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
- ...

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

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]


- 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: RR = 0.18!
- Strong bias because of mis-allocation and exclusion of risk time.
- Immortal time bias

Danish study [7]


- 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 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
t▶ 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
- 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

<table>
<thead>
<tr>
<th>Diabetes duration</th>
<th>Insulin duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well DM</td>
<td>DM/Ins</td>
</tr>
<tr>
<td>0</td>
<td>319088</td>
</tr>
<tr>
<td>1</td>
<td>2703</td>
</tr>
<tr>
<td>2</td>
<td>2703</td>
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<td>3</td>
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</tr>
<tr>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>Sum</td>
<td>319088</td>
</tr>
</tbody>
</table>

Model for cancer incidence rates

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

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.
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.

References

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
▶ ...