoma
- Increased iodine uptake and thyroid cancer

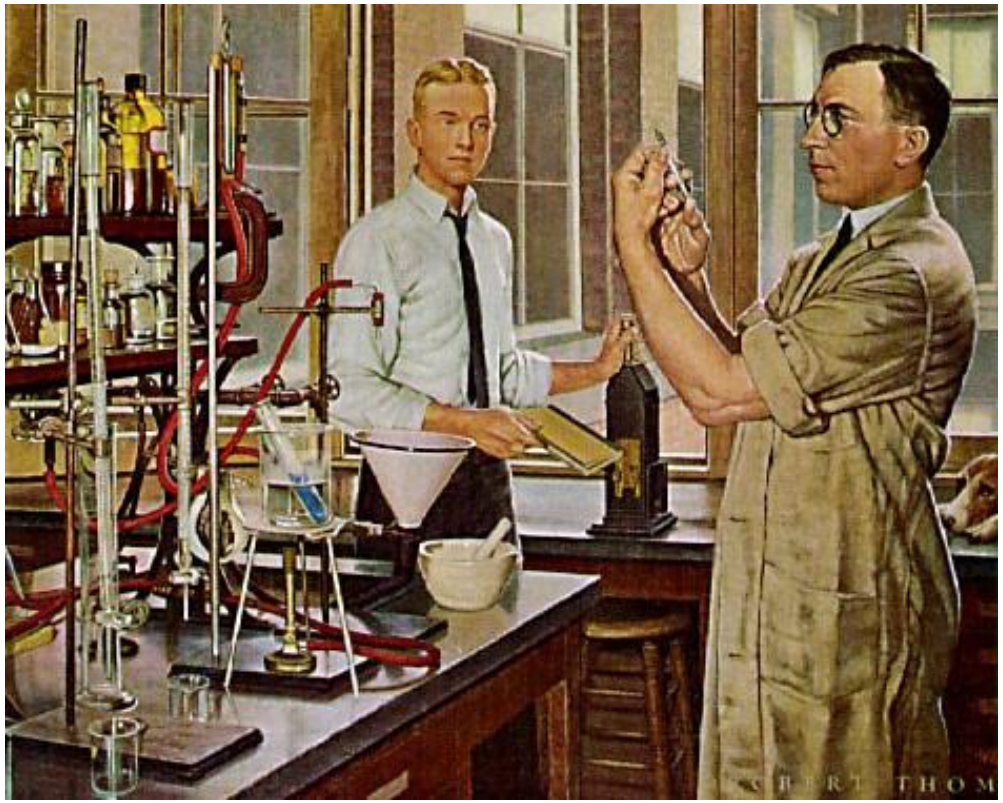
Renehan et al. Arch Phys Biochem 2008 (updated)

Insulin analogue has more IGF-I 'look'



Kaarsholm & Ludvigsen. Receptor 1995;5:1–8
Pires & Chacra. Arq Bras Endocrinol Metabol 2008;52:268–78

The next two talks



What's happen in the last 20 months

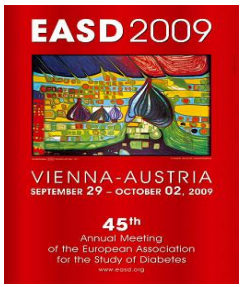
June 2009

the aftermath

June 2010

March 2011

The 'BIG FOUR'



American Cancer Society®

American Diabetes Association®

Consensus meeting

Linking diabetes and cancer: a consensus on complexity

Pathophysiological conditions characterised by hyper- and in several examples differ from conve

Renehan, Smith, Kirkman *Lancet* commentary

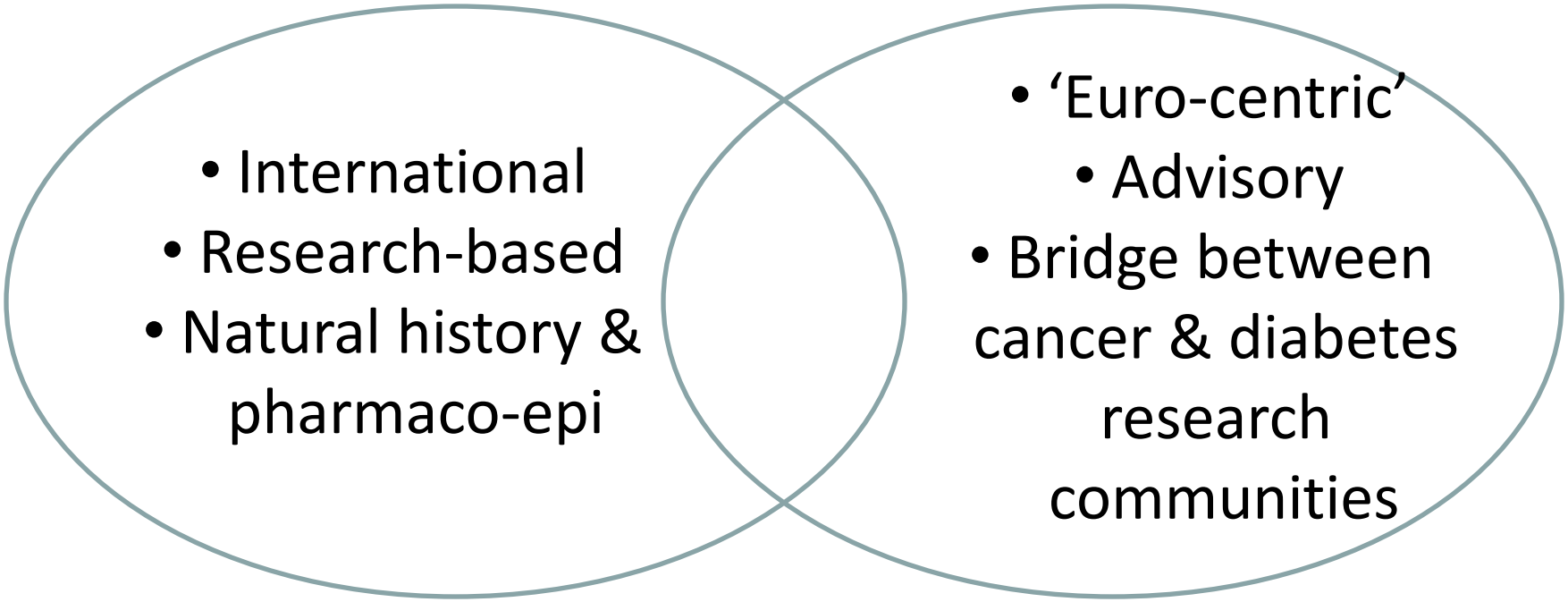
+

many more commentaries

Diabetes and Cancer Research Consortium

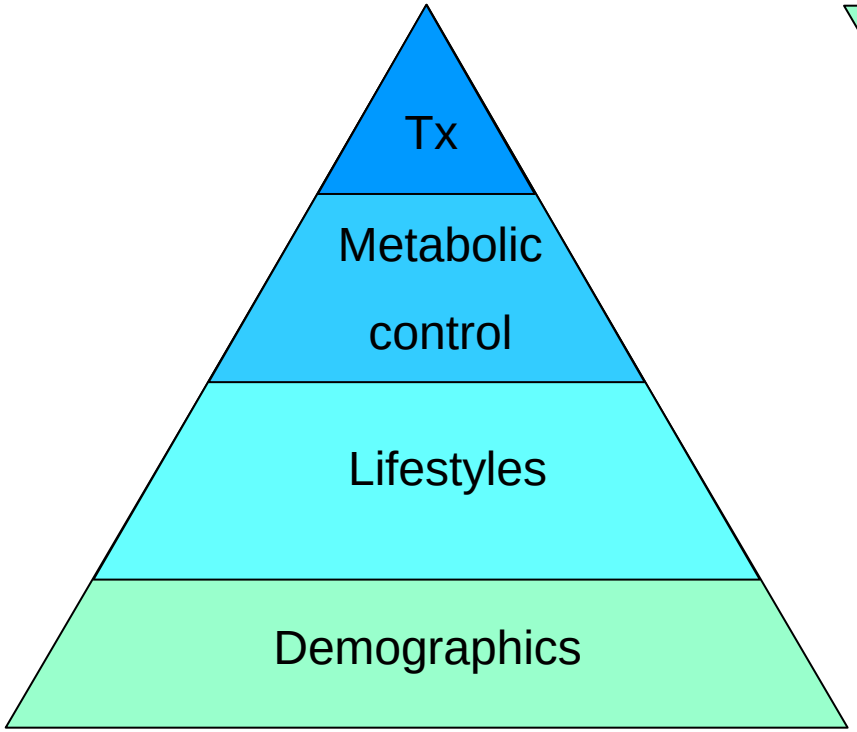
Second generation of analyses in complex datasets

EASD linked initiatives

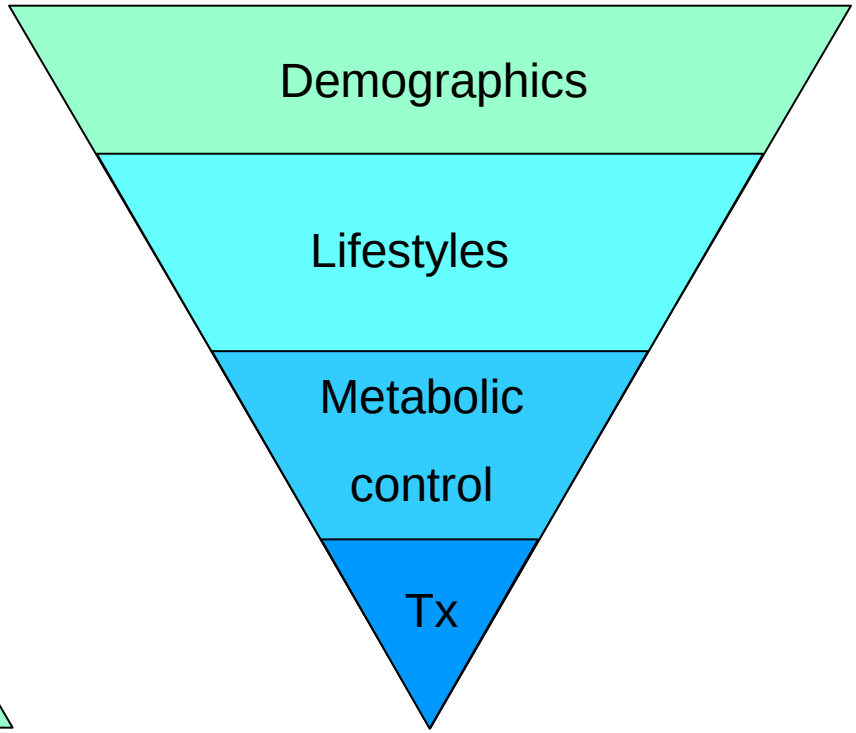


Perspectives

Diabetes Perspective (top-down)



Oncology Perspective (bottom-up)



Diabetes-cancer research consortium:

framework so far

- Cancer incidence (rather than mortality)
- Gender & site-specific approach
- Important confounders
  - e.g. BMI, smoking
- Time-varying analyses, varying dose, immortal time bias

Summary

- Obesity is associated with risk of several cancer types
- Diabetes is associated with risk of several cancer types, likely in many cases to be independent of BMI
- Diabetes & increased cancer mortality – needs research
- Insulins may increase cancer risk; metformin may reduce
- Future – 2nd generation analyses more sophisticated