Metformina e Insulina

Dott. Maurizio Nizzoli
U.O. Endocrinologia e Malattie Metaboliche
U.O. Medicina Interna
O.C. G.B. Morgagni - Forlì

Bari,
7-10 novembre 2013

Conflitto d'interessi

Onorari da: Eli Lilly
Sanofi-Aventis
MSD

Diabete e Cancro

Bari,
7-10 novembre 2013

1910

A Statistical Study in Cancer Death-Rates

Cancer and Diabetes,

Both diseases have very much the same age distribution. They stand almost alone as being on the increase, while other causes of death show declining rates. The aetiology of both diseases is obscure. Both being diseases of old age…

… If there were a common factor in the causation of the dual increase a correlation between these diseases might be discovered.

Maynard GD. Biometrika 1910 ; 7: 276-304

American Diabetes Association / American Cancer Society: Consensus Report 2010

Bari,
7-10 novembre 2013

Type 2 diabetes and cancer share many risk factors, but potential biologic links between the two diseases are incompletely understood.

Cancer and diabetes are diagnosed within the same individual more frequently than would be expected by chance, even after adjusting for age.

Giovannucci E et al. Diabetes Care 2010;33(7):1674-85.

Incidenza di cancro in pz con diabete: meta-analisi

Bari,
7-10 novembre 2013

Cancro	Autore	anno	[12]	RR	CI
Tutti	Noto	2011	39 10 20	**1.1**	1.04 – 1.17
Mammella	Boyle Liao Larsson	2012 2011 2007	16	**1.27** **1.23** **1.20**	1.16 – 1.39 1.18 – 1.27 1.12 – 1.28
Vescica	Larsson	2006	21	**1.24**	1.08 – 1.42
Tratto Biliare	Ren	2011	5	**1.43**	1.18 – 1.72
Colangiocarcinoma	Jing	2012	24	**1.6**	1.38 – 1.87
Colon retto	Deng	2012	16	**1.26**	1.20 – 1.31
Endometrio	Friberg	2007	17	**2.1**	1.75 – 2.53
Esofago	Huang	2012	25	**1.30**	1.12 -1.50
Stomaco	Tian	2012	18	**1.11**	1.00 – 1.24
HCC	Wang	2012	9	**2.01**	1.61 – 2.51
Rene	Larsson	2011	14	**1.42**	1.06 – 1.91
Fegato	Gao	2010	15	**3.33**	1.82 – 6.1
Linfoma NH	Mitri	2008	35	**1.19**	1.04 – 1.35
Pancreas	Ben	2011		**1.94**	1.66 – 2.27
Prostata	Kasper	2006	19	**0.84**	0.76 – 0.93

Summary of the Association of Diabetes and Cancer Mortality

Study group	Cancer evaluated	Risk	95% CI
Campbell et al 2012 (men) (65)	Breast	RR 4.20[a]	2.20-8.04
	Hepatic	RR 2.26[a]	1.89-2.70
	Oropharyngeal	RR 1.44[a]	1.07-1.94
	Pancreatic	RR 1.40[a]	1.23-1.59
	Bladder	RR 1.22[a]	1.01-1.47
	Colon	RR 1.15[a]	1.03-1.29
	Prostate	RR 0.88[a]	0.79-0.97
Campbell et al 2012 (women) (65)	Hepatic	RR 1.40[a]	1.05-1.86
	Endometrial	RR 1.33[a]	1.08-1.65
	Pancreatic	RR 1.31[a]	1.14-1.51
	Colon	RR 1.18[a]	1.04-1.33
	Breast	RR 1.16[a]	1.03-1.29
Currie et al 2012 (66)	All cancers	HR 1.09[b]	1.06-1.13
	Breast	HR 1.32[b]	1.17-1.49
	Prostate	HR 1.19[b]	1.08-1.31
	Bladder	HR 1.16[b]	1.02-1.32
	Lung	HR 0.84[b]	0.77-0.92

Diabete e rischio di cancro: fattori interferenti

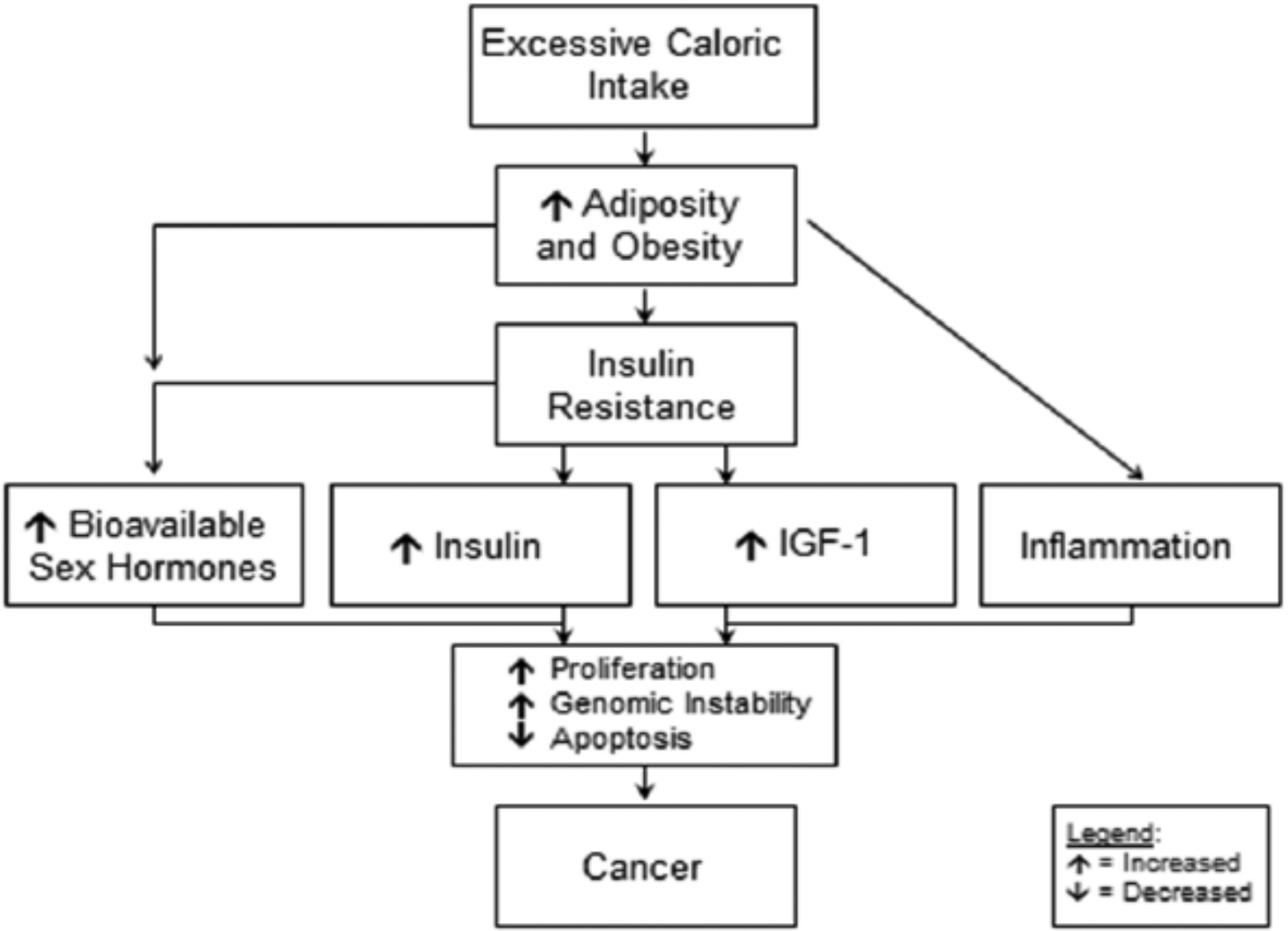
Bari,
7-10 novembre 2013

- Tipo di diabete: tipo 1 / tipo 2
- Obesità
- Durata della malattia
- Grado di compenso metabolico
- Comorbilità
- Tipo di terapia
- Dieta e attività fisica

DIABETES AND CANCER—AN AACE/ACE CONSENSUS STATEMENT

ENDOCRINE PRACTICE Vol 19 No. 4 July/August 2013

Bari,
7-10 novembre 2013



Bari,
7-10 novembre 2013

Effetto della chirurgia bariatrica

	Surgery Group (#/ 10,000 person-yr)	Control Group (#/ 10,000 person-yr)
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
Non-disease causes		
Accident	3.7	2.7
Poisoning	1.9	0.6
Suicide	2.7	1.2

Adams TD et al. N Engl J Med 2007;357:753-761.

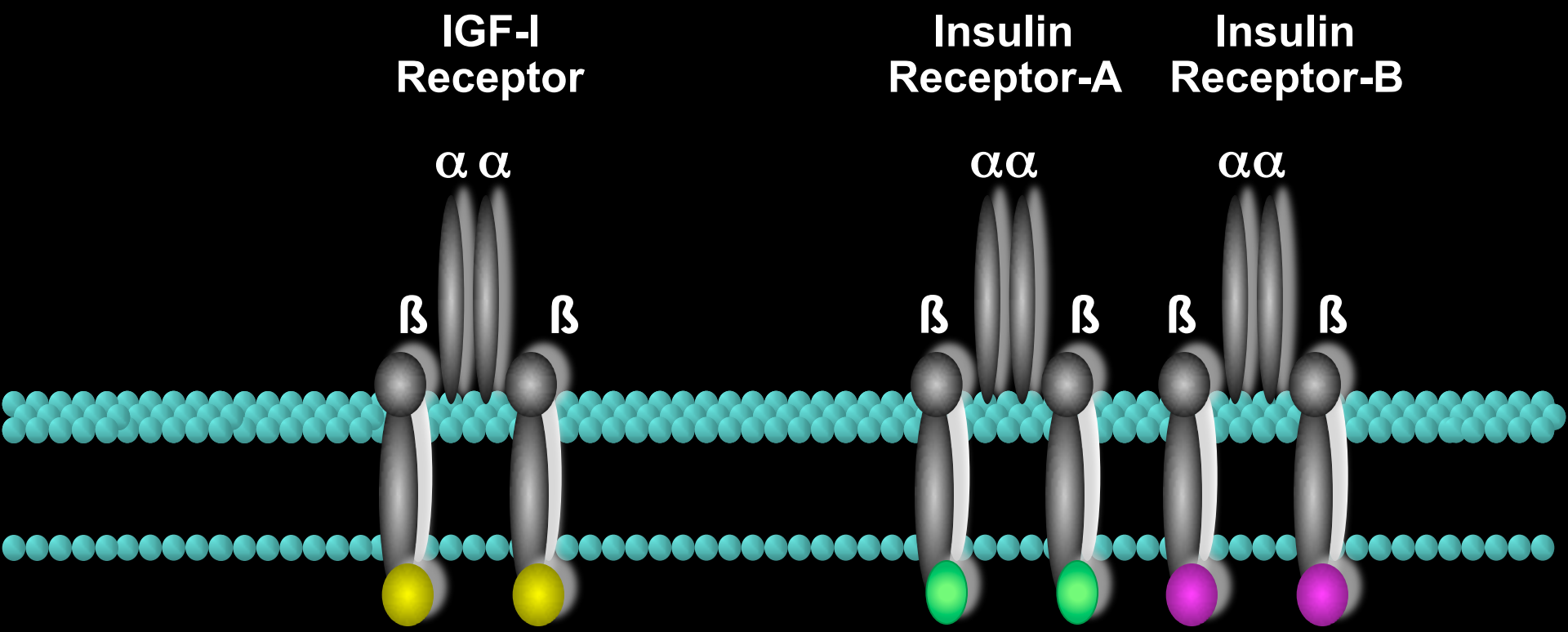
Insulina, IGF-1 e Cancro

Bari,
7-10 novembre 2013

Marker	Risk of Associated Cancer	Population	Reference
C-Peptide	*Increased*		
	•Colorectal	Physicians' Health Study	Ma et al. 2004
		EPIC	Jenab et al 2007
		NYUWHS	Kaaks et al 2000
	•Endometrial	EPIC	Cust et al 2007
	•Advanced Prostate	Physicians Health Study	Ma et al. 2008
Insulin	*Increased*		
	•Endometrial	Women's Health Initiative	Gunter et al 2008
	•Colorectal	Women's Health Initiative	Gunter et al 2009
	Conflicting Results		
	•Pre-menopausal Breast	Women's Health Initiative	Gunter et al 2008
		Nurses' Health Study	Eliassen et al 2007
IGF-I	*Increased*		
	•Colorectal	Meta-Analyses	Chen et al 2009, Rinaldi et al 2010
	•Pre-menopausal Breast		Chen et al 2009
	•Prostate		Chen et al 2009
			Roddam et al 2008
			Renehan et al 2004

IGF-1 Receptor and Insulin Receptors

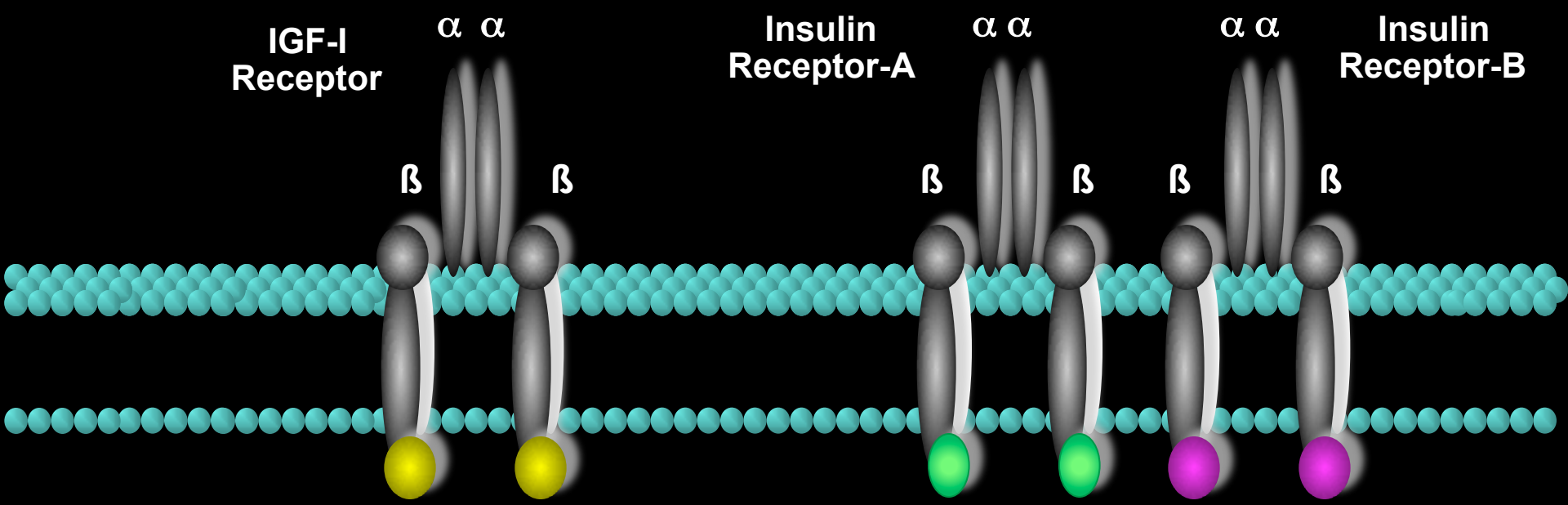
Bari,
7-10 novembre 2013



- Questi due recettori condividono la via intracellulare del segnale ormonale
- L'insulina ha una ridotta affinità per il recettore IGF-1R, ma a concentrazioni elevate è in grado di attivare anche questo recettore

IGF-1 Receptor and Insulin Receptors

Bari,
7-10 novembre 2013



MAP K

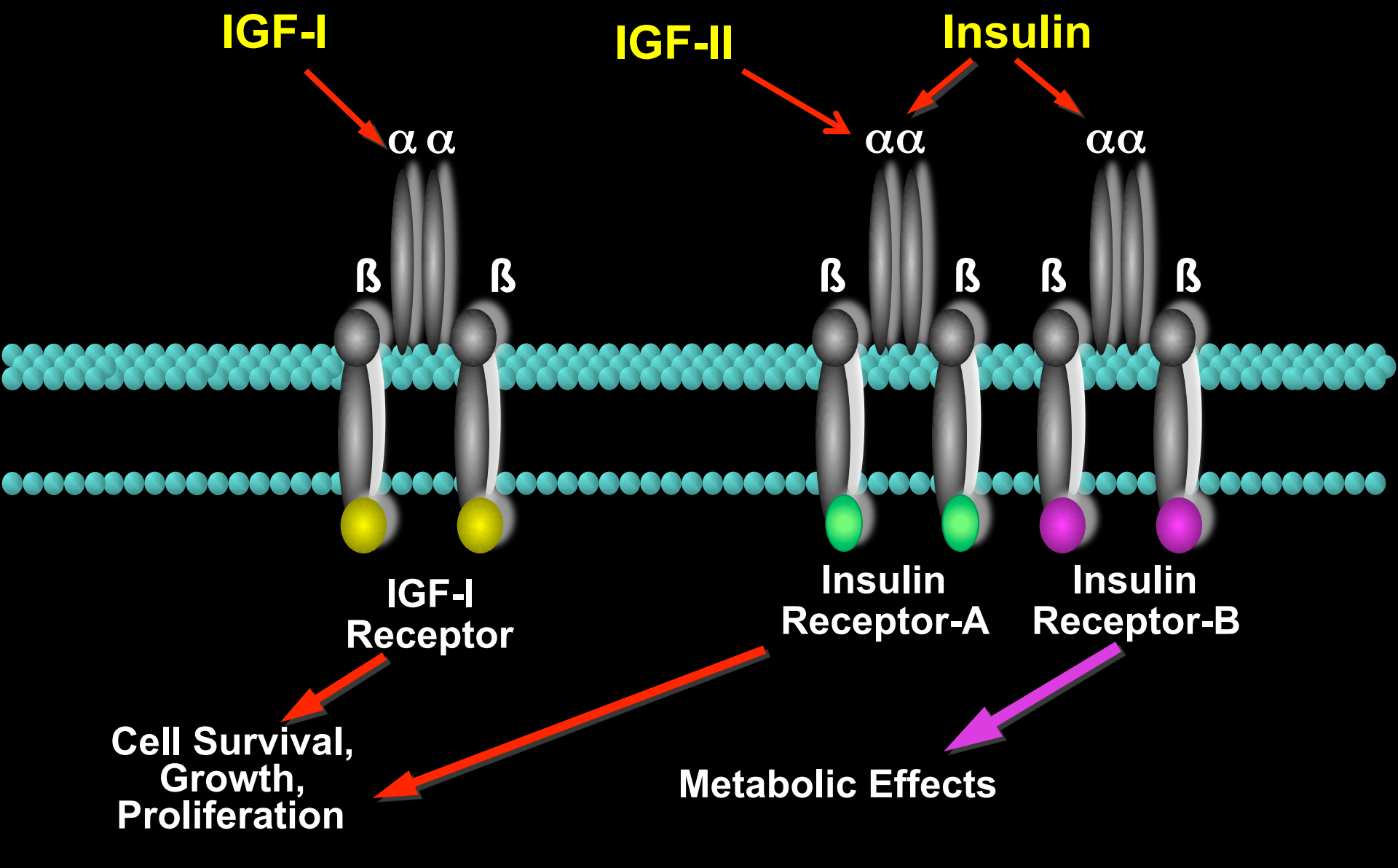
PI3 K

VIA MITOGENA

VIA METABOLICA

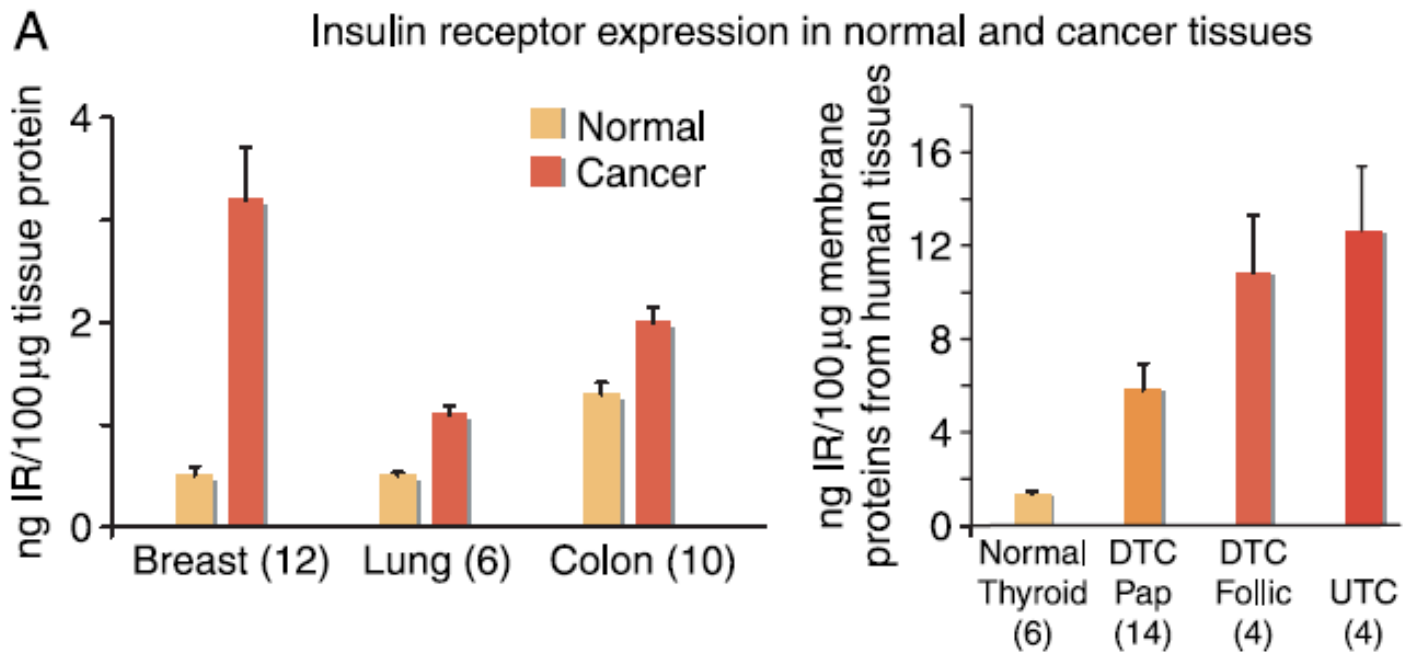
IGF-1 Receptor and Insulin Receptors

Bari,
7-10 novembre 2013



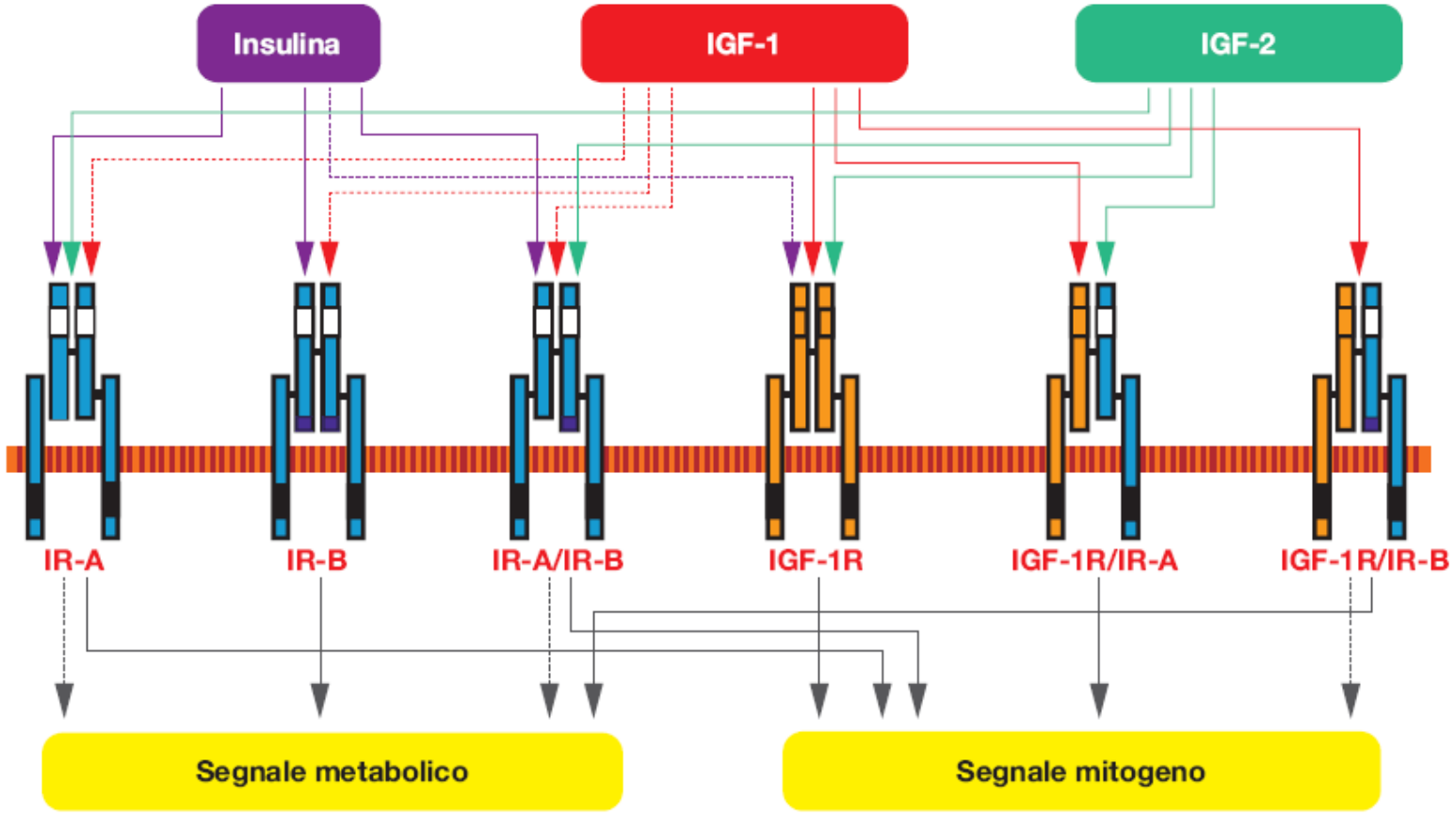
IGF-1 Receptor and Insulin Receptors

Bari,
7-10 novembre 2013



IGF-1 Receptor and Insulin Receptors

Bari,
7-10 novembre 2013



Recettori dell'insulina (IR-A e IR-B), recettore dell'IGF-1 (IGF-1R) e recettori ibridi (IR-A/IR-B, IGF-1R/IR-A e IGF-1R/IR-B)

Diabete e cancro

Bari,
7-10 novembre 2013

Effetto proliferativo

L'insulina ha certamente un ruolo nel favorire la progressione e l'aggressività del tumore, ma verosimilmente non contribuisce alla comparsa di nuovi tumori

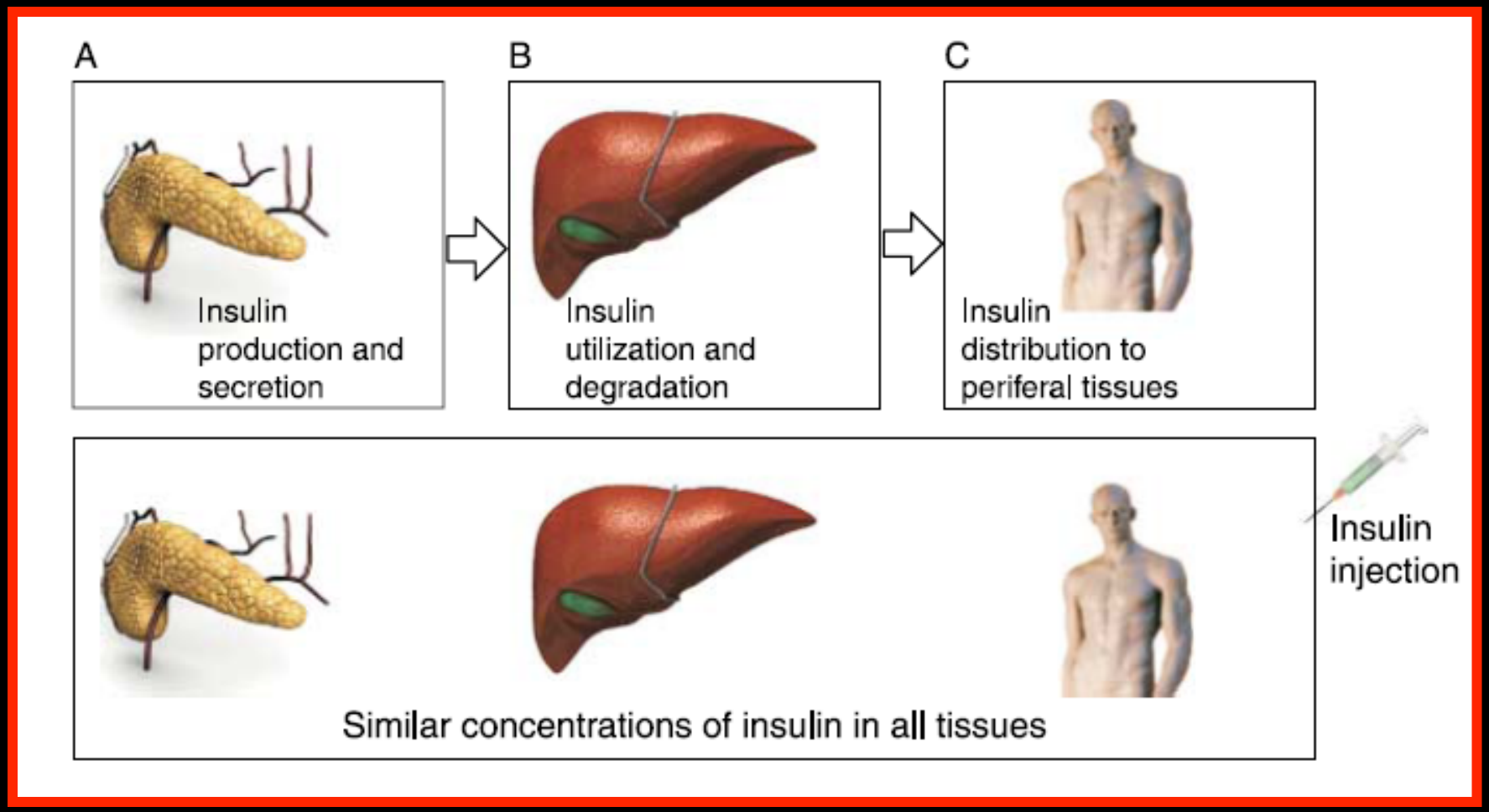
INFIAMMATORIO CRONICO → Adipochine → Effetto mutageno ?

Incident cancers in large randomized trials of glucose lowering

Bari,
7-10 novembre 2013

Trials	N°	Follow up	Intensive %	Control %	RRR
All intensive UKPDS	2729	10	0.44	0.44	0.98 (0.64-1.52)
Insulin UKPDS	911	10	0.46	0.48	0.94 (0.55-1.62)
Glyburide UKPDS	615	10	0.44	0.48	0.91 (0.49-1.67)
Metformina UKPDS	342	10	0.35	0.49	0.71 (0.29-1.76)
VADT	892	10.7	0.48	0.42	1.15 (0.65-2.05)
ACCORD	5128	5.6	1.3	1.2	1.08 (0.90-1.3)
ADVANCE	5571	5	0.43	0.43	1.00 (0.78-1.29)

Sede di iniezione ?



Mitogenicità analoghi in vitro

Bari,
7-10 novembre 2013

Tipo insulina	Affinità recettore insulina	Potenza metabolica	Affinità recettore IGF-1	Potenza mitogenica
Umana	100	100	100	100
Lispro	84	82	156	66
Aspart	92	101	81	58
Glargine	86	60	641	783
Detemir	18	27	16	11

Zib I – Diabetes Obesity Metabolism 2006; 8: 611-620

Glargine e rischio di cancro

Bari,
7-10 novembre 2013

Studio	Risultati	limiti
Germania: 127.031 pz	▪Aumento del rischio nei pz glargine vs NPH all'analisi cruda ▪Aumento del rischio con glargine dopo aggiustamento per la dose di insulina	▪Esposizione breve all'insulina ▪Non aggiustamento per per BMI con bias da indicazione
Regno Unito: 62.809 pz	▪Non evidenza di rischio con glargine	▪Minore eterogeneità tra i pz trattati con insulina vs le altre analisi di registro
Svezia: 114.841 pz	▪Non aumento del rischio di neoplasia ▪Rischio di ca della mammella nei pz trattati con glargine, ma non in quelli con glargine + altre insuline	▪Limitato numero di neoplasie ▪Differenze nelle caratteristiche demografiche dei pz
Scozia: 49.197 pz	▪Aumento complessivi di neoplasie nei trattati con glargine, ma non in quelli con glargine + altre insulina	▪Differenze demografiche tra i gruppi ▪Bias di allocazione

Similar risk of malignancy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: findings from a 5 year randomised, open-label study

- RCT della durata 5 anni glargine vs NPH in 1.024 pazienti DMT2. End-point primario: progressione della retinopatia diabetica (studio di non inferiorità).

Incidenza di progressione: *14.2% in glargine vs 15.7% in NPH.**

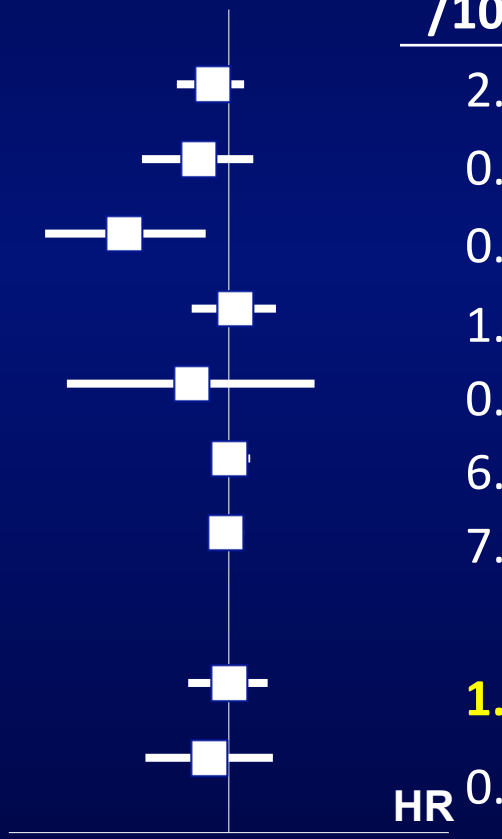
- Analisi post-hoc sull'incidenza di neoplasie. Esposizione cumulativa >4aa. La frequenza di neoplasie emergenti nel corso del trattamento è stata: *11.1% (57/20) glargine vs 12.3% (62/31) NPH: RR 0.90 (95% IC 0.64-1.26)*. Non si rileva aumento del cancro al seno. *§*

*Rosenstock J, et Al.
Diabetologia. 2009 Sep;52(9):1978-88. Epub 2009 Jul 13.

§ Rosenstock J, et Al.
Diabetologia. 2009 Sep;52(9):1971-3. Epub 2009 Jul 16.

Additional Outcomes

	HR (95% CI)	P	Insulin /100 py	Standard /100 py
Angina	0.95 (0.85, 1.05)	0.29	2.07	2.17
Unstable	0.91 (0.76, 1.08)	0.28	0.66	0.72
New angina	0.72 (0.56, 0.93)	0.01	0.27	0.38
Worsening	1.02 (0.89, 1.16)	0.80	1.29	1.26
Amputation	0.89 (0.60, 1.31)	0.55	0.13	0.14
CV Hosp	1.00 (0.95, 1.07)	0.90	6.98	6.91
Non-CV Hosp	0.99 (0.94, 1.05)	0.85	7.90	7.93
Any Cancer	**1.00 (0.88, 1.13)**	**0.97**	**1.32**	**1.32**
Cancer Death	0.94 (0.77, 1.15)	0.52	0.51	0.54



Studio ORIGIN

Bari,
7-10 novembre 2013

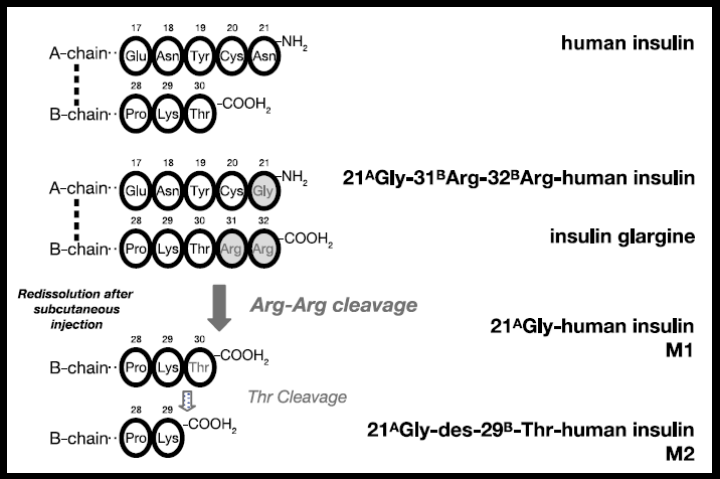
Neoplasie	Glargine	Controllo
INCIDENZA	1.32/100/anno	1.32/100/anno
MORTALITA'	0.51/100/anno	0.54/100/anno

- HbA1c e la terapia ipoglicemizzante non modificano il rischio
- Non vi è alcuna relazione con la dose di insulina
- Nessuna differenza di sede (mammella, colon, prostata, polmone, melanoma)

Bordeleau et al. ADA 2013

Diabetes Care 35:2647–2649, 2012

Dopo la somministrazione di glargine, l'esposizione anche a dosi sovraterapeutiche è marginale, perché glargine è rapidamente e quasi completamente processata a M1 che media l'effetto metabolico dell'insulina



type 1 di-
is rapidly
metabolic

Metabolism of Insulin Glargine After Repeated Daily Subcutaneous Injections in Subjects With Type 2 Diabetes

CONCLUSIONS—After subcutaneous injection, glargine was minimally detectable in blood, whereas its metabolite M1 accounted for most (>90%) of the plasma insulin concentration and metabolic action of the injected glargine.

Metformina e rischio di cancro e prognosi

Bari,
7-10 novembre 2013

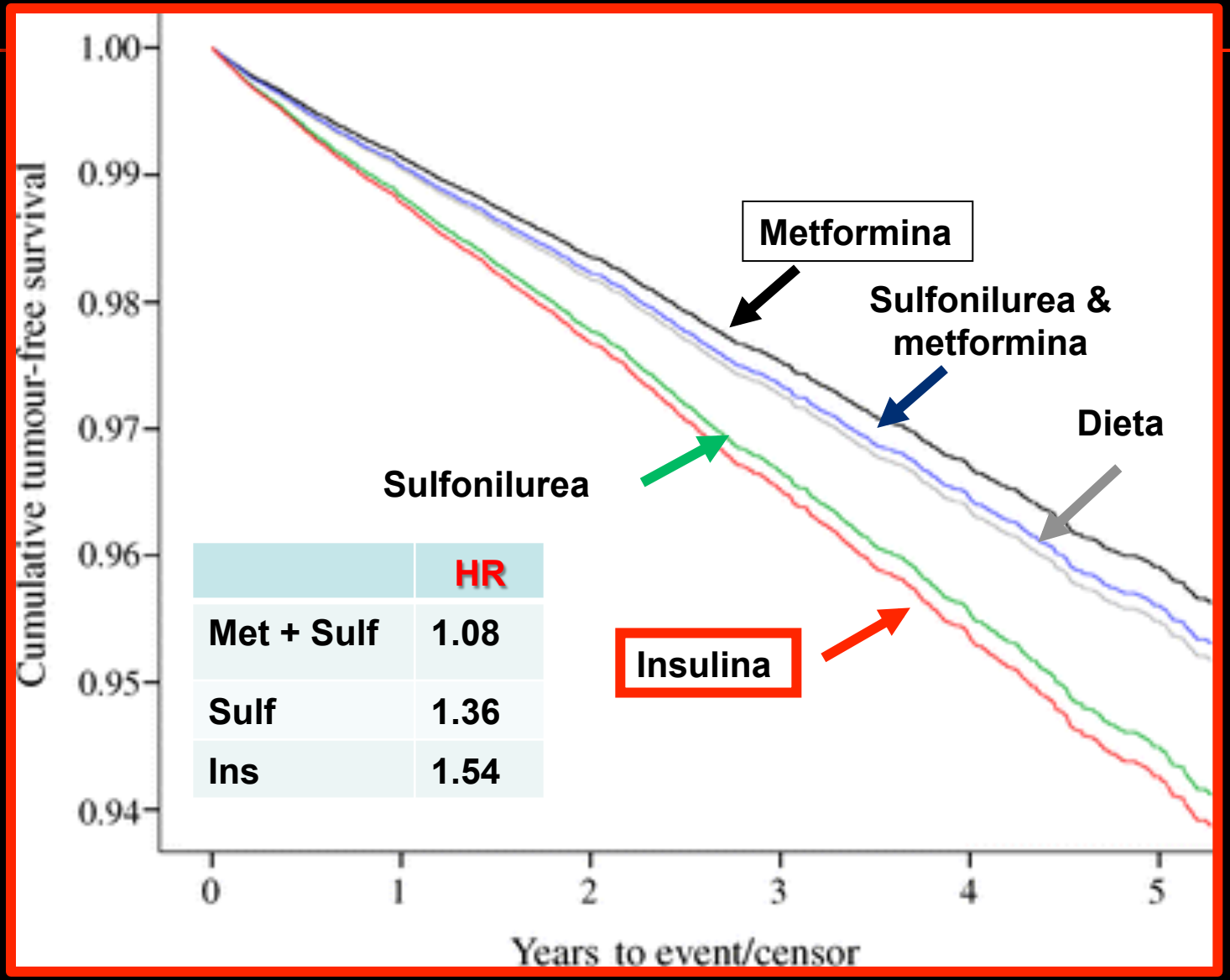
Tutti tipi di cancro		
	HR	95% CI
Incidenza	0.68	0.52
Mortalità	0.70	0.51

Tipi di cancro		
	HR	
Colon	0.64	S
Mammella	0.70	NS
Pancreas	0.20 – 0.38	S
Fegato	0.33	S
Prostata	0.56 – 1.62	NS

Decensi A. et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res. 2010; 3: 1451 - 1461

Terapia del diabete e cancro

Bari,
7-10 novembre 2013



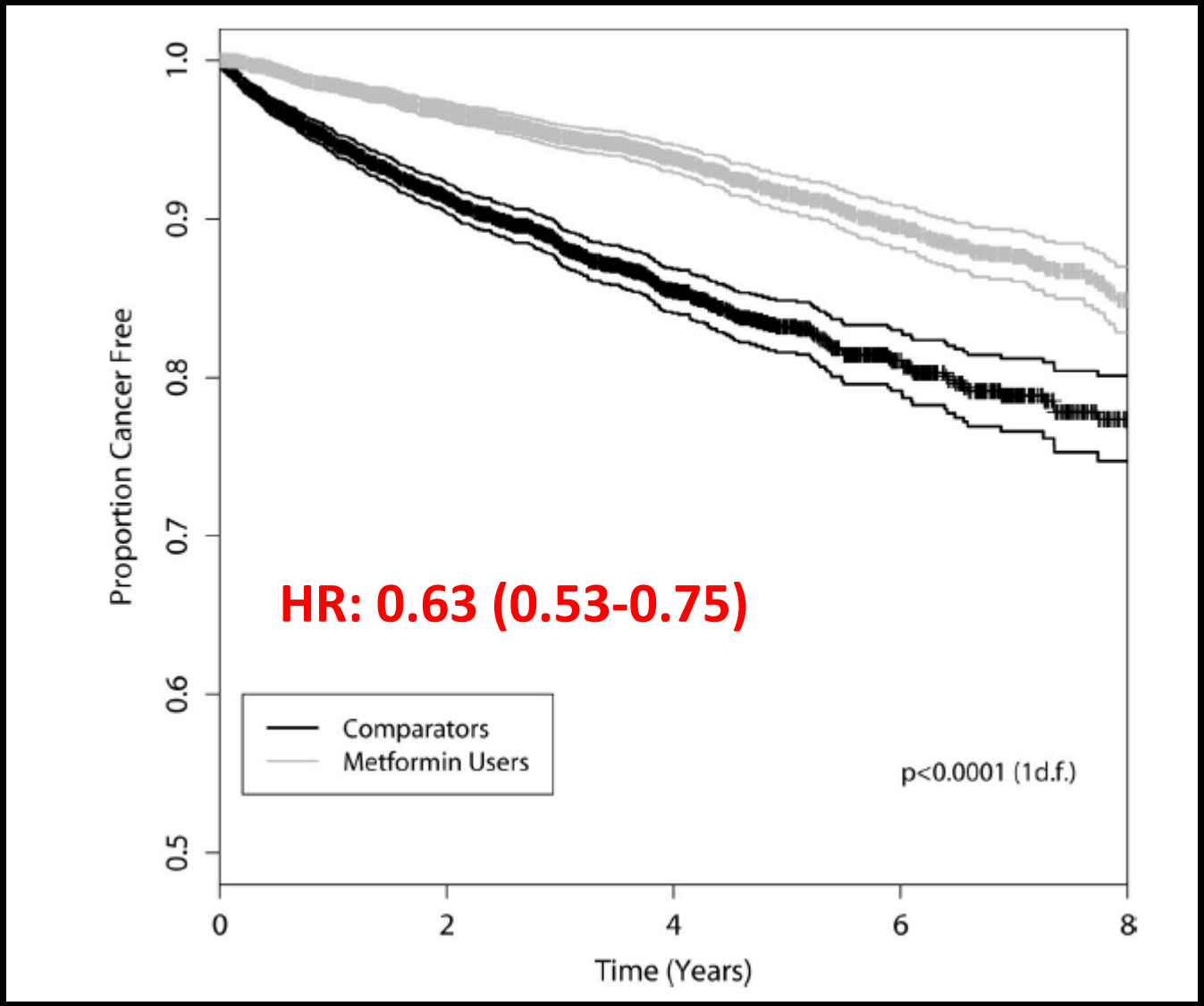
Currie CJ et Al "The influence of glucose lowering therapies on cancer risk in type 2 diabetes". Diabetologia 52; 1766-1777, 2009

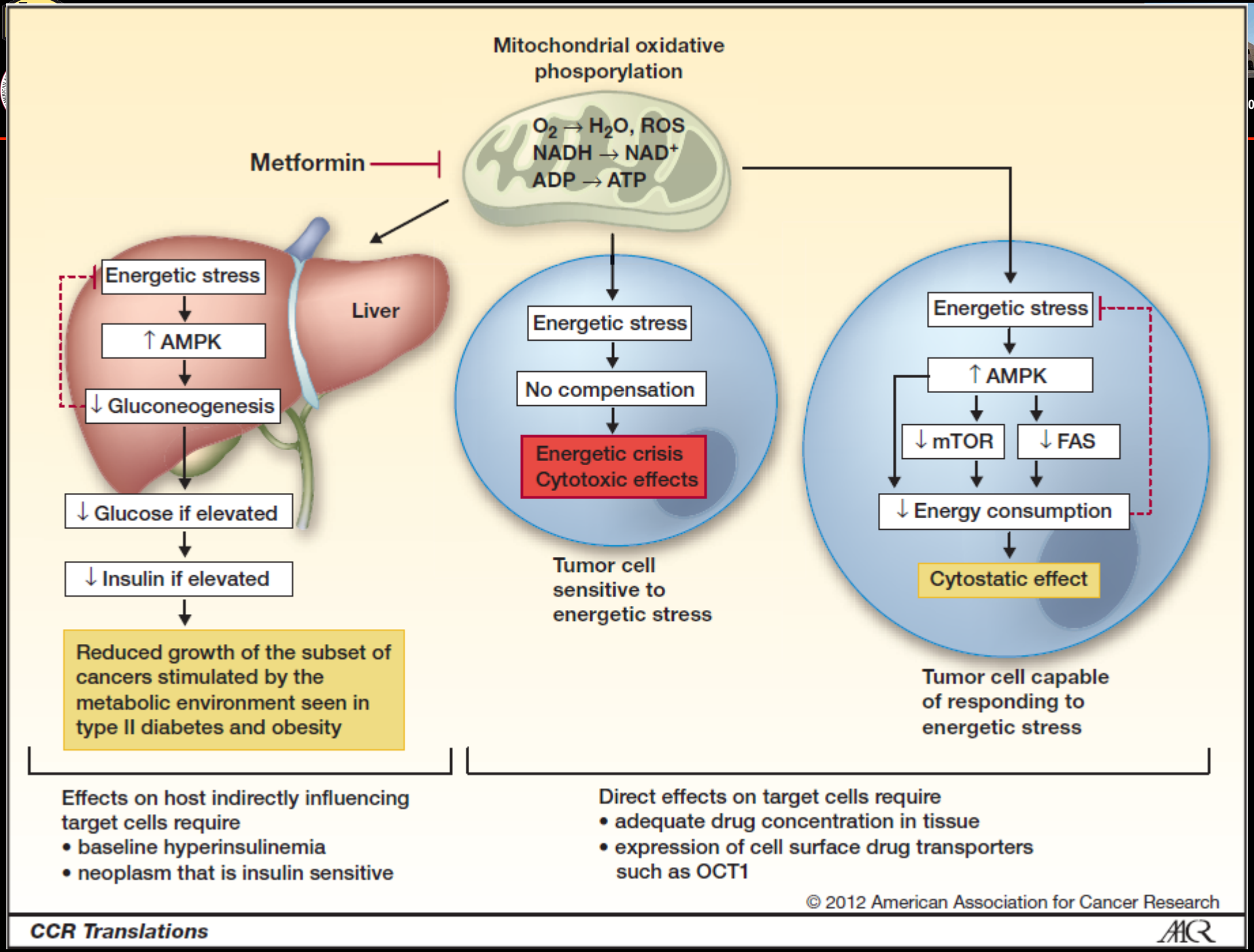
New Users of Metformin Are at Low Risk of Incident Cancer

Diabetes Care 32:1620–1625, 2009

A cohort study among people with type 2 diabetes

Bari,
7-10 novembre 2013



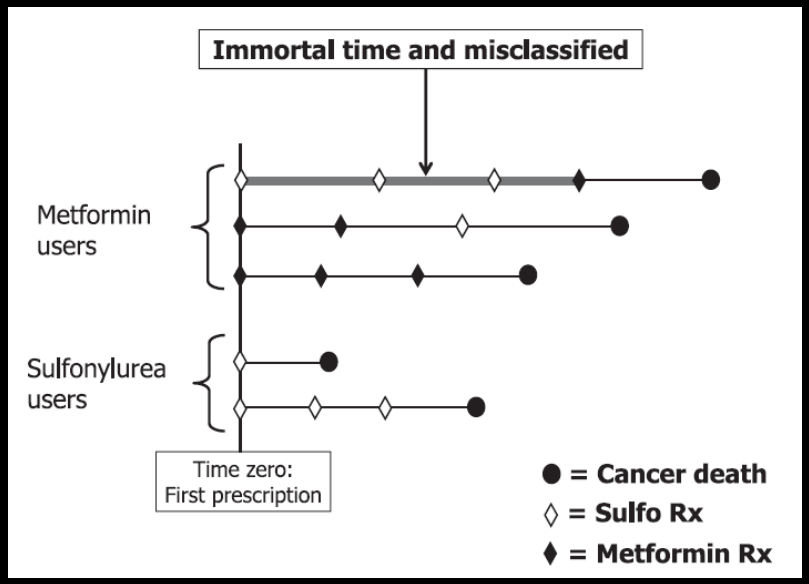


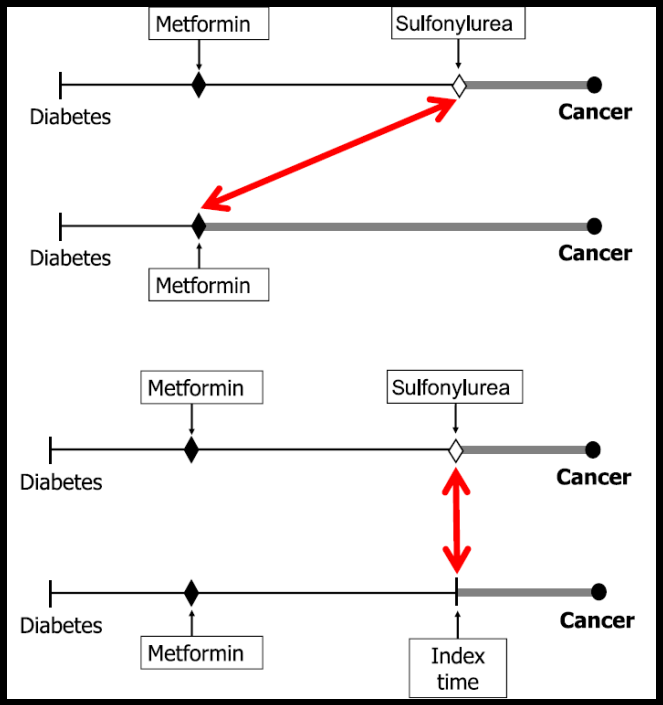
Metformin and the Risk of Cancer

Time-related biases in observational studies

Samy Suissa, PhD[1,2]
Laurent Azoulay, PhD[1,3]

Bari,
7-10 novembre 2013





CONCLUSIONS—Although observational studies are important to better understand the effects of drugs, their proper design and analysis is essential to avoid major time-related biases. With respect to metformin, the scientific evidence of its potential beneficial effects on cancer would need to be reassessed critically before embarking on further long and expensive trials.

Diabetes Care 35:2665–2673, 2012

Clinical Trials studying Metformin and Cancer

Bari,
7-10 novembre 2013

Trial Number	Type of Trial	Phase	Tumor Type	Stage	Primary Outcome
NCT01266486	Single arm, Open-Label	Phase II	**Breast Cancer**	Early stage	**pS6K, p4E-BP-1, pAMPK**
NCT01302002	Non-Randomized, Open Label	Phase 0	**Breast Cancer**	Operable stage I and II	**Proliferation and apoptosis**
NCT00897884	Single arm, non-randomized	-	**Breast Cancer**	Operable T1-4 (T1≥1cm), Nx	**Proliferation**
NCT00984490	Single arm, open label	-	**Breast Cancer**	Stage I and II	**Proliferation**
NCT01310231	Randomized, double-blind, placebo controlled	Phase II	**Breast Cancer**	Metastatic	**Progression free survival**
NCT01101438	Randomized, double blind, placebo controlled	Phase III	**Breast Cancer**	Early stage	**Invasive disease free survival**
NCT00930579	Non-randomized, Open label	Phase II	**Breast Cancer**	DCIS or operable invasive breast cancer	**AMPK / mTOR signaling**
NCT01205672	Single arm, open label	-	**Endometrial Cancer**	All candidates for surgical staging	**Insulin / glucose metabolism and mTOR signaling**
NCT01333852	Randomized, double blind, placebo controlled	-	**Head & Neck Cancer**	Metastatic or recurrent	**Disease control at 12 weeks**
NCT01210911	Randomized, placebo, controlled	Phase II	**Pancreatic Cancer**	Locally advanced or metastatic	**6 month survival**
NCT01167738	Randomized, open label	Phase II	**Pancreatic Cancer**	Metastatic	**Progression free survival at 6 months**
NCT01215032	Single arm, open label	-	**Prostate Cancer**	Castration resistant	**PSA response**
NCT01243385	Single arm, open	Phase II	**Prostate Cancer**	Locally advanced	**Progression free**

Conclusioni 1°

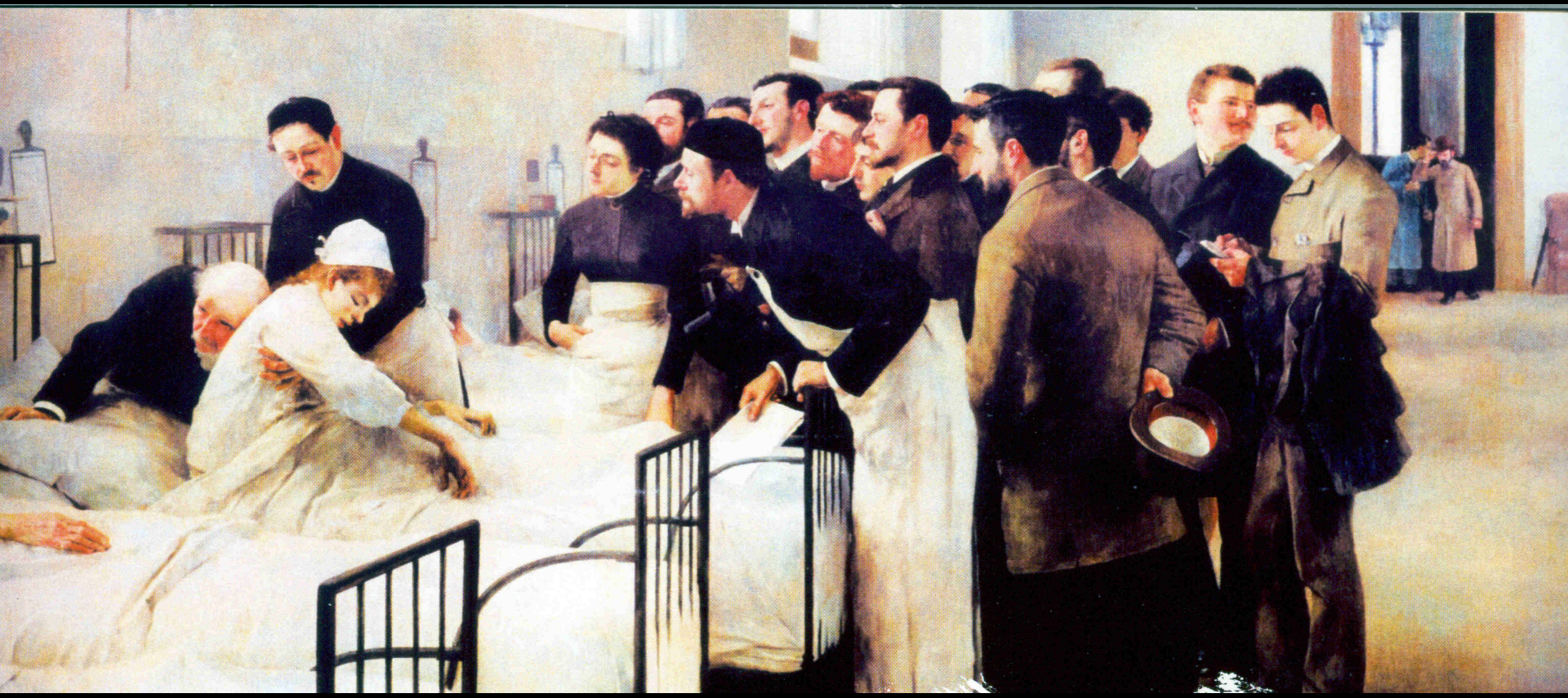
Bari,
7-10 novembre 2013

- L'associazione tra diabete e rischio neoplastico è stata osservata e sostanzialmente confermata
- Numerosi sono i fattori confondenti che rendono difficile identificare un chiaro rapporto di causa ed effetto
- L'asse insulina / IGF-1 sembra avere un ruolo: appare certo un effetto proliferativo, meno convincente l'effetto carcinogenetico

Conclusioni 2°

Bari,
7-10 novembre 2013

- Sono numerosi gli studi osservazionali e le metanalisi che attribuiscono alla terapia insulinica (in particolare agli analoghi) un effetto favorevole e alla metformina un effetto protettivo nei confronti del rischio di neoplasia.
- Molti di questi studi sono metodologicamente poco corretti
- Il maggior rischio attribuito all'insulina glargine sembra molto ridimensionato
- Sono necessari ulteriori studi RCT per potere avere una risposta definitiva (sono in corso numerosi trials per la metformina)



Vi ringrazio per l'attenzione