Cancer in diabetes patients: Basing a wrong conclusion on a wrong or on a correct analyses.

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Diabetes and Cancer

Persons with diabetes have long been known to have increased incidence rates and mortality rates from cancer [1, 2, 3]:

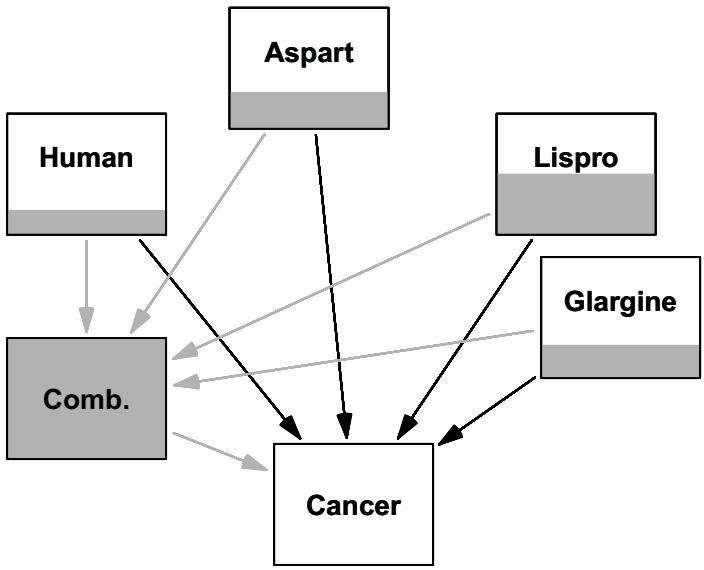
- Pancreas
- Liver
- Colon / Rectum
- Corpus uteri
- Lung
- Kidney
- ...

Diabetologia, September 2009:

- **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, and P. T. Sawicki, Diabetologia, 52:1732–1744, Sep 2009.
- **Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden.** J. M. Jonasson, R. Ljung, M. Talbäck, B. Haglund, S. Gudbjörnsdottir, and G. Steineck, Diabetologia, 52:1745–1754, Sep 2009.
- **Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group.** H. M. Colhoun and the SDRN Epidemiology Group, Diabetologia, 52:1755–1765, Sep 2009.
- **The influence of glucose-lowering therapies on cancer risk in type 2 diabetes.** C. J. Currie, C. D. Poole, and E. A. Gale, Diabetologia, 52:1766–1777, Sep 2009.
- **Does diabetes therapy influence the risk of cancer?** U. Smith and E. A. Gale, Diabetologia, 52:1699–1708, Sep 2009.

Hemkens et al. [4]

- Data: Insurance database from Germany
- Entry: Newly started treatment for DM
- Exposure:
  Monotherapy (4 classes) throughout follow-up
  - Initial dose
  - Cumulative dose over the entire follow-up
- Outcome: All cancers
- Model: Cox (time since treatment start?)

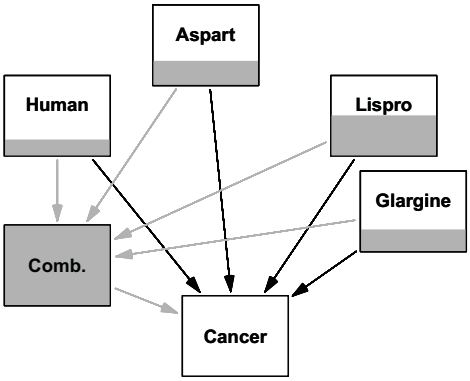


Problems (Hemkens et al.

- Assumes that those who go on to combination therapy are irrelevant, *i.e.* all effects are *instantaneous*.
- The time on monotherapy *before* combination therapy is discarded:

  > *We defined four study groups according to the treatment received: human insulin, aspart, lispro and glargine. Eligible participants were those exposed to only one of these agents during follow-up.*

- . . . thus all cancer rates are too small
- . . . and not necessarily with the same amount
- Conditioning on the future



The gray part of the follow-up time is discarded based on knowledge of the future exit from the groups.

Currie et al. [5]

- Data: THIN database
  (clinical records from GPs)
- "Cohort" of OAD initiators.
- Time-varying exposure,
  i.e. follow-up classified by *current* (maximal?) treatment:
  - Metformin
  - SU
  - Met+SU
  - Insulins: Human basal / Human biphasic / Glargine / other Analog

Currie et al. [5]

- Model: Cox (time since treatment start)
- Persons censored at therapy change:

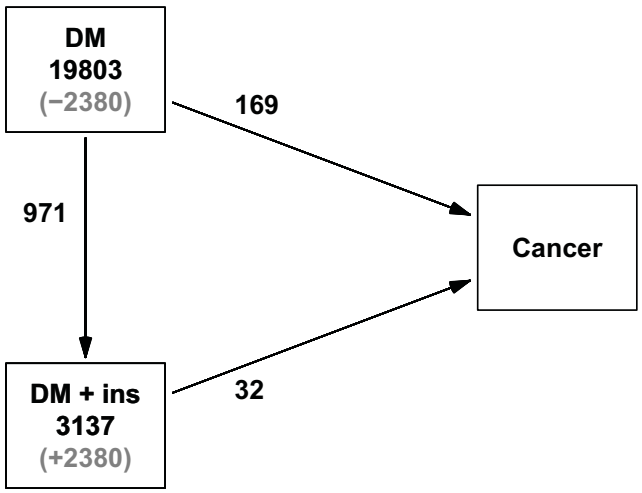
  Cohort membership was terminated by progression to a record of the primary or secondary outcomes of interest, right censoring at the final observation of the database, transfer out of the practice, or treatment switching.

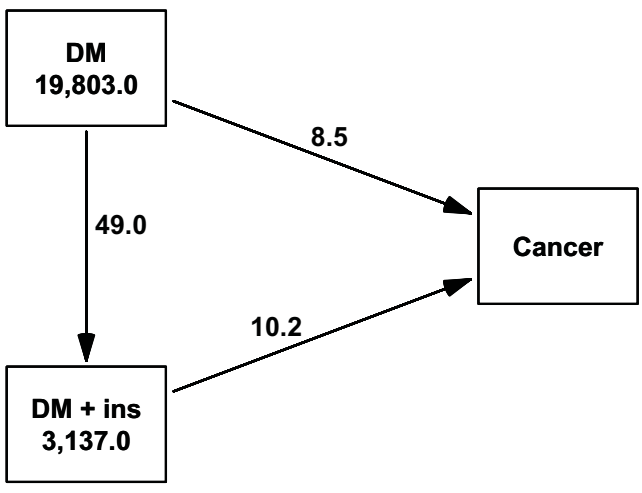
- Censoring is **not** independent of the disease outcome

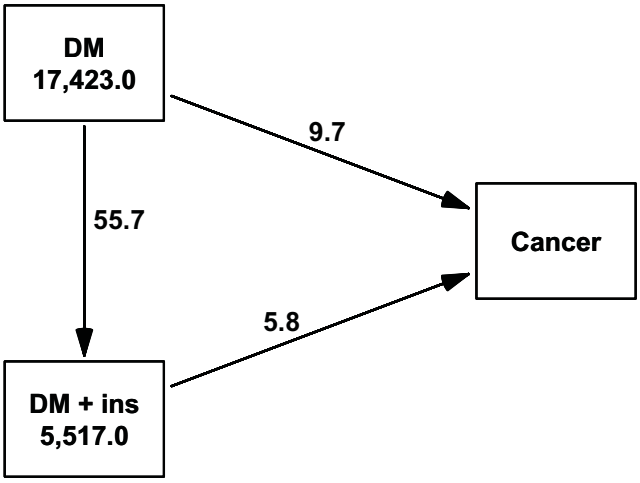
Yang et.al [6]

Associations of Hyperglycemia and Insulin Usage With the Risk of Cancer in Type 2 Diabetes: The Hong Kong Diabetes Registry.
Yang *et al:* Diabetes, vol. 59, May 2010, pp. 1254 ff.

- Data: DM register of Hong Kong
- Cohort based on any exposure in entire follow-period.
- Additional matching of insulin users to non-users.
- Insulin vs. non-insulin: $\mathrm{RR} = 0.18$!
- Strong bias because of mis-allocation and exclusion of risk time.
- Immortal time bias





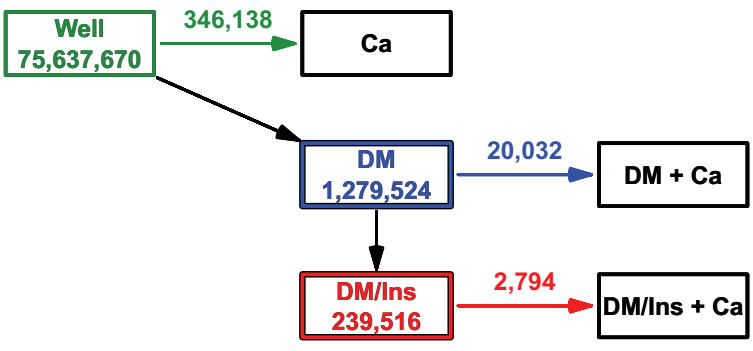


Danish study [7]

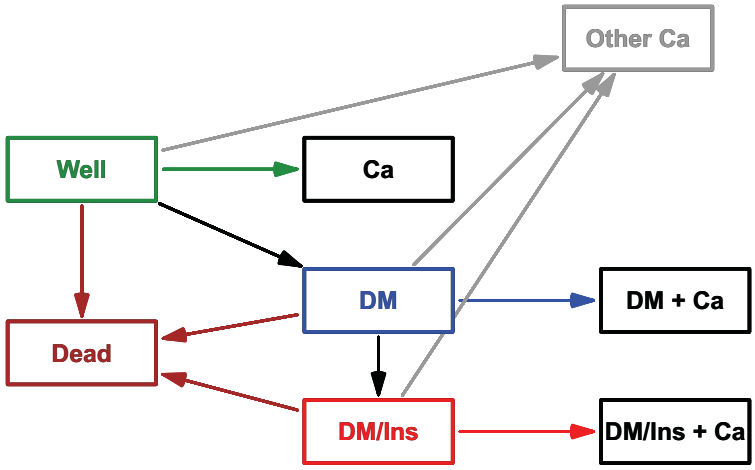
Cancer occurrence in Danish diabetic patients: duration and insulin effects. B. Carstensen, D. R. Witte, and S. Friis. Diabetologia, e-pub ahead of print, Nov 2011.

- Describe cancer incidence rates among diabetes patients in Denmark.
- and how rates vary relative to the non-DM population with:
  - duration of diabetes
  - duration of insulin use
- for all types of cancer
- and for specific sites of cancer

Follow-up of the Danish population



Follow-up of the Danish population



Follow-up in the population

Persons are followed 1 Jan 1995 to:

event: first primary cancer of a given type

censoring:
- diagnosis of any other primary cancer
- death
- 31 Dec 2009

Tabulation & analysis

Follow-up time (person-years) and events (cancer diagnosis) were classified by:

- sex
- current age in 1-year classes
- current date in 1-year classes
- date of birth in 1-year classes
- state of follow-up: Well / DM / DM/Ins
- duration of DM in 6 month classes
- duration of insulin use in 6 month classes

Poisson analysis using class midpoints as continuous variables.

How the data looks — events

	Diabetes duration			Insulin duration		
	Well	DM	DM/Ins	Well	DM	DM/Ins
0	319088	4331	255	319088	17927	781
1	0	2703	196	0	0	407
2	0	2322	222	0	0	329
3	0	1917	238	0	0	248
4	0	1714	210	0	0	181
5	0	1356	211	0	0	133
6	0	1023	216	0	0	132
7	0	828	231	0	0	85
8	0	633	169	0	0	61
9	0	479	180	0	0	46
10	0	297	131	0	0	22
11	0	194	120	0	0	17
12	0	100	62	0	0	11
13	0	30	15	0	0	3
Sum	319088	17927	2456	319088	17927	2456

Model for cancer incidence rates

$$\begin{aligned}\text{rate} = & f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\ & \times t(\text{DM-duration}) \\ & \times s(\text{Ins-duration})\end{aligned}$$

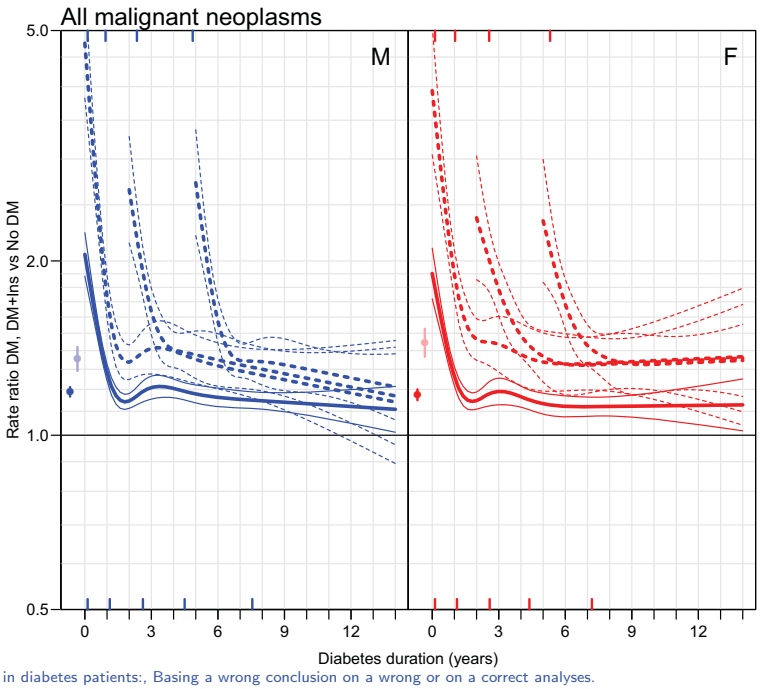
Functions t and s give the **combined** effects of:

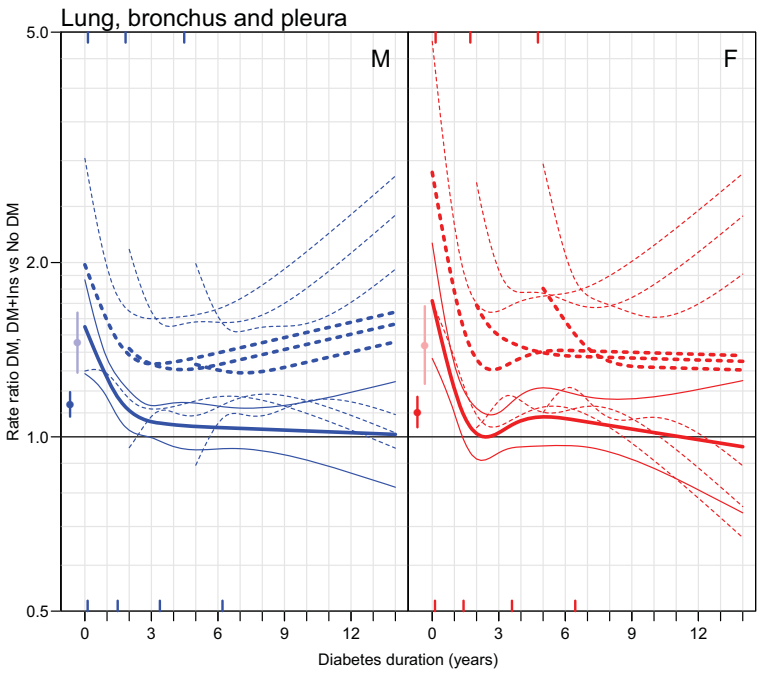
- duration / cumulative dose
  (slowly increasing/decreasing from time 0)
- allocation (jump at time 0) & common risk factors
  (confounding by indication)

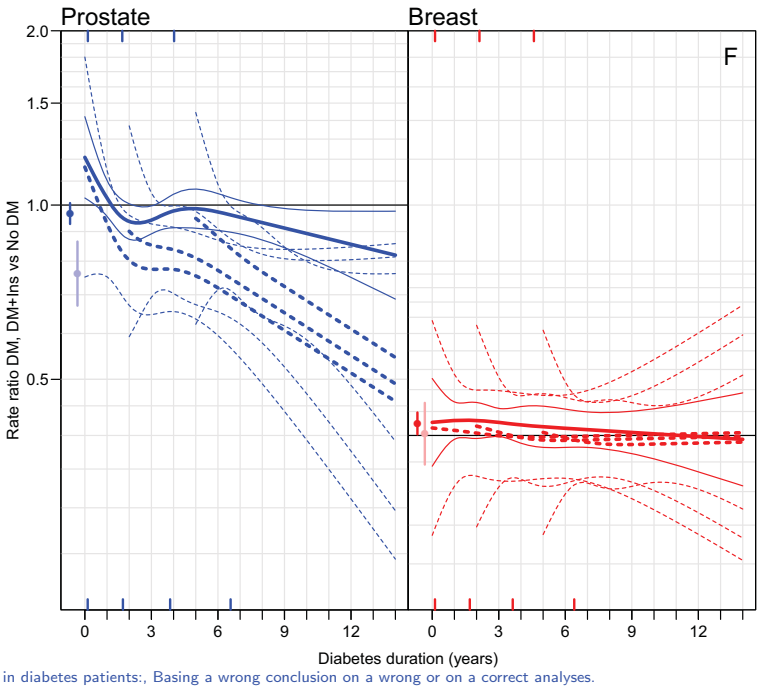
There is **no way** to separate these two effects.

Modelling in R

```
m1 <- glm( D ~ Ns(ax,knots=a.kn) +
               detrend( Ns(px,knots=p.kn), px ) +
               Ns(cx,knots=c.kn) +
               state +
               Ns( DMDur,knots=d.kn) +
               Ns(InsDur,knots=d.kn) +
               offset( log(y) ),
               family = poisson,
               data = subset(data,sex==sx) )
```


All malignant neoplasms
M
F
Rate ratio DM, DM+Ins vs No DM
5.0
2.0
1.0
0.5
0
3
6
9
12
Diabetes duration (years)


Lung, bronchus and pleura
M
F
Rate ratio DM, DM+Ins vs No DM
5.0
2.0
1.0
0.5
0
3
6
9
12
Diabetes duration (years)


Prostate
Breast
F
Rate ratio DM, DM+Ins vs No DM
2.0
1.5
1.0
0.5
0
3
6
9
12
Diabetes duration (years)

Interpretation

Findings are consistent with:

- Common risk factors for DM and cancer (obesity, lack of physical exc., eating habits . . .)
- More intense surveillance for cancer following DM diagnosis
- Reverse causation: Undiagnosed cancers lead to DM diagnosis
- Effect of insulin in either direction:
  A cumulative effect of insulin increasing cancer risk cannot be excluded even if RR decrease by insulin duration for most cancer sites — there is a strong mortality selection.

Methodological points for FU-studies

- Follow all persons till death or exit from study — never censor persons due to status change, model effect of the status change.
- Only classify follow-up (risk time, events) by currently known features:
  Do not condition on the future.
- Multiple time scales necessary (age, calendar time, duration)

Morale:

- Always draw *all* your boxes.
- Define what they mean.
- When do persons enter.
- When do they exit:
  - as events
  - as censorings (is this independent of the event process?)
- What is counted as events; what is not.

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Diabetologia, Nov 2011.

The epidemic of matching

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Avoid confounding

Confounding of the

- exposure effect on
- the outcome

arises when:

- the confounder is associated with the exposure
- the confounder is associated with the outcome

Sometimes the former can be fixed, but rarely the latter

Avoid confounding

How do you fix the association between a confounder, such as

- age at diagnosis, exposure, ...
- sex

and the exposure, such as:

- IUD
- congenital malformation
- childhood cancer

...you make sure that the confounder distribution is the same among exposed and non-exposed!

$\Rightarrow$ Match your cohort study.

Avoid confounding

What if you cannot fix the confounder distribution?

- Control for the confounder
- Include it in a model

which will allow you to

- Model the exposure effect
- Test for interaction
- ...

Avoid the "clinical trial" thinking

When you match the control group it is no more representative for the un-exposed.

Analyses based only on the control group are meaningless, such as a Kaplan-Meier curve...

...only comparisons are relevant.

The precision of the estimates from the control group is smaller that it would have been if you had taken the entire group

Don't think it's a clinical trial

Instead of

Match, Waste, Compare

you should

Use all, Analyze, Report!