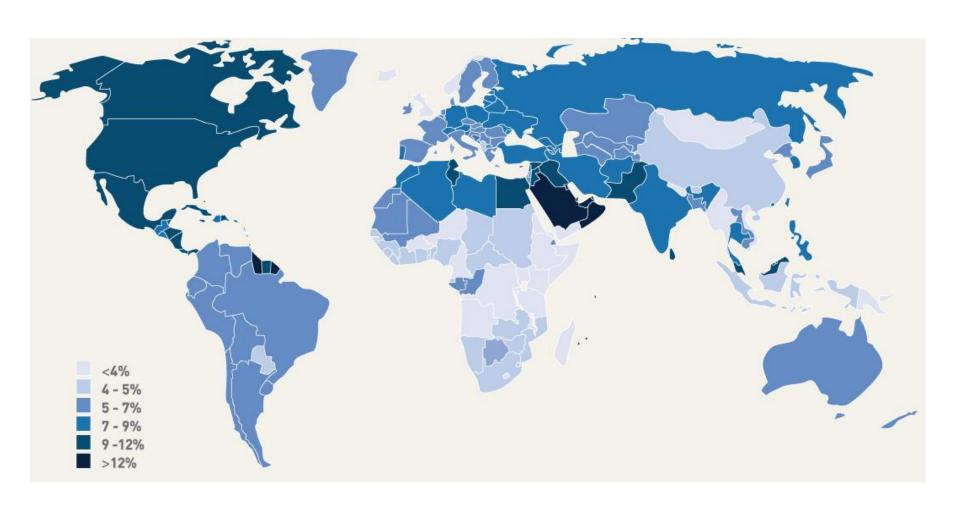
# Diabetes: a risk factor for cancer

Dr. Cesare Berra

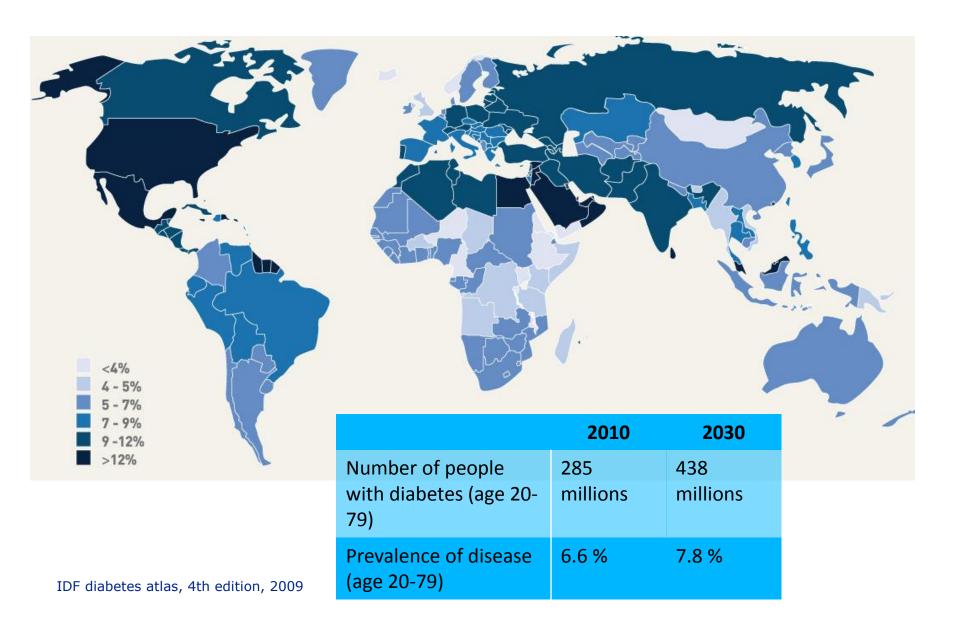
## Disclosure information:

No conflict of interests declared

### **Prevalence diabetes 2010**



### **Prevalence diabetes 2030**

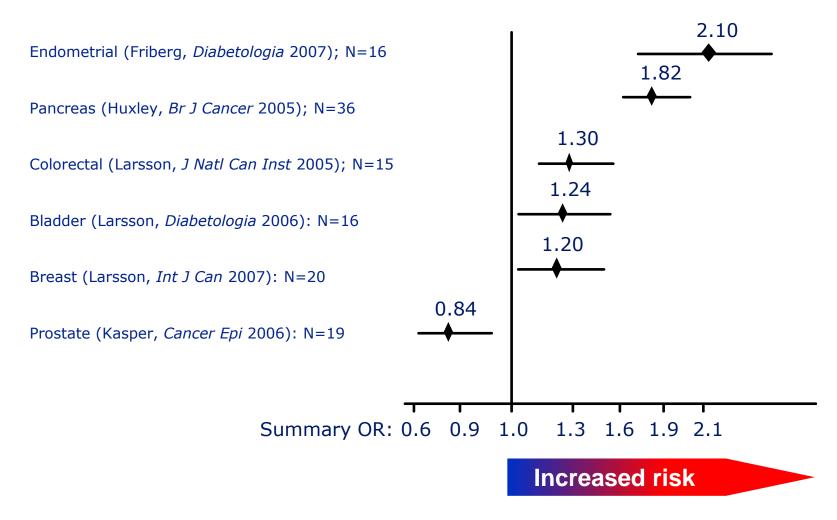


# Diabetes and cancer incidence: analysis from Tayside, Scotland

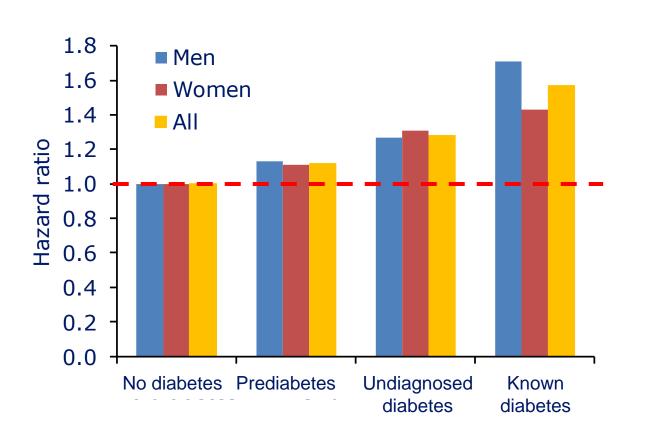
	Adjusted RR (95% CI)	Adjusted RR (95% CI) (excluding outcomes in first year)
Any malignant cancer C00-97	0.99 (0.90-1.09)	1.05 (0.93-1.18)
Pancreas C25	3.06 (1.73-5.39)	2.85 (1.27-6.43)
Liver C22	2.93 (1.40-6.14)	3.50 (1.38-8.91)
Oesophagus C15	1.70 (0.98-2.95)	1.74 (0.91-3.32)
Colon C18-19	1.46 (1.07-2.01)	1.56 (1.05-2.32)
Breast C50	1.05 (0.75-1.47)	1.05 (0.71-1.57)
Prostate C61	0.77 (0.54-1.09)	0.76 (0.50-1.17)

Codes after cancer type indicate diagnosis code in the ICD-10 diagnosis classification system

# Diabetes and cancer risk: meta-analyses of 2005–2007 studies



### **Diabetes and cancer mortality**



**Disease progression** 

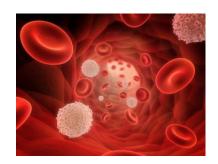
# Waist to hip ratio more strongly associated with risk of cancer than BMI

Body size measurement	Category	Pooled effect estimate (95% CI)	
ВМІ	Male (colon cancer)	1.59 (1.35–1.86)	
	Female (colon cancer)	1.22 (1.08-1.39)	
	Male (rectal cancer)	1.16 (0.93-1.54)	
	Female (rectal cancer)	1.23 (0.98-1.54)	
Waist circumference	Male (colon cancer)	1.68 (1.36-2.08)	
	Female (colon cancer)	1.48 (1.19-1.84)	
	Male (rectal cancer)	1.26(0.90-1.77)	
	Female (rectal cancer)	1.23 (0.81-1.86)	
Waist-to-hip ratio	Male (colon cancer)	1.91 (1.46-2.49)	
	Female (colon cancer)	1.49 (1.23-1.81)	
	Male (rectal cancer)	1.93 (1.19-3.13)	
	Female (rectal cancer)	1.20 (0.81-1.78)	

# What other factors could be contributing to the increased risk...?

Three hypotheses:

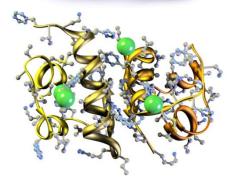
1. Chronic inflammation



2. Hyperglycaemia



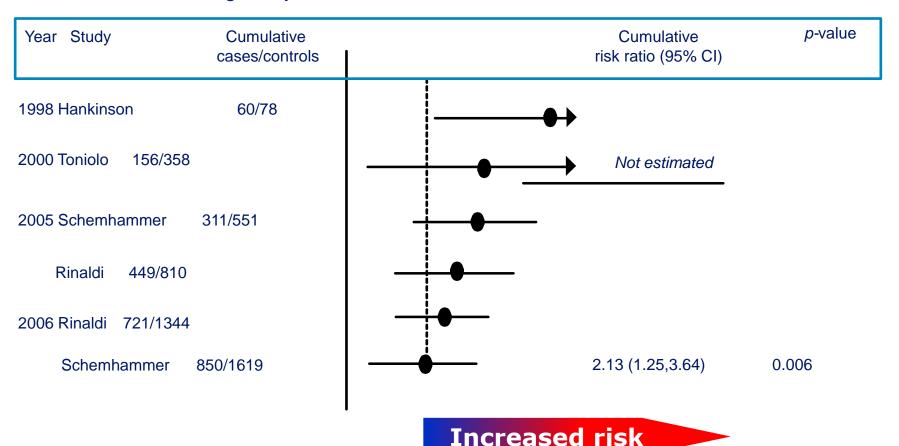
3. Insulin/IGF-1



# High circulating levels of IGF-1 associated with increased risk of breast cancer

#### **Associations with IGF-1**

Breast cancer under age 50 years



### Insulin receptor and IGF-1 receptor activation associated with poor breast cancer survival

#### Research Article

Phosphorylated Insulin-Like Growth Factor-I/Insulin Receptor Is Present in All Breast Cancer Subtypes and Is Related to Poor Survival

Jennifer H. Law, Golaren Habibi, Kaiji Hu, Hamid Masoudi, Michelle Y.C. Wang, Anna L. Stratford, Lugene Park, Julia M.W. Gee, Pauline Finlay, Helen E. Jones, Robert I. Nicholson, Joan Carboni, Marco Gottardis, Michael Pollak, and Sandra E. Dunn

"Laboratory for Orcegoromic Bossach, Department of Pudatries, Experimental Medicins, and Medical Guestics, Child and Family Research Institute, University of British Cokumbia, Vancourous British Cokumbia, Canada Fancous Contro for Carcer Research, Welsh Scholars, Canada Control Control Control Control Control Conference on Canada Myers Signife Oncodegy Drug Discovery, Princetors, by Jersey, and "Department of Orcelogic Loady Dates Research Institute of the Jessish General Hospital and McGill University, Montreal, Quebec, Canada

Drugs that target the insulin-like growth factor-I receptor (IGF-IR) and/or insulin receptor (IR) are currently under investigation for a variety of malignancies including breast cancer. Although we have previously reported that IGF-IR expression in primary breast tumors is common, the activation status of this receptor has not been examined in relation to survival. Phosphorylated IGF-IR/IR (P-IGF-IR/IR) and its downstream signaling partner phospho-S6 (P-S6) were evaluated immunohistochemically in tumor tissue microarrays representing 438 cases of invasive breast cancer. P-IGF-IR/IR (n = 114; P = 0.046) and total levels of IR (n = 122; P = 0.009)were indicative of poor survival, whereas total IGF-IR (n = 112; P = 0.304) was not. P-IGF-IR/IR and P-S6 were coordinately expressed in primary breast tumors (likelihood ratio, 11.57;  $P = 6.70 \times 10^{-4}$ ). Importantly, P-IGF-IR/IR was detected in all breast cancer subtypes (luminal, 48.1%; triple negative, 41.9%; and HER2, 64.3%). In vitro, the IGF-IR/IR inhibitor BMS-536924 decreased phospho-RSK and P-S6, and significantly suppressed the growth of breast cancer cell lines MCF-7, SUM149, and AU565 representing the luminal, triple negative, and HER2 subtypes, respectively, in monolayer and soft agar. BMS-536924 also inhibited growth in tamoxifen resistant MCF-7 Tam-R cells while having little effect on immortalized normal breast epithelial cells. Thus, we can determine which patients have the activated receptor and provide evidence that P-IGF-IR/IR is a prognostic factor for breast cancer. Beyond this, P-IGF-IR/IR could be a predictive marker for response to IGF-IR and/or IR-targeted therapies, as these inhibitors may be of benefit in all breast cancer subtypes including those with acquired resistance to tamoxifen. [Cancer Res 2008;68(24):10238-46]

The insulin-like growth factor-I receptor (IGF-IR) has become an attractive molecular target for cancer treatment given as it is

Note: Supplementary data for this article are available at Cancer Research Online

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expressed in a wide range of tumors including those that arise in the breast. Several studies indicate that IGF-IR activation is associated with the growth, invasion, and metastasis of breast cancer (1) and where estrogen receptor (ER) is present, also interplays with this steroid hormone receptor to promote growth (2). The expression of constitutively active IGF-IR in the mammary gland leads to the development of tumors (3) while overexpression of a constitutively activated IGF-IR (CD8-IGF-IR) is sufficient to cause transformation of immortalized human mammary epithelial cells and growth in immunocompromised mice (4). Conversely, silencing IGF-IR with small molecules inhibits the growth of mammary cells (IGF-IR-Sal) expressing constitutively activated IGF-IR in a xenograft model (3). As well, IGF-IR neutralizing antibodies suppress the growth of breast cancer cells implanted as xenografts (5). Furthermore, transgenic mice that express activated IGF-IR in the mammary gland under a doxycycline inducible promoter developed tumors at 2 months of age (6). Thus IGF-IR signaling is important for the development of breast tumors and cancers continue to depend upon this pathway for sustained growth and survival.

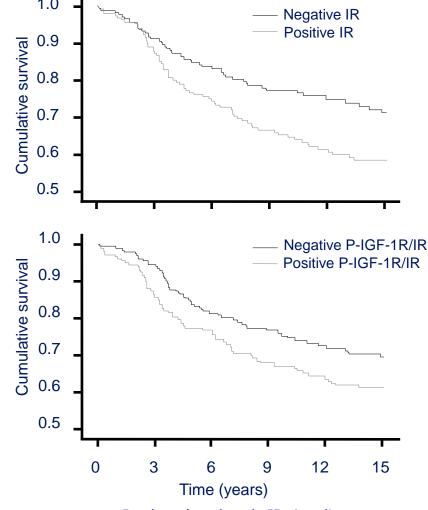
Given the importance of IGF-IR in tumor growth, it has become an attractive molecular target for therapy and small molecules as well as antibodies are being developed to inhibit this pathway (7-10). Although most of them are directed against IGF-IR, some also inhibit insulin receptors (IR), which could be additionally beneficial given that IGF-IR and IR form heterodimers (11, 12) and that the IR itself has been shown to be important in cancers (13). For example, two recent dual specificity inhibitors, BMS-554417 and BMS-536924, were found to target both the IGF-IR and IR and were active in vivo (4, 14, 15). Although these compounds can lead to hyperglycemia, there is recent preclinical evidence that this adverse effect can be attenuated by the use of metformin.5

The IGF-IR pathway is also implicated in resistance to targeted therapies including those that target the ER and the epidermal growth factor receptor (EGFR) family members EGFR and HER2. For example, IGF-IR is reportedly up-regulated during the acquisition of tamoxifen resistance. The continuous exposure of MCF-7 cells to tamoxifen resulted in the eventual emergence of resistant cells, called MCF-7 Tam-R, which use IGF-IR for their growth (16, 17). Activation of the IGF-IR signaling cascade has also been reported in models of resistance to agents that target

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<sup>6</sup>J. Carboni, unpublished data

Cancer Res 2008; 68: (24). December 15, 2008



#### ARTICLE

# 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

R. Ruiter · L. E. Visser · M. P. P. van Herk-Sukel · J. W. W. Coebergh · H. R. Haak · P. H. Geelhoed-Duijvestijn · S. M. J. M. Straus · R. M. C. Herings · B. H. Ch. Stricker

Received: 23 May 2011 / Accepted: 19 August 2011 / Published online: 29 September 2011 © The Author(s) 2011. This article is published with open access at Springerlink.com

Conclusion/interpretation Users of insulin glargine and users of other insulin analogues had a lower risk of cancer in general than those using human insulin. Both associations might be a consequence of residual confounding, lack of adherence or competing risk. However, as in previous studies, we demonstrated an increased risk of breast cancer in users of insulin glargine in comparison with users of human insulin.

# RESEARCH

# Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis

Isabelle N. Colmers BScH, Samantha L. Bowker PhD, Sumit R. Majumdar MD, Jeffrey A. Johnson PhD

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Interpretation: The limited evidence available supports the hypothesis that thiazolidine-diones, particularly pioglitazone, are associated with an increased risk of bladder cancer among adults with type 2 diabetes.

Open Access Research



## Risk of cancer in patients using glucoselowering agents: a nationwide cohort study of 3.6 million people

Charlotte Andersson, Allan Vaag, Christian Selmer, Michelle Schmiegelow, Rikke Sørensen, Jesper Lindhardsen, Gunnar H Gislason, Lars Køber, Christian Torp-Pedersen, Christian Torp-Pedersen,

**Conclusions:** Use of most glucose-lowering agents including sulfonylureas was associated with a comparable increased risk of cancer shortly after initiation of treatment and subsequently a decline to the risk of the background population. This suggests that the relation is not causal.

## Target of treatment in T2D

Organizzazioni	HbA <sub>1c</sub> (%)	FPG (mmol/L)	PPG (mmol/L)	
ADA-EASD <sup>1</sup>	<7	_	_	
IDF-Europe <sup>2</sup>	<6.5	<6.0 (<110*)	<8.0 (<140*)	
AACE <sup>3</sup>	≤6.5	<6.1 (<110*)	<7.8 (<140*)	
NICE <sup>4</sup>	<6.5**	_	<8.5 (<153*)	
DDG <sup>5</sup>	<6.5	_	_	

<sup>\*</sup>mg/dL

FPG: fasting plasma glucose; PPG: postprandial glucose; ADA: American Diabetes Association; IDF: International Diabetes Federation; AACE: American Association of Clinical Endocrinologists; NICE: National Institute of Clinical Excellence;

DDG: Deutschen Diabetes-Gesellschaft (German Diabetes Association)

- 1. Nathan DM, et al. Diabetologia. 2009;52:17-30.
- 2. IDF. Global Guidelines 2005.
- 3. Rodbard HW, et al. Endocr Pract. 2007;13(Suppl. 1):1-68.
- 4. NICE clinical guideline 87. Quick reference guide. May 2009.
- 5. Matthaei S, et al. German Diabetes Association guidelines. October 2008.

<sup>\*\* &</sup>lt; 7.5% for people receiving ≥2 oral glucose-lowering drugs or those requiring insulin

### **Personalized Therapy**

Skyler J, et al. Diabetes Care 2009;32:187

### A1c <7.0%

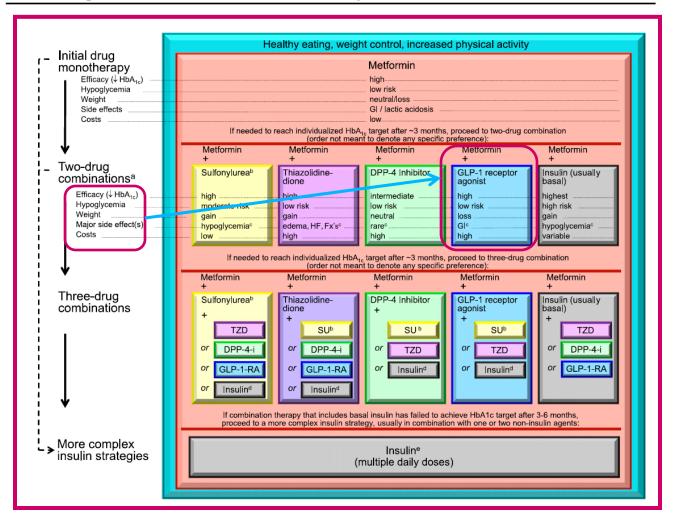
- Short duration of diabetes
- Long life expectancy
- No significant cardiovascular disease

### A1c > 7.0%

- History of severe hypoglycemia
- Limited life expectancy
- Long-standing diabetes
- Advanced micro- and macrovascular complications

# Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



# Treating diabetic patients with chemotherapy: single centre experience of toxicity and outcomes Final publication number 1549PD Seligmann J et al.

#### **Background**

- 1:8 people aged 60-79 in the UK are diabetic
- They have an increased risk of
  - Infection
  - Hospital admission and in-hospital mortality
  - Several solid organ cancers
  - Complications following surgery and adjuvant chemotherapy for solid organ cancers
- Limited data exists about the experience of diabetic patients with palliative chemotherapy

### **Methods and results**

- A retrospective cohort study comparing diabetic patients with age, treatment and disease matched non-diabetic controls during the first 18 weeks of chemotherapy
- Population: 292 patients with advanced colorectal or gynaecological cancer

Outcome	OR	95% CI	p-value
Acute admission	3.32	1.8-5.8	<0.0001
Early stopping	2.17	1.25-3.85	0.008
of chemotherapy			
Reduced use of	0.56	0.34-0.95	0.03
2 <sup>nd</sup> line treatment			

### **Results and conclusions**

#### Other important results

- Common causes for diabetic patient admissions
  - infection (41%), poor glycaemic control (17%)
- Independent prognostic factors
  - primary site, performance status, age

#### **Conclusions**

- Diabetic patients experience more acute complications on chemotherapy possibly limiting further treatment options
- A prospective study would clarify the contributing factors and inform management of diabetic patients with cancer

### **Comments**

How may influence this outcomes the metabolic balance (levels of HbA1c)?

The age and/or the presence of compliations of diabetes could be important?

use of steroids and the percentage of diabetes induced by: an open problem.

### Thank you for your attention

Dr. Cesare Berra