DIABETES AND CANCER
AN AACE/ACE CONSENSUS STATEMENT

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ENDOCRINE PRACTICE Vol 19 No. 4 July/August 2013 675

Preface

- The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) convened a task force to develop a consensus on the association of obesity, diabetes, and diabetes management with cancer.
- The consensus is based on a conference with 30 global experts in New York City; followed by an exhaustive analysis of the evidence to understand factors associated with cancer development in obesity and diabetes and to evaluate the potential cancer risk of antihyperglycemic medications.
- The purpose of the consensus is to provide practical recommendations and implications for practice to physicians, clinicians, general healthcare, patients and scientists; and to highlight future research needs.

Presentation Outline

- Epidemiology
- Molecular Mechanisms
- Pathophysiology
- Diabetes Management and Cancer Risk
- Regulatory Position
- Implications for Practice
- Future Research and Conclusion

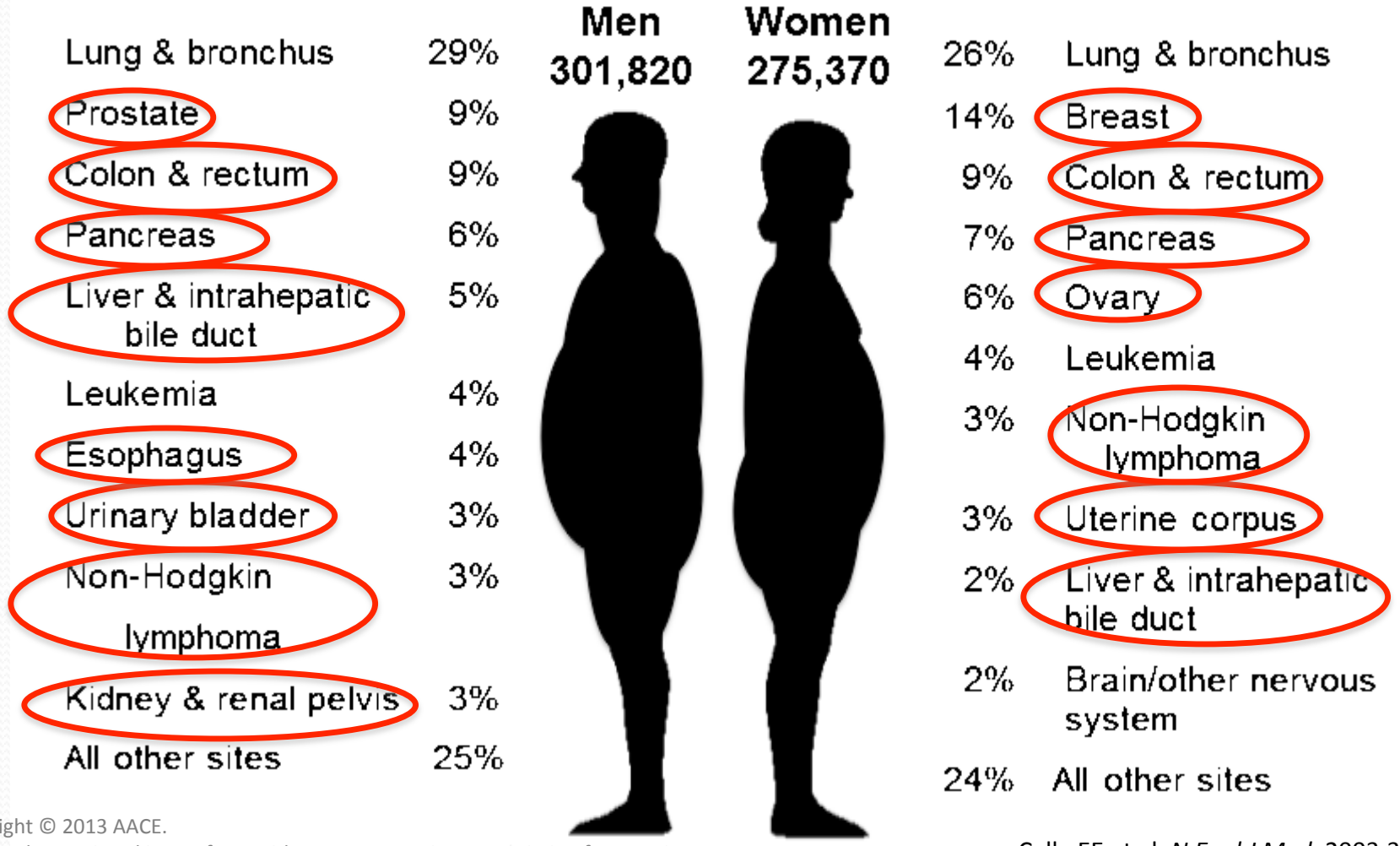
Epidemiology

Obesity Linked to Specific Cancers

- Each year, 100,500 new cases of cancer are caused by obesity:
  - Breast 33,000
  - Endometrial, 20,700
  - Kidney, 13,900
  - Colorectal, 13,200
  - Pancreas, 11,900.
  - Esophagus, 5,800.
  - Gallbladder, 2,000

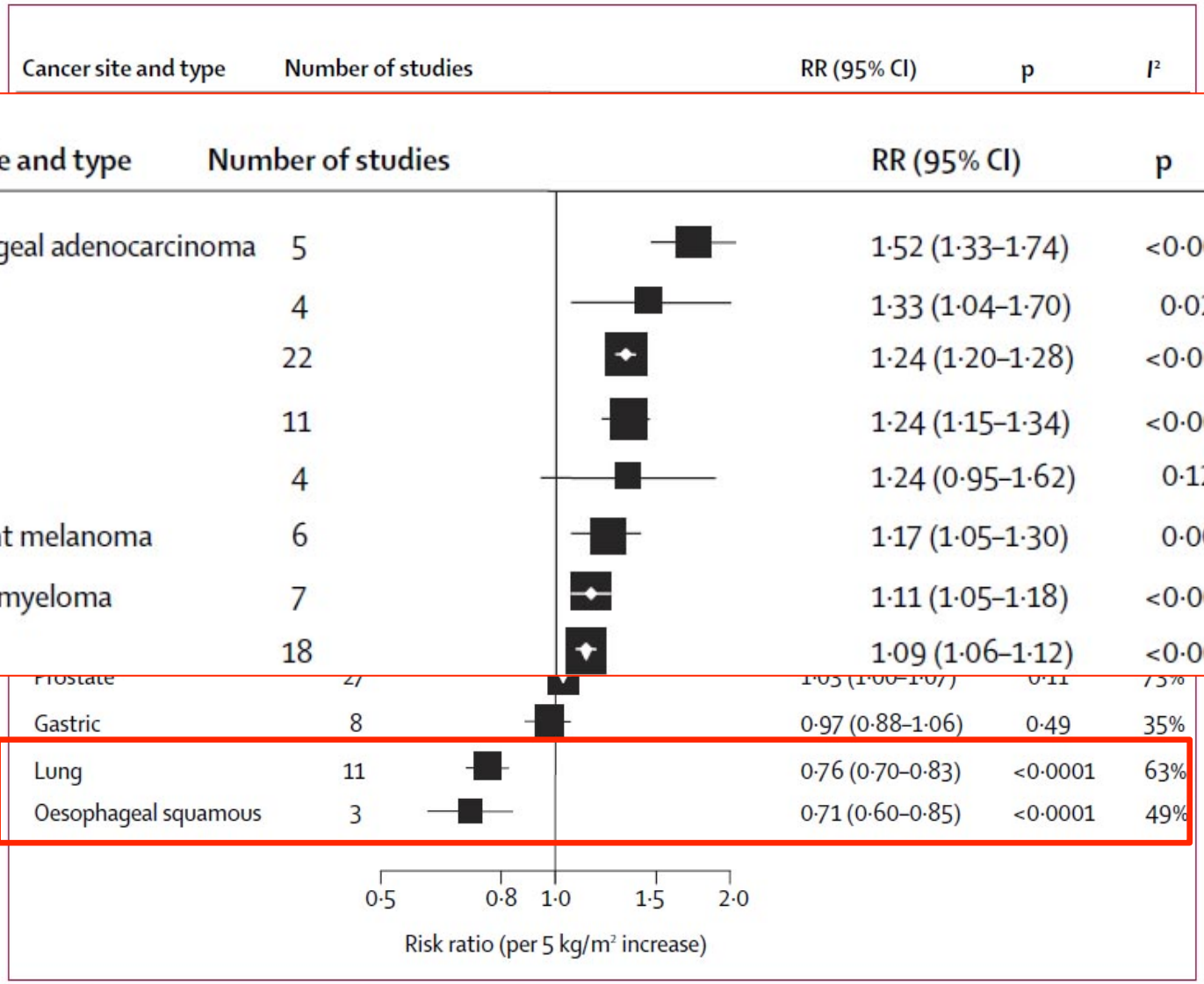
American Institute for Cancer Research Press Kit, November 5, 2009

Cancer Deaths Associated with Obesity



Calle EE et al. *N Engl J Med.* 2003;348:1625-38

BMI & Cancer Risk (men)



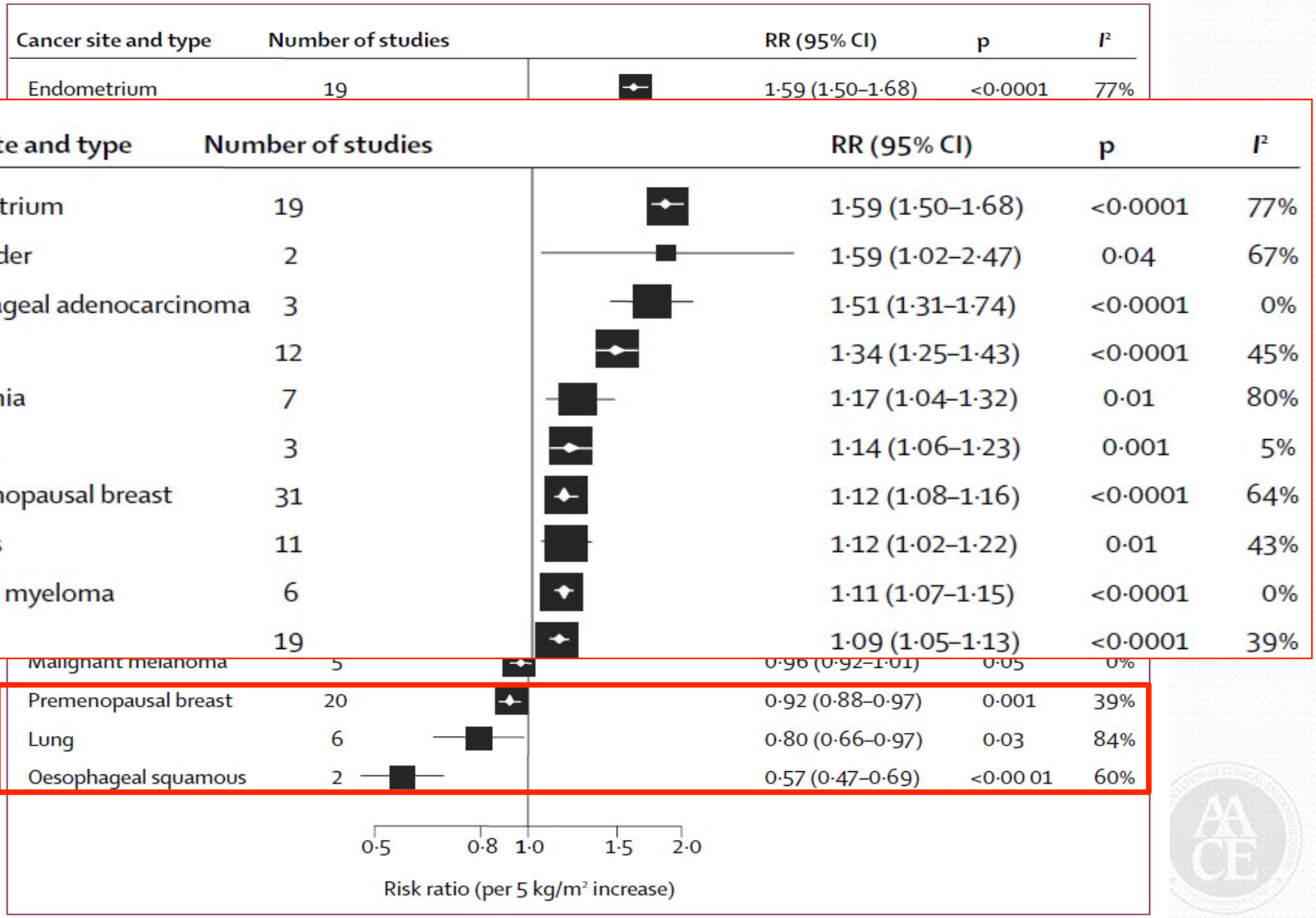
Cancer site and type	Number of studies	RR (95% CI)	p	I^2
Oesophageal adenocarcinoma	5	1·52 (1·33–1·74)	<0·0001	24%
Thyroid	4	1·33 (1·04–1·70)	0·02	77%
Colon	22	1·24 (1·20–1·28)	<0·0001	21%
Renal	11	1·24 (1·15–1·34)	<0·0001	37%
Liver	4	1·24 (0·95–1·62)	0·12	83%
Malignant melanoma	6	1·17 (1·05–1·30)	0·004	44%
Multiple myeloma	7	1·11 (1·05–1·18)	<0·0001	7%
Rectum	18	1·09 (1·06–1·12)	<0·0001	3%
Prostate	27	1·03 (1·00–1·07)	0·11	73%
Gastric	8	0·97 (0·88–1·06)	0·49	35%
Lung	11	0·76 (0·70–0·83)	<0·0001	63%
Oesophageal squamous	3	0·71 (0·60–0·85)	<0·0001	49%

0·5 0·8 1·0 1·5 2·0

Risk ratio (per 5 kg/m² increase)

Renehan AG et al. *Lancet*. 2008;371:569-578

BMI & Cancer Risk (women)



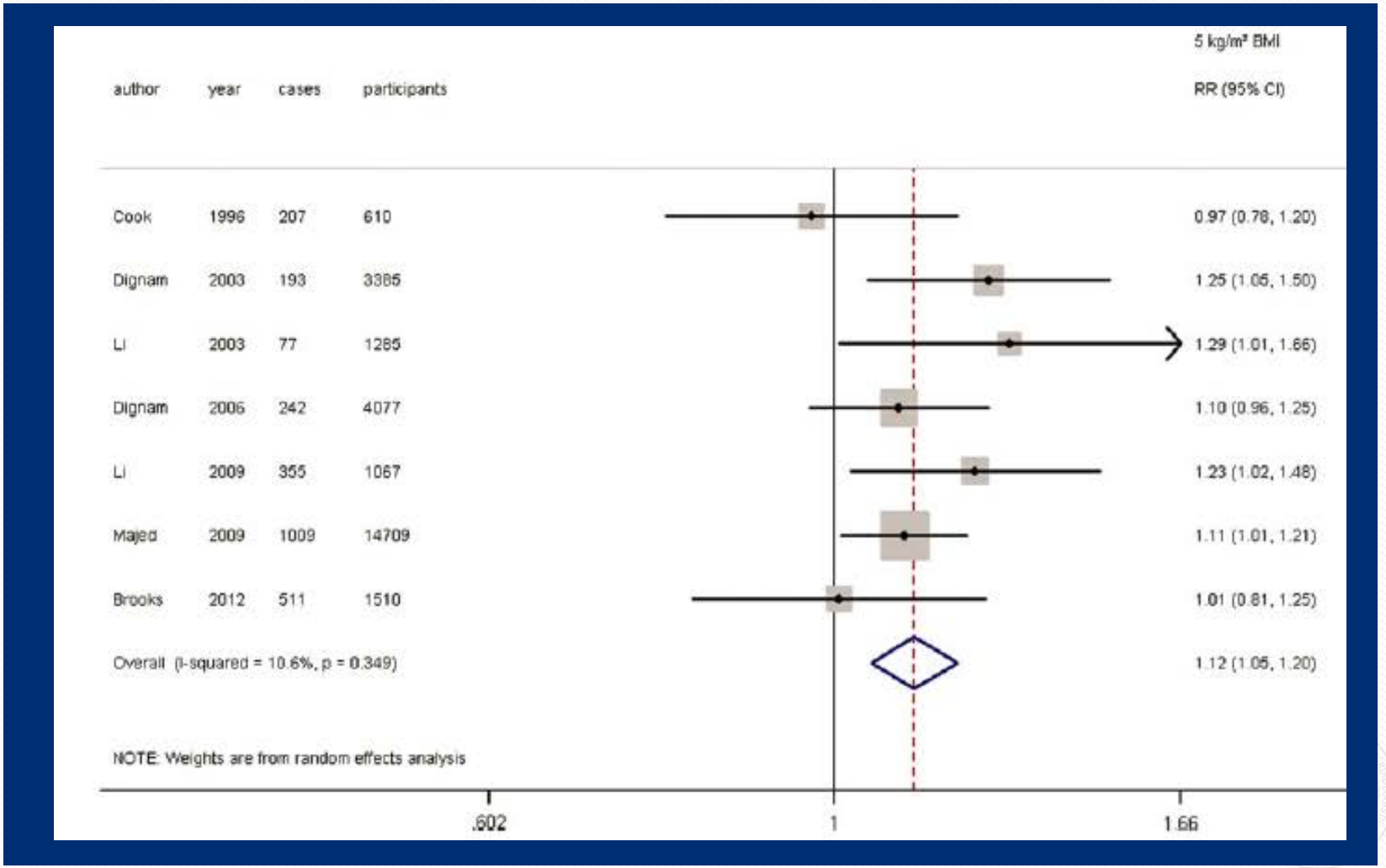
Cancer site and type	Number of studies	RR (95% CI)	p	I^2
Endometrium	19	1·59 (1·50–1·68)	<0·0001	77%
Gallbladder	2	1·59 (1·02–2·47)	0·04	67%
Oesophageal adenocarcinoma	3	1·51 (1·31–1·74)	<0·0001	0%
Renal	12	1·34 (1·25–1·43)	<0·0001	45%
Leukaemia	7	1·17 (1·04–1·32)	0·01	80%
Thyroid	3	1·14 (1·06–1·23)	0·001	5%
Postmenopausal breast	31	1·12 (1·08–1·16)	<0·0001	64%
Pancreas	11	1·12 (1·02–1·22)	0·01	43%
Multiple myeloma	6	1·11 (1·07–1·15)	<0·0001	0%
Colon	19	1·09 (1·05–1·13)	<0·0001	39%
Malignant melanoma	5	0·96 (0·92–1·01)	0·05	0%
Premenopausal breast	20	0·92 (0·88–0·97)	0·001	39%
Lung	6	0·80 (0·66–0·97)	0·03	84%
Oesophageal squamous	2	0·57 (0·47–0·69)	<0·00 01	60%

0·5 0·8 1·0 1·5 2·0

Risk ratio (per 5 kg/m² increase)

Renehan AG et al. *Lancet*. 2008;371:569-578

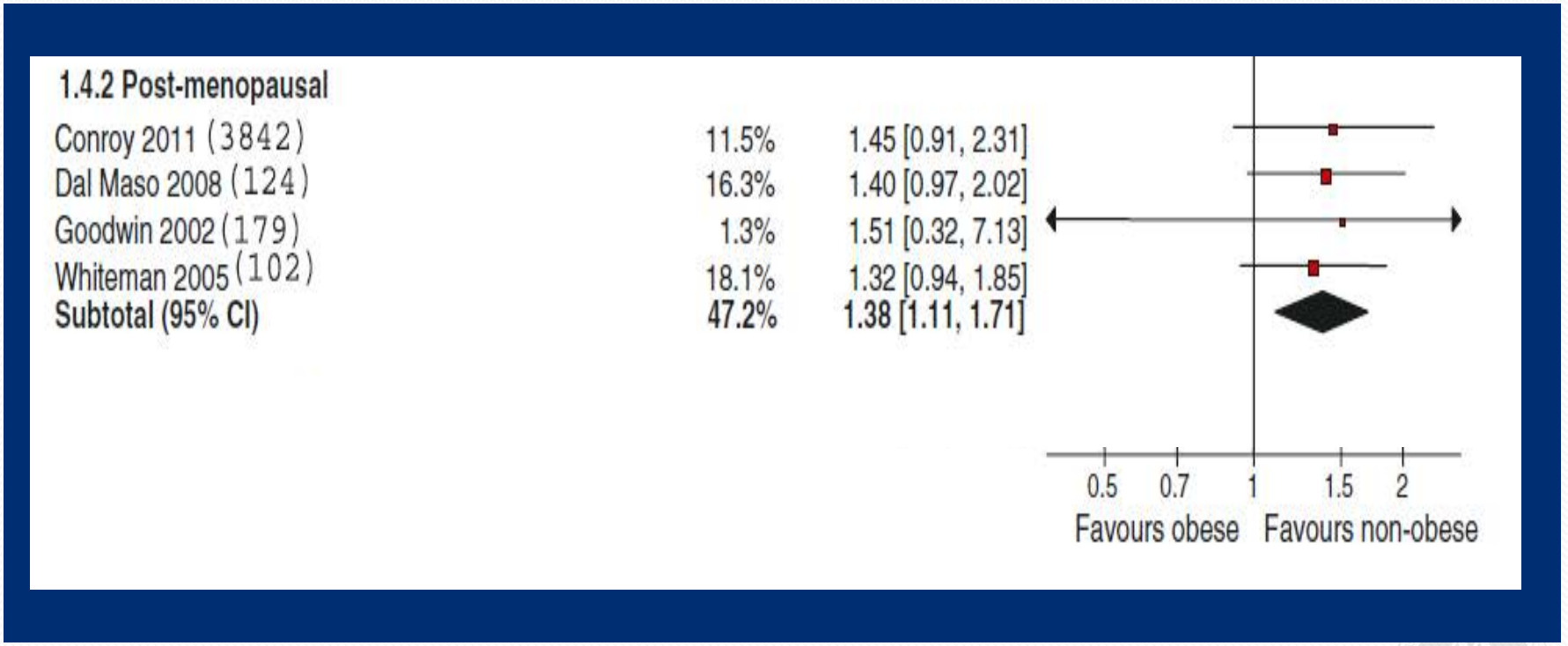
BMI & risk of second primary cancer



Druesne-Pecollo N et al. *Breast Cancer Res Treat.* 2012;135:647-54

BMI (post-diagnosis) & breast cancer

Breast cancer-specific survival



Niraula S et al. *Breast Cancer Res Treat.* 2012;134:769-81

Fasting Insulin and Breast Cancer Risk

- Case-control design
- 99 premenopausal T1-3, No-1, Mo BC
- 99 age-matched premenopausal controls with non-proliferative breast biopsies

Insulin Quintile	Level (pmol/L)	Odds Ratio (95% CI) for Breast Cancer (age, weight adjusted)
I	≤ 35	1.0
II	>35 - ≤41	1.19 (0.49 – 2.89)
III	>41 - ≤47	1.33 (0.53 – 3.35)
IV	>47 - ≤58	1.19 (0.48 – 2.93)
V	>58 - ≤180	3.72 (1.32 – 10.5)

P (insulin) = 0.02 (2-tail)

Del Giudice ME. *Breast Cancer Res Treat*. 1998;47:110-20

Meta-Analyses of RR of Cancer in Different Organs of Patients with Diabetes

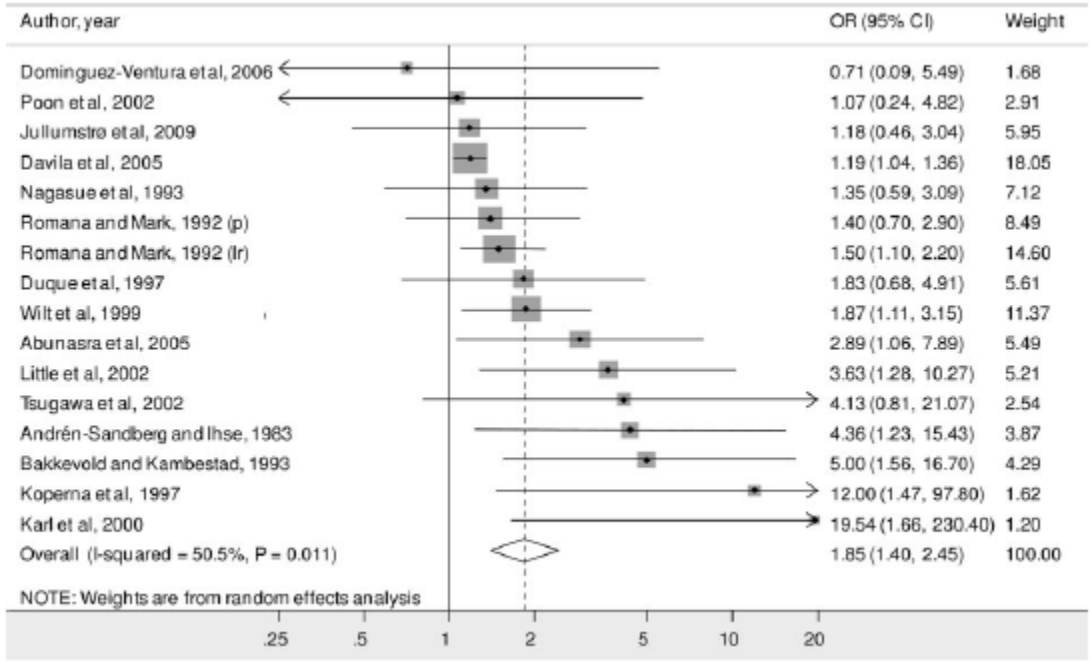
Cancer		RR (95% CI)
Liver (El-Serag *et al*. 2006)	13 case–control studies 7 cohort studies	2.50 (1.8–3.5) 2.51 (1.9–3.2)
Pancreas (Huxley *et al*. 2005)	17 case–control studies 19 cohort studies	1.94 (1.53–2.46) 1.73 (1.59–1.88)
Kidney[a] (Lindblad *et al*. 1999, Washio *et al*. 2007)	1 cohort study 1 cohort study	1.50 (1.30–1.70) 2.22 (1.04–4.70)
Endometrium (Friberg *et al*. 2007)	13 case–control studies 3 cohort studies	2.22 (1.80–2.74) 1.62 (1.21–2.16)
Colon–rectum (Larsson *et al*. 2005)	6 case–control studies 9 cohort studies	1.36 (1.23–1.50) 1.29 (1.16–1.43)
Bladder (Larsson *et al*. 2006)	7 case–control studies 3 cohort studies	1.37 (1.04–1.80) 1.43 (1.18–1.74)
Non-Hodgkin's lymphoma (Mitri *et al*. 2008)	5 cohort studies 11 case–control studies	1.41 (1.07–1.88) 1.12 (0.95–1.31)
Breast (Larsson *et al*. 2007)	5 case–control studies 15 cohort studies	1.18 (1.05–1.32) 1.20 (1.11–1.30)
Prostate (Kasper & Giovannucci 2006)	9 case–control studies 10 cohort studies	0.89 (0.72–1.11) 0.81 (0.71–0.92)

[a]Data on kidney cancer were not obtained from meta-analysis; CI, confidence interval; RR, relative risk.

Vigneri P et al. *Endocr Relat Cancer.* 2009;16:1103-23

Diabetes and Cancer Mortality

- Post-operative cancer patients with T2DM have ~85% higher overall mortality compared to patients without T2DM
  - adjusted for confounders the increased mortality is ~50%

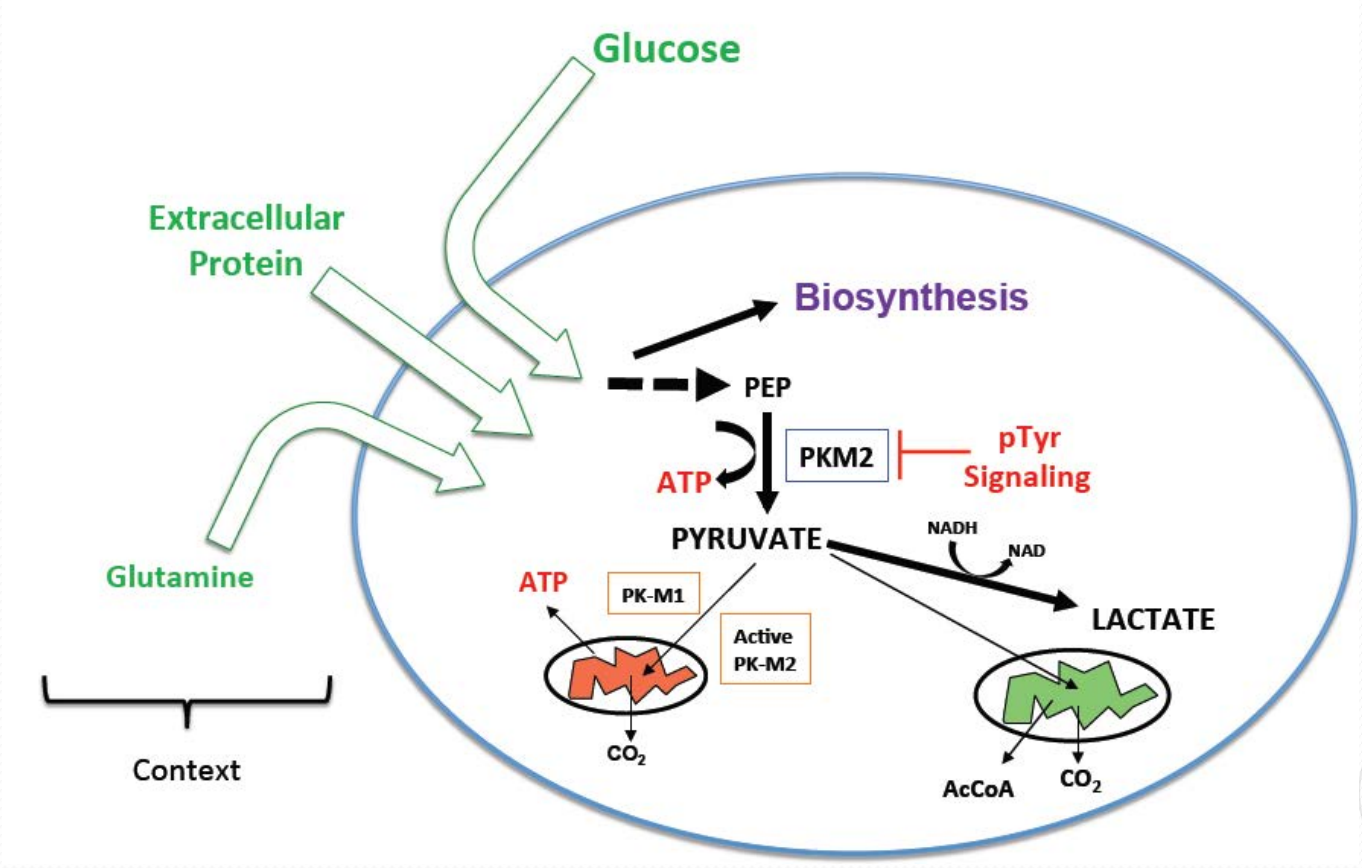


Barone BB et al. *Diabetes Care*. 2010;33:931-9

Molecular Mechanisms

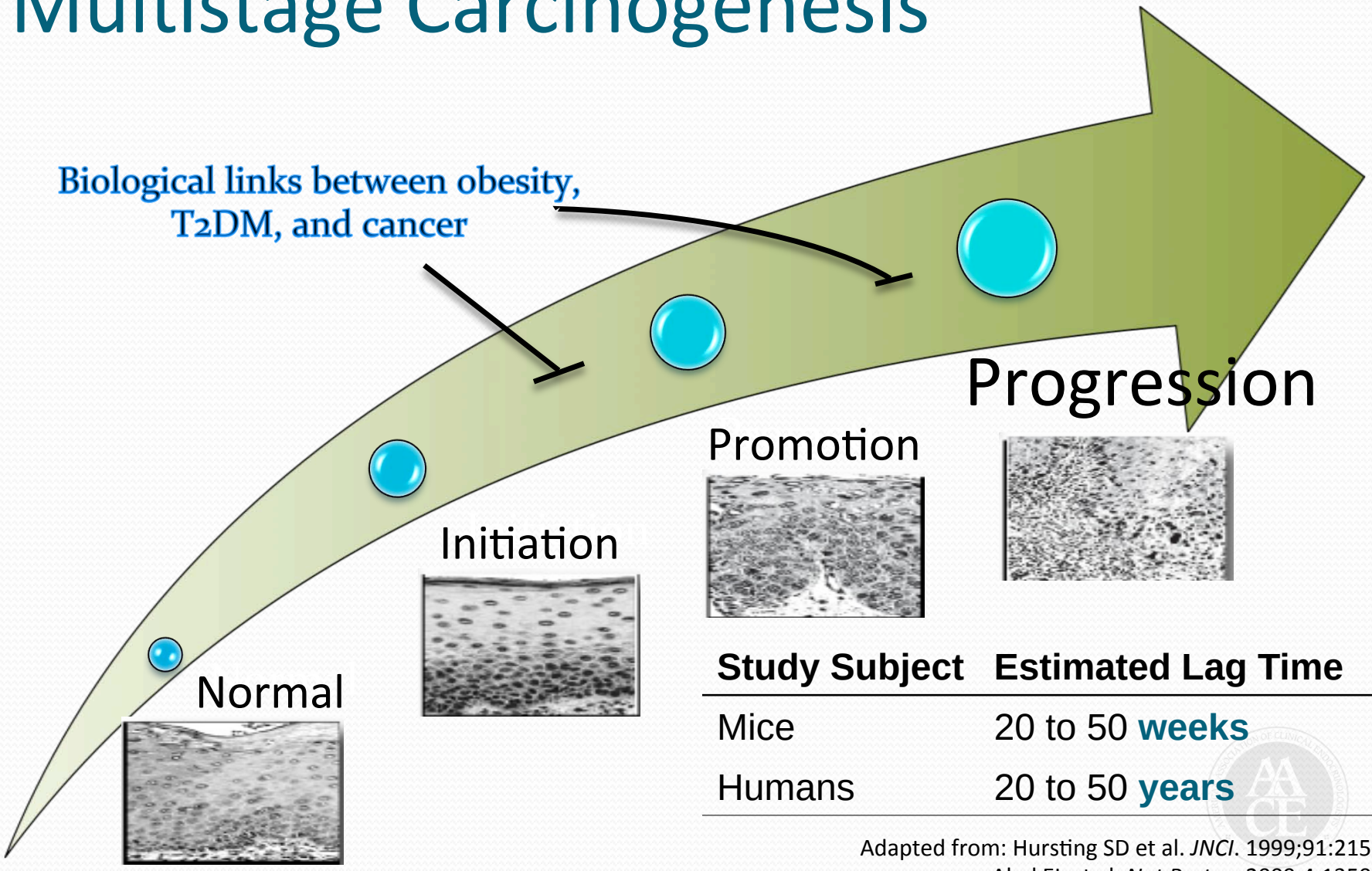
Cellular Requirements for Tumor Biosynthesis

- Tumor cells depend on multiple energy sources not just glucose
- Genetic mutations and altered metabolism also support tumor growth



Vander Heiden MG et al. *Science*. 2009;324:1029-1033
Christofk HR et al. *Nature.* 2008; 452:230-233

Multistage Carcinogenesis



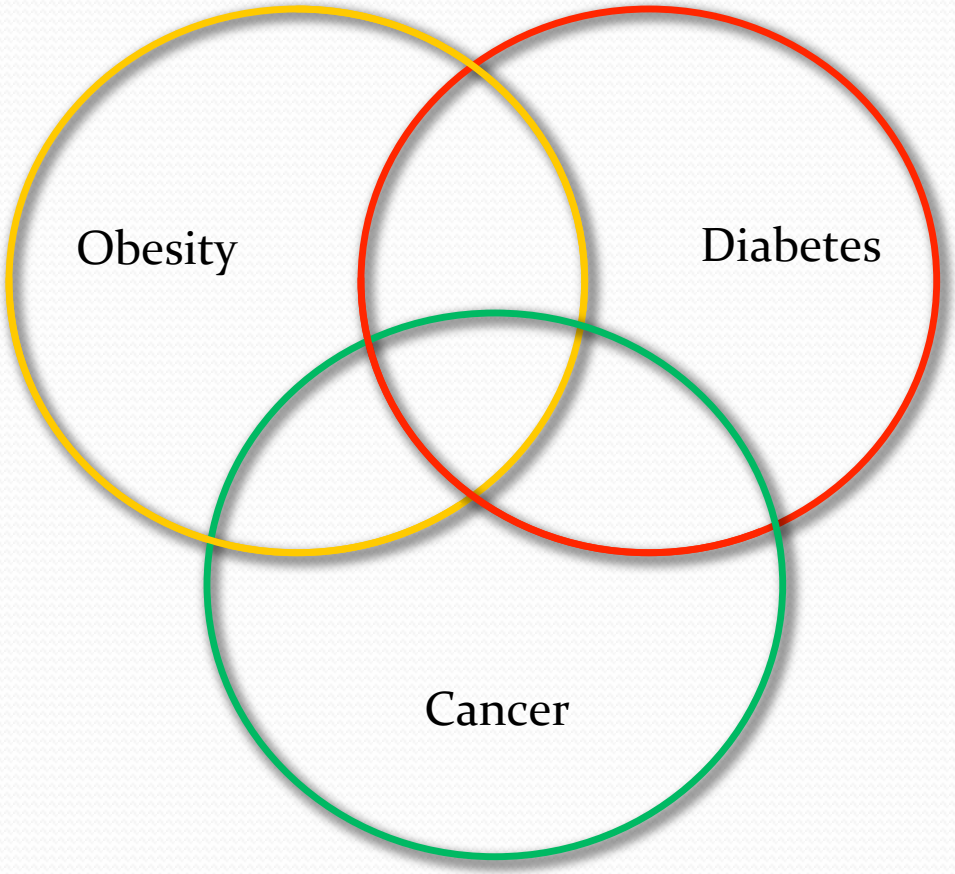
Study Subject	Estimated Lag Time
Mice	20 to 50 **weeks**
Humans	20 to 50 **years**

Adapted from: Hursting SD et al. *JNCI*. 1999;91:215-25
Abel EL et al. *Nat Protoc*. 2009;4:1350-62
Loeb LA et al. *Cancer Res*. 2008;68:6863-72

Pathophysiology

How Can the Metabolic Syndrome, Obesity, and Type 2 Diabetes Affect Cancer Development and Metastases?

Nutrients
IGF-I
Leptin
Adiponectin
Cytokines
Chemokines
Estrogen

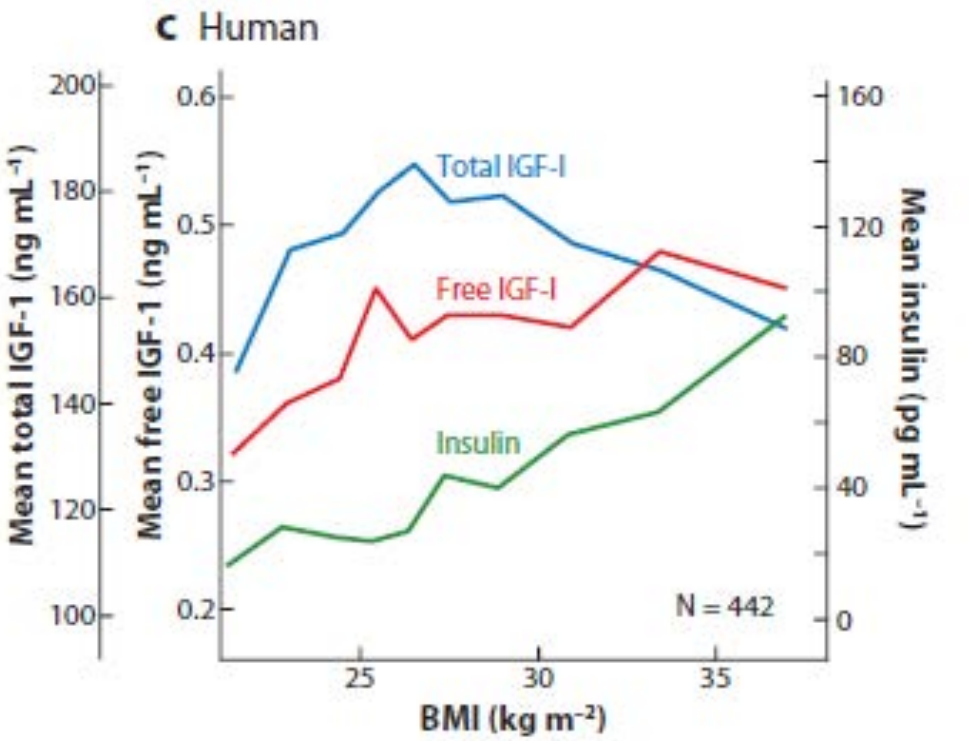


Hyperinsulinemia
Hyperglycemia
Hyperlipidemia

LeRoith D. Presented at: AACE Annual Meeting; May. 2013

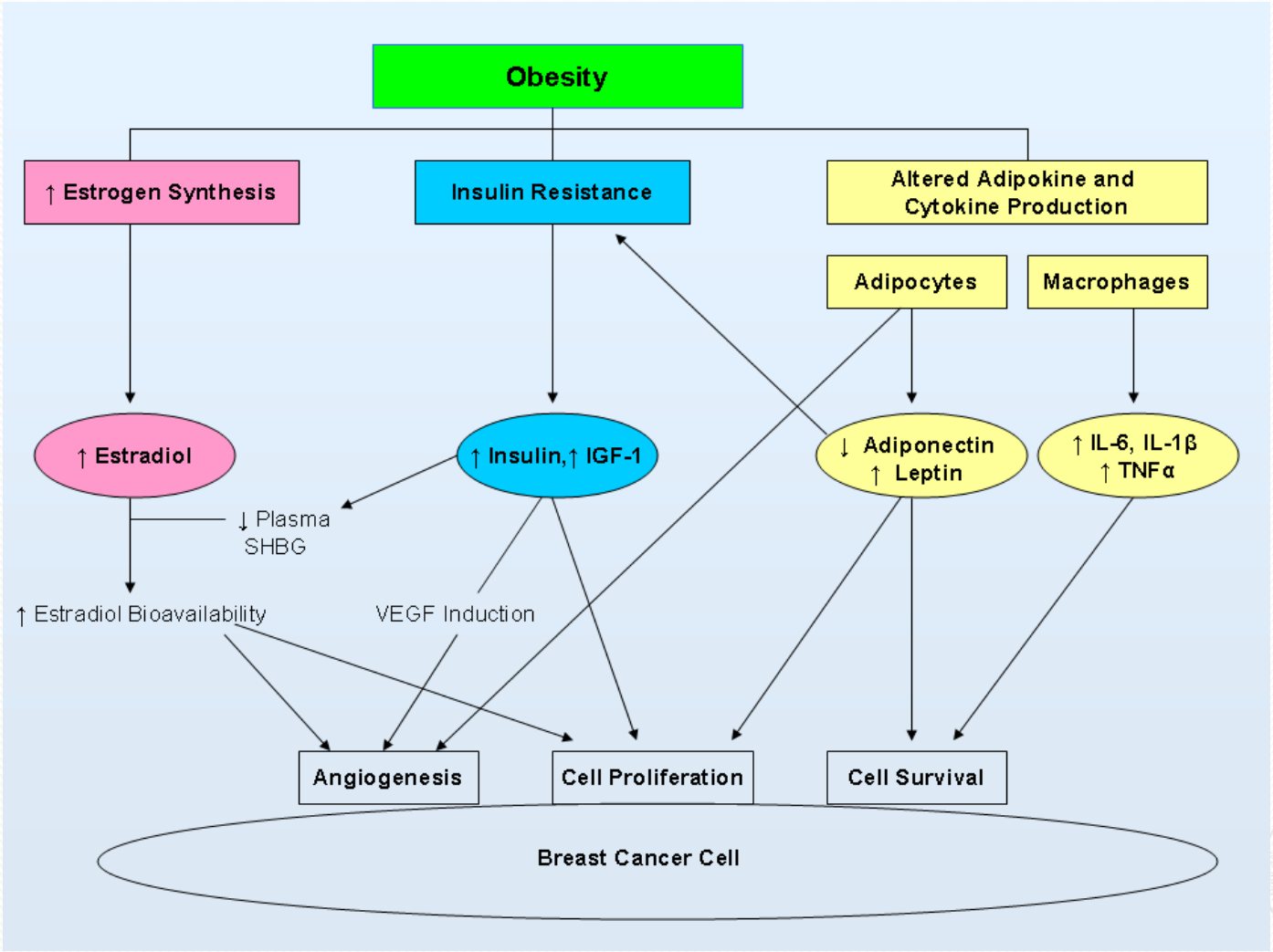
Obesity, Insulin, and IGF-1

- Increased BMI has been directly related to increased insulin and free insulin-like growth factor-1 (IGF-1) levels.



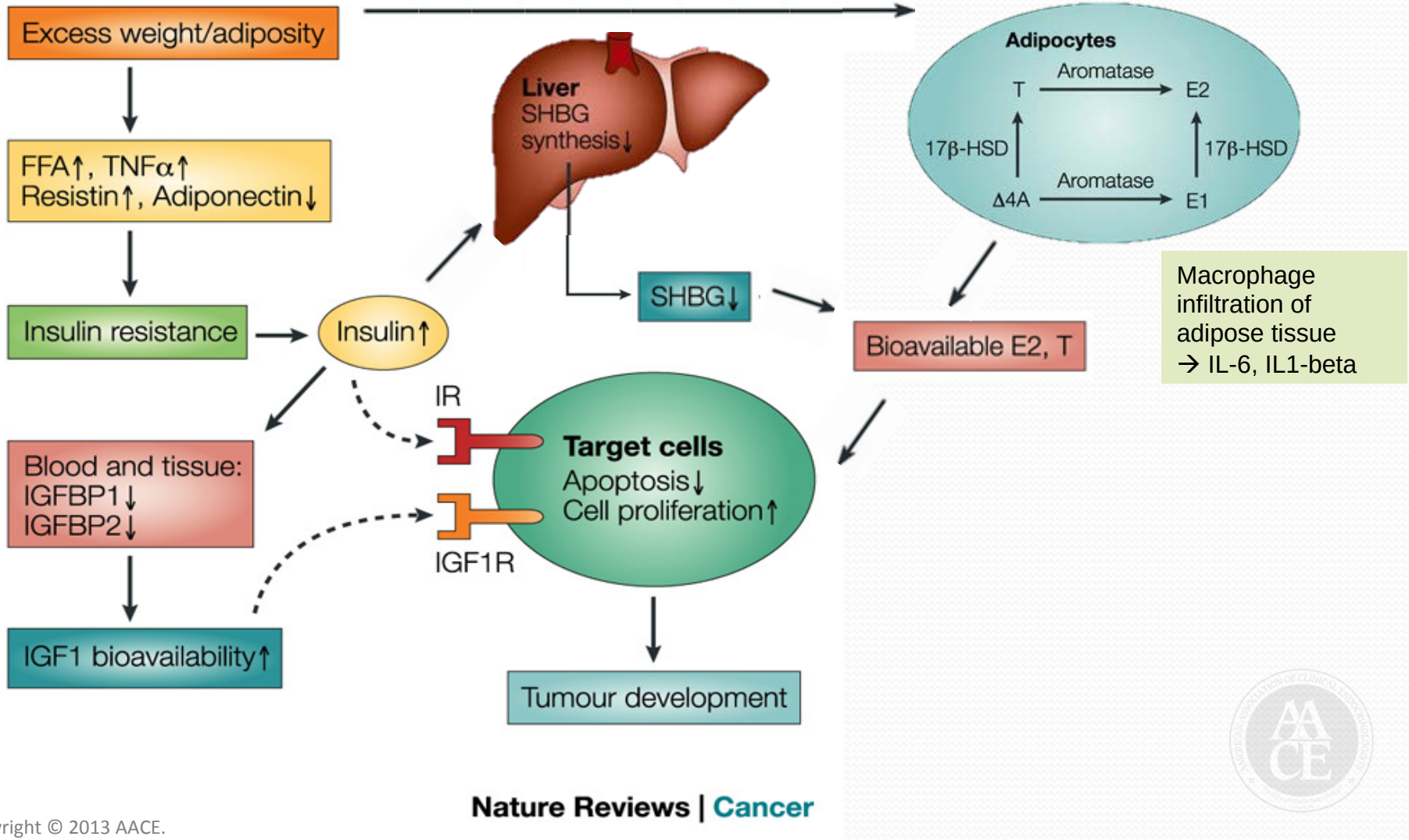
Roberts DL et al. *Annu Rev Med.* 2010;61:301-16

Pathways Linking Obesity with Breast Cancer



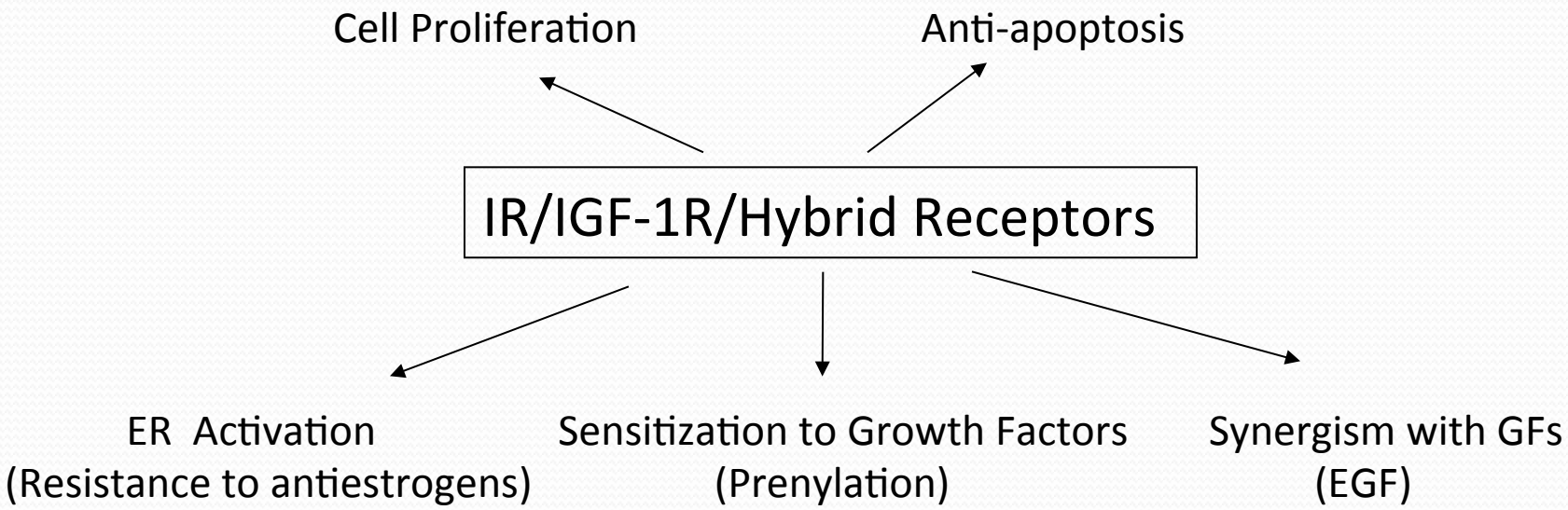
Dannenberg A. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

Potential Mechanisms Linking Diabetes and Cancer



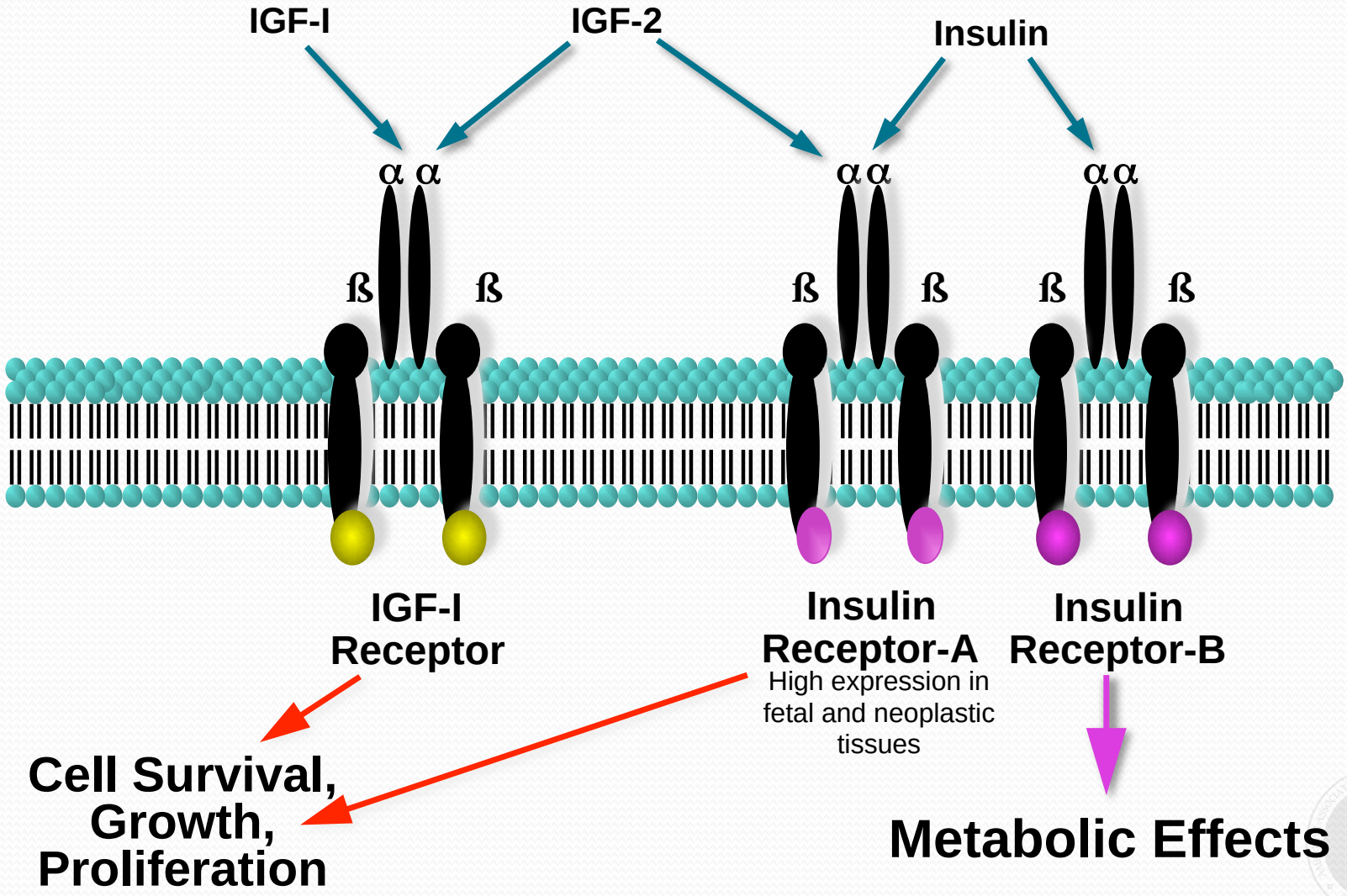
Calle EE et al. *Nat Rev Cancer*. 2004;4:579-91

Hyperinsulinemia and Cancer (Direct Effects)



Fantus IG. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

Insulin, Insulin-like Growth Factors, and Receptors



LeRoith D. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

Hyperinsulinemia and Cancer (Indirect Effects)

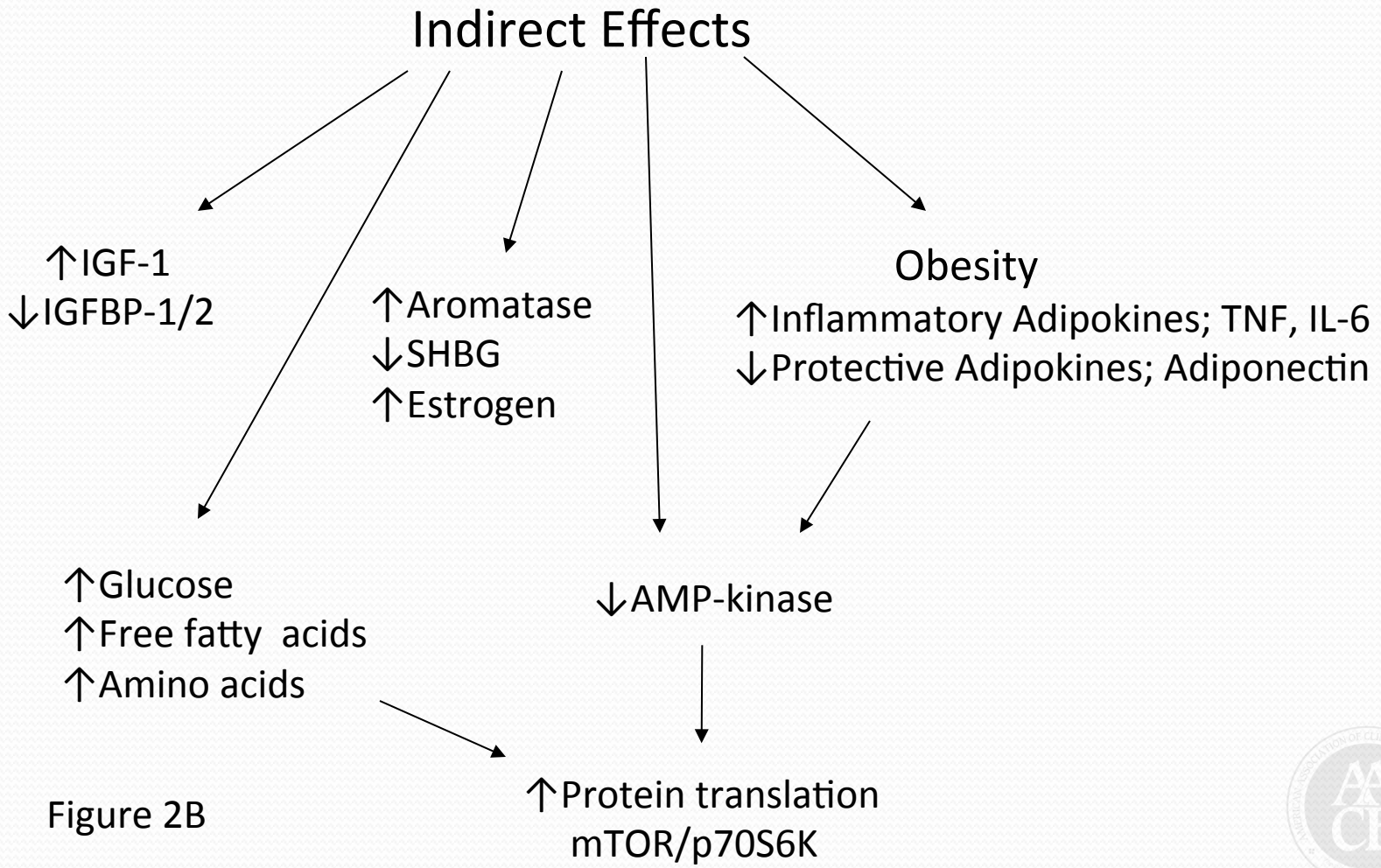
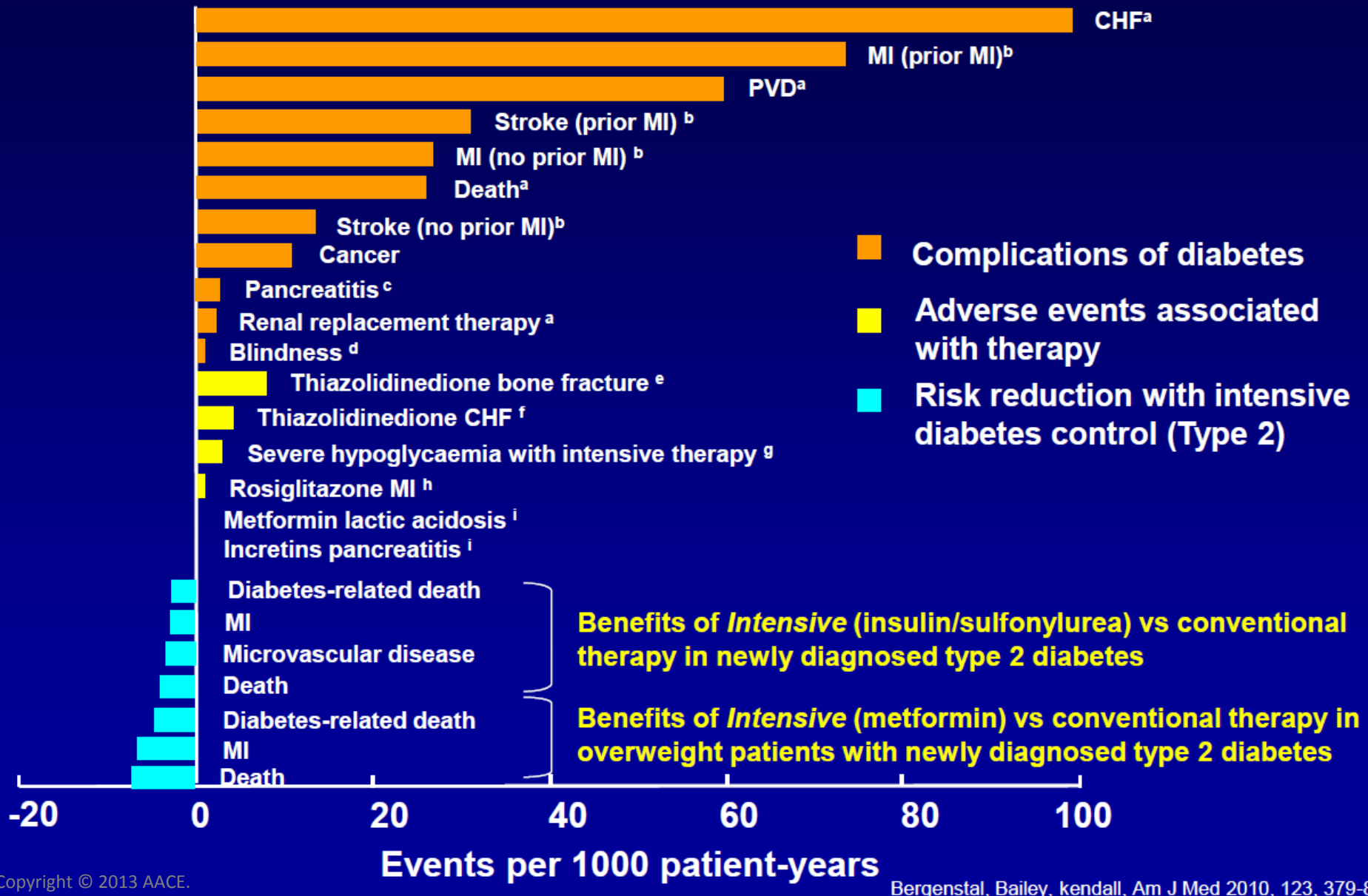


Figure 2B

Fantus IG. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

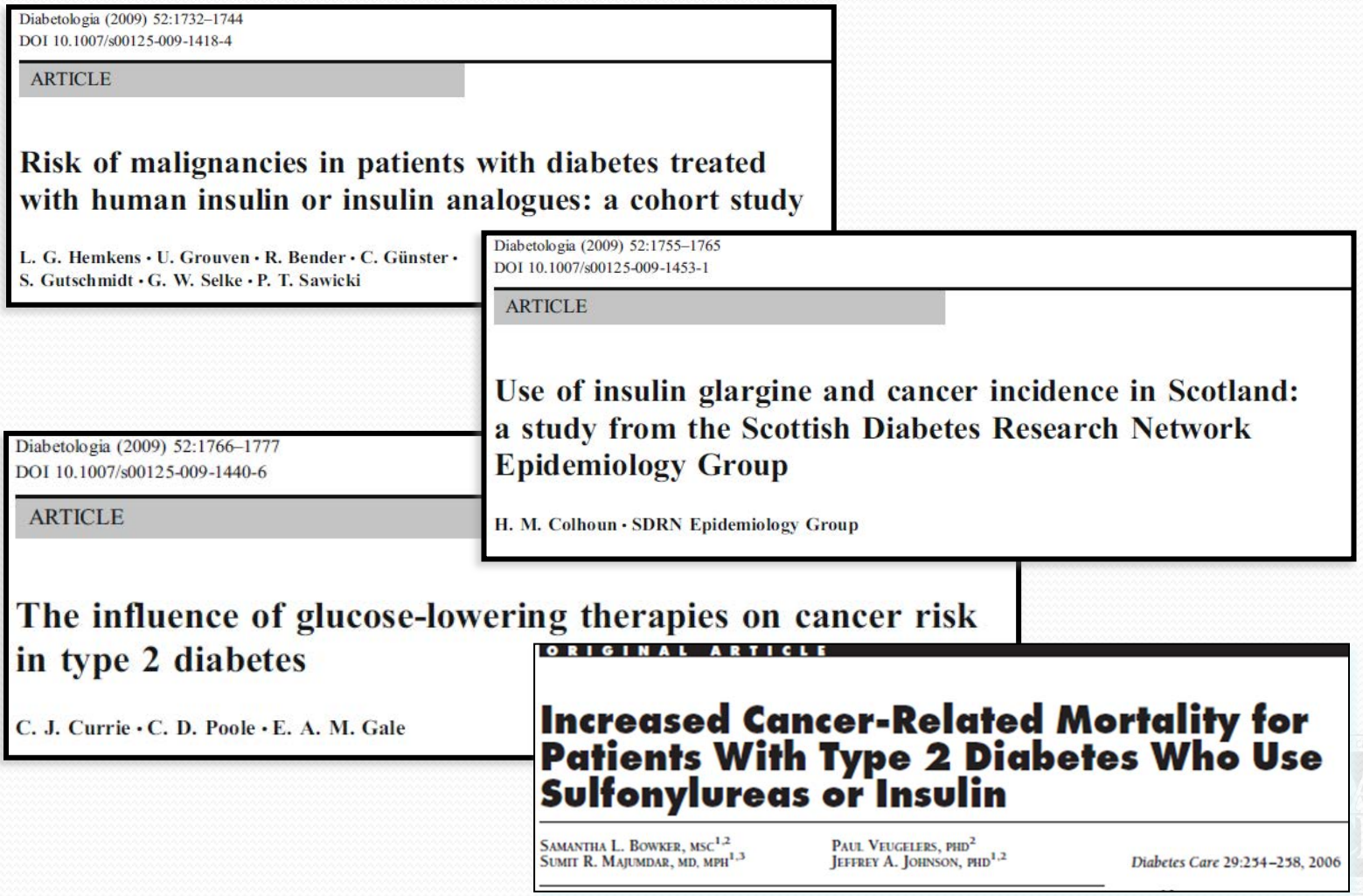
Diabetes Management & Cancer Risk

Risk-benefit of diabetes versus therapy



Bergenstal, Bailey, kendall, Am J Med 2010, 123, 379-84

Insulin Therapy and Cancer



Diabetologia (2009) 52:1732–1744
DOI 10.1007/s00125-009-1418-4

ARTICLE

Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study

L. G. Hemkens · U. Grouven · R. Bender · C. Günster · S. Gutschmidt · G. W. Selke · P. T. Sawicki

Diabetologia (2009) 52:1755–1765
DOI 10.1007/s00125-009-1453-1

ARTICLE

Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group

H. M. Colhoun · SDRN Epidemiology Group

Diabetologia (2009) 52:1766–1777
DOI 10.1007/s00125-009-1440-6

ARTICLE

The influence of glucose-lowering therapies on cancer risk in type 2 diabetes

C. J. Currie · C. D. Poole · E. A. M. Gale

ORIGINAL ARTICLE

Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin

SAMANTHA L. BOWKER, MSC[1,2]
SUMIT R. MAJUMDAR, MD, MPH[1,3]
PAUL VEUGELERS, PHD[2]
JEFFREY A. JOHNSON, PHD[1,2]

Diabetes Care 29:254–258, 2006

Malignant Neoplasm in Diabetic Patients with Different Insulin Doses (Glargine vs. Human Insulin)

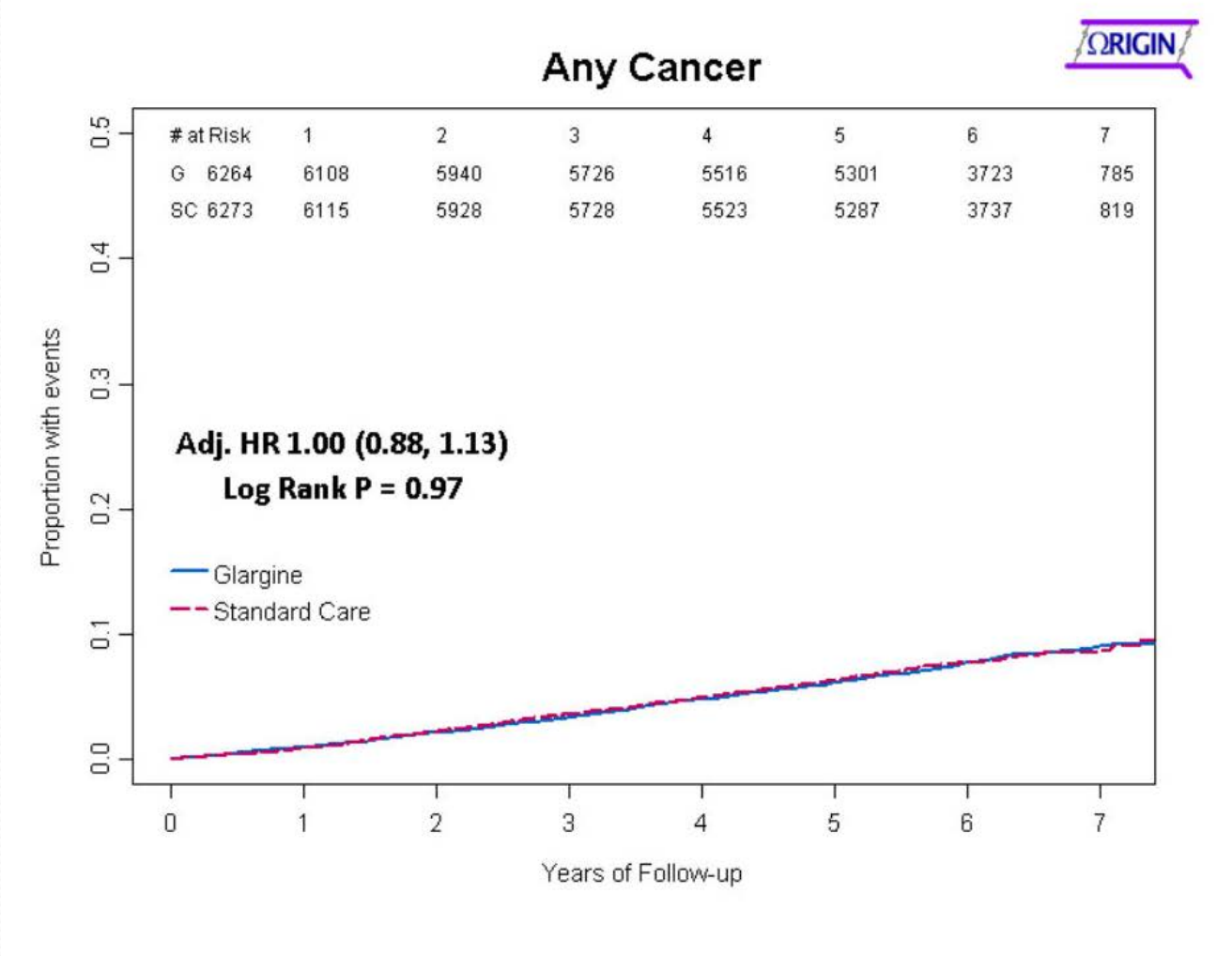
- N=127,031 T1 and T2 insulin-treated patients. 95,804 human insulin, 23,855 glargine, followed up to 4.4 years (mean 1.6 years), cancer-free in preceding 3 years.

	Incidence per 1,000 patient-years (95% CI)		
	<20 U/d	20-40 U/d	>40 U/d
Glargine	18.6 (16.5-20.7)	20.3 (17.9-22.9)	52.6 (42.9-63.8)
Human Insulin	17.3 (16.1-18.6)	23.6 (22.3-25.0)	31.0 (29.6-32.3)

Note high rates of new cancer in the study

Hemkens LG et al. *Diabetologia.* 2009; 52:1732-44

ORIGIN Trial Results



Presented at: *72nd Scientific Sessions of the American Diabetes Association*, 2012

The ORIGIN Trial: Lack of Association of Insulin Glargine with Malignancy

	Insulin	Control	P-value
Cancer death	3.0%	3.0%	N.S.
Breast cancer	0.4%	0.4%	N.S.
Lung cancer	1.3%	1.1%	N.S.
Colon cancer	1.2%	1.1%	N.S.
Prostate cancer	2.1%	2.2%	N.S.
Melanoma	0.2%	0.3%	N.S.
Other cancer	3.7%	3.9%	N.S.
Total cancers	8.9%	9.0%	N.S.

N.S., not significant

ORIGIN Trial Investigators, Gerstein HC et al. *N Engl J Med*. 2012;367:319-28

Meta-analysis: Insulin Glargine and Cancer Risk

- Findings from an European Medicines Agency (EMA)-commissioned database study indicate significantly decreased risk of all cancer and prostate cancer (glargine vs. non-glargine use).

Cancer Type	Cancer Incidence Summary Relative Risk (95% CI)
All cancer	0.90 (0.82 – 0.99)
Colorectal	0.84 (0.74 – 0.95)
Breast	1.11 (1.00 – 1.22)
Prostate	1.30 (1.00 – 1.28)

Boyle P et al. Presented at: *72nd Session of the American Diabetes Association.* 2012. Poster 1332-P

Meta-analysis: Insulin Glargine and Cancer Risk

- Data from the Inovalon MORE 2 registry and the Kaiser Permanente Northern California (KPNC) database showed no significant increased risk of all cancer incidence (glargine vs. NPH use)

Database	All Cancer Incidence Hazard Ratio (95% CI)
Inovalon MORE 2 Registry	1.12 (0.95 – 1.32)
KPNC	0.90 (0.90 – 1.00)

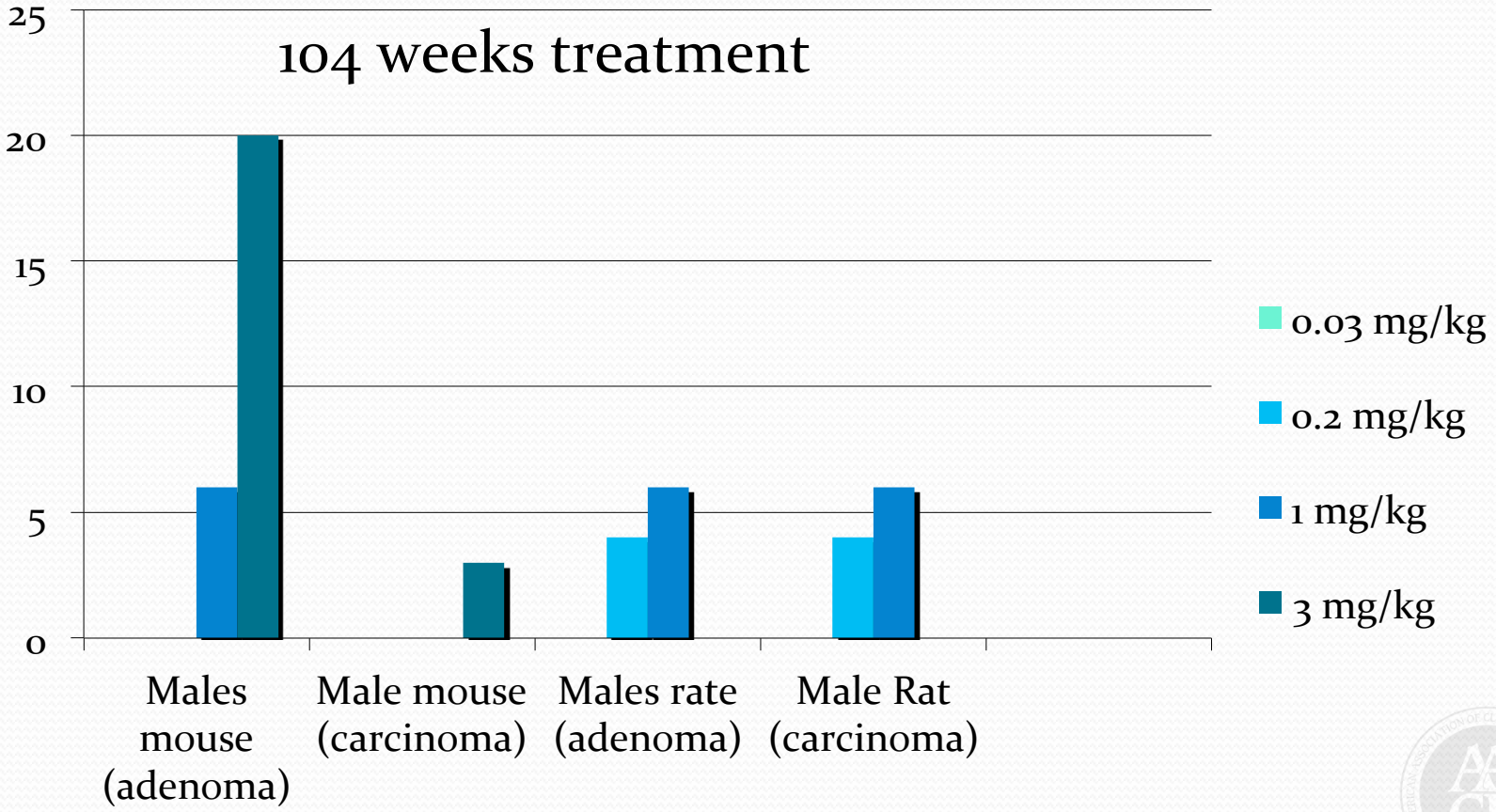
Sturmer T et al. *Diabetes Care.* 2013 Jul 22 [Epub ahead of print]
Habel L. Presented at: *72nd Session of the American Diabetes Association.* 2012. CT-SY13

Incretin-based Therapies and Cancer

- Studies Demonstrating Effects of GLP-1 agonists on Rodent C Cells:
  - Treatment with GLP-1 agonists caused an increase in number of C cells; prolonged treatment was associated with development of medullary thyroid cancer (MTC)
  - Treatment with liraglutide stimulated increases in serum calcitonin in rodents
  - Rats treated with weekly exenatide for 2 years had increased incidence of thyroid C-cell neoplasms (adenomas and carcinomas) in males and females at all doses tested.
    - *Human relevance of findings are unknown*

Nauck M. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

Percentage of Male Mice or Rats Who Developed C cell Adenomas or Carcinomas with Liraglutide Treatment



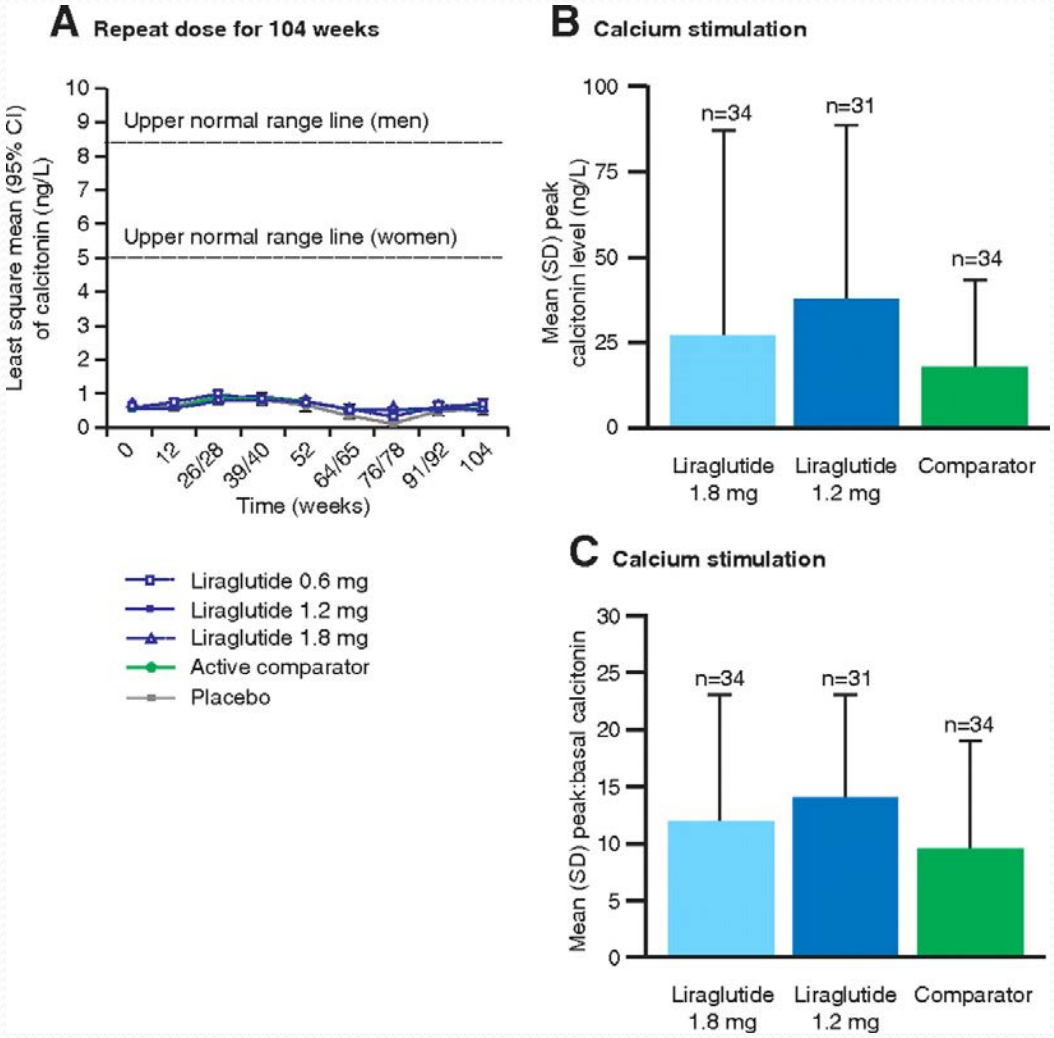
Bjerre Knudsen L et al. *Endocrinology*. 2010;151:1473-86

GLP-1 Agonists and Thyroid Carcinoma

- Thyroid C-cell carcinomas in rats with glucagon like peptide-1 (GLP-1) receptor agonist exposure are not believed to be a cause of concern in humans:
  - Rodents have ~45x more C-cells than humans
  - Only rodent C-cell lines express functional GLP-1 receptors

Bjerre Knudsen L et al. *Endocrinology*. 2010;151:1473-86

GLP-1 Agonists and Calcitonin



- Plasma calcitonin levels did not increase in patients with T2DM treated with liraglutide or comparator for two years in the Phase III LEAD-2 & -3 trials (Figures A, B, and C)
- Plasma calcitonin also did not increase in LEAD-6 (liraglutide vs. exenatide BID)

Bjerre Knudsen L et al. *Endocrinology*. 2010;151:1473-86
Hegedüs L et al. *J Clin Endocrinol Metab*. 2011;96:853-60

Thyroid Neoplasms in RCTs

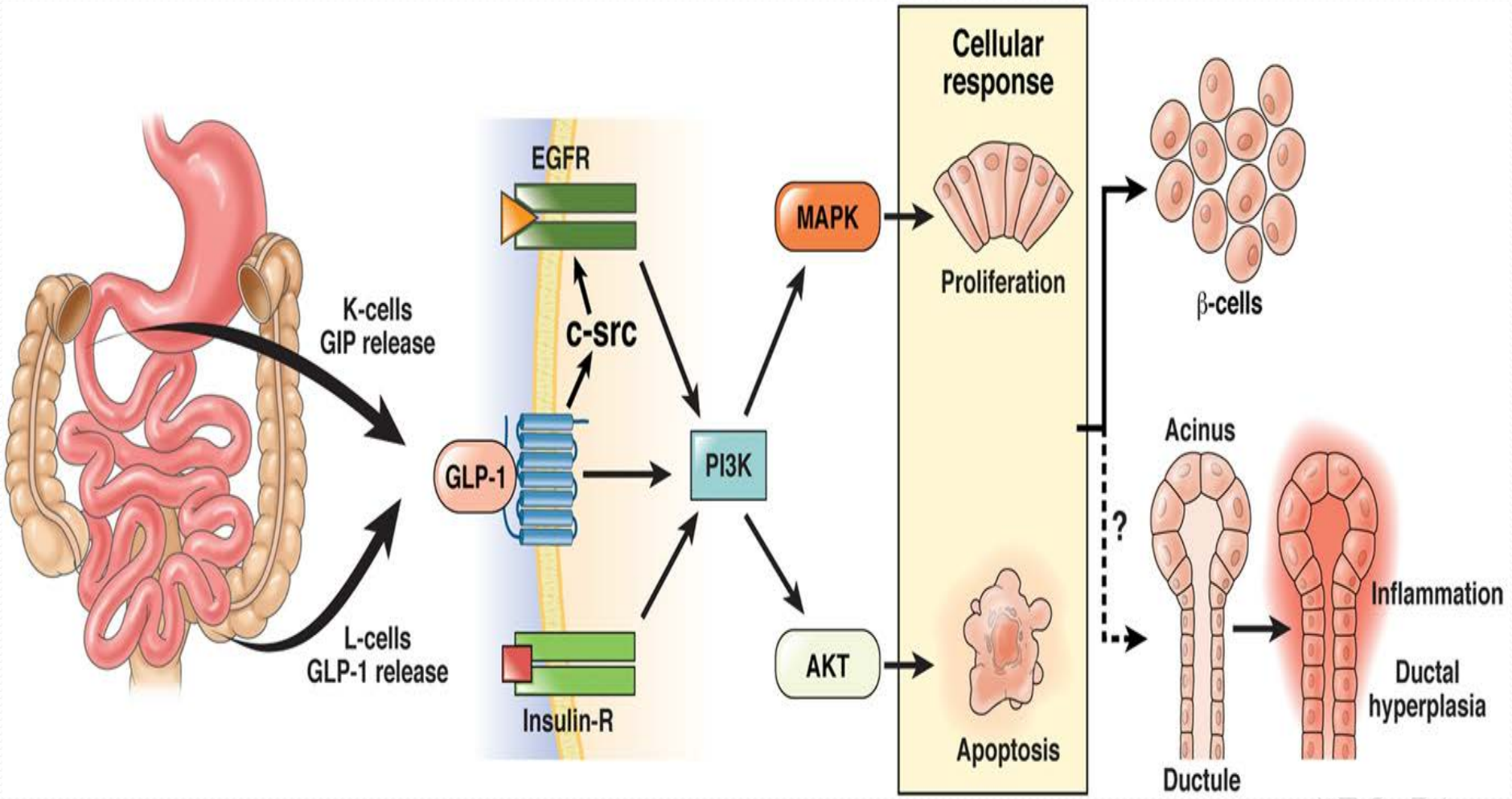
- No great disparity in the incidence of thyroid neoplasms has been observed between GLP-1 receptor agonists and placebo or active comparator.

GLP-1 Agonist	Treatment Group	Incidence Rate
Liraglutide	Liraglutide	1.3 cases per 1000 patient-years
	Placebo	1.0 cases per 1000 patient-years
Exenatide BID	Exenatide BID	0.3 cases per 100 patient-years
	Comparator	0 cases per 100 patient-years

BID, twice daily; GLP, glucagon-like peptide; RCT, randomized controlled trial

Novo Nordisk. VICTOZA (liraglutide) U.S. Prescribing Information, April 2012
MacConell L et al. *Diabetes Metab Syndr Obes*. 2012;5:29-41

GLP-1 agonists increase β-cell mass in rodents



Spranger J et al. *Gastroenterology.* 2011;141:20-3

Sitagliptin & Pancreatic Cancer

- Animal studies are conflicting:
  - Sitagliptin was associated with increased pancreatic ductal proliferation (8/8 rats), ductal metaplasia (3/8) and pancreatitis (1/8)
    - In *human islet amyloid polypeptide transgenic **rat** model* of type 2 diabetes
    - Potential risk factors for pancreatic cancer
  - Sitagliptin exposure (± metformin) for one year in mice was associated with no increase in pancreatitis, ductal metaplasia, or neoplasia compared to the no treatment group.

Matveyenko AV et al. *Diabetes.*2009;58:1604-15
Aston-Mourney K et al. *Am J Physiol Endocrinol Metab.* 2013;305:E475-84

GLP-1 Receptor Agonists
Pancreatic ductal metaplasia and tumors?

- Butler – Nauck debate at EASD 2011:
  - "For now, this analysis of the FDA database does not establish that pancreatitis, pancreatic and thyroid cancer are caused by GLP-1 based therapy. It simply raises the level of concern that they may be and that the appropriate prospective studies are required to rule them out."
  - "…at least a decade between the occurrence of the initiating mutation…"
  - "At least five more years are required for the acquisition of metastatic ability…"

Elashoff M et al. *Gastroenterology*. 2011;141:150-60
Matvenyenko AV et al. *Diabetes* .2009;58:1604-15
Yachida S et al. *Nature*. 2010;467:1114-7

Incretin-Based Therapies and Cancer - Pancreas

Exenatide Clinical Studies:

- Pancreatic Cancer
  - Exenatide Incidence: 0.5/1,000 pt-yrs
  - Insulin incidence: 1.6/1,000 pt-yrs
  - Placebo incidence: 0/1,000 pt-yrs.
- Adverse Events Reported:
  - Pancreatic cancer: 6.7/100,000 pt-yrs
- German Adverse Events Database 2011
  - Pancreatic cancer 11 cases in 4 years
    - 15,000 to 25,000 patients treated yearly
    - Average duration of treatment 12 months

Amylin. BYETTA (Exenatide) U.S. Prescribing Information, February 2013
Arzneimittelkommission der deutschen Ärzteschaft, *Dtsch Arztebl* 2011; 108: A-1080

Could GLP-1 Be a "Good Guy"?

- GLP-1 is a potent inducer of cAMP and inhibitor of **breast cancer** cell proliferation
- Treatment of CT26 **colon cancer** cells and of CT26 tumor-bearing mice with *exenatide* → increased tumor apoptosis, reduced growth and survival in CT26 colon cancer
- Human ***neuroblastoma*** SH-SY5Y: *GLP-1 and exenatide* stimulate cell proliferation and increase cell viability, enhance neuroprotection

Ligumsky H et al. *Breast Cancer Res Treat.* 2012;132:449
Koehler JA et al. *Endocrinology.* 2011;152:3362
Li Y et al. *J Neurochem.* 2010;113:1621

Regulatory Communications (Incretin Mimetics)

- European Medicines Agency (EMA):
  - "Presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines."
  - "With regard to pancreatic cancer, data from clinical trials do not indicate an increased risk…"
- FDA:
  - "Patients should continue to take their medicine as directed until they talk to their health care professional…"
  - "…health care professionals should continue to follow the prescribing recommendations in the drug labels."

Investigation into GLP-1 Based Therapies Concluded. July 2013. http://www.ema.europa.eu/ema/index.jsp...
FDA Safety Communication. March 2013. http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm

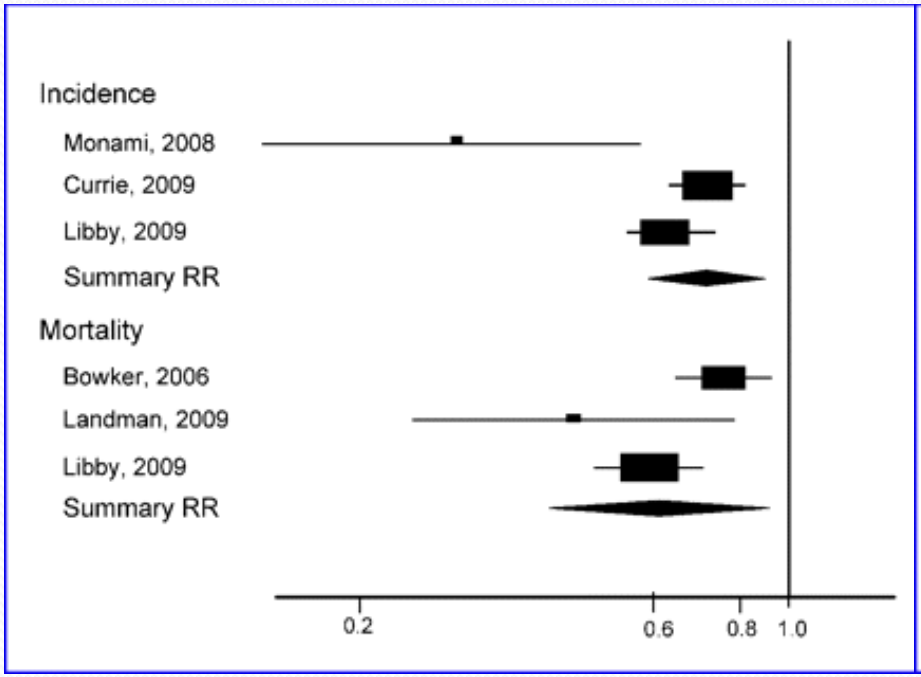
Meta-Analysis of Metformin and Cancer

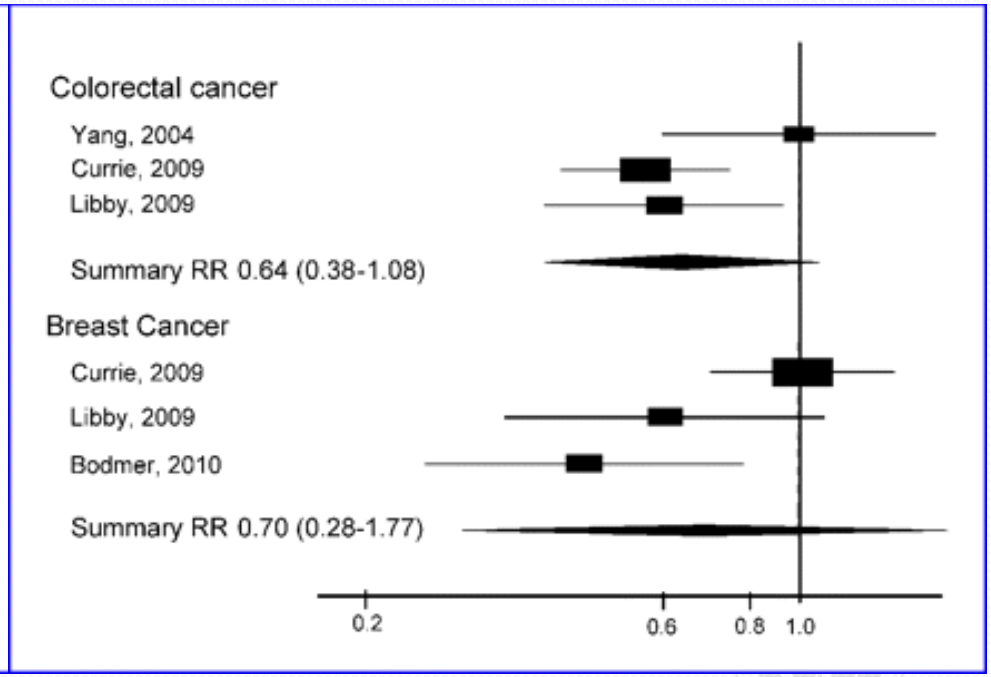
All Cancer

- 5 observational studies
  - 4 cohort, 1 case control
- N=29,792, average follow-up ~6 years

Colorectal and breast cancer

- 4 observational studies
  - 2 cohort, 2 case control
- N=18,668, average follow-up ~4 years

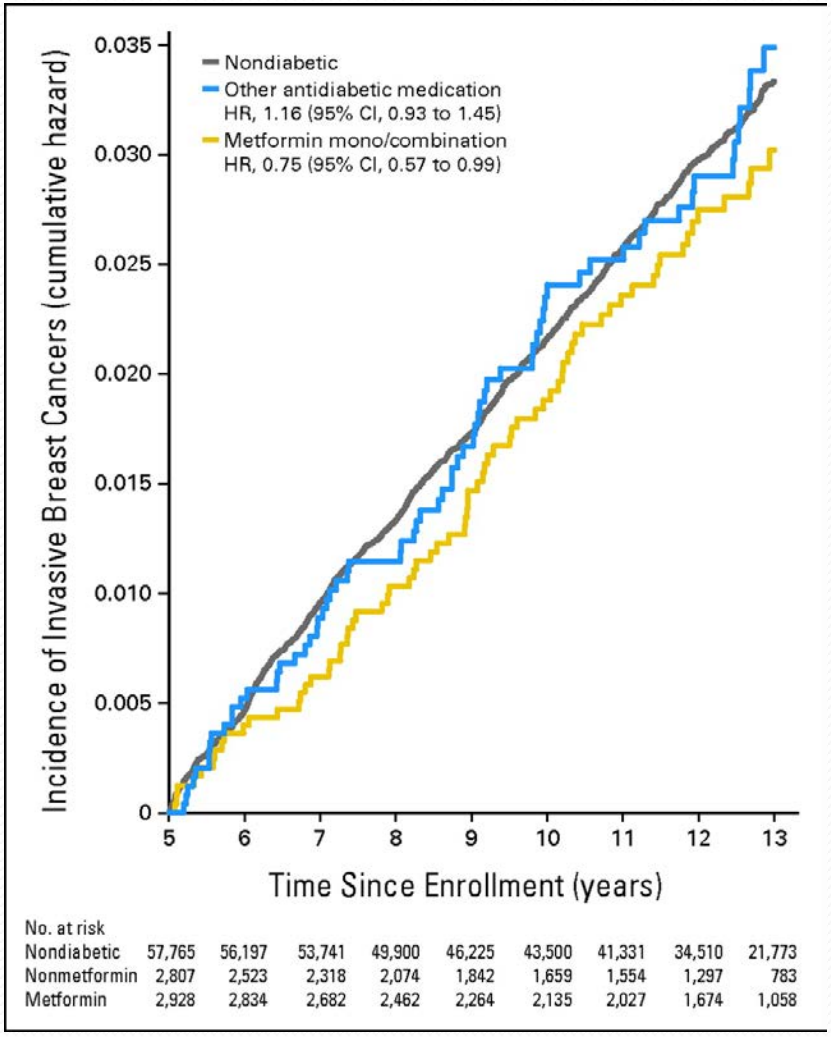




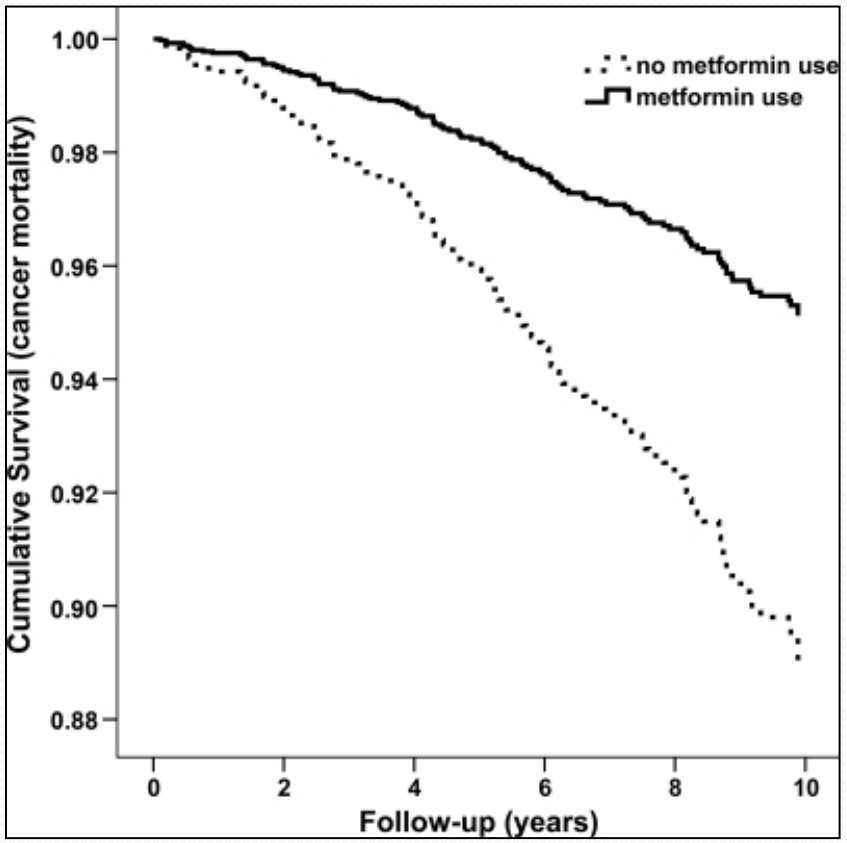
Decensi A et al. *Cancer Prev Res.* 2010;3:1451-61

Metformin and Cancer

Breast Cancer Incidence



Cancer Mortality



Chlebowski RT et al. *J Clin Oncol*. 2012;30:2844-52
Landman GW et al. *Diabetes Care.* 2010;33:322-6

CT.gov "Metformin and Cancer" Search (September 18, 2013)

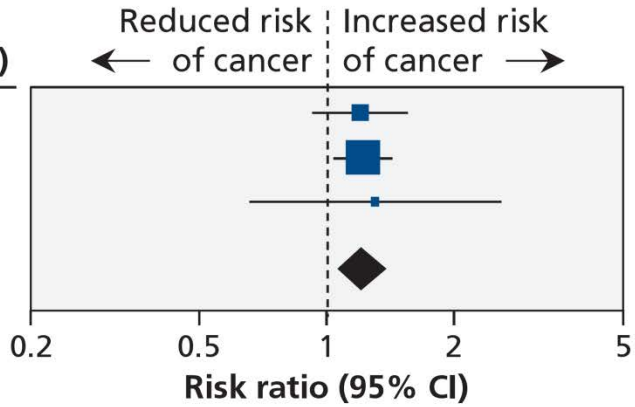
- 81 open studies returned
- 53 relevant to cancer
  - Breast: 16
  - Colorectal: 8
  - Prostate: 6
  - Gynecologic: 5
  - Pancreatic: 4
  - Leukemia: 4
  - Other Cancers: 10 (lung, skin, head/neck, heme, etc.)
- Most studies investigating improved patient response to chemotherapy, improved survival, or chemoprevention.

http://clinicaltrials.gov/ct2/results?term=metformin+and+cancer&recr=Open&pg=1

Do Thiazolidinediones (TZDs) Cause Cancer?

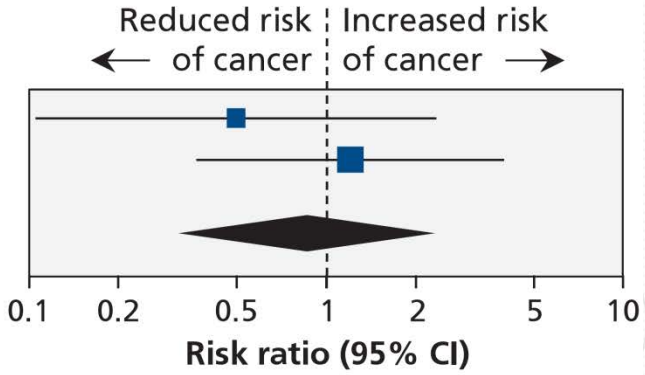
Pioglitazone:

Study	Exposed *n/N*	Comparison *n/N*	Risk ratio (95% CI)
Lewis et al.[10]	90/30 173	791/162 926	1.2 (0.9–1.5)
Neumann et al.[19]	175/155 535	1 841/1 335 525	1.22 (1.05–1.43)
Tseng[20]	10/2 545	155/52 383	1.30 (0.66–2.58)
Overall			1.22 (1.07–1.39)
Heterogeneity: $I^2 = 0\%$			



Rosiglitazone:

Study	Intervention *n/N*	Control *n/N*	Risk ratio (95% CI)
Kahn et al.[16]	2/1456	8/2895	0.50 (0.11–2.34)
Home et al.[17]	6/2220	5/2227	1.20 (0.37–3.94)
Overall	8/3676	13/5122	0.87 (0.34–2.23)
Heterogeneity: $I^2 = 0\%$			



Colmers IN et al. *CMAJ*. 2012;184:E675-E683

Thiazolidinediones and Cancer

- PROactive: A prospective randomized, controlled multicenter study of the effect of pioglitazone on CV events in patients with T2DM
- Pioglitazone (n=2605); Placebo (n=2633)
- Incidence of malignancy was similar in both groups
  - 97 (3.7%) pioglitazone, 99 (3.8%) placebo
- However:
  - Fewer breast cancer cases with pioglitazone
    - 3 (0.1%) pioglitazone, 11 (0.4%) placebo
  - More bladder cancer cases with pioglitazone
    - 14 (0.5%) pioglitazone, 5 (0.2%) placebo

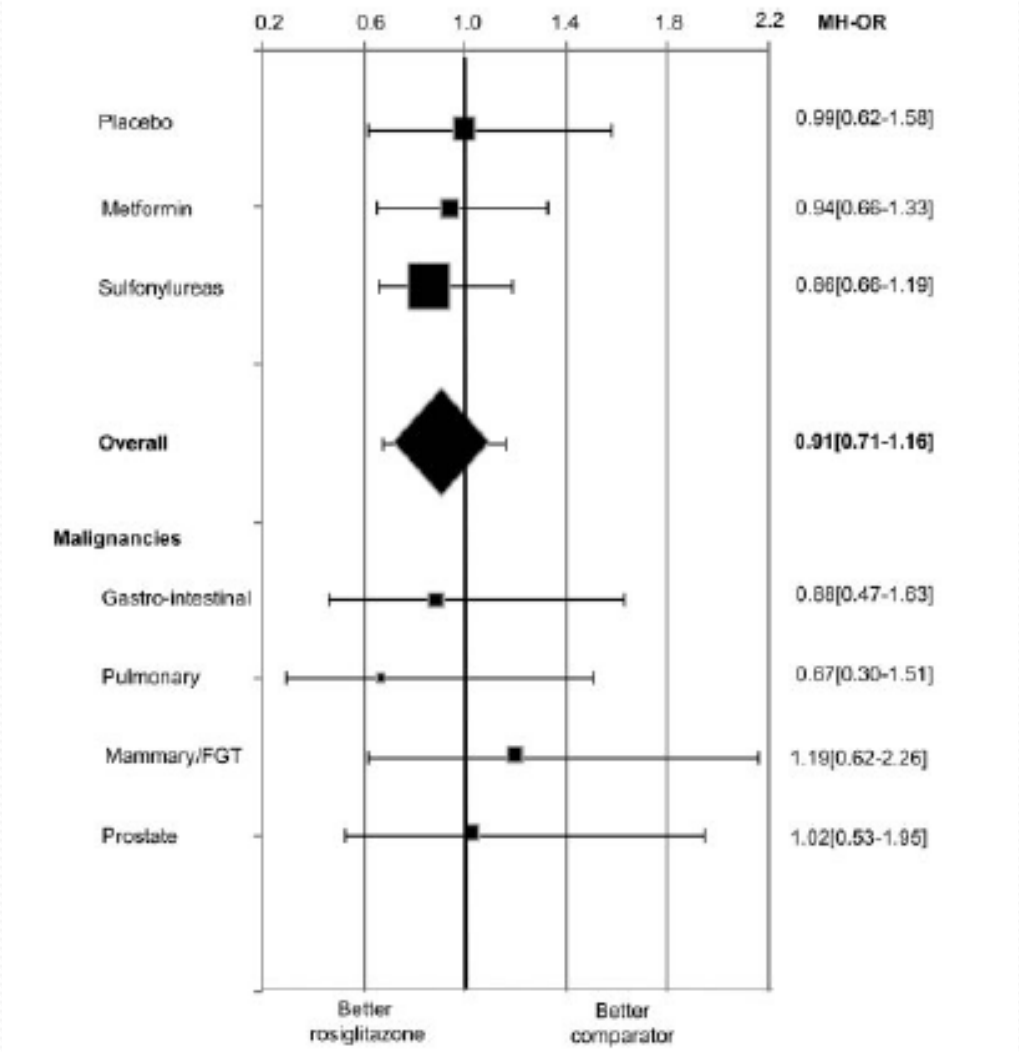
Dormandy J et al. *Drug Saf.* 2009;32:187-202

FDA Safety Communication (Pioglitazone and Bladder Cancer)

- Five-year interim data from the Kaiser Permanente Northern California health plan indicated no significant increase in the risk of bladder cancer with pioglitazone (HR 1.2, 95% CI 0.9 to 1.5)
  - Nominally significant increased risk for use >2 years (HR 1.4, 95% CI 1.03 to 2.0)
- Practitioners should "not use pioglitazone in patients with active bladder cancer," and should use "with caution in patients with a prior history of bladder cancer."

FDA Safety Communication. June 2011. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm

Rosiglitazone Meta-analysis



- Included 80 clinical trials
- Rosiglitazone (N=16,332) vs. Comparator (N=12,522)
- Rosiglitazone combined with placebo or other treatments did not significantly modify cancer risk (OR 0.91, 95% CI 0.71-1.16)
- The incidence of malignancies was significantly lower in rosiglitazone-treated patients than in control groups at **0.23 vs. 0.44 cases/100 patient-years (*P*<0.05)**

Monami M et al. *Diabetes* Care. 2008;31:1455-60

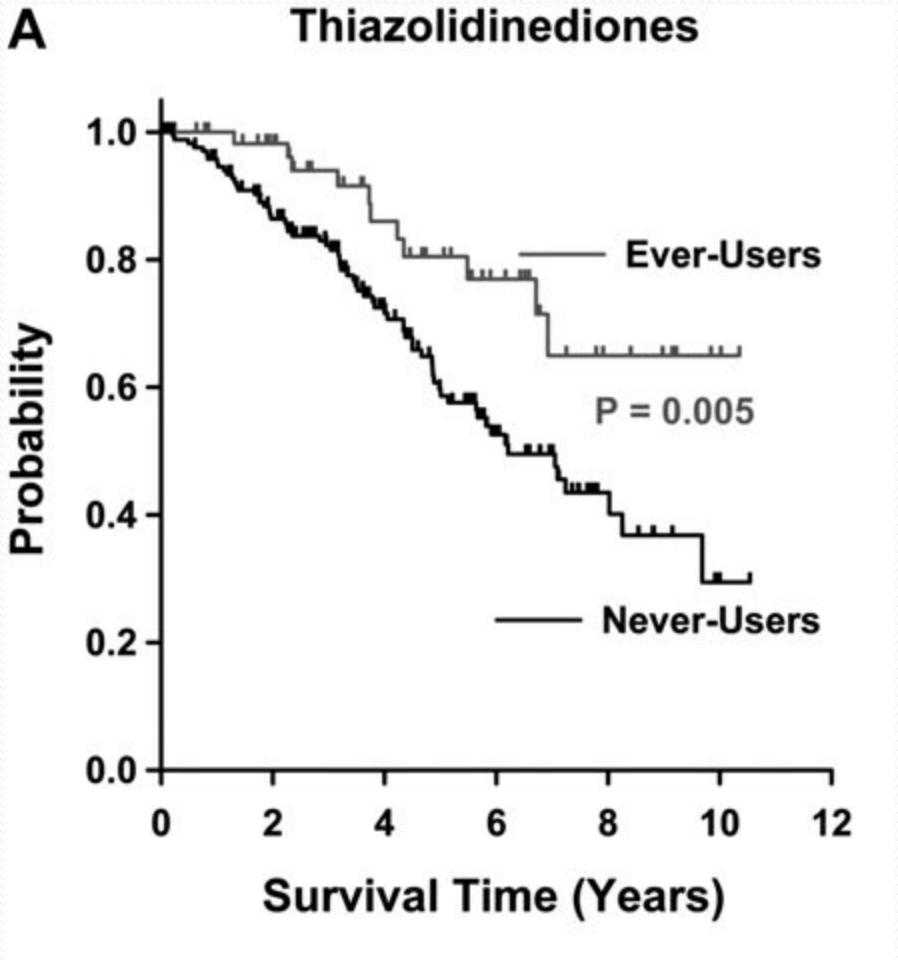
RECORD Study

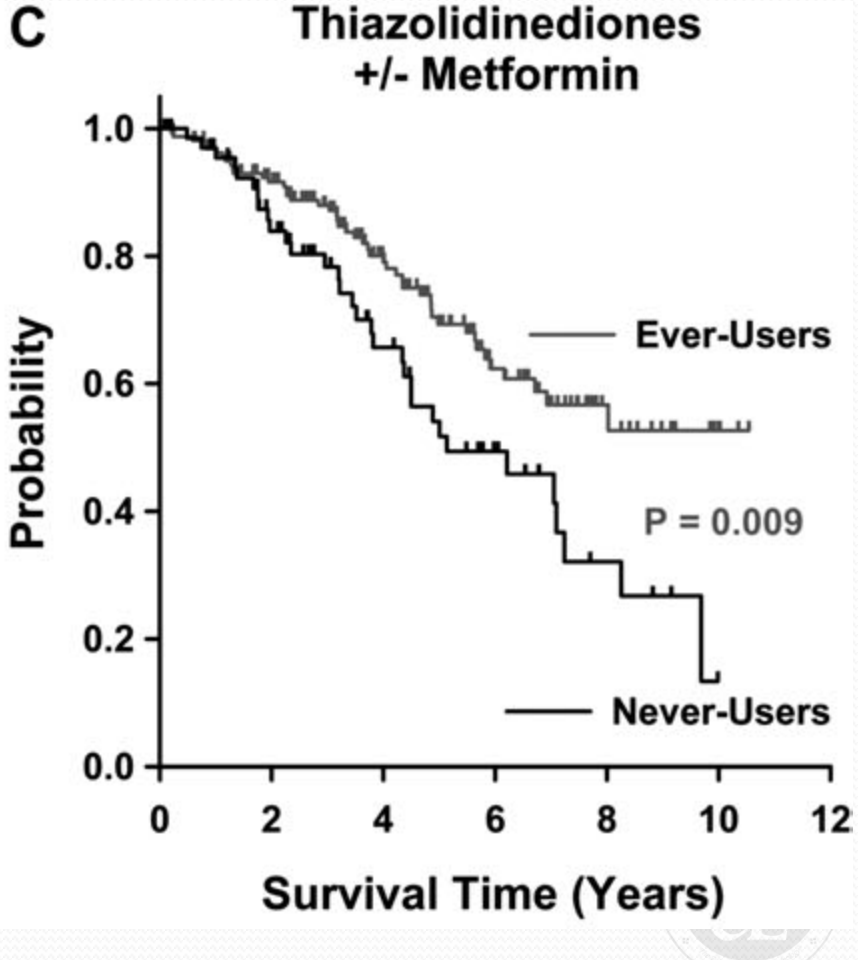
Variable	Background Sulfonylurea		Background Metformin	
	Metformin	Rosiglitazone	Sulfonylurea	Rosiglitazone
n	1,122	1,103	1,105	1,117
Study exposure, (person-years)	6,126	6,110	6,146	6,228
Malignancies, n (%)	69 (6.1)	56 (5.1)	74 (6.7)	57 (5.1)
Rate (per 100 person-years)*	1.15	0.94	1.23	0.93
Hazard ratio (95% CI)	1.22 (0.86-1.74)		1.33 (0.94-1.88)	

*Adjusted for study exposure; CI, confidence interval; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes

Home PD et al. *Diabetologia*. 2010;53:1838-45

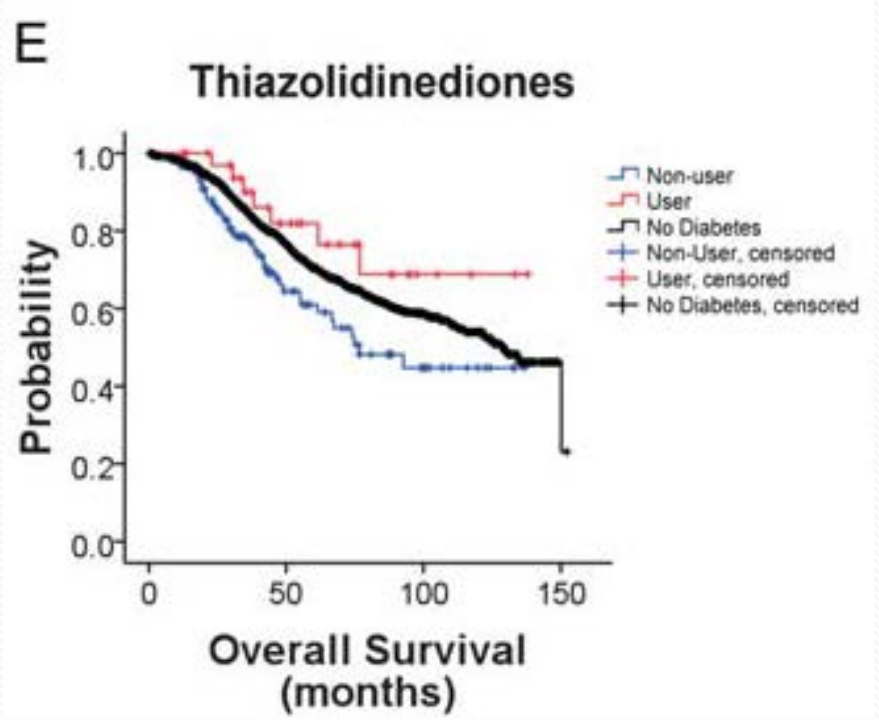
TZDs and Prostate Cancer

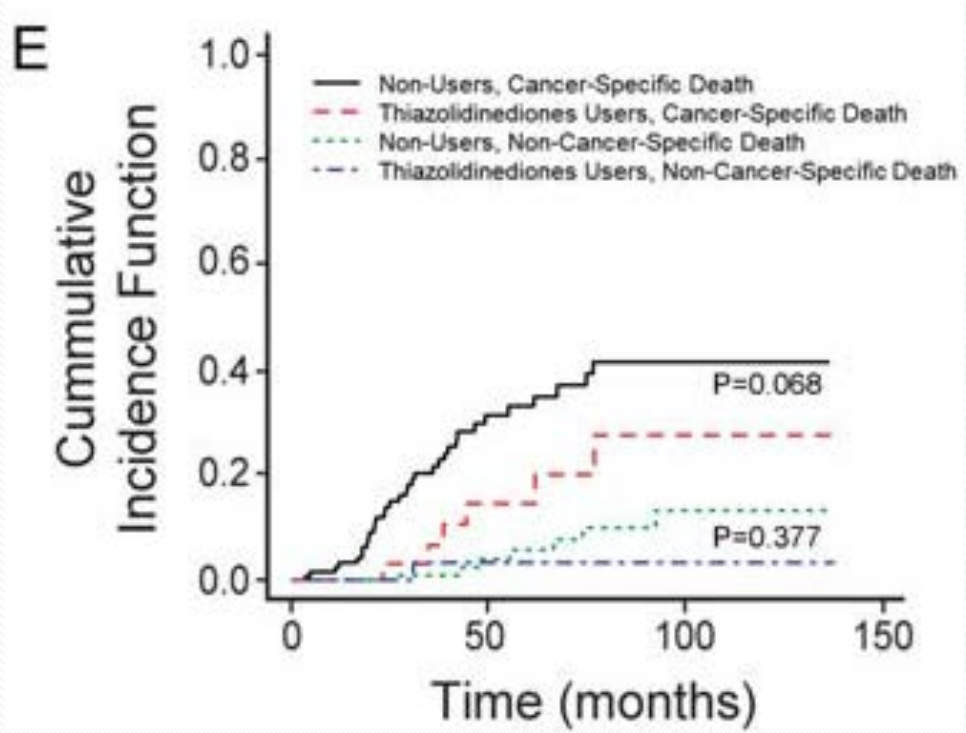




He XX et al. *Ann Oncol*. 2011;22:2640-5

TZDs and HER2+ Breast Cancer





He XX et al. *Ann Oncol*. 2012;23:1771-80

Association of TZDs with Decreased Cancer Incidence

- Lung:
  - Govindarajan, et al. (2007). *J Clin Oncol* 25(12): 1476-1481.
  - Lai, et al. (2012). *Clin Lung Cancer* 13(2): 143-148.
- Liver:
  - Chang, et al. (2012). *Hepatology* 55(5): 1462-1472.
- Colon/rectum:
  - Chang, et al. (2012). *Hepatology* 55(5): 1462-1472.
- Cancers in general:
  - van Staa, et al. (2012). *Diabetologia* 55(3): 654-665.
  - Yang, et al. (2012). *Diabetes Res Clin Pract* 97(1): e11-15.
- No clear evidence of an association between use of pioglitazone and risk of the incident cancers examined.
  - Koro, et al. (2007). *Pharmacoepidemiol Drug Saf* 16(5): 485-492.
  - Ferrara, et al. (2011). *Diabetes Care* 34(4): 923-929.

Sodium-Glucose Cotransporter 2 Inhibitors

- Dapagliflozin, which is currently approved in Europe only, was implicated with an increased incidence of breast and bladder cancer.
  - The increased incidence was *not statistically significant*
- Canagliflozin which was recently approved in the United States has not been associated with a cancer-related safety signal of concern.

Kim Y et al. *Diabetes Metab Syndr Obes*. 2012;5:313-27
USFDA Briefing document (NDA 202293 - Dapagliflozin). 2011

SGLT2 Inhibitors - Potential Signal Identified from Dapagliflozin Clinical Data

- Interim clinical data – May 2011 cutoff
  - Overall incidence of malignancies or unspecific tumors was balanced
  - However, imbalance in some tumor types was noted

Adverse Events	Dapagliflozin (N=4559)	All Control (N=2239)
Any Malignant or Unspecified Tumor	65 (1.4%)	29 (1.3%)
Bladder	**7 (0.15%)**	**0 (0%)**

Reilly TP. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

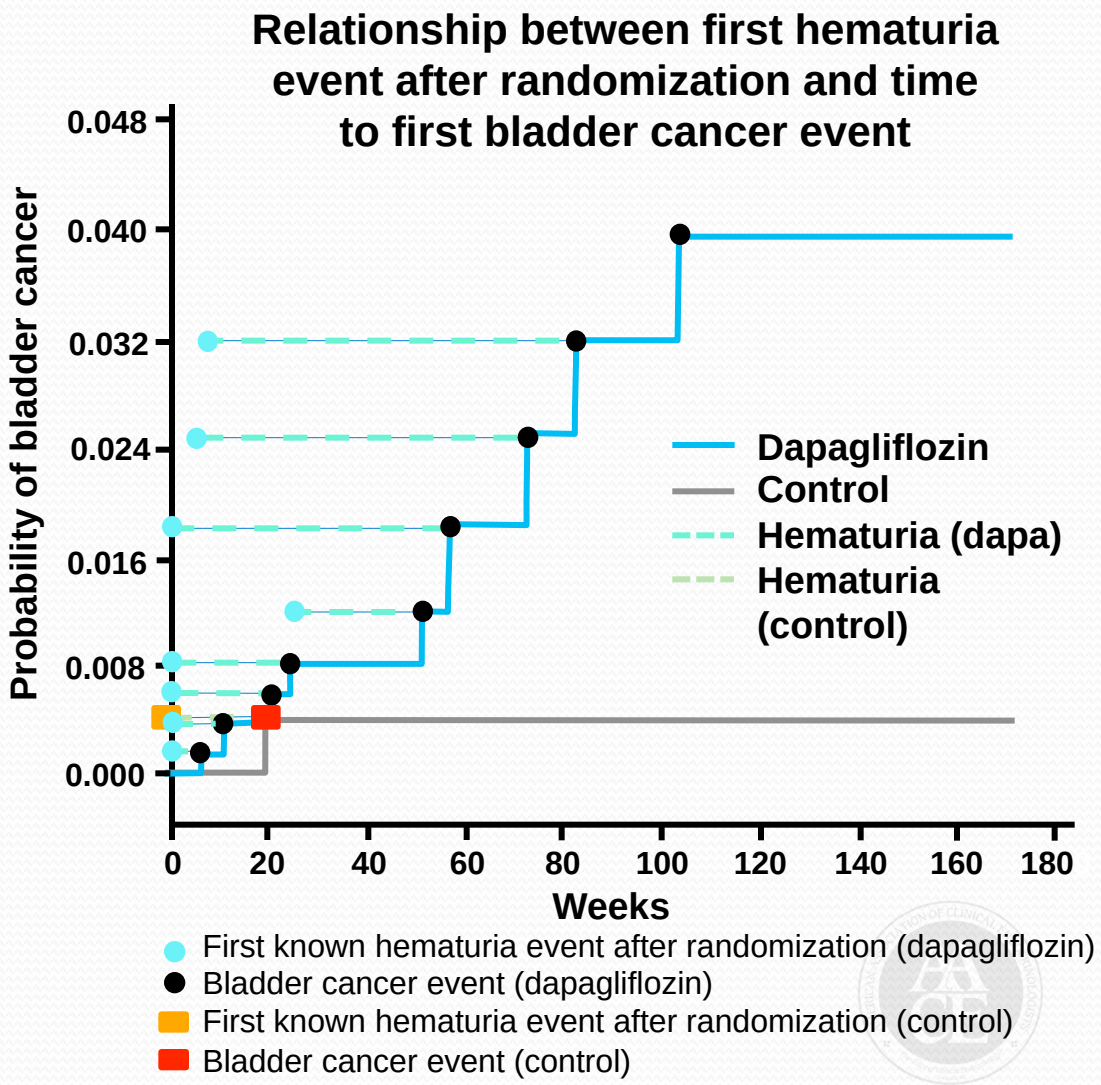
Bladder Cancers in Dapagliflozin Studies Were Likely Pre-existent

	Dapagliflozin	Control
Subjects	5501	3184
Exposure	5874 pt-y	3216 pt-y
Subjects with Events	9 of 5501 (0.16%)	1 of 3184 (0.03%)
Incidence rate (95% CI)	0.15 (0.07, 0.29)	0.03 (0.00, 0.17)

Incidence Rate Ratio: 5.176
(95% CI: 0.678, 233.92)

***Database Cut of 15 July 2011**

Dapagliflozin:
control exposure ratio ~ 1.8



Reilly TP. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

Diabetes Medications and Cancer Risk

Medication Class	Cancer Risk Summary
Insulin	No evidence of cancer risk from RCTs
Incretins	
GLP-1 agonists	No evidence of MTC or pancreatic cancer in humans
DPP-4 Inhibitors	No evidence of MTC or pancreatic cancer in humans
Metformin	No discernible cancer risk Possible protective benefits on cancer outcomes
Thiazolidinediones	
Rosiglitazone	No evidence of cancer risk
Pioglitazone	Possible risk of bladder cancer at chronic high doses (>24 months and >28,000-mg cumulative dose)
SGLT2 Inhibitors	No evidence of cancer risk

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1; MTC, medullary thyroid carcinoma; SGLT2, sodium-glucose cotransporter 2

Does Bariatric Surgery Affect Mortality? (Utah Obesity Surgery Study)

- Retrospective cohort design:
  - 9949 gastric bypass patients
  - 9628 severely obese (BMI ≥35 kg/m²) driver's license applicants (control)

	Surgery Group (n/ 10,000 person-yrs)	Control Group (n/ 10,000 person-yrs)
All causes of death	37.2	61.1
CV disease	8.5	19.3
Diabetes	0.3	3.5
Cancer	**5.4**	**15**
Other disease	11.4	17

Adams TD et al. *N Engl J Med.* 2007;357:753-61

SOS Study: Obesity-related Cancers Decrease with Surgically-induced Weight Loss

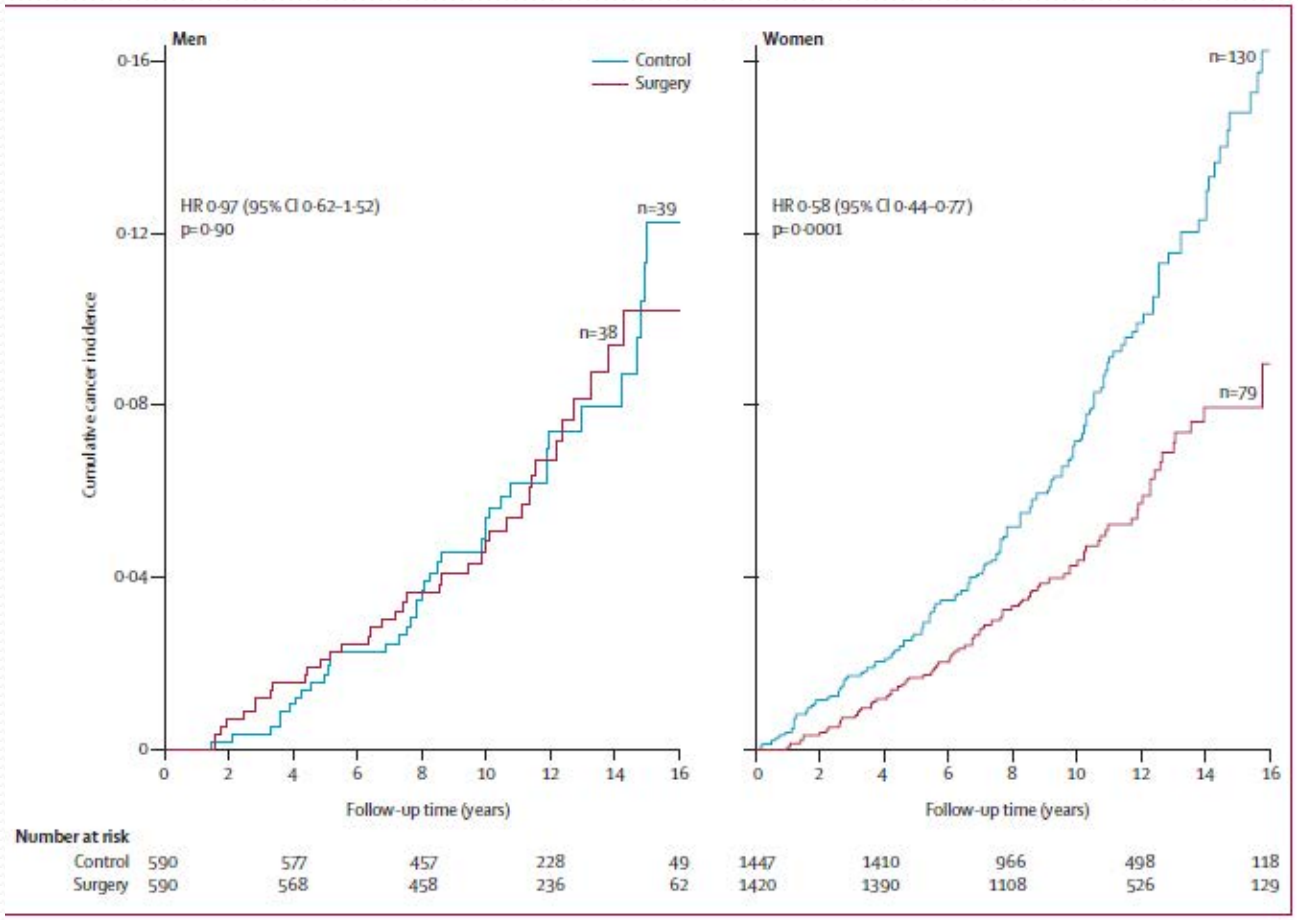


Figure 3: The unadjusted cumulative fatal plus non-fatal cancer incidence from the start of the intervention by sex in surgically treated obese individuals and in obese control individuals

Sjostrom L et al. *Lancet.* 2009;10:653-62

Implications for Practice

Implications for Practice (Cancer Screening)

- Cancer screening and counseling on lifestyle changes, should be a part of regular preventive care in people with obesity and/or diabetes.
- Conversely, people who develop cancer at an early age should be screened for metabolic abnormalities.
- Cancer screening tests of proven benefit for malignancies (breast cancer, colon cancer, skin cancer, etc.) in at-risk individuals should begin relatively early.

Implications for Practice (Diabetes Treatments)

- The current totality of evidence on diabetes treatments and cancer risk should not change clinical practice.
- The practitioner must decide if remote yet plausible cancer risks weight more heavily than suboptimal glycemic control and a higher likelihood of diabetes complications in patients.
- Healthcare professionals should have greater confidence in prescribing all FDA-approved antihyperglycemic medications according to current clinical practice recommendations.

Future Research and Conclusion

Future Research Needs

- Questions about the relative contributions of obesity and diabetes to cancer development remain.
  - What role, if any, does various levels of hyperglycemia play?
  - Do patients with diabetes and controlled glucose have a decreased risk of cancer compared to those with uncontrolled glucose?
- Future studies of medications should be designed to detect cancer-related outcomes in addition to efficacy and safety outcomes.
- Randomized controlled trials of sufficient size and duration are needed to minimize bias, confounding, and chance.

Conclusion

- Epidemiology demonstrates a significant increase of cancer in obesity, insulin-resistant states, and ultimately diabetes; early cancer screening is critical in patients with these conditions.
- There is currently insufficient evidence to warrant withholding of the use of certain glucose-lowering medications on the basis of cancer concerns.
- Further collaborative research between clinicians, as well as basic, clinical, and epidemiologic researchers, is necessary to complete the evidence on these complex issues.