Diabetes and Cancer

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▸ Do diabetes patients get cancer more often than non-diabetics?
  — cancer incidence studies

▸ Do cancer patients with diabetes die earlier than cancer patients without diabetes?
  — 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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Diabetes and Cancer problems

How does incidence/survival/mortality depend on disease and treatment?
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- You cannot randomize people to
  - Diabetes
  - OAD
  - Insulin
  - ...
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  - confined to an extreme high-risk group
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So, no trials exist or will be done
Diabetes and Cancer problems

How does incidence/survival/mortality depend on disease and treatment?

▶ All studies are observational
▶ All studies are subject to confounding by indication
▶ There is no remedy for this
▶ What I show is therefore a description of cancer occurrence in (various groups of) diabetes patients.
▶ Causal interpretations are purely speculation.
Diabetes and Cancer problems

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Cancer mortality & treatment

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

|                               | Patients | Deaths | RR  | 95% c.i.    |
|-------------------------------|----------|--------|-----|-------------|
| Oral antidiabetica:           |          |        |     |             |
| Metformin                     | 6,969    | 245    | 1.0 | (ref)       |
| Sulfonylurea                  | 3,340    | 162    | 1.3 | (1.1–1.6)   |
| Insulin use:                  |          |        |     |             |
| No insulin use                | 8,866    | 323    | 1.0 | (ref)       |
| Insulin use                   | 1,443    | 84     | 1.9 | (1.5–2.4)   |

This general pattern is repeatedly reported since then.
The (not so) recent scare

- Diabetologia published 4 papers and an editorial in the summer 2009, pointing (weakly) to a possible promoting effect of Glargine, an insulin analog from Sanofi-Avensis. [2, 3, 4, 5, 6].
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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.
Graphical overview
Graphical overview

Well

DM

Ca (W)

Ca (DM)
Graphical overview

Well

DM

Ca (W) → Dead (Ca)

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Graphical overview

Well

DM

Ca (W)
Dead (O)
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Ca (DM)
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Cancer incidence

Well

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DM

Ca (DM)

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Well

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DM

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Cancer survival

Well

DM

Ca (W) Dead (Ca)
Dead (O)
Ca (DM) Dead (Ca)
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Dead (Ca)
Cancer mortality

Well

DM

Dead (O)

Ca (W)

Dead (Ca)

Ca (DM)

Dead (Ca)

Dead (O)
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Well

DM

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Dead (Ca)

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The Danish study

- Cancer incidence study in the total population.
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- Outcome: Rate-ratio of cancer occurrence between DM-paitiens and non-DM persons in the entire population
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- Comparing diabetes patients with non-diabetes patients.
- Outcome: Rate-ratio of cancer occurrence between DM-patients and non-DM persons in the entire population.
- Results broadly confirm previous findings [7, 8]
All malignant neoplasms
Oesophagus
Stomach
Colorectal cancer
Ascending colon
Transverse colon
Descending and sigmoid colon
Rectum
Liver
Pancreas
Lung, bronchus and pleura
Melanoma of skin
Breast
Cervix uteri
Corpus uteri
Ovary, fallopian tube etc.
Prostate
Testis
Kidney
Urinary bladder
Brain
Thyroid
Hodgkin's lymphoma
Non–Hodgkin lymphoma
Multiple myeloma
Leukaemia

RR, DM vs. non–DM

0.5 0.7 1.0 1.5 2.0 3.0 4.0 5.0

13553
10293
272
73
345
159
2003
1415
361
428
201
169
620
373
702
441
778
673
2040
1292
352
246
17
2420
240
157
0
634
0
351
2664
44
0
379
228
1228
289
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The Danish study — overall

- All cancers: $RR = 1.2$

- Digestive system: $RR \approx 1.2$, varying between sites

- Liver: $RR_{Men} = 4$, $RR_{Women} = 1.8$

- Pancreas: $RR = 2.8$

- Lung: $RR = 1.15$

- Endometrium: $RR = 1.6$

- Kidney: $RR = 1.7$

- Bladder: $RR_{Men} = 1.2$, $RR_{Women} = 1.0$

- Prostate: $RR = 0.95$

- Brain, lymphomas: $RR = 1.2$
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How the Danish study really was

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Ca (W)
Dead (O)

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  - Non-ins user long term RR: 1.1
  - Insulin user long term RR: 1.3
Questions on incidence

- Does cancer incidence vary with diabetes duration?
Questions on incidence

- Does cancer incidence vary with diabetes duration?
- Does cancer incidence vary with duration of insulin use?
Questions on incidence

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

Rate ratio DM+Ins vs DM

Insulin duration (years)

M F
Cumulative risk of cancer

This is asking the question(s):

- What fraction of patients will have a cancer diagnosis within the next $X$ years?
Cumulative risk of cancer

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- What fraction of patients will have a cancer diagnosis within the next $X$ years?
- Take into account that patients die too

NOTE: this also involves the mortality rates!
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DM

DM+Ins

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Dead (O)

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Cumulative risk of cancer

Well
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DM
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Dead (O)
DM+Ins
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Dead (O)
Cumulative risk of cancer

Age at start: 60 years
Age at start: 65 years
Age at start: 70 years

10 year cumulative risks of cancer and death

Age at start: 60 years
Age at start: 65 years
Age at start: 70 years
Conclusion

1. Detection “bias”
Conclusion

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2. ⇒ overall effects on incidence must evaluated in the long term
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4. Insulin treated generally higher than non-insulin treated.
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5. Lung cancer elevated only for insulin treated.
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5. Lung cancer elevated only for insulin treated.
6. No signal for breast cancer
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4. Insulin treated generally higher than non-insulin treated.
5. Lung cancer elevated only for insulin treated.
6. No signal for breast cancer
7. Smaller incidence rates for prostate, more so by time.
Coarse survival study of Danish cancer pt.:  

- Subdivide all newly diagnosed cancer patients (1995–2009) by diabetes status at date of cancer diagnosis:
Coarse survival study of Danish cancer pts:

- Subdivide all newly diagnosed cancer patients (1995–2009) by diabetes status at date of cancer diagnosis:
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Mortality rate-ratio relative to the non-diabetic cancer patients 27/ 32
Coarse survival study of Danish cancer patients:

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  - Diabetes, treated with medication other than insulin
  - Diabetes, treated with insulin

- Mortality rate-ratio relative to the non-diabetic cancer patients
Mortality of (all) Danish cancer ptts:

- Colorectal
- Liver
- Pancreas
- Lung
- Melanoma
- Breast
- Cervix uteri
- Endometrium
- Ovary
- Prostate
- Kidney
- Bladder

Mortality RR vs. non-DM

No med | OAD | Insulin
-------|-----|-------
3633 | 2362 | 973
262 | 376 | 237
1095 | 758 | 602
2877 | 1891 | 1034
781 | 373 | 187
3221 | 1428 | 719
209 | 78 | 56
747 | 411 | 206
366 | 191 | 108
2817 | 1692 | 593
577 | 365 | 206
1661 | 1031 | 425

No medication (No med)
Interpretation

- Causality is unknown — all studies are necessarily observational

- Possible contributing factors to excess risk:
  - Reverse causation: A latent cancer deteriorates the diabetic condition
  - Common risk factors: Obesity, sedentary lifestyle, eating habits...

- Actual effects of drugs:
  - Metformin: Inhibition of tumour growth
  - Insulin: Promotion of tumour growth
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Conclusion

- 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
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