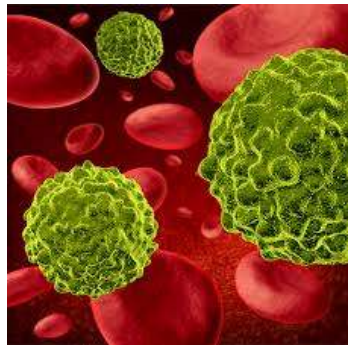
Epidemiology of cancer in diabetes

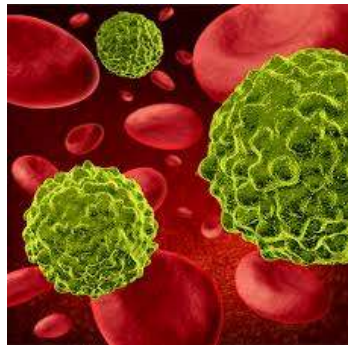
Nan Hee Kim, MD, Ph.D.

Korea University Medical School



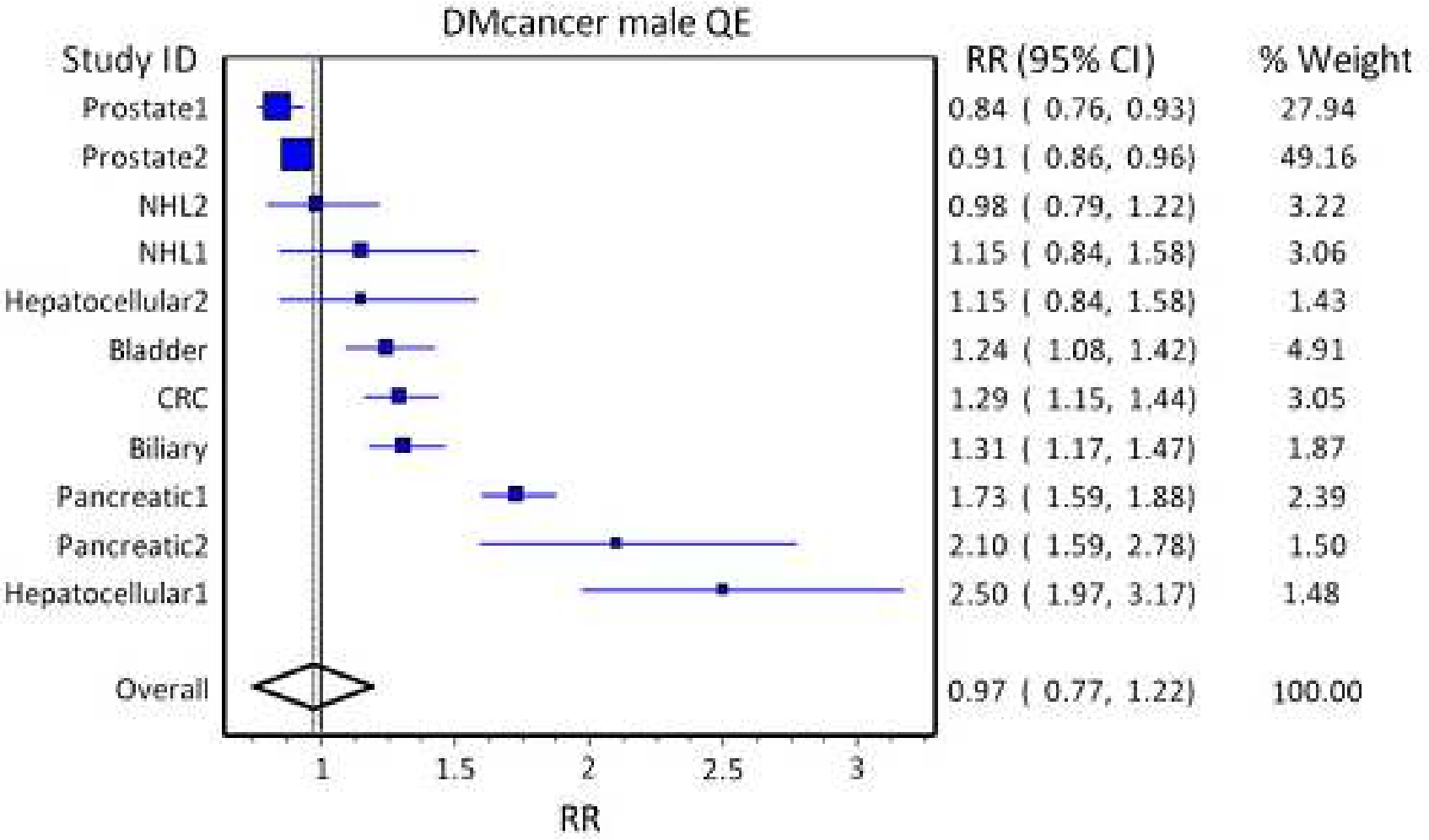
Contents

- Association of diabetes and cancer
- Possible mechanisms of this association
  - Hyperinsulinemia
  - IGF-I
- Treatment of diabetes and cancer



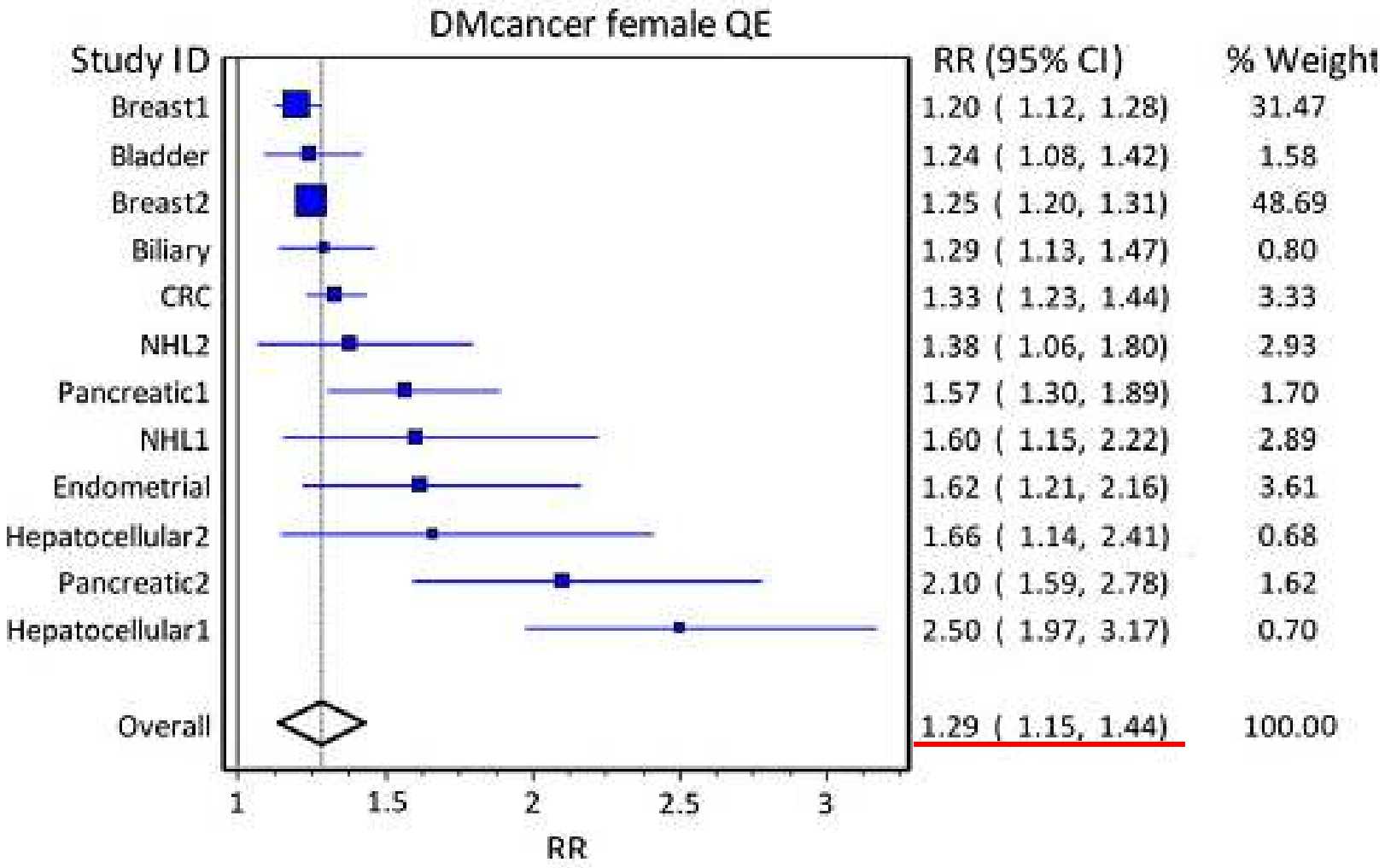
Association of diabetes and cancer

Pooled risk of cancer in diabetic men



Onitilo AA, Cancer Causes Control 23: 2012

Pooled risk of cancer in diabetic women



Onitilo AA, Cancer Causes Control 23: 2012

Diabetes affects mortality in cancer

Table 3 Summary of meta-analyses of survival in cancer patients with diabetes

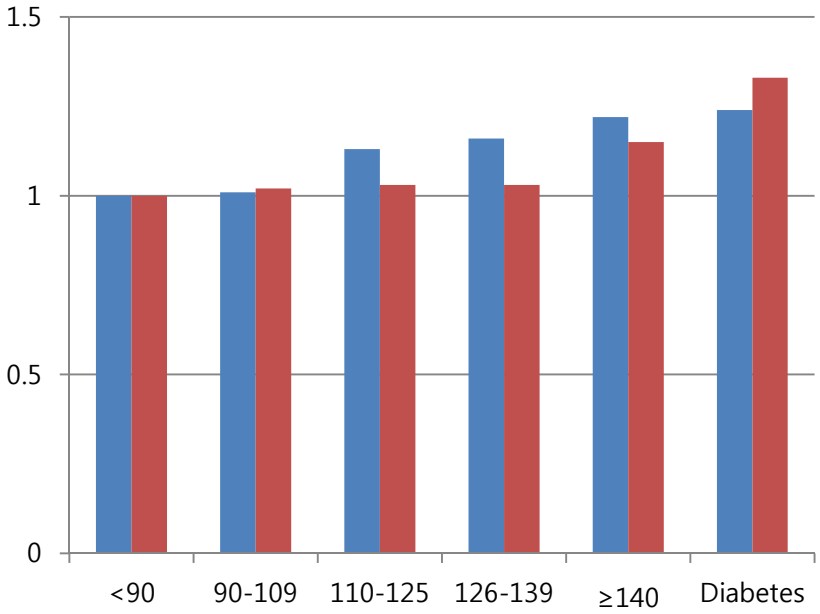
Cancer site (number of studies)	First author	HR (95 % CI) of death (all cause)
All cancer types (23)	Barone [115]	1.41 (1.28–1.55)
Breast (8)	Peairs [116]	1.49 (1.35–1.65)
Prostate (4)	Snyder [117]	1.57 (1.12–2.20)

Onitilo AA, Cancer Causes Control 23: 2012

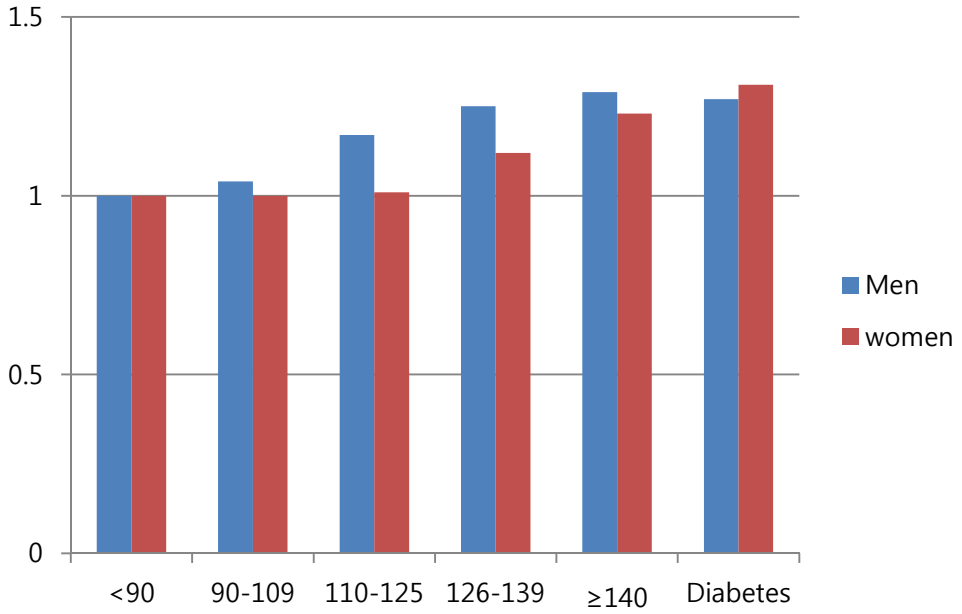
Fasting Serum Glucose Level and Cancer Risk in Korean Men and Women

10yr prospective cohort study of more than one million Koreans who received Health insurance from the National Health Insurance Corp.

Cancer incidence by FPG levels



Cancer mortality by FPG levels



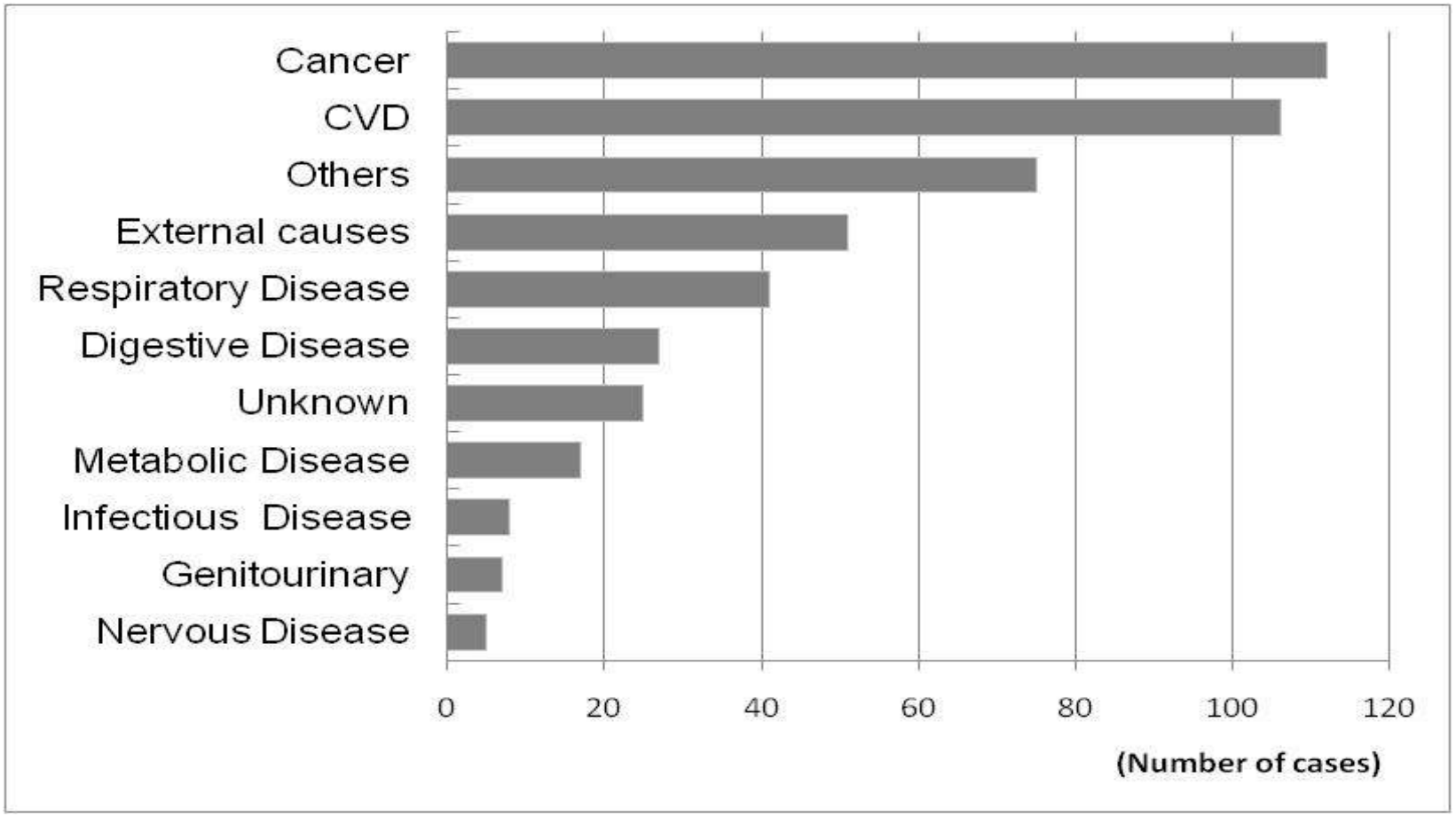
Diabetes: FPG ≥126 or medication

Jee SH, JAMA 293: 194-202, 2005

Plasma glucose regulation and mortality in Korea

: A pooled analysis of three community-based cohort studies

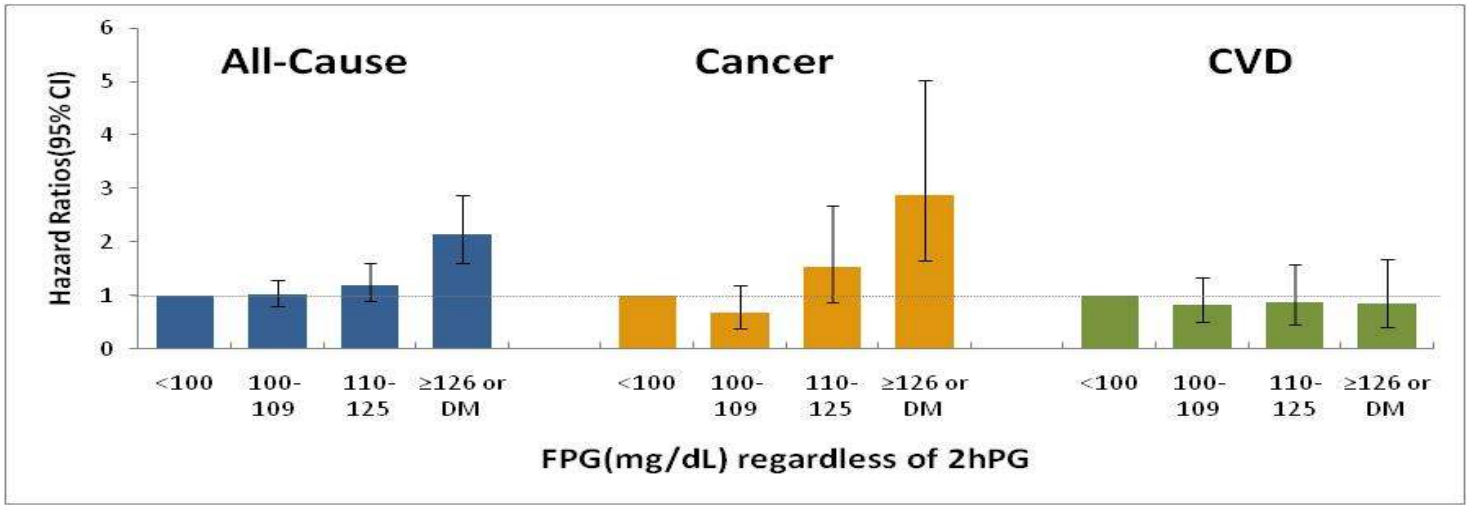
Yonchon, Jungeup, and Ansan studies, N=3801
Median f/u: 11yr, N. of all-cause death: 474



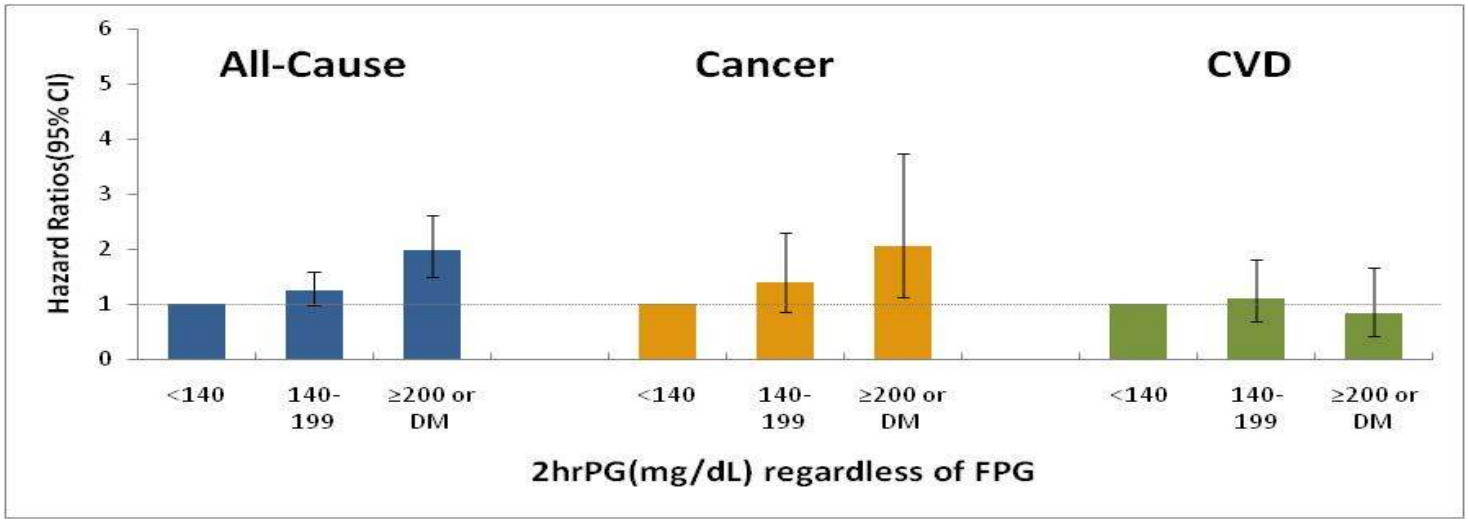
The Committee on the Epidemiology of Diabetes, KDA (Diabetes Metab J, in press)

Plasma glucose regulation and mortality in Korea

a) FPG



b) 2hPG

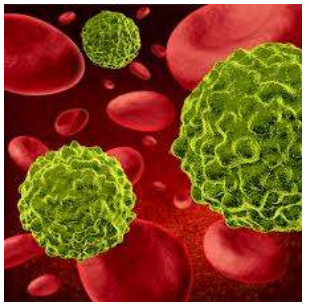


HR: Adjusted for age, sex, study center, BMI, systolic blood pressure, total cholesterol, HDL-cholesterol and smoking status.

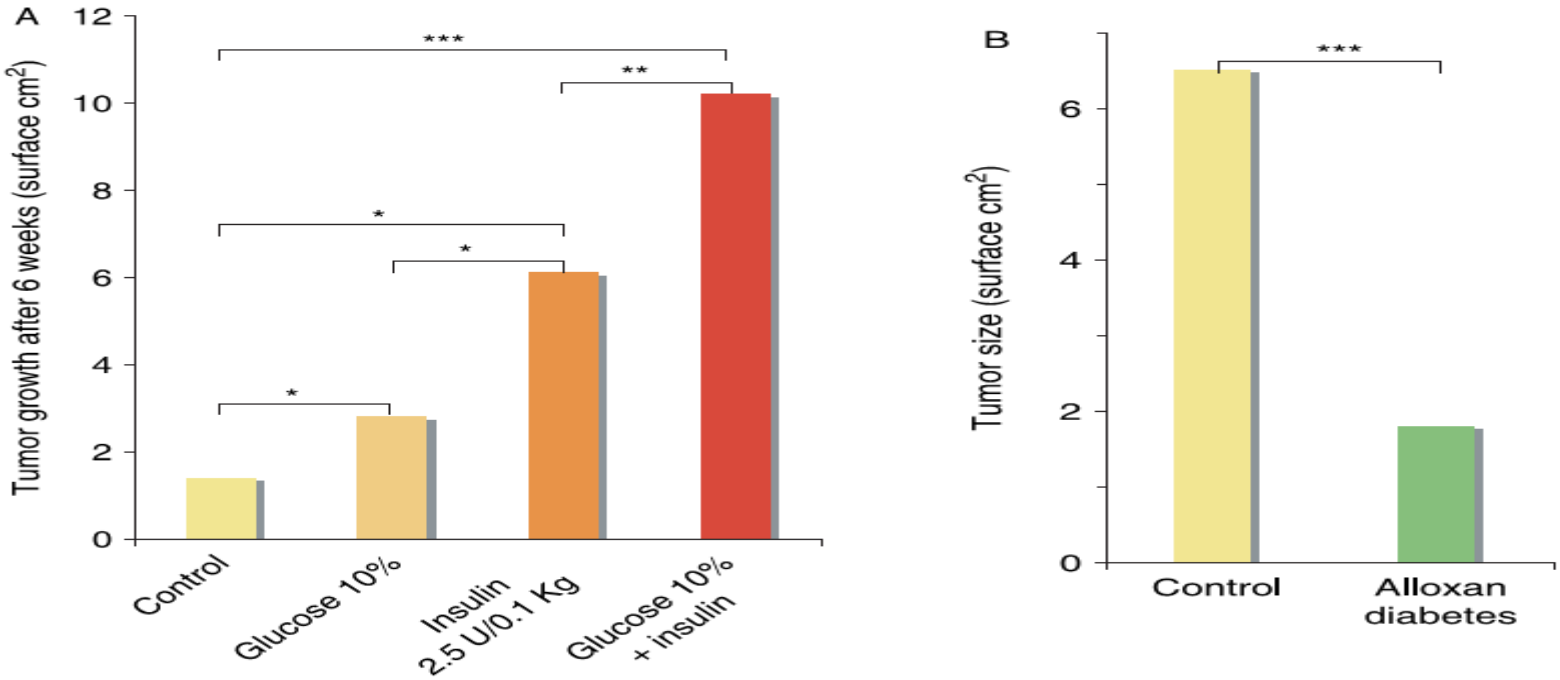
Linking mechanisms between diabetes and cancer

Hyperinsulinemia

Increased Insulin-like growth factor-I (IGF-I) activity



Effects of insulin administration and deprivation on mammary tumor growth

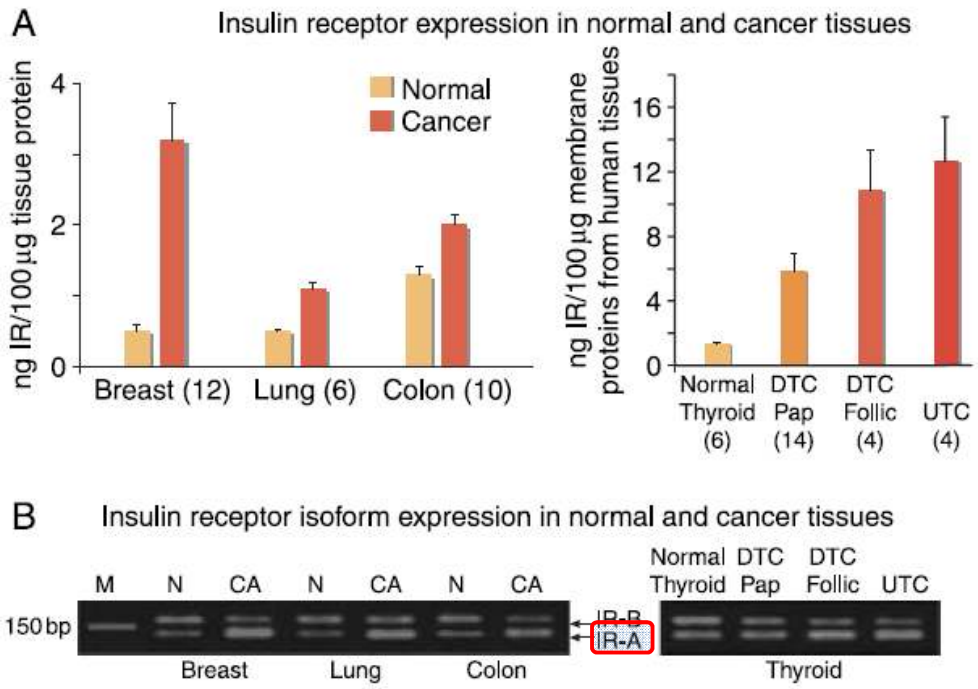


- Administration of insulin produced a significant increase in tumor growth
- Mammary tumor showed regression after induction of alloxan diabetes, which represents insulin deficiency

Heuson J, Cancer Res 32:233-238, 1972, Heuson J, Cancer Res 32:226-232, 1972

Insulin receptor (IR) contents and IR isoform expression in cancer

- Many cancer cells have an increased IR contents, especially IR-A
- By binding to overexpressed IR-A, insulin may facilitate the growth of tumors



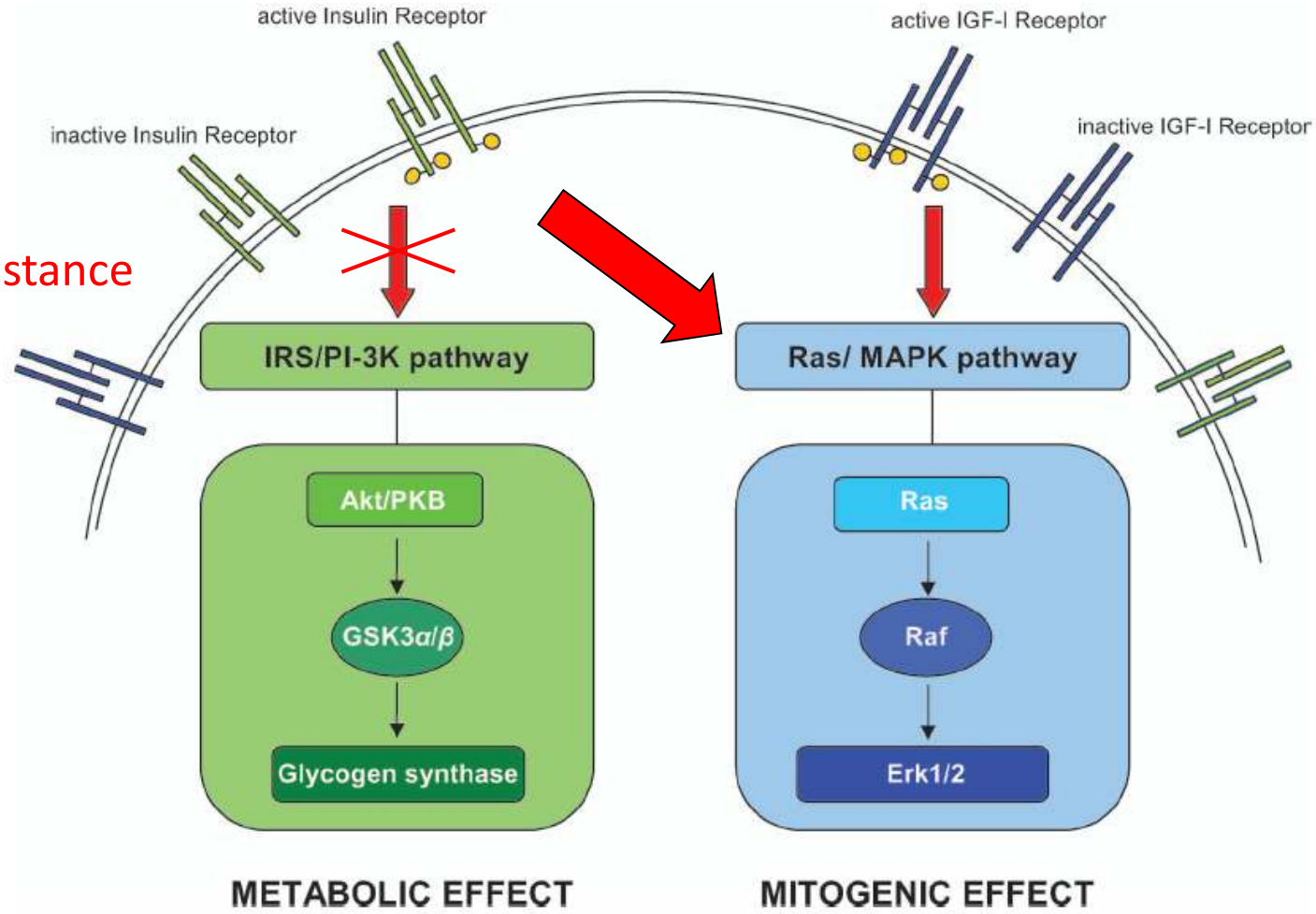
Vigneri P, Endocrine-Related Cancer 16: 2009

Insulin and IGF-1 receptor signaling

Hyperinsulinemia

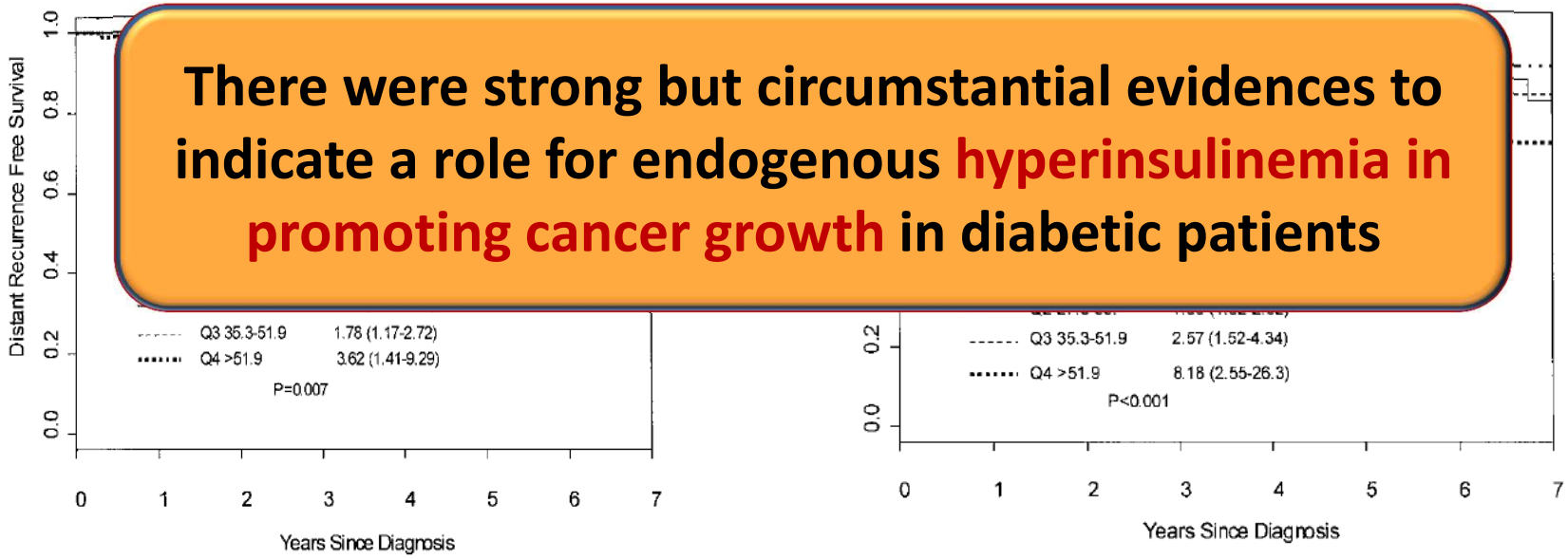
Hyperinsulinemia

Insulin resistance



Fasting insulin and outcome in breast cancer

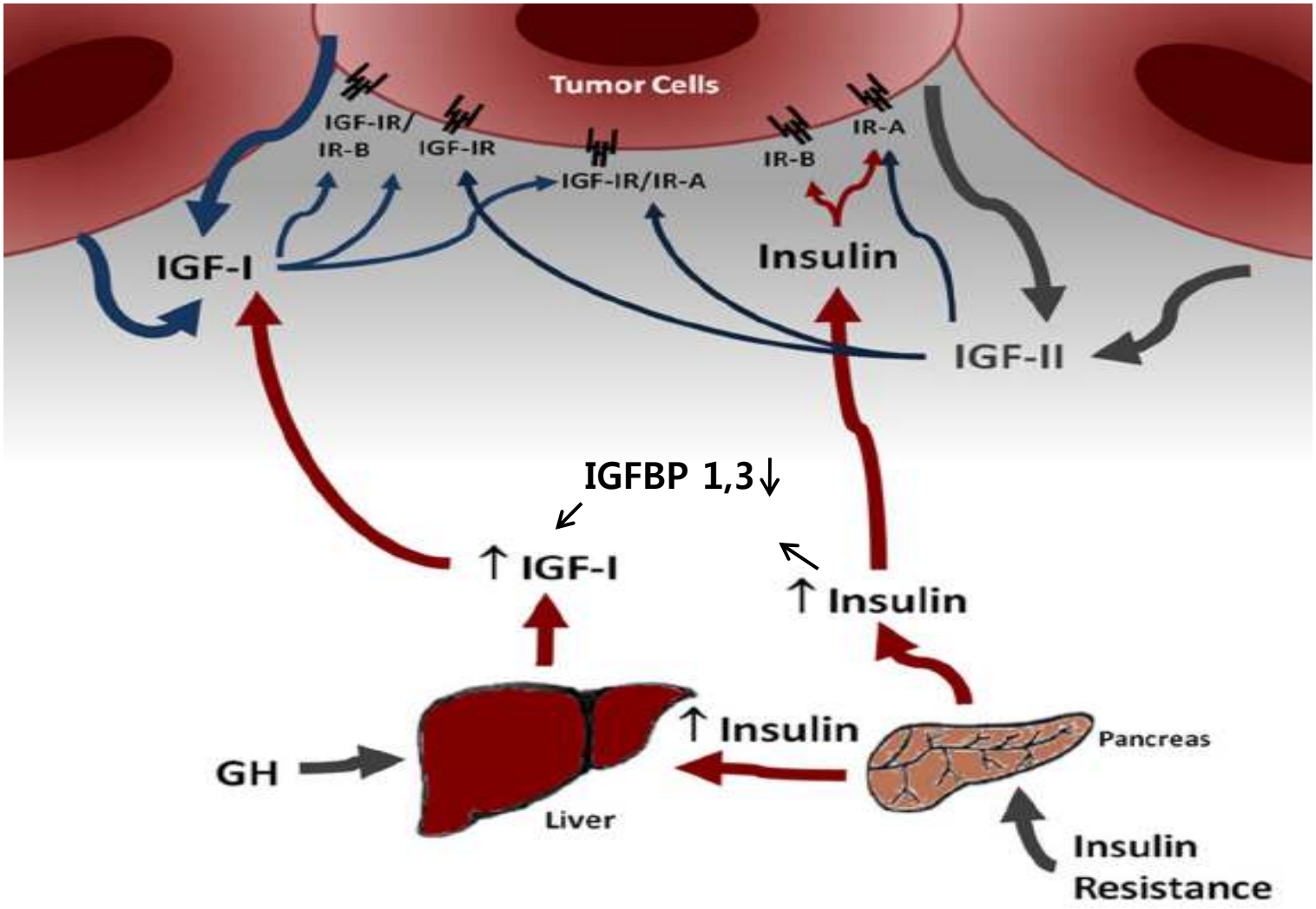
In a cohort of 512 women without diabetes, who had early stage breast cancer, higher serum insulin level was associated with worse outcome



There were strong but circumstantial evidences to indicate a role for endogenous hyperinsulinemia in promoting cancer growth in diabetic patients

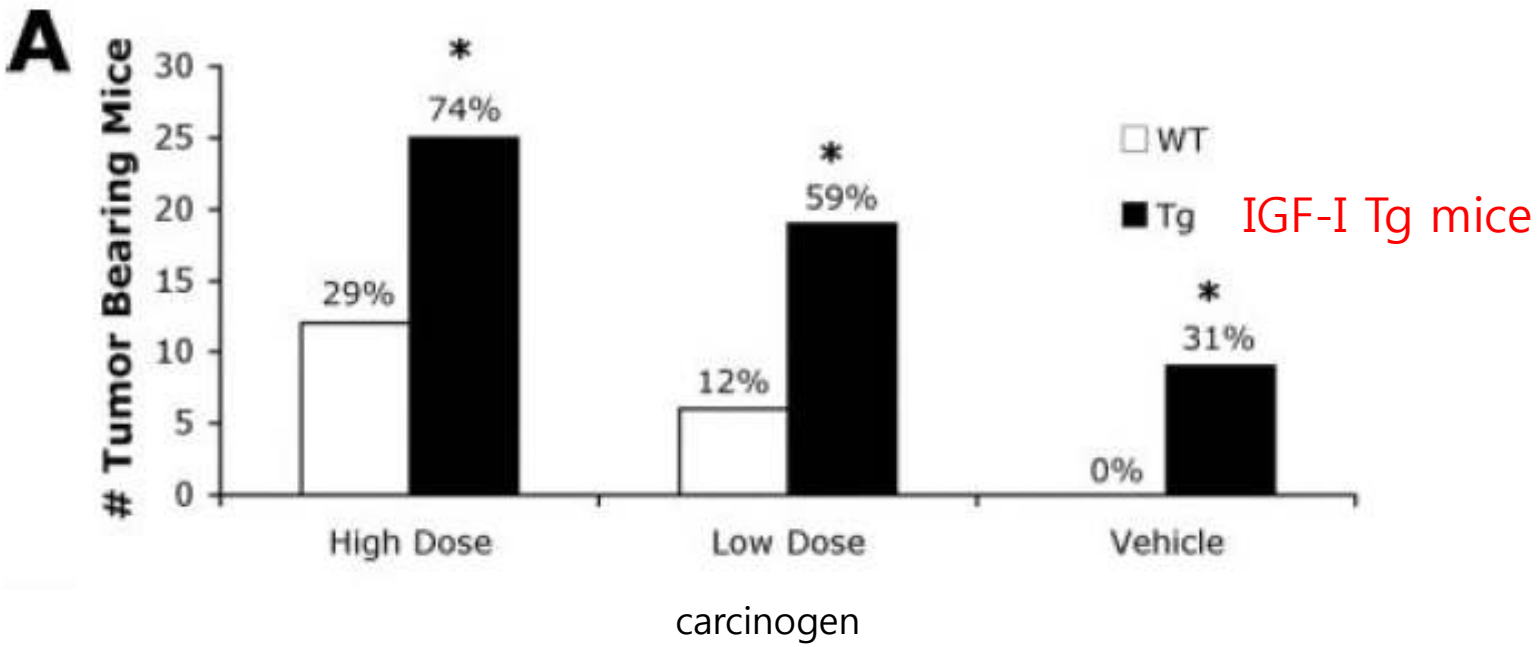
Pamela J, J Clin Oncol 20: 2001

Signaling of IGFs in tumor cells



Gallagher EJ. Endocrinology 152, 2011

Overexpression of IGF-I stimulates mammary tumorigenesis

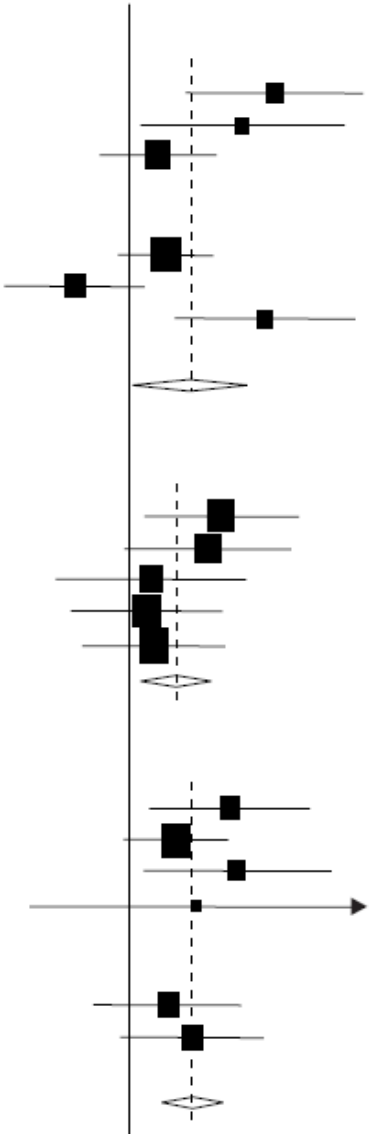


IGF-I Tg mice

De Ostrovich KK, Am J Pathol 173: 2008

Comparison of highest and lowest serum IGF-I levels by cancer site

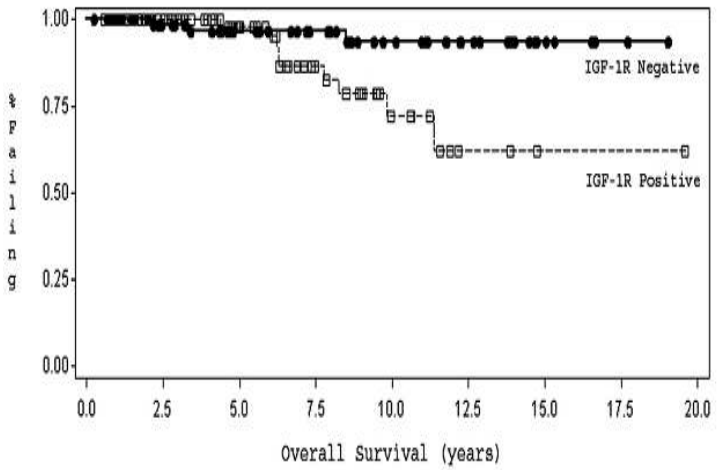
(a) Prostate cancer			
Cohort studies			
Chan 1998[5]	152/152	Quartiles	4·32 (1·76–10·6)
Harman 2000[24]	72/203	Tertiles	3·11 (1·11–8·74)
Stattin 2000[25]	149/298	Quartiles	1·32 (0·73–2·39)
All cohort studies			2·43 (1·11–5·32)
Case-control studies			
Wolk 1998[22]	224/224	Quartiles	1·43 (0·88–2·33)
Finne 2000[23]	179/486	Quartiles	0·57 (0·28–1·16)
Chokkalingam 2001[26]	128/306	Quartiles	3·92 (1·58–9·70)
All case-control studies			1·42 (0·56–3·60)
All studies			1·83 (1·03–3·26)
(b) Colorectal cancer			
Cohort studies			
Ma 1999[7]	193/318	Quintiles	2·51 (1·15–5·46)
Giovannucci 2000[27]	79/158	Tertiles	2·18 (0·94–5·01)
Kaaks 2000[28]	102/200	Quintiles	1·23 (0·47–3·22)
Probst-Hensch 2001[29]	135/661	Quintiles	1·18 (0·55–2·53)
Palmqvist 2002[30]	168/336	Quartiles	1·27 (0·62–2·63)
All studies			1·58 (1·11–2·27)
(c) Pre-menopausal breast cancer			
Cohort studies			
Hankinson 1999[6]	76/105	Tertiles	2·88 (1·21–6·85)
Toniolo 2000[32]	172/486	Quartiles	1·60 (0·91–2·81)
Muti 2002[34]	69/267	Quartiles	3·12 (1·13–8·60)
Krajeik 2002[35]	66/66	Quartiles	2·01 (0·33–12·40)
All cohort studies			2·08 (1·37–3·15)
Case-control studies			
Del Giudice 1998[31]	99/99	Quintiles	1·47 (0·66–3·27)
Yu 2002[33]	178/170	Tertiles	1·92 (0·88–4·20)
All case-control studies			1·68 (0·96–2·95)
All studies			1·93 (1·38–2·69)



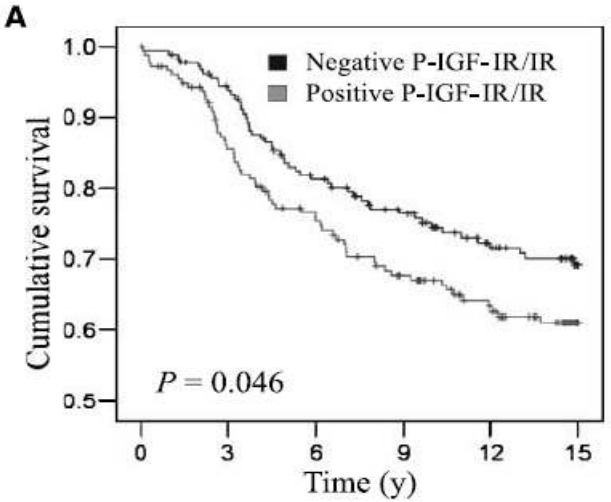
Renehan AG, Lancet 353: 2004

IGF-IR expression and prognosis of cancer

- IGF-IR expression was associated with lower overall survival in node-negative breast cancer patients



- Phosphorylated IGF-IR/IR staining in 438 invasive breast cancer tissues



- IGF-I activation has been associated with resistance to chemo- and radiation therapy
- There are ongoing clinical trials evaluating the efficacy of drugs targeting the IGF1R

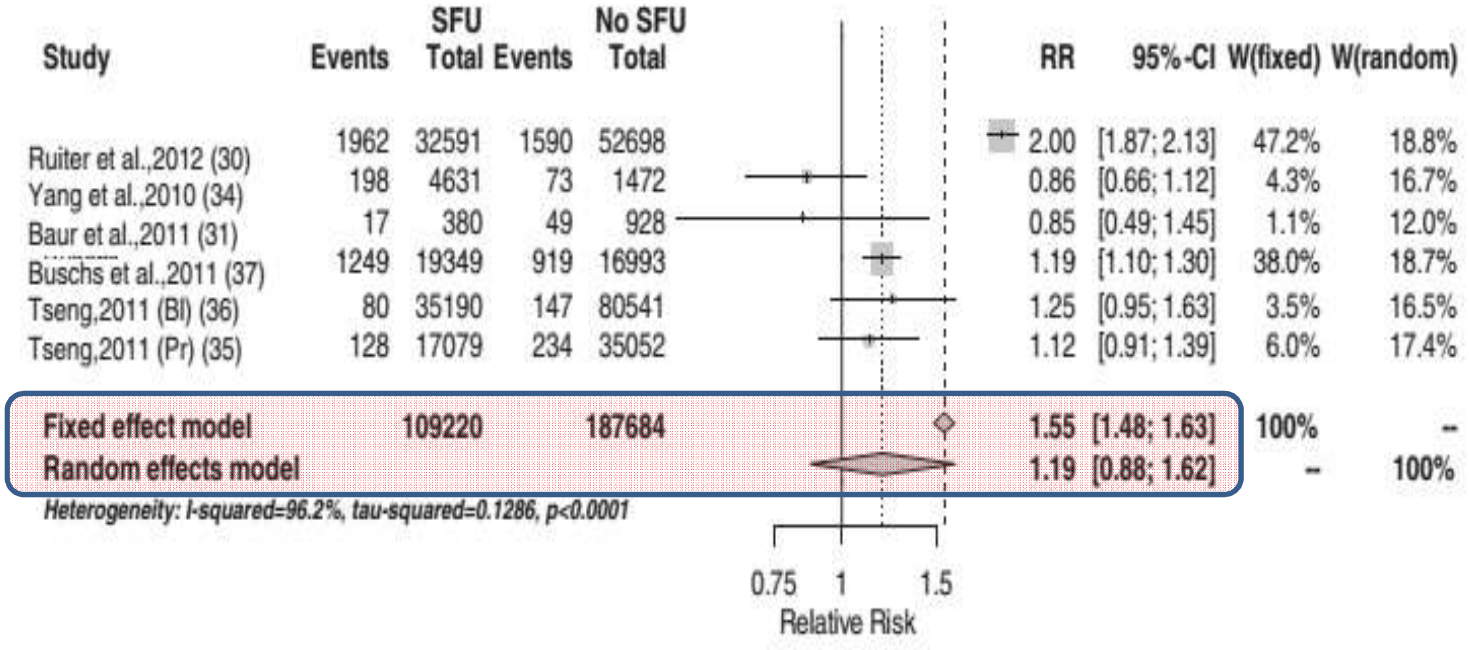
Taunk NK, Radiother Oncol 96:204-8, 2010, Law JH, Cancer Res 68; 2008

Anti-diabetic medications and cancer

-Especially metformin & insulin

Sulfonylurea & cancer: meta-analysis

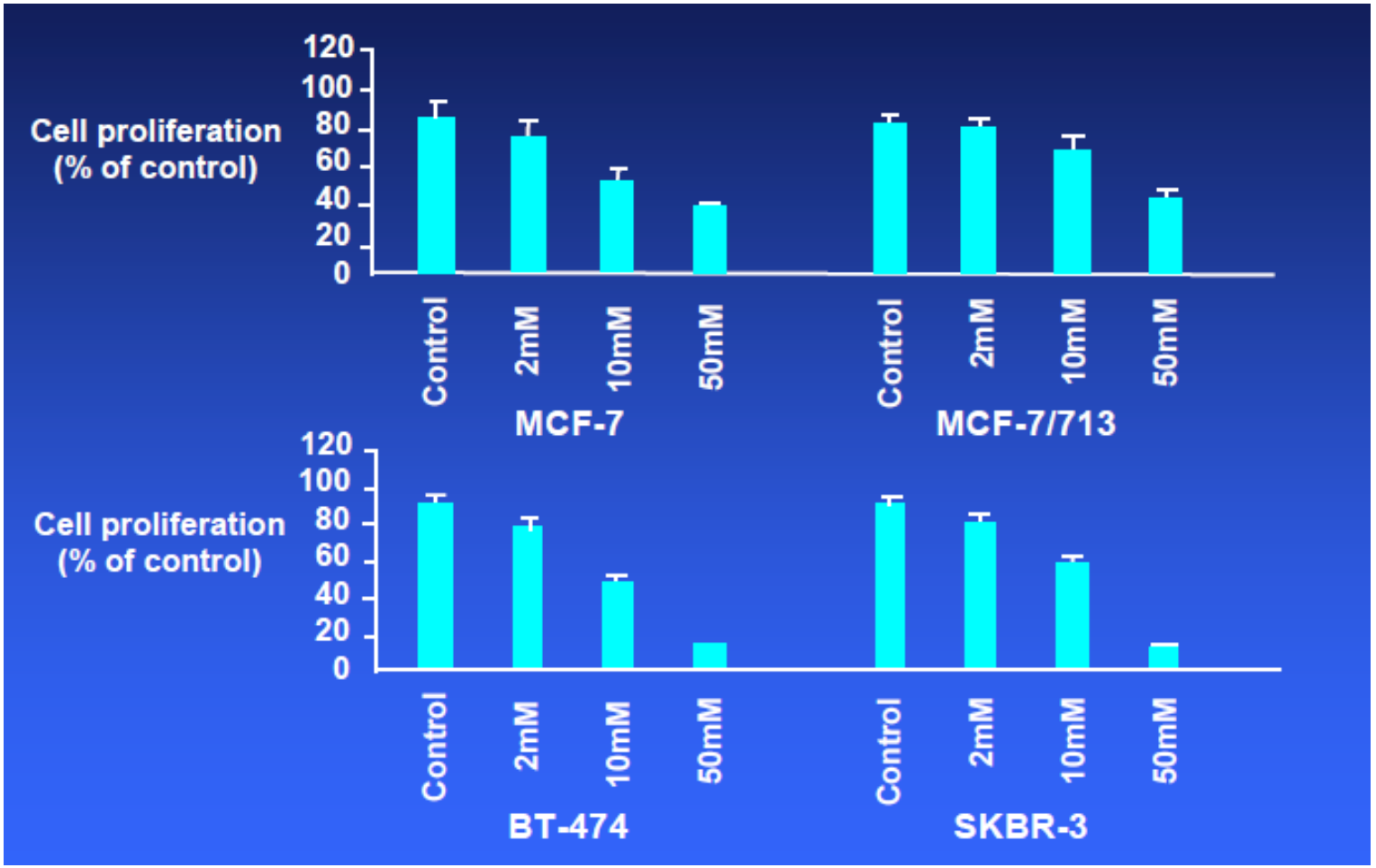
Cohort studies



However, Gliclazide [HR=0.67 95% CI=0.51-0.89] and glibenclamide [HR=0.65 95% CI=0.49-0.83] were associated with reduced risk of cancer

Thakkar B, Metabolism 62; 922-934, 2013

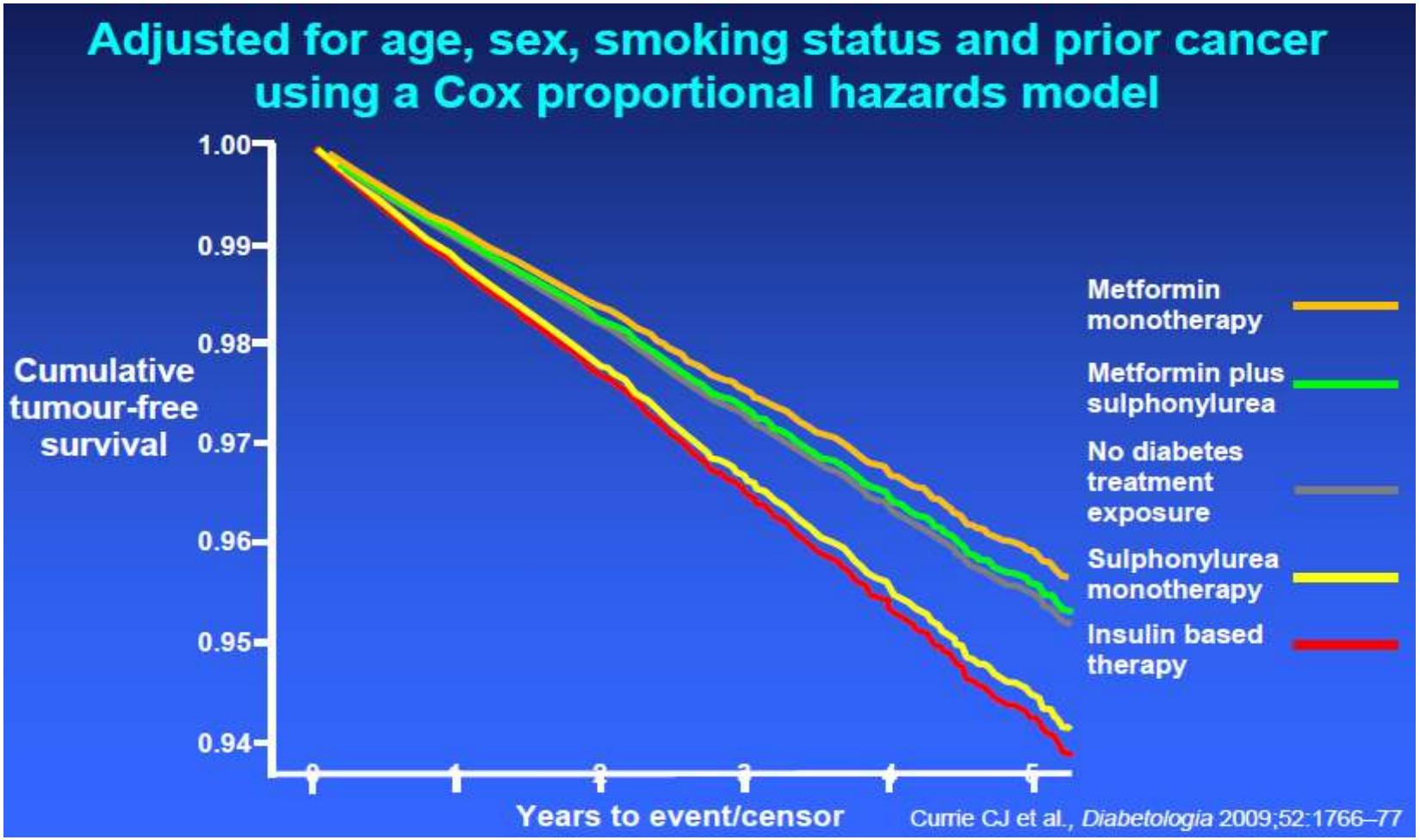
Anti-cancer effect of metformin on breast cancer cell lines



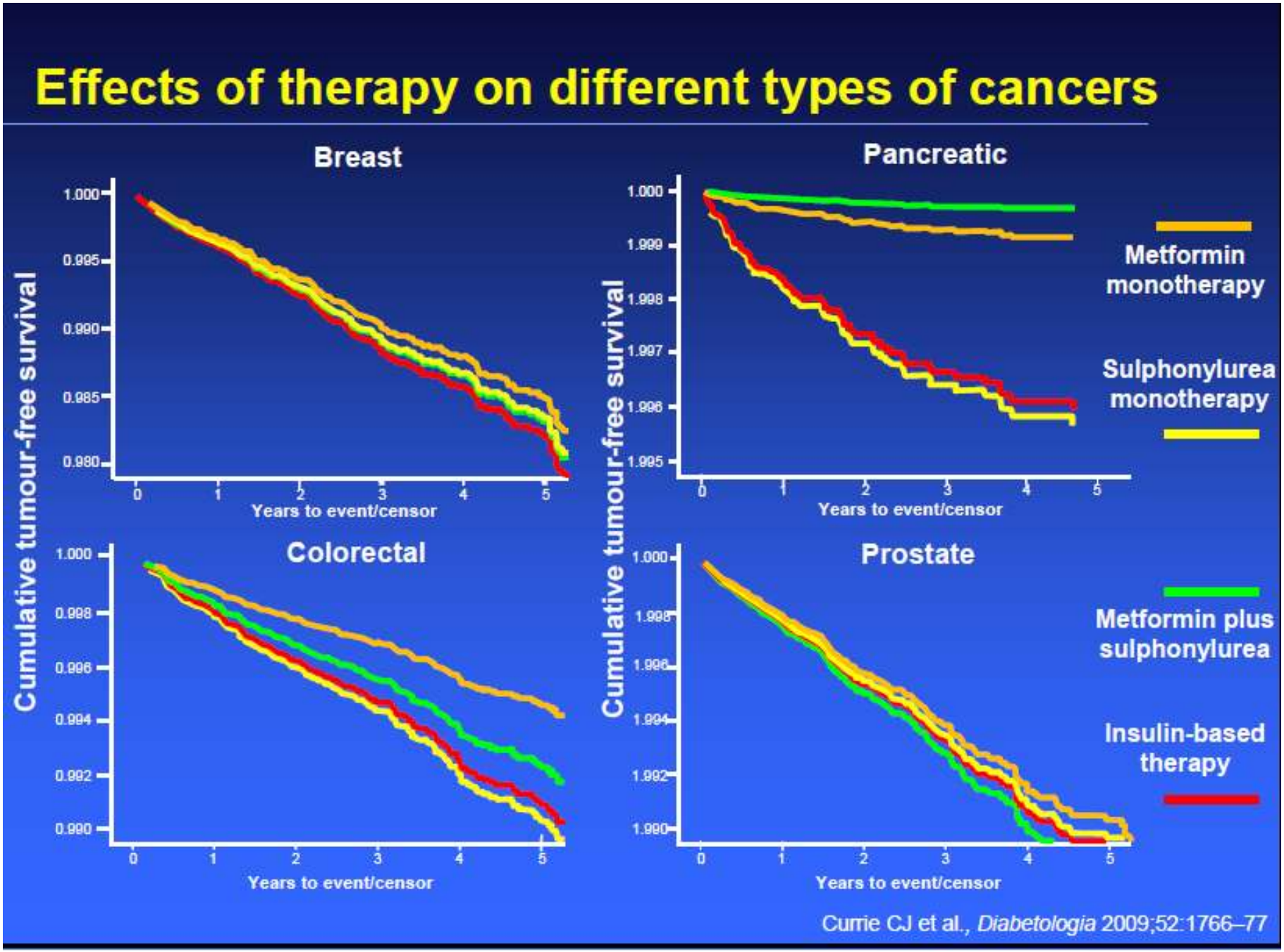
Alimova I, Cell cycle 8:909-915,2009

General Practice Database Study (GPDS) in UK

Retrospective cohort study of people treated in UK general practices (N=62809)
Who have recently initiated treatment



Effects of therapy on different types of cancers



Currie CJ et al., *Diabetologia* 2009;52:1766–77

Metformin & Breast Cancer

GP database study in UK

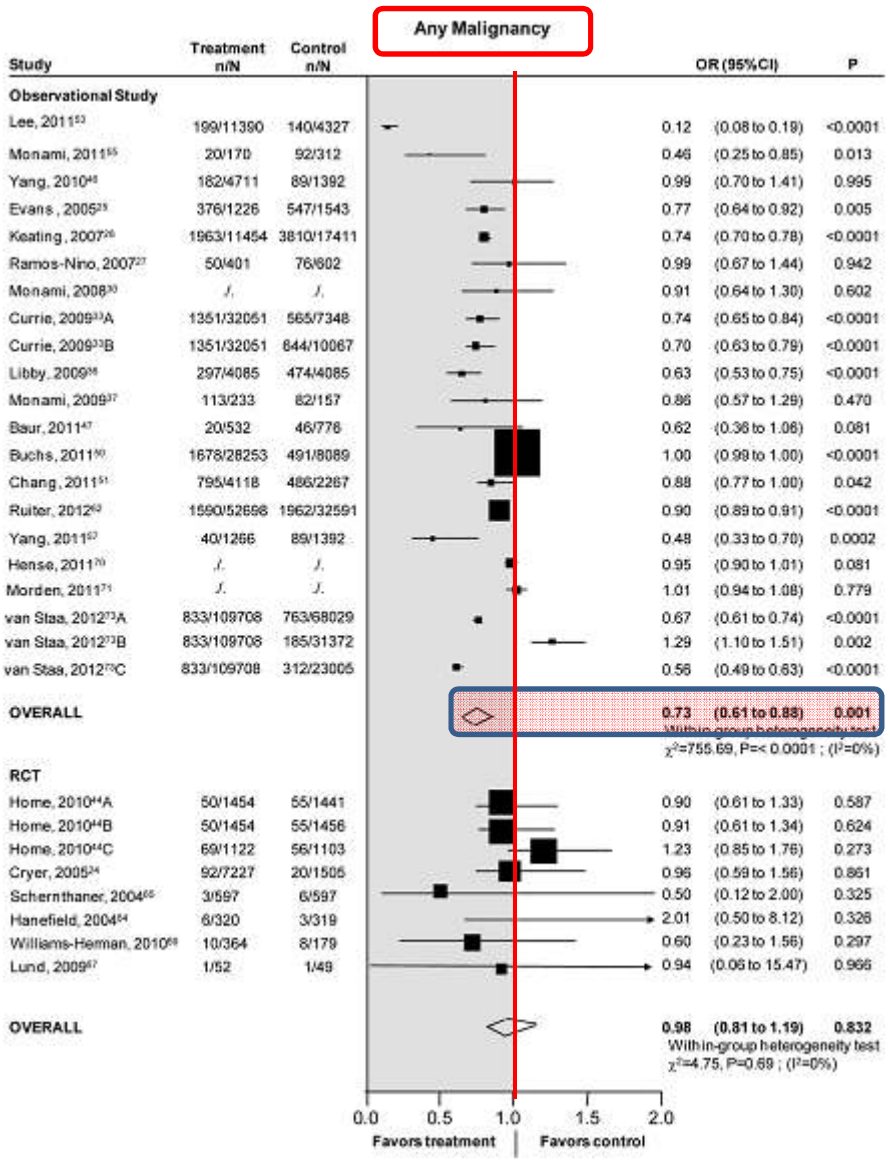
Table 3—*Breast cancer risk in users of oral antidiabetic drugs and users of insulin*

Drug and no. prescriptions	Case patients	Control patients	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)†	*P* value‡
n	305	1,153			
Metformin					
None	140	540	1.00 (referent)	1.00 (referent)	
1–9	64	205	1.21 (0.86–1.72)	1.20 (0.82–1.78)	0.35
10–39	84	288	1.16 (0.85–1.60)	1.09 (0.76–1.55)	0.65
≥40 (≥5 yrs)	17	120	0.55 (0.31–0.97)	0.44 (0.24–0.82)	0.01
Sulfonylureas					
None	138	492	1.00 (referent)	1.00 (referent)	
1–9	62	243	0.87 (0.61–1.23)	0.85 (0.58–1.24)	0.39
10–39	71	292	0.87 (0.62–1.20)	0.79 (0.55–1.15)	0.22
≥40	34	126	0.96 (0.62–1.49)	1.03 (0.62–1.69)	0.92
Thiazolidinediones					
none	285	1,084	1.00 (referent)	1.00 (referent)	
1–4	4	24			
5–9	4	15			
≥10	12	30	1.59 (0.80–3.17)	1.76 (0.84–3.68)	0.13
Insulin					
none	262	1,022	1.00 (referent)	1.00 (referent)	
1–9	18	49	1.51 (0.86–2.66)	1.74 (0.95–3.21)	0.07
10–29	11	40	1.13 (0.57–2.26)	1.30 (0.62–2.70)	0.49
≥30	14	42	1.35 (0.72–2.54)	1.51 (0.76–3.01)	0.24

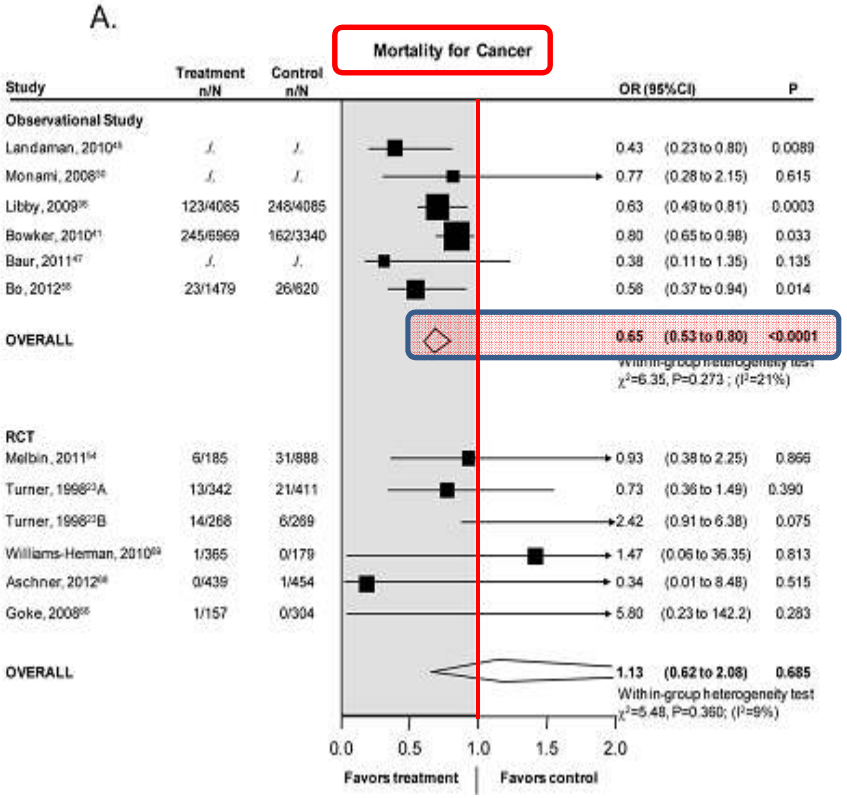
Data are n unless otherwise indicated. *Adjusted for age, sex, general practice, and calendar time by matching. †Adjusted for age, sex, general practice, and calendar time by matching and further adjusted for each other plus use of prandial glucose regulators, acarbose, estrogens, smoking, BMI, diabetes duration, and A1C ‡*P* values relate to the adjusted model.

Bodmer M, Diabetes care 33:1304-08, 2010

Metformin & Cancer: meta-analysis



27% reduction of all malignancy
35% reduction of cancer mortality



Franciosi M, Plos one 8:e71583, 2013

A.

Liver Cancer

Study	Treatment n/N	Control n/N	OR (95%CI)	P
Observational Study				
Hassan, 2010[43]	44/98	78/110	0.30 (0.20 to 0.60)	<0.0001
Kavaguchi, 2009[34]	4/9	134/232	0.59 (0.15 to 2.24)	0.433
Lee, 2011[53]	45/11236	28/4215	0.06 (0.02 to 0.16)	<0.0001
Oliveira, 2008[32]	./.	./.	0.73 (0.34 to 1.56)	0.418
Donadon, 2010[42]	18/71	172/334	0.15 (0.04 to 0.50)	0.003
Nkontchou, 2011[56]	2/26	37/74	0.19 (0.04 to 0.79)	0.029
Lai, 2012[61]	158/16282	66/3067	0.49 (0.37 to 0.66)	<0.0001
Ruiter, 2012[62]	16/52698	15/32591	0.67 (0.53 to 0.86)	0.001
OVERALL			**0.34 (0.19 to 0.60)**	**0.0003**

Colorectal cancer

Study	Treatment n/N	Control n/N	OR (95%CI)	P
Observational Study				
Lee, 2011[53]	30/11221	26/4213	0.36 (0.13 to 0.98)	0.047
Chung, 2008[28]	34/79	66/121	0.70 (0.30 to 1.40)	0.364
Lewis, 2008[29]A	415/1537	881/2711	0.77 (0.67 to 0.88)	<0.0001
Lewis, 2008[29]B	352/3720	599/6093	0.96 (0.83 to 1.10)	0.349
Oliveira, 2008[32]	./.	./.	0.67 (0.52 to 0.85)	0.001
Currie, 2009[33]A	./.	./.	0.56 (0.40 to 0.78)	0.001
Currie, 2009[33]A	./.	./.	0.59 (0.43 to 0.81)	0.001
Libby, 2009[38]	40/4085	76/4085	0.60 (0.38 to 0.94)	0.027
Ferrara, 2011[52]	./.	./.	1.00 (0.90 to 1.20)	1.000
Ferrara, 2011[52]	./.	./.	0.90 (0.70 to 1.20)	0.444
Ruiter, 2012[62]	228/52698	299/32591	0.91 (0.88 to 0.94)	<0.0001
Bodmer, 2012[59]	416/2770	504/3669	1.11 (0.96 to 1.28)	0.146
Morden, 2012[71]	./.	./.	0.94 (0.72 to 1.22)	0.646
van Staa, 2012[73]A	75/10708	63/68029	0.74 (0.53 to 1.03)	0.076
van Staa, 2012[73]B	75/10708	24/31372	0.89 (0.56 to 1.42)	0.631
van Staa, 2012[73]C	75/10708	15/23005	1.05 (0.60 to 1.83)	0.867
OVERALL			**0.83 (0.74 to 0.92)**	**0.001**
			Within-group heterogeneity test	

A.

Pancreatic cancer

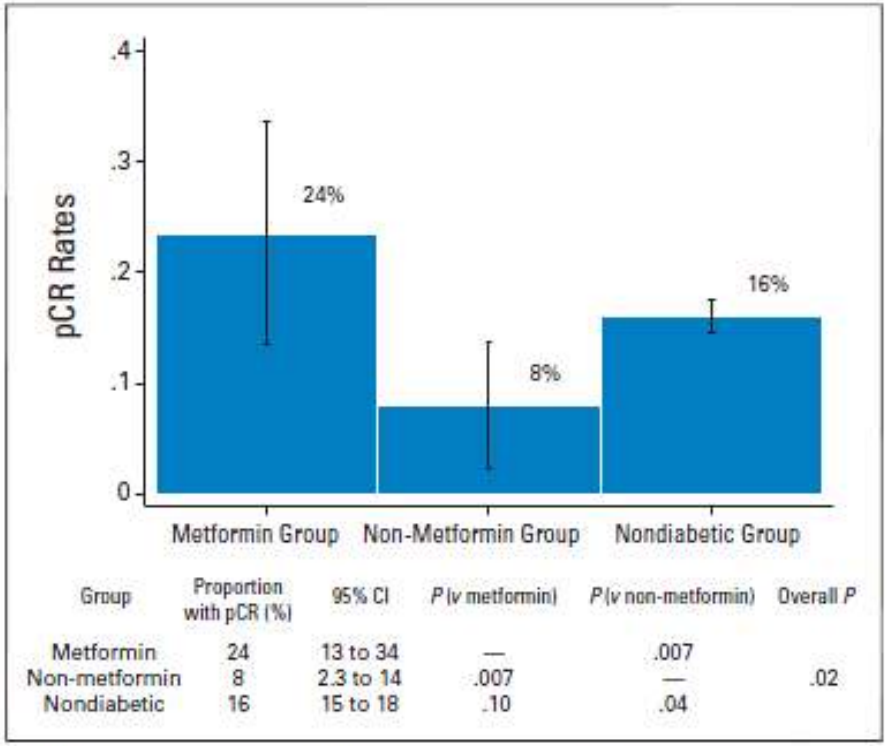
Study	Treatment n/N*	Control n/N*	OR (95%CI)	P
Observational Study				
Lee, 2011[53]	21/11212	7/4194	0.15 (0.03 to 0.79)	0.023
Oliveira, 2008[32]	./.	./.	1.26 (0.80 to 1.99)	0.320
Currie, 2009[33]A	./.	./.	0.20 (0.11 to 0.37)	<0.0001
Currie, 2009[33]B	./.	./.	0.22 (0.12 to 0.38)	<0.0001
Li, 2009[35]	117/191	142/177	0.38 (0.22 to 0.69)	0.0009
Ferrara, 2011[52]	./.	./.	1.20 (1.00 to 1.50)	0.078
Ruiter, 2012[62]	60/52698	106/3259	0.73 (0.66 to 0.80)	<0.0001
Bodmer, 2012[60]	./.	./.	0.87 (0.57 to 1.21)	0.468
Morden, 2011[71]	./.	./.	1.25 (0.89 to 1.75)	0.196
van Staa, 2012[73]A	88/109708	128/68029	0.43 (0.32 to 0.56)	0.320
van Staa, 2012[73]B	88/109708	20/31372	1.26 (0.77 to 2.05)	0.354
van Staa, 2012[73]C	88/109708	74/23005	0.25 (0.18 to 0.34)	<0.0001
OVERALL			**0.56 (0.36 to 0.86)**	**0.009**
			Within-group heterogeneity test	

Stomach Cancer

Study	Treatment n/N*	Control n/N*	OR (95%CI)	P
Observational Study				
Lee, 2011[53]	24/11215	10/4197	1.41 (0.42 to 4.73)	<0.0001
Ruiter, 2012[62]	47/52698	70/32591	0.83 (0.76 to 0.90)	<0.0001
OVERALL			**0.83 (0.76 to 0.91)**	<0.0001
			Within-group heterogeneity test	
			χ^2=73.39, P=<0.0001; (I^2=0%)	

Franciosi M, Plos one 8:e71583, 2013

Metformin and Pathologic Complete Responses to Neoadjuvant Chemotherapy in Diabetic Patients With Breast Cancer



Group	Proportion with pCR (%)	95% CI	P (v metformin)	P (v non-metformin)	Overall P
Metformin	24	13 to 34	—	.007	
Non-metformin	8	2.3 to 14	.007	—	.02
Nondiabetic	16	15 to 18	.10	.04	

Fig 1. Proportions of pathologic complete response (pCR) between study groups. Comparison of pCR rates between the study groups (graph) and pairwise statistical comparisons of pCR rates between the study groups.

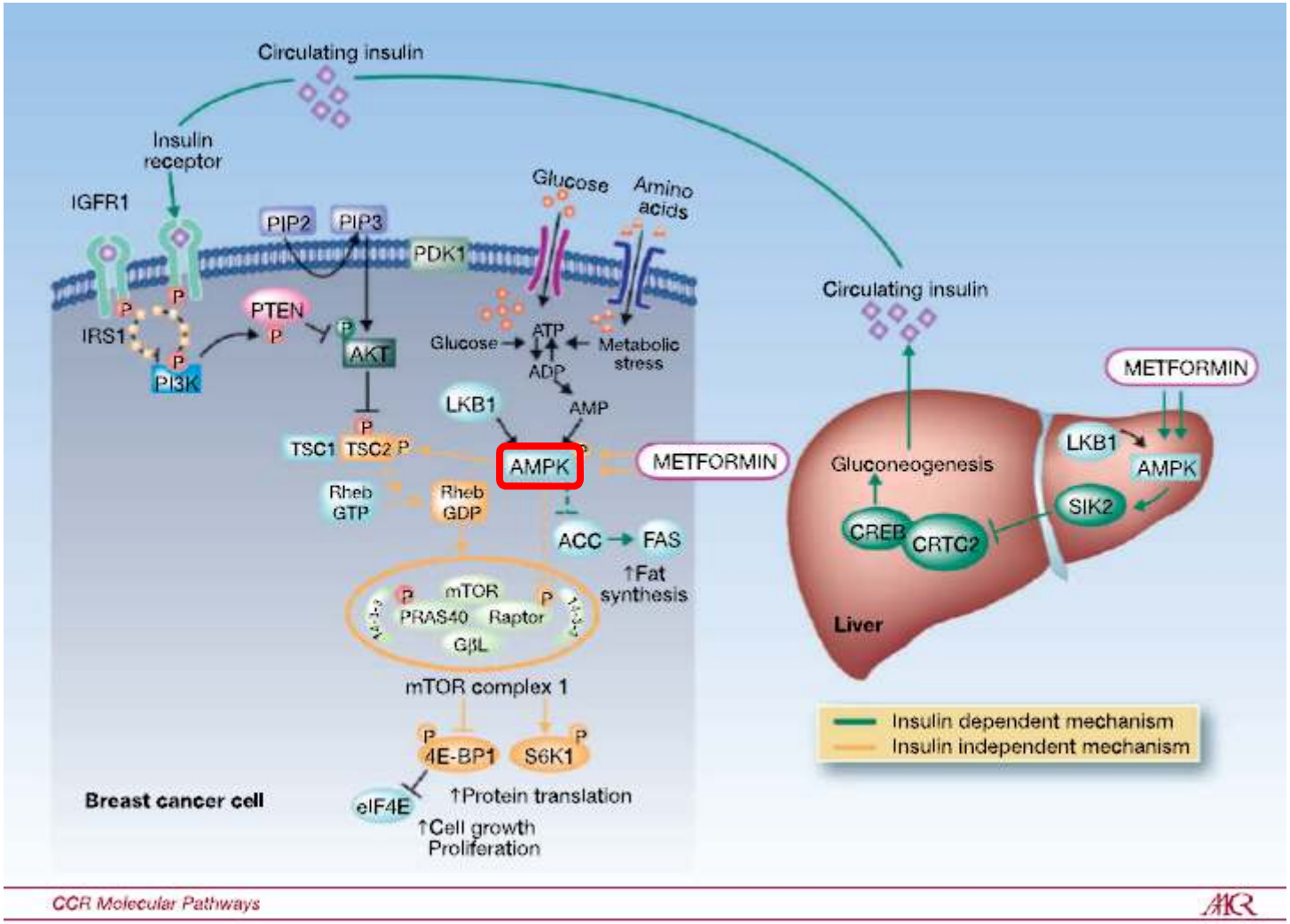
Table 2. Multivariate Logistic Regression Model for Pathologic Complete Response

Variable	Odds Ratio	95% CI	P
Diabetes, yes *v* no	0.44	0.20 to 1.00	.05
Age, ≥ 50 years *v* < 50 years	0.89	0.70 to 1.14	.36
Metformin use, yes *v* no	2.95	1.07 to 8.17	.04
Clinical stage, III *v* I and II	0.60	0.47 to 0.77	< .001
Tumor grade, 3 *v* 1 and 2	2.66	1.89 to 3.73	< .001
Hormone receptor status, ER positive and/or PR positive *v* both negative	0.34	0.26 to 0.44	< .001
HER-2 status, positive *v* negative	2.38	1.86 to 3.05	< .001
Neoadjuvant taxane use, yes *v* no	2.30	1.65 to 3.20	< .001
BMI			
Overweight *v* normal/ underweight	0.77	0.56 to 1.04	.09
Obese *v* normal/ underweight	1.16	0.88 to 1.55	.299

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; BMI, body mass index.

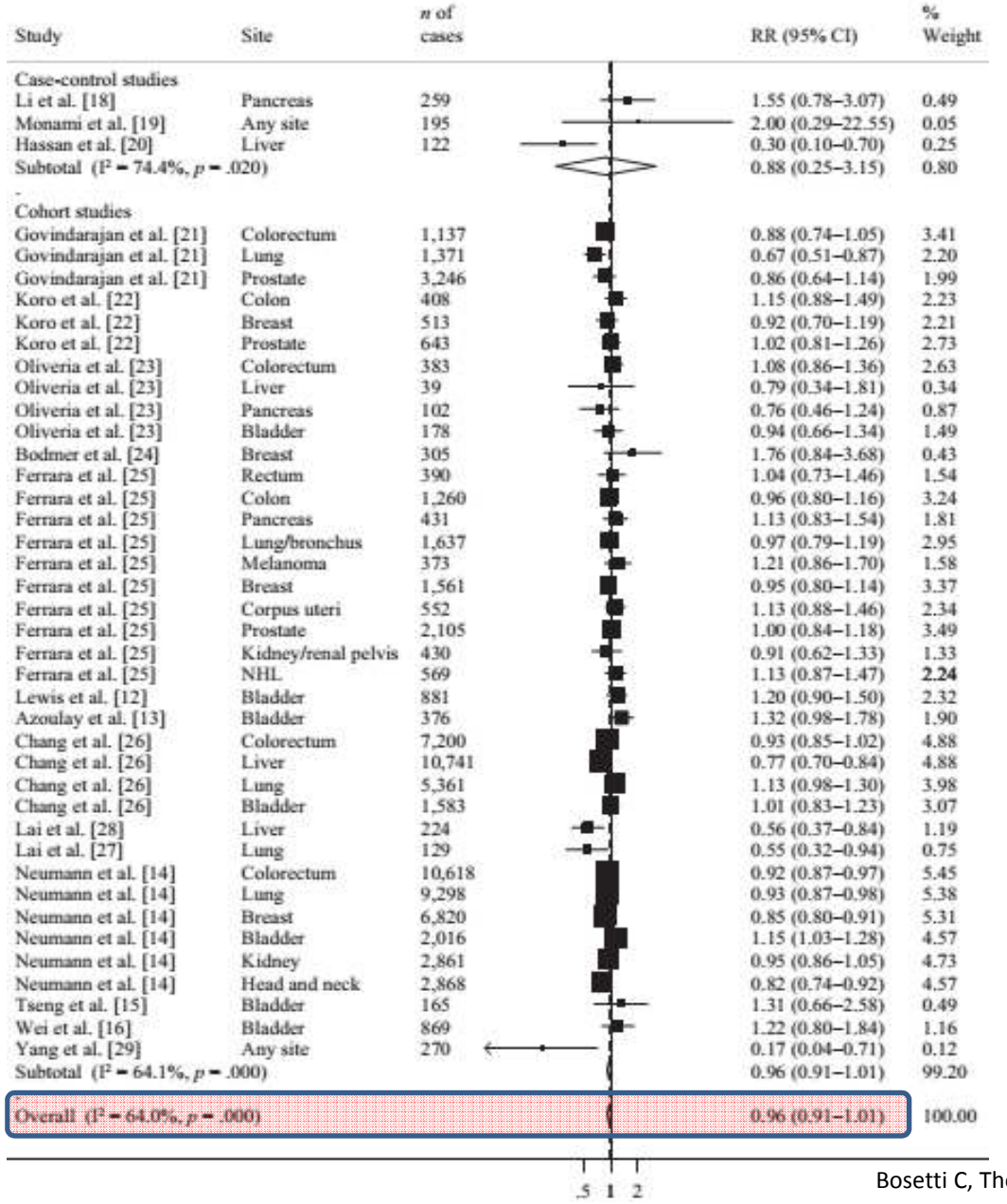
Jiralerspong S, Clin Oncol 27:3297-3302, 2009

Metformin & Cancer



TZD and cancer

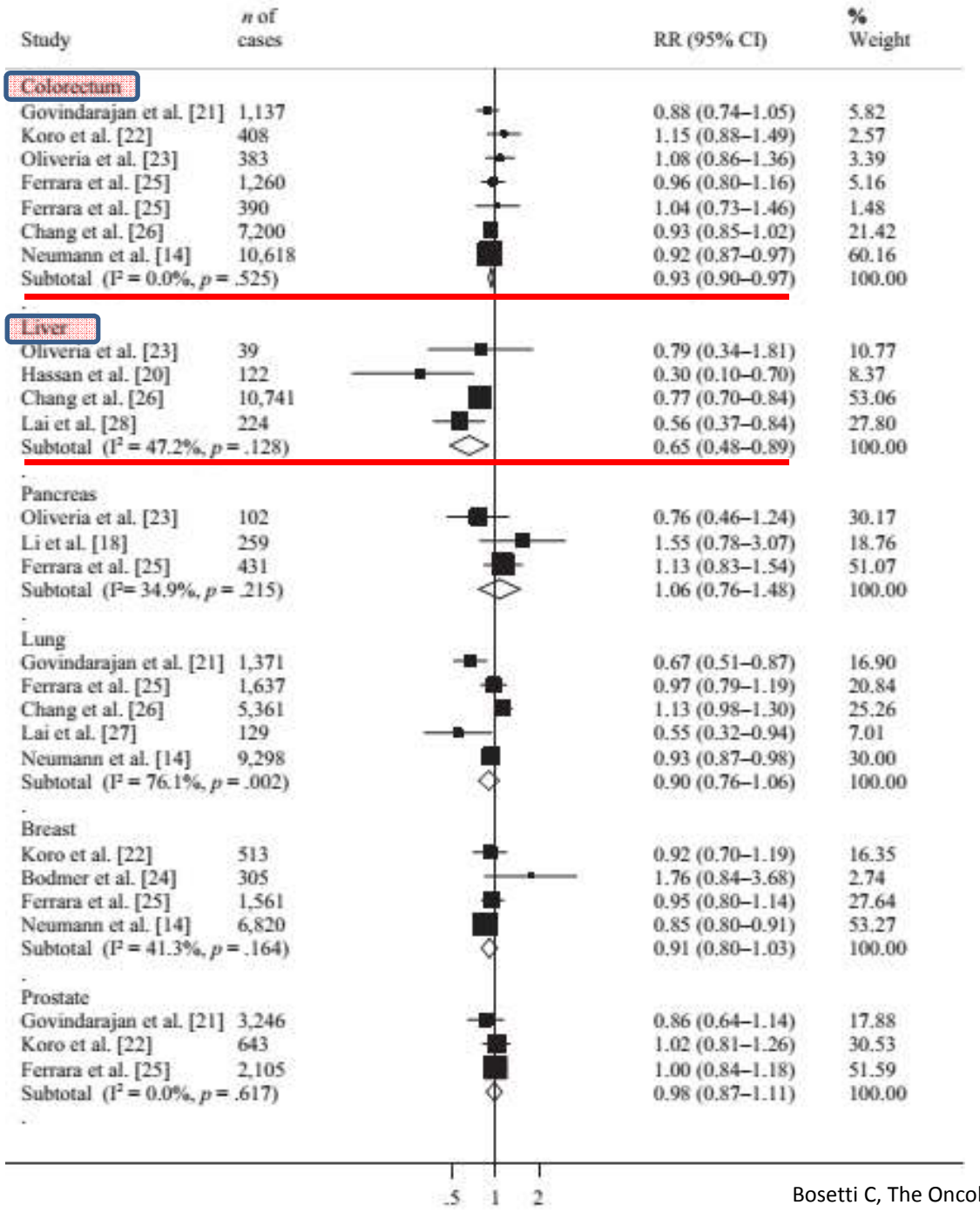
TZD and cancer: a meta-analysis



Study	Site	*n* of cases	RR (95% CI)	% Weight
Case-control studies				
Li et al. [18]	Pancreas	259	1.55 (0.78–3.07)	0.49
Monami et al. [19]	Any site	195	2.00 (0.29–22.55)	0.05
Hassan et al. [20]	Liver	122	0.30 (0.10–0.70)	0.25
Subtotal (I^2 = 74.4%, p = .020)			0.88 (0.25–3.15)	0.80
Cohort studies				
Govindarajan et al. [21]	Colorectum	1,137	0.88 (0.74–1.05)	3.41
Govindarajan et al. [21]	Lung	1,371	0.67 (0.51–0.87)	2.20
Govindarajan et al. [21]	Prostate	3,246	0.86 (0.64–1.14)	1.99
Koro et al. [22]	Colon	408	1.15 (0.88–1.49)	2.23
Koro et al. [22]	Breast	513	0.92 (0.70–1.19)	2.21
Koro et al. [22]	Prostate	643	1.02 (0.81–1.26)	2.73
Oliveria et al. [23]	Colorectum	383	1.08 (0.86–1.36)	2.63
Oliveria et al. [23]	Liver	39	0.79 (0.34–1.81)	0.34
Oliveria et al. [23]	Pancreas	102	0.76 (0.46–1.24)	0.87
Oliveria et al. [23]	Bladder	178	0.94 (0.66–1.34)	1.49
Bodmer et al. [24]	Breast	305	1.76 (0.84–3.68)	0.43
Ferrara et al. [25]	Rectum	390	1.04 (0.73–1.46)	1.54
Ferrara et al. [25]	Colon	1,260	0.96 (0.80–1.16)	3.24
Ferrara et al. [25]	Pancreas	431	1.13 (0.83–1.54)	1.81
Ferrara et al. [25]	Lung/bronchus	1,637	0.97 (0.79–1.19)	2.95
Ferrara et al. [25]	Melanoma	373	1.21 (0.86–1.70)	1.58
Ferrara et al. [25]	Breast	1,561	0.95 (0.80–1.14)	3.37
Ferrara et al. [25]	Corpus uteri	552	1.13 (0.88–1.46)	2.34
Ferrara et al. [25]	Prostate	2,105	1.00 (0.84–1.18)	3.49
Ferrara et al. [25]	Kidney/renal pelvis	430	0.91 (0.62–1.33)	1.33
Ferrara et al. [25]	NHL	569	1.13 (0.87–1.47)	**2.24**
Lewis et al. [12]	Bladder	881	1.20 (0.90–1.50)	2.32
Azoulay et al. [13]	Bladder	376	1.32 (0.98–1.78)	1.90
Chang et al. [26]	Colorectum	7,200	0.93 (0.85–1.02)	4.88
Chang et al. [26]	Liver	10,741	0.77 (0.70–0.84)	4.88
Chang et al. [26]	Lung	5,361	1.13 (0.98–1.30)	3.98
Chang et al. [26]	Bladder	1,583	1.01 (0.83–1.23)	3.07
Lai et al. [28]	Liver	224	0.56 (0.37–0.84)	1.19
Lai et al. [27]	Lung	129	0.55 (0.32–0.94)	0.75
Neumann et al. [14]	Colorectum	10,618	0.92 (0.87–0.97)	5.45
Neumann et al. [14]	Lung	9,298	0.93 (0.87–0.98)	5.38
Neumann et al. [14]	Breast	6,820	0.85 (0.80–0.91)	5.31
Neumann et al. [14]	Bladder	2,016	1.15 (1.03–1.28)	4.57
Neumann et al. [14]	Kidney	2,861	0.95 (0.86–1.05)	4.73
Neumann et al. [14]	Head and neck	2,868	0.82 (0.74–0.92)	4.57
Tseng et al. [15]	Bladder	165	1.31 (0.66–2.58)	0.49
Wei et al. [16]	Bladder	869	1.22 (0.80–1.84)	1.16
Yang et al. [29]	Any site	270	0.17 (0.04–0.71)	0.12
Subtotal (I^2 = 64.1%, p = .000)			0.96 (0.91–1.01)	99.20
Overall (I^2 = 64.0%, p = .000)			0.96 (0.91–1.01)	100.00

.5 1 2

Bosetti C, The Oncologist 18; 148-156, 2013



Bosetti C, The Oncologist 18; 148-156, 2013

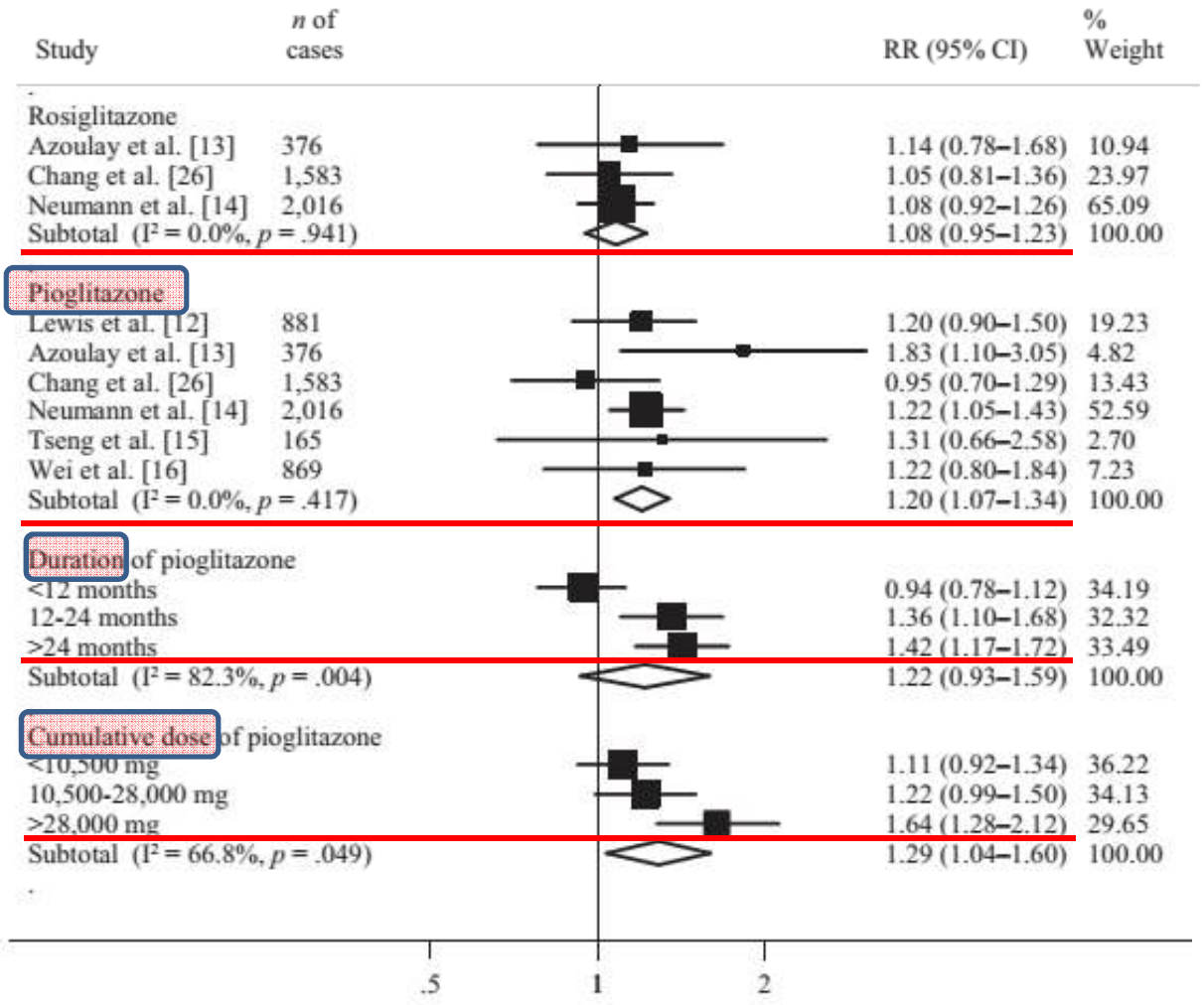
Pioglitazone and bladder cancer

- Preclinical studies suggested an association between pioglitazone use and the development of bladder cancerous tumors in male rats

- The FDA reviewed 93 post-marketing reports of bladder cancer in T2DM patients between 2004 and 2009 and found a 4-fold increase in the risk of bladder cancer among pioglitazone users

- On June 2011, FDA issued a warning of increased bladder cancer risk associated with pioglitazone, French Medicines Agency suspended the use of pioglitazone

TZD and bladder cancer



Bosetti C, The Oncologist 18; 148-156, 2013

The Risk of Bladder Cancer in Korean Diabetic Subjects Treated with Pioglitazone

Sun Ok Song*, Kwang Joon Kim*, Byung-Wan Lee, Eun Seok Kang, Bong Soo Cha, Hyun Chul Lee

Division of Endocrinology and Metabolism, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

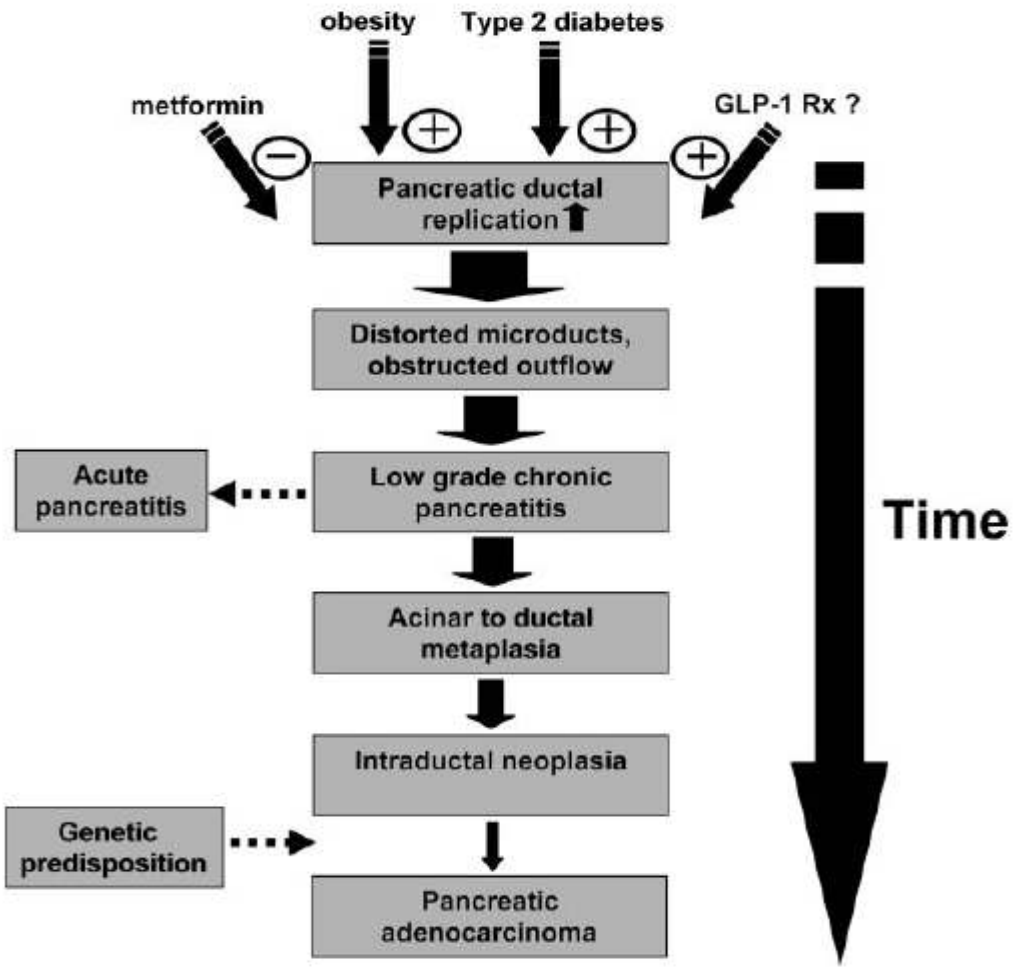
- Retrospective, matched case-control study
- Case group with diabetic patients with bladder cancer (n=329) vs. age-sex-matched diabetic patients (n=685)

Table 2. Independent variables predicting bladder cancer

Variable	OR	95% CI for OR	*P* value
Alcohol	1.563	0.941-2.598	0.085
Smoking	11.643	6.563-20.655	<0.001
History of pioglitazone use	2.09	0.260-16.814	0.488
Coexisting cancer	6.113	2.247-16.627	<0.001
Hemoglobin	0.779	0.689-0.880	<0.001
Albumin	0.968	0.645-1.453	0.876

Song SO, Diabetes Metab J 36; 371-378, 2012

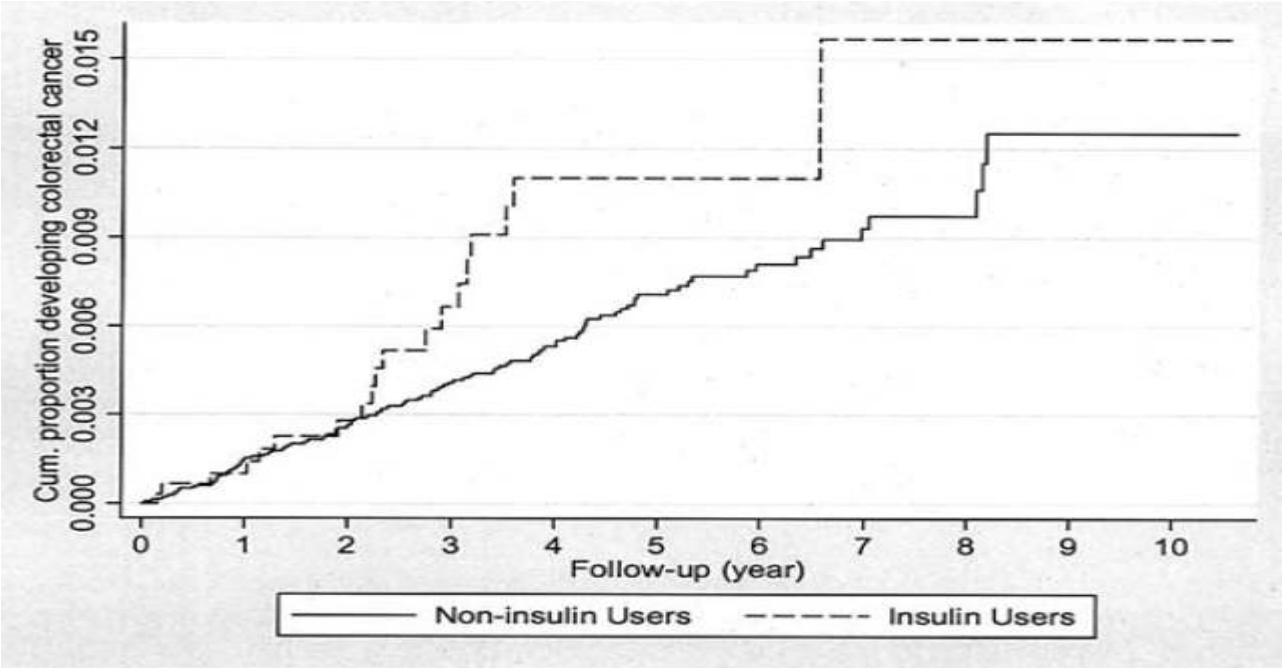
GLP-1-based therapy and cancer



Insulin and cancer

Insulin therapy and colorectal cancer

- Retrospective case-control study of the General Practice Research Database from UK
- Insulin users (at least > 1yr, N=3160) vs. noninsulin-using T2DM patients (N=24918) for occurrence of colorectal cancer
- Age 74.9±8.4 yrs, f/u 5.6±1.8 yrs



insulin users

noninsulin users

Yang Y, Gastroenterology 127: 2004

Insulin therapy and colorectal cancer

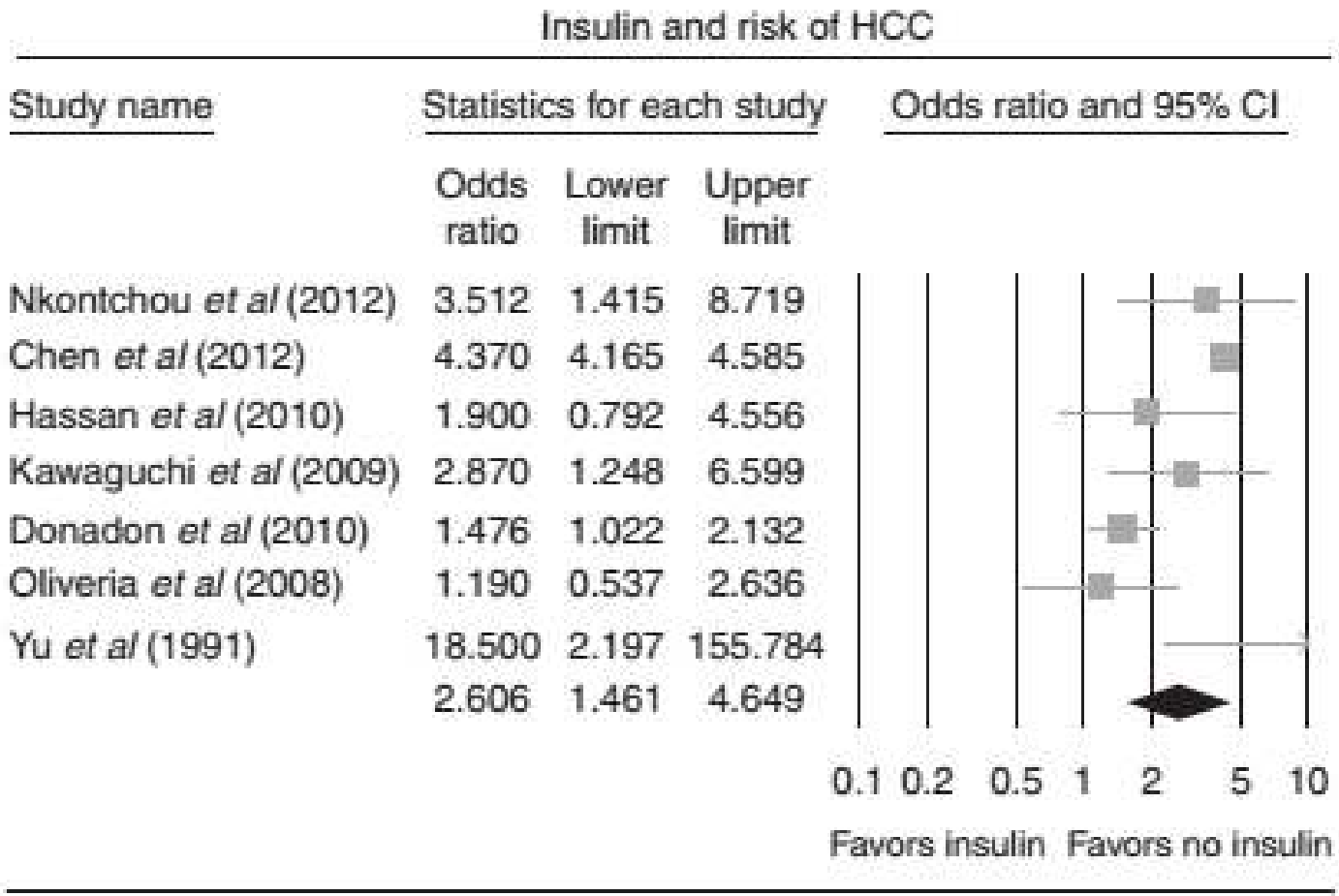
Nested case-control analysis (matched for age, duration of DM)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No insulin therapy (reference)	1.0	1.0
≥1 year and <3 years of insulin use	1.2 (0.6-2.6)	1.4 (0.6-2.9)
≥3 years and <5 years of insulin use	2.2 (0.9-5.5)	2.9 (1.1-7.7)
≥5 years of insulin use	2.8 (0.9-8.5)	4.7 (1.3-16.7)
Each incremental year of insulin therapy	1.13 (0.99-1.3)	1.2 (1.03-1.4)

Adjusted for sex, history of cholecystectomy, smoking, duration of diabetes, BMI, use of metformin, sulfonylurea, or NSAID

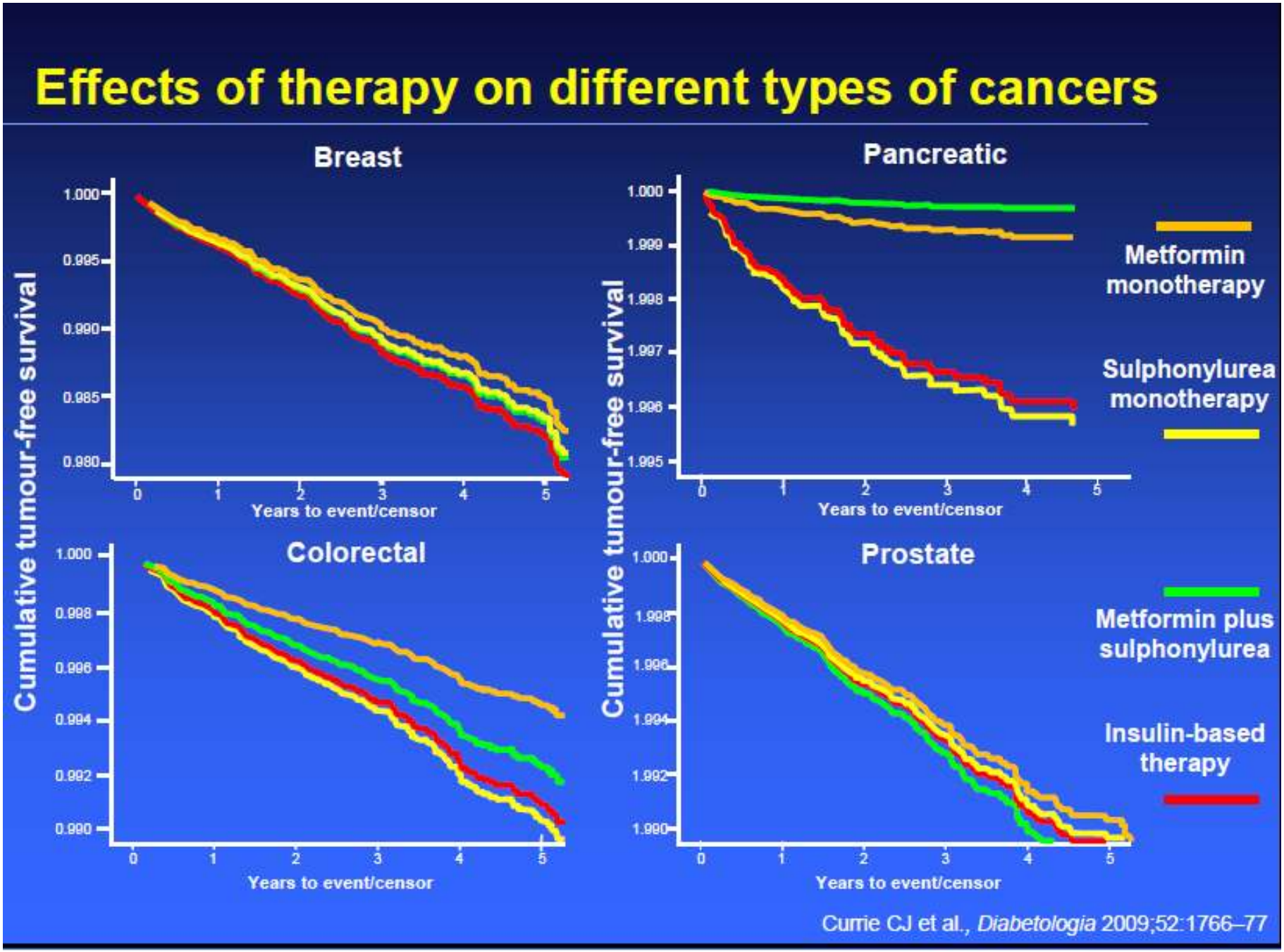
Yang Y, Gastroenterology 127: 2004

Insulin and hepatocellular carcinoma



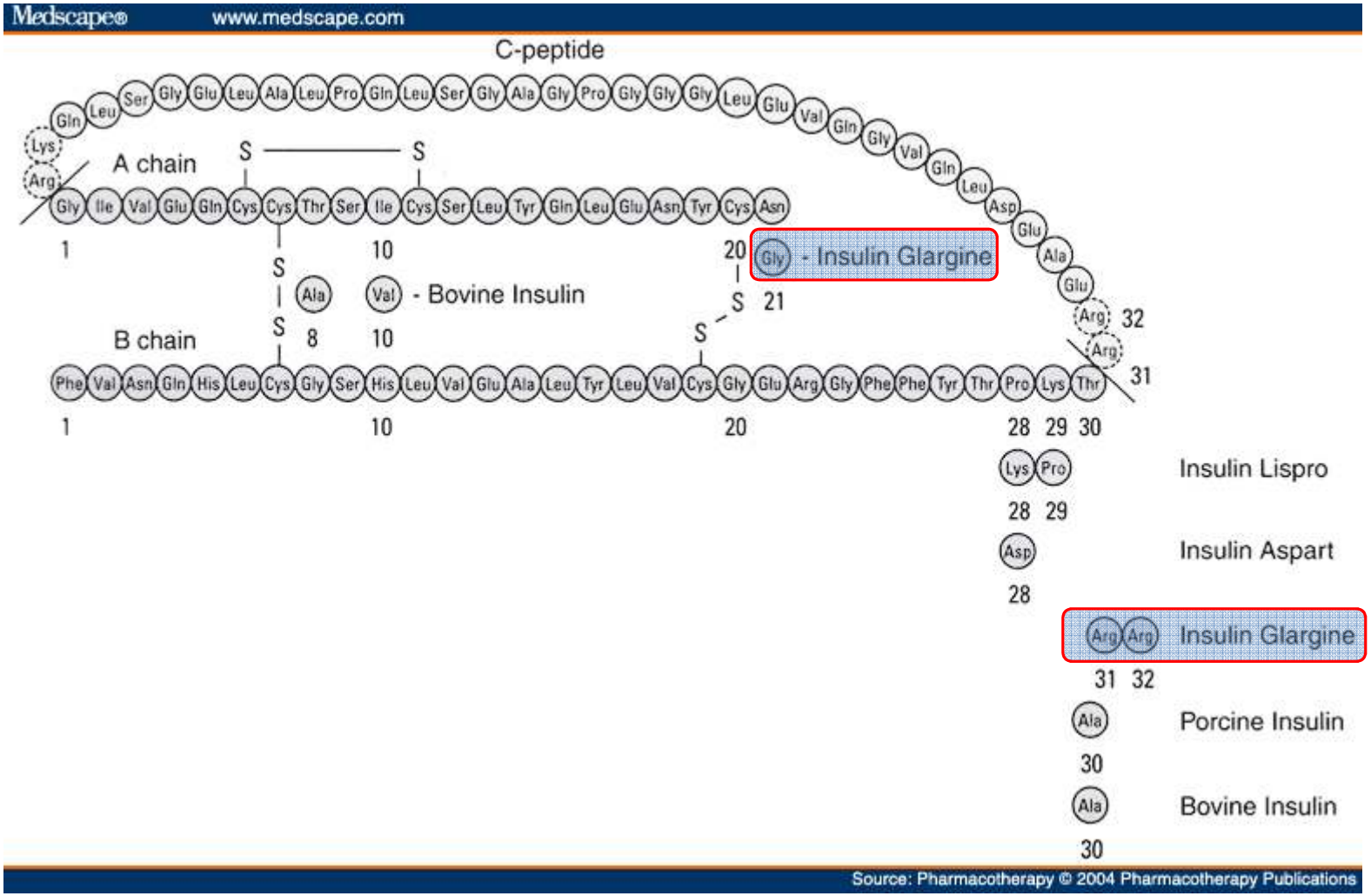
Yang Y, Gastroenterology 127: 2004

Effects of therapy on different types of cancers



Currie CJ et al., *Diabetologia* 2009;52:1766–77

Insulin analogues



Insulin analogues and mitogenicity

Analog	Insulin receptor affinity (%)	Insulin receptor off-rate (%)	IGF-I receptor affinity (%)	Mitogenic potency (%)
Human insulin	100	100	100	100
B10Asp	205 ± 20	14 ± 1	587 ± 50	975 ± 173
Aspart	92 ± 6	81 ± 8	81 ± 9	58 ± 22
Lispro	84 ± 6	100 ± 11	156 ± 16	66 ± 10
Glargine	86 ± 3	152 ± 13	641 ± 51	783 ± 132
A21Gly	78 ± 10	162 ± 11	42 ± 11	34 ± 12
B31B32diArg	120 ± 4	75 ± 8	2,049 ± 202	2,180 ± 390
Detemir	46 ± 5/18 ± 2	204 ± 9	16 ± 1	11

Kurtzhals P, Diabetes 29: 2000

Insulin glargine & cancer: a German study

- German statutory health insurance database
- Diabetic patients without known malignancies and had received first-time therapy exclusively with human insulin, aspart, lispro, glargine
- N=127031, f/u 1.63 yrs

	HR (95% CI, reference group: human insulin)		
Covariates	Aspart	Lispro	Glargine
None	0.86	0.85	0.85 (0.79-0.93)
Age, sex	0.95	0.90	0.86 (0.79-0.94)
Age, sex, dose	1.01	0.99	1.14 (1.05-1.24)
Final model			
10 IU	1.00	0.99	1.09 (1.00-1.19)
30 IU	1.02	0.98	1.19 (1.10-1.30)
50 IU	1.04	0.98	1.31 (1.20-1.42)

Hemkens LG, Diabetologia 52; 2009

Limitations

1. Allocation bias

Human insulin group	Insulin glargine group
Type 1 & type 2 diabetes	Type 2 diabetes only
OHA 77.2% (SU 66.7%)	OHA 92.1% (SU 79.8%)
More frequent hospitalization before enrollment	Older
NPH insulin &/or RI	Insulin glargine only
Basal, basal plus, & basal bolus	Basal only

2. No information of confounding factors
(BMI, diabetes duration and smoking)

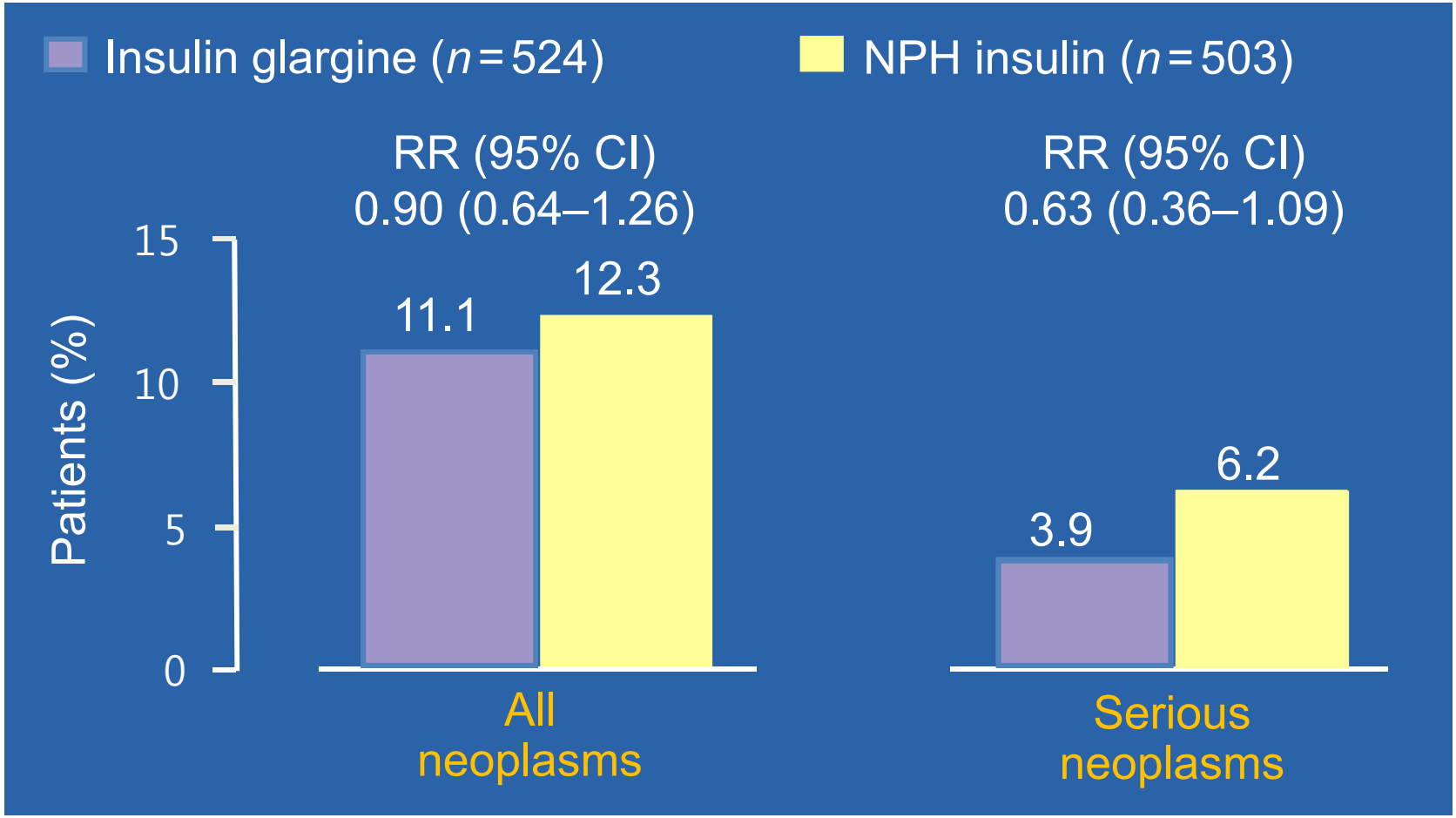
3. Large number of exclusion
(participants who changed insulin type)

The three other analyses published in *Diabetologia*

Country and population	Main allegations concerning Lantus	Remarks
Sweden N=114,841	• No increased risk of cancer overall • Higher risk of breast cancer only in patients taking glargine alone but not in patients taking glargine plus other insulins	• Low number of breast cancers • allocation bias
Scotland N=49,197	• Higher overall cancer rate in patients treated with glargine alone, but not in patients treated with glargine plus other insulin	• Inconsistency in cancer findings among fixed and incidence cohorts • allocation bias
UK N=62,809	• No evidence of increased risk of cancer with glargine compared with human insulin	• Less heterogeneity between insulin-treated patients than in the other analyses

Currie, Diabetologia 2009;52:1766–77
Jonasson, Diabetologia 2009;52:1745–54
Colhoun, SDRN Epidemiology Group. Diabetologia 2009;52:1755–65

Cancer rates in the 5-year randomized controlled trial (insulin glargine *vs.* NPH insulin)



Rosenstock J. Diabetologia **52**:1971–3, 2009

Insulin glargine metabolism after subcutaneous injection

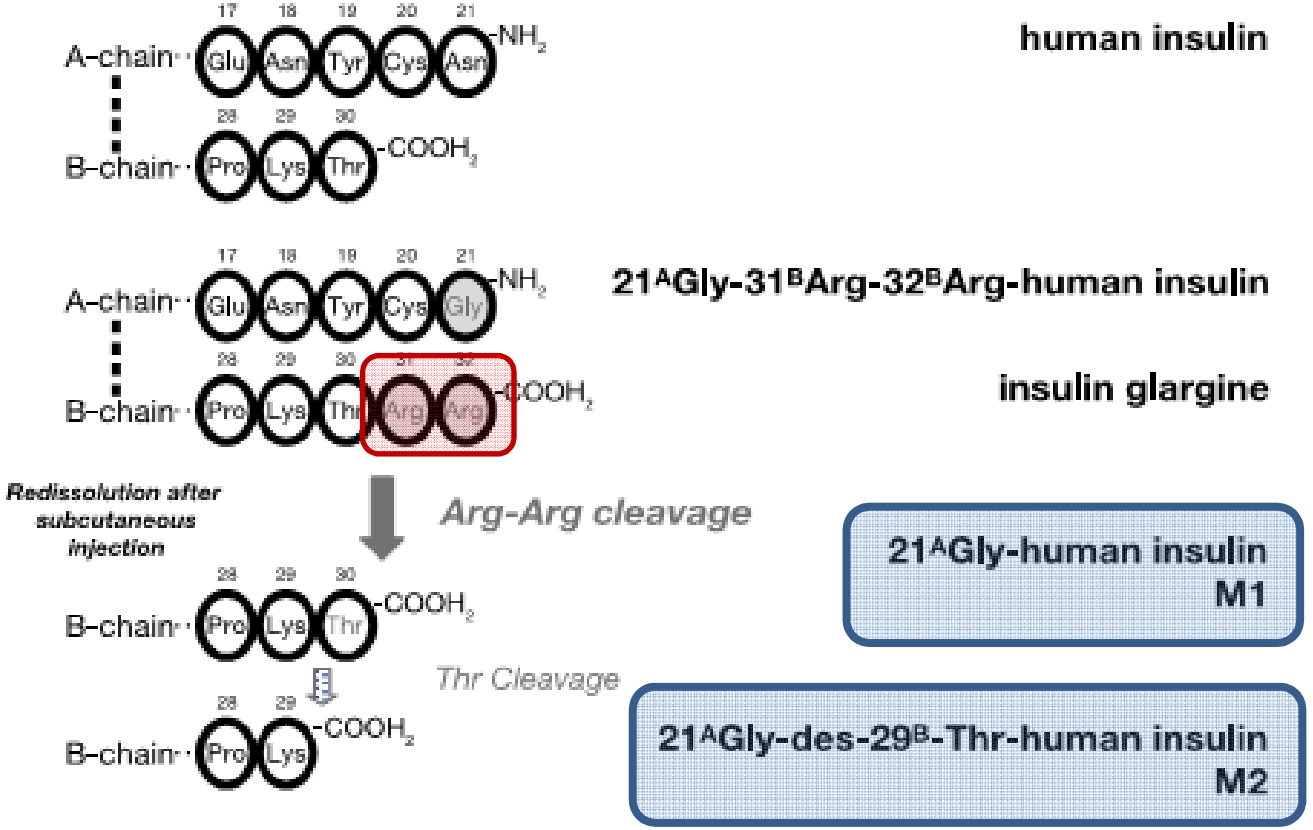
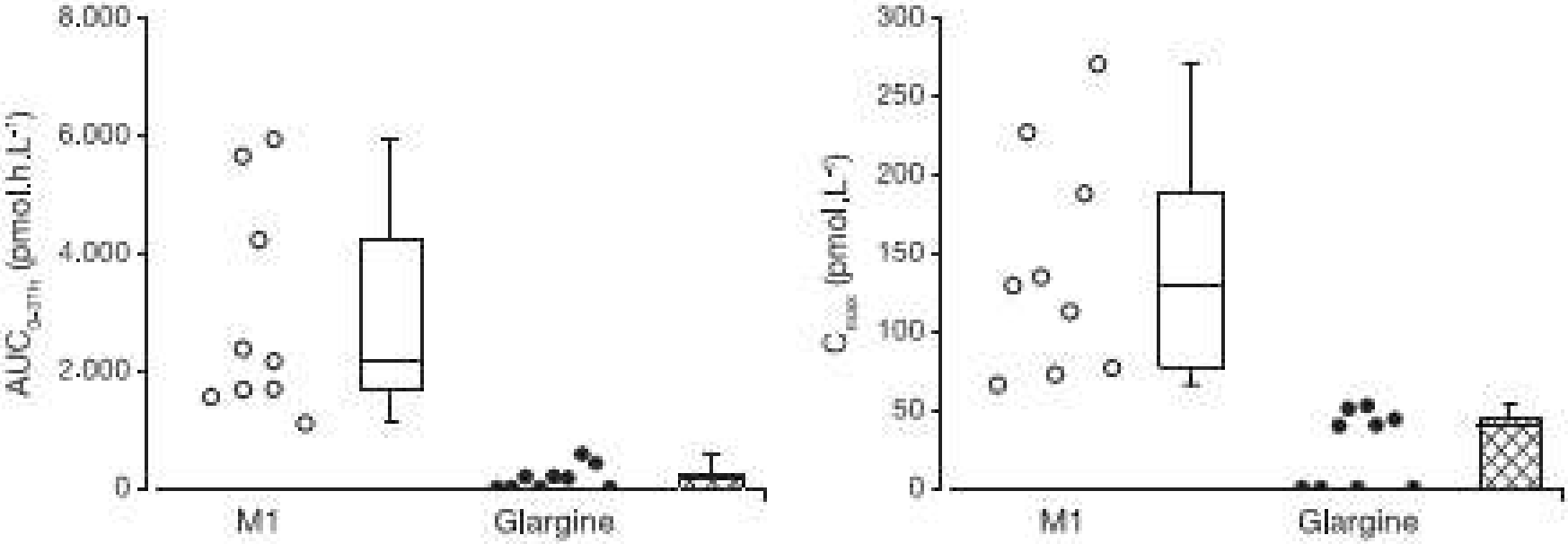


Figure 1—*Insulin glargine maturation and metabolism after subcutaneous injection. Enzymatic removal of the COOH-terminal basic arginine pair yields 21^{A}-Gly-human insulin metabolite M1, the principal active moiety of glargine. Subsequent cleavage of 30^{B}-threonine yields M2.*

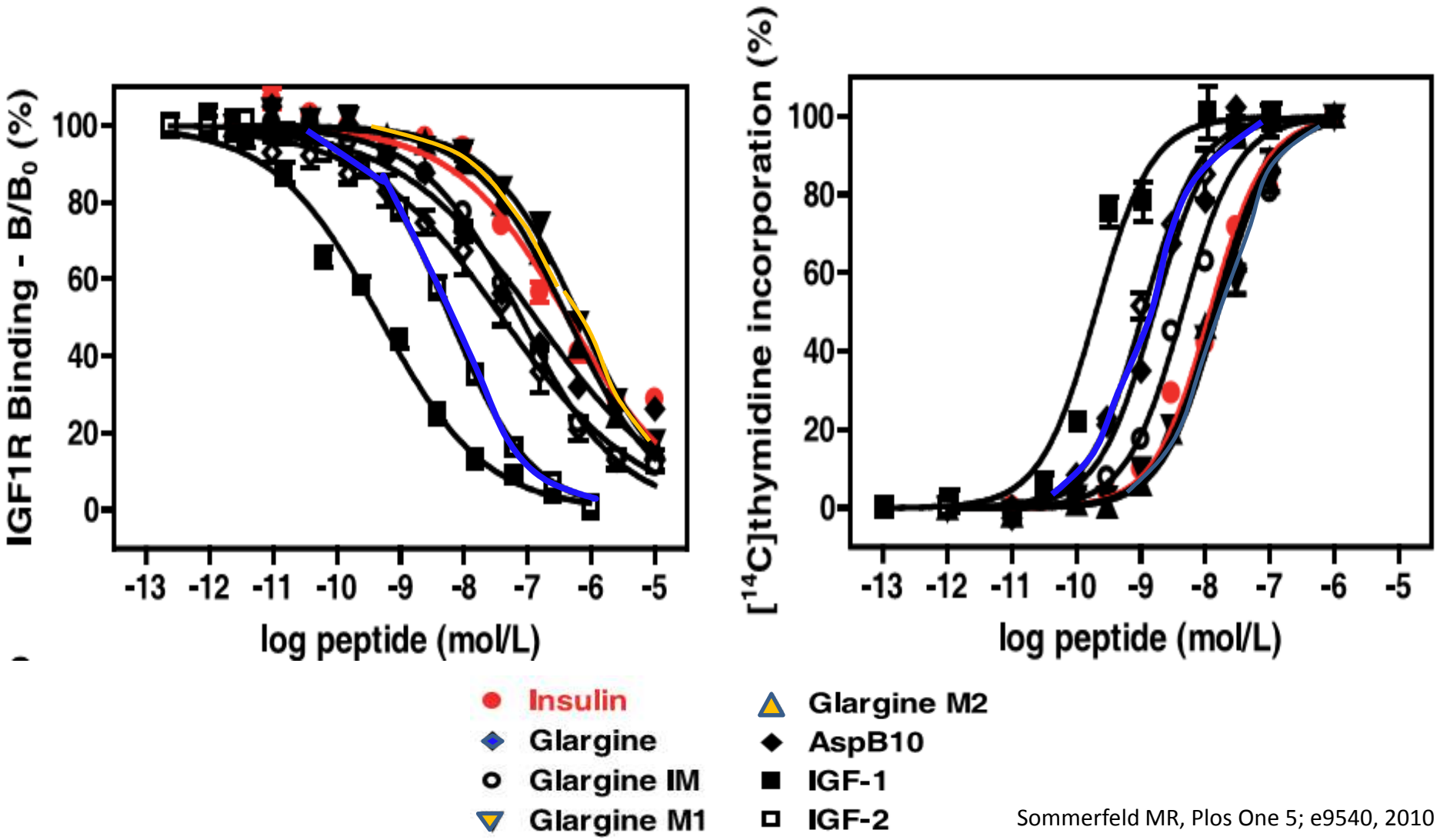
Bolli GB, Diabetes care 35; 2626-2630, 2012

Metabolism of insulin glargine after daily subctaneous injections in T2DM



Lucidi P, Diabetes care 35; 2647-2649, 2012

Activity of insulin analogs on the human IGF1R and mitogenic potential



Sommerfeld MR, Plos One 5; e9540, 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

- 12,537 people with CV risk factors plus IFG, IGT, or T2DM
- Insulin glargine vs. standard care
- During median 6.2yr f/u, there was no significant difference in cancer incidence (HR=1.00)

N Engl J Med 367;319-28, 2012

Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database

Blin P, Diabetologia 55; 644-653, 2012

Cancer Risk Associated with Insulin Glargine among Adult Type 2 Diabetes Patients – A Nationwide Cohort Study

Chang C, Plos One 6; e21368, 2011

The chapter on whether insulin glargine is an independent risk factor for cancer may now be closed

71, 2011

Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: results from a large population-based follow-up study

Ruiter R, Diabetologia 55; 51-62, 2012

Insulin Glargine and Cancer Risk in Patients with Diabetes: A Meta-Analysis

Tang X, Plos one 7; e51814, 2012

Problems of and clinical implications observational studies

- Several methodological problems in observational studies
  : allocation bias, lack of adjusting for confounding factors, reverse causality, short follow-up time, detection bias…

- Randomized controlled study with cancer occurrence as a primary outcome is hard to carry out

- Better designed, less biased observational studies should be needed

Conclusion (I)

- Cancer should be recognized as an important complication and cause of death of type 2 diabetes

- As hyperinsulinemia is a major contributing factor in the development of cancer, exogenous insulin exposure has been linked to a higher risk of cancer, whereas metformin linked to a lower risk of cancer

Conclusion (II)

- Therefore, cancer risk can potentially be modified by lifestyle changes and metformin in diabetes

- Although some medications may be associated with the increased risk of cancer, clinicians should continue to consider the benefits of optimal glycemic control over any presumed cancer risks in the management of diabetes

Thank you for your attention!

- Cancer screening
  There is no DM-specific cancer screening recommandations
- In DM pats, overall cancer screening rate is lower
- TZD ca감소하는 경향인데 방광암은 느는 이유
- GLP1

tiated enough. Such considerations should not currently influence our treatment decisions regarding the potential prescription of GLP-1 receptor agonists or DPP-4 inhibitors within a treatment regimen for type 2 diabetes.

Ca. mortality 증가:

- 1. It is unclear if diabetes makes the cancer more aggressive, or host mechanism to resistant to ca progression
- Diabetic pts receive less appropriate anti-ca tx
- Response to the CTx is worse

T1DM

- No increased risk of breast, pancreatic, c-r, kidney cancer, but increased stomach (pernicious anemia. H pylori), endometrial, and cervical ca (higher incidence of irregular mens and fertility disorders in T1DM)

Liver, pancreatic ca가 많은 이유

Colon ca: in addition to hyperinsulinemia, they have slow bowel transit time and high fecal bile acid concentration

NNH: number needed to harm is 5 cases of bladder cancer per 100,000 pys