Bendix Carstensen

Steno Diabetes Center Gentofte, Denmark http://BendixCarstensen.com

3rd Update: Diabetes and Cardiovascular Disease

http://BendixCarstensen.com/3rdUpdate

Roma, April 2012

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 - cancer survival studies
- Combination (ignoring the cancer diagnosis): Do diabetes patients die more frequently from cancer than non-diabetics?
 - cancer mortality studies

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So, no trials exist or will be done

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- What I show is therefore a description of cancer occurrence in (various groups of) diabetes patients.
- Causal interpretations are purely speculation.

Cancer mortality & treatment

Bowker et al. [1] found for cancer mortality:

	Patients	Deaths	RR	95% c.i.
Oral antidiabetica:				
Metformin Sulfonylurea	6,969 3,340	245 162		(ref) (1.1–1.6)
Insulin use:				
No insulin use Insulin use	8,866 1,443	323 84	1.0 1.9	(ref) (1.5–2.4)

This general pattern is repeatedly reported since then.

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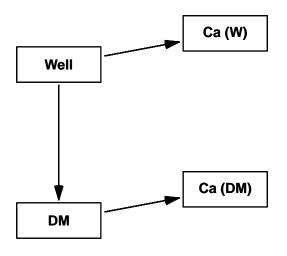
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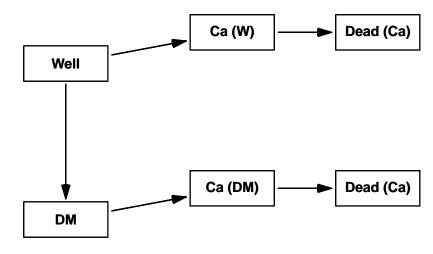
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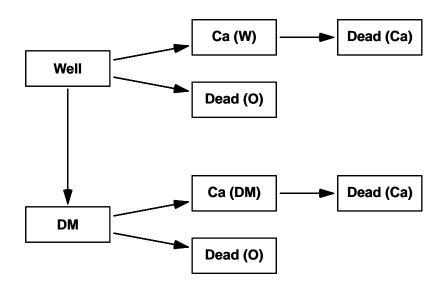
There is biological reason to suspect insulin/analogs for a role in cancer promotion.

But evidence is weak and data are limited.

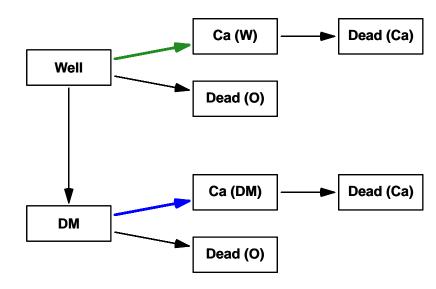




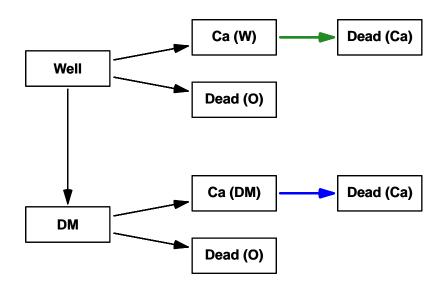




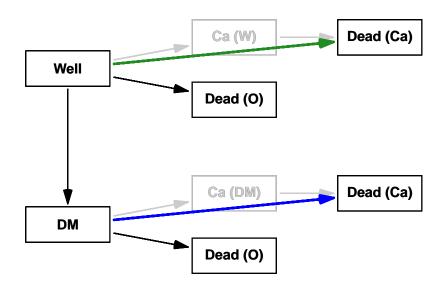
Cancer incidence



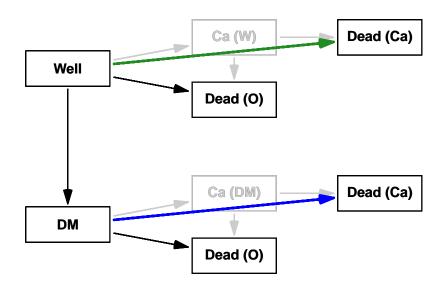
Cancer survival



Cancer mortality



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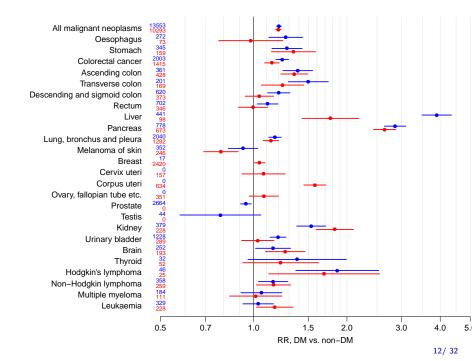


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- Results broadly confirm previous findings [7, 8]



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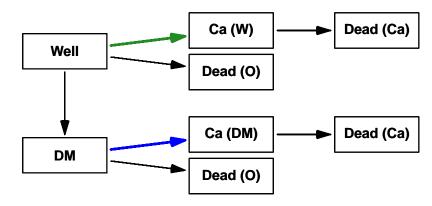
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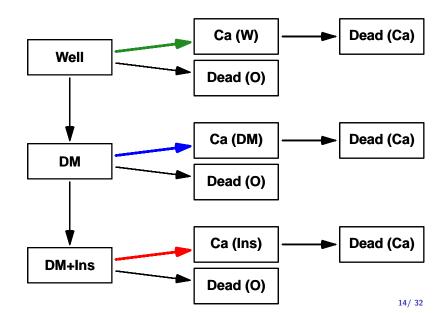
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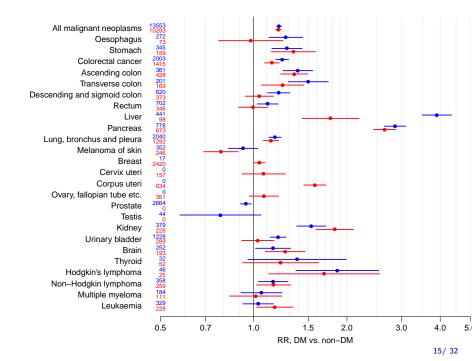
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- ▶ Brain, lymphomas: RR = 1.2

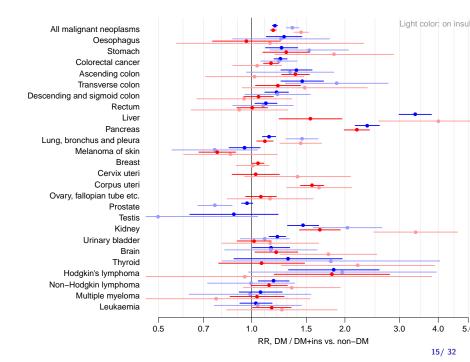
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Questions on incidence

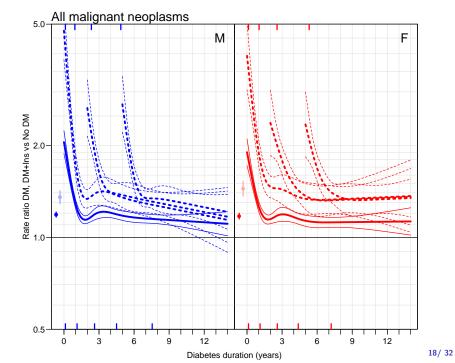
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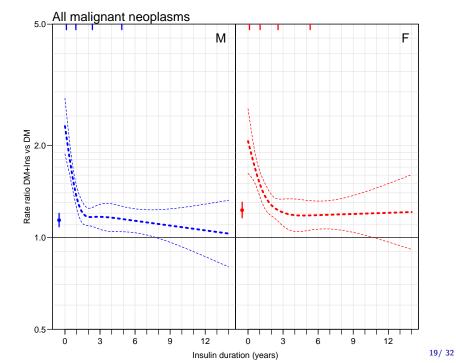
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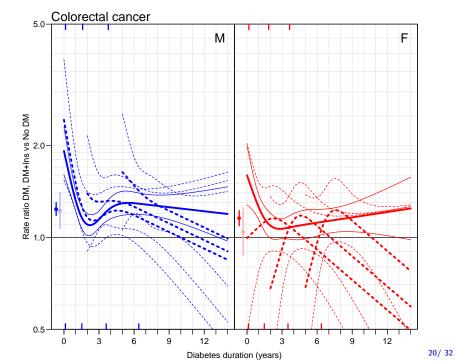
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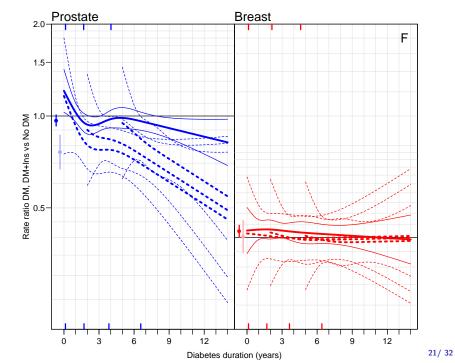
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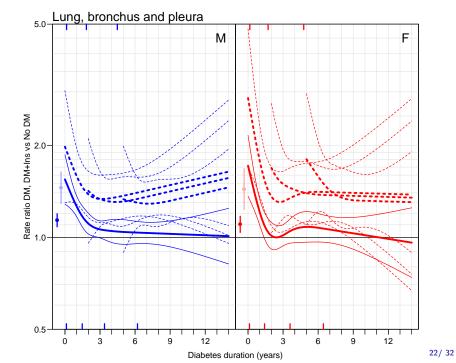
- ▶ Does cancer incidence vary with diabetes duration?
- Does cancer incidence vary with duration of insulin use?
- What is the cumulative risk of cancer?











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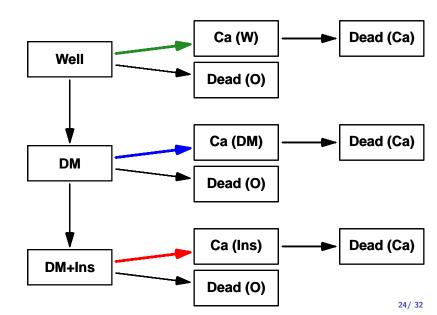
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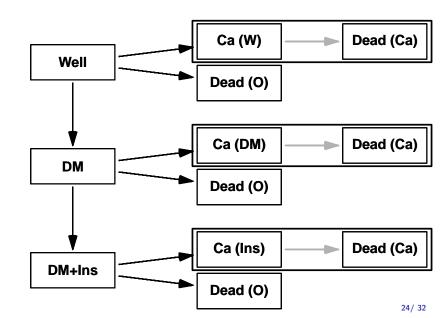
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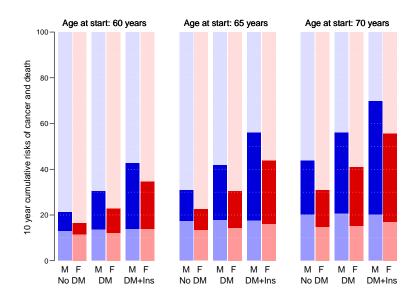
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- NOTE: this also involves the mortality rates!







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- Smaller incidence rates for prostate, more so by time.

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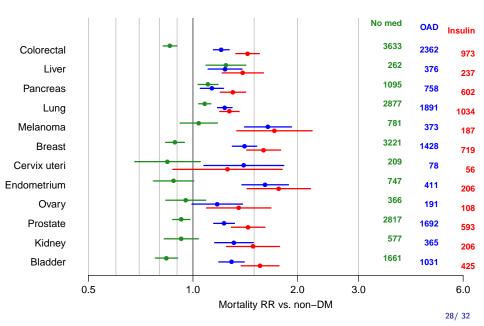
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- Mortality rate-ratio relative to the non-diabetic cancer patients

Mortality of (all) Danish cancer ptt:



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 - Metformin: Inhibition of tumour growth
 - Insulin: Promotion of tumour growth

- ▶ Diabetes patients have overall 20% higher rates of cancer
- Varies dramatically by duration highest in the beginning
- ▶ Long-term excess is 10% for ptt. not on insulin
- ▶ Long-term excess is 30% for ptt. on insulin
- Overall analyses suggest that patients on Metformin relative to SU have lower:
 - Cancer rates
 - Mortality rates

References



S.L Bowker, S.R. Majumdar, P. Veugelers, and J.A Johnson.

Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin.

Diabetes Care 29:254-258, 2006, 29:254-258, 2006.



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

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

Diabetologia, 52:1732-1744, Sep 2009.



J. M. Jonasson, R. Ljung, M. Talbäck, B. Haglund, S. Gudbjörnsdóttir, and G. Steineck.

Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden.

Diabetologia, 52:1745-1754, Sep 2009.



H. M. Colhoun and the SDRN Epidemiology Group.

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

Diabetologia, 52:1755-1765, Sep 2009.



C. J. Currie, C. D. Poole, and E. A. Gale.
The influence of glucose-lowering therapies on cancer risk in type 2 diabetes.

Diabetologia. 52:1766–1777. Sep 2009.



U. Smith and E. A. Gale.

Does diabetes therapy influence the risk of cancer? Diabetologia, 52:1699–1708, Sep 2009.



H. O. Adami, J. McLaughlin, A. Ekbom, C. Berne, D. Silverman, D. Hacker, and I. Persson.

Cancer risk in patients with diabetes mellitus.

Cancer Causes Control. 2:307–314. Sep 1991.



L. Wideroff, G. Gridley, L. Mellemkjær, W. H. Chow, M. Linet, S. Keehn, K. Borch-Johnsen, and J. H. Olsen.

Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark.

J. Natl. Cancer Inst., 89:1360-1365, Sep 1997.



B. Carstensen, D. R. Witte, and S. Friis.

Cancer occurrence in Danish diabetic patients: duration and insulin effects. *Diabetologia*, 55(4):948–958, Apr 2012.