Diabetes and Cancer

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Diabetes and Cancer

Two main questions:

▶ 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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- You cannot randomize people to
  - Diabetes
  - OAD
  - Insulin
  - ...
Diabetes and Cancer problems

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  - confined to an extreme high-risk group
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  - Diabetes
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  - Insulin
  - ...

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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:

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Deaths</th>
<th>RR</th>
<th>95% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral antidiabetica:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>6,969</td>
<td>245</td>
<td>1.0</td>
<td>(ref)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>3,340</td>
<td>162</td>
<td>1.3</td>
<td>(1.1–1.6)</td>
</tr>
<tr>
<td><strong>Insulin use:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No insulin use</td>
<td>8,866</td>
<td>323</td>
<td>1.0</td>
<td>(ref)</td>
</tr>
<tr>
<td>Insulin use</td>
<td>1,443</td>
<td>84</td>
<td>1.9</td>
<td>(1.5–2.4)</td>
</tr>
</tbody>
</table>

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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- Some were methodologically flawed.

There is biological reason to suspect insulin/analogs for a role in cancer promotion. But evidence is weak and data are limited.
Graphical overview

Well

 DM
Graphical overview

Well ➔ Ca (W)

Well ➔ DM

DM ➔ Ca (DM)
Graphical overview

Well

DM

Ca (W) → Dead (Ca)

Ca (DM) → Dead (Ca)
Graphical overview

Well

DM

Ca (W)  →  Dead (Ca)

Dead (O)

Ca (DM)  →  Dead (Ca)

Dead (O)

DM

Ca (W)  →  Dead (Ca)

Dead (O)

Well

DM

Ca (DM)  →  Dead (Ca)

Dead (O)
Cancer survival

Well

DM

Ca (W) → Dead (Ca)

Dead (O)

Ca (DM) → Dead (Ca)

Dead (O)
Cancer mortality

Well

DM

Ca (W)
Dead (Ca)

Dead (O)

Ca (DM)
Dead (Ca)

Dead (O)
Cancer mortality

- **Well**: Dead (Ca)
  - **Ca (W)**: Dead (Ca)
  - **Dead (O)**: Dead (Ca)
- **DM**: Dead (Ca)
  - **Ca (DM)**: Dead (Ca)
  - **Dead (O)**: Dead (Ca)

Diagrams show transitions from Well to Dead (Ca) and from DM to Dead (Ca).
The Danish study

- Cancer incidence study in the total population.
The Danish study

- Cancer incidence study in the total population.
- Comparing diabetes patients with non-diabetes patients.
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- Outcome: Rate-ratio of cancer occurrence between DM-patients 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
The Danish study — overall

- All cancers: $RR = 1.2$
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- All cancers: $\text{RR} = 1.2$
- Digestive system: $\text{RR} \approx 1.2$, varying between sites
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- Liver: $RR_{Men} = 4$, $RR_{Women} = 1.8$
The Danish study — overall

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- Digestive system: $RR \approx 1.2$, varying between sites
- Liver: $RR_{Men} = 4$, $RR_{Women} = 1.8$
- Pancreas: $RR = 2.8$
The Danish study — overall

- All cancers: RR = 1.2
- Digestive system: RR ≈ 1.2, varying between sites
- Liver: $RR_{Men} = 4$, $RR_{Women} = 1.8$
- Pancreas: RR = 2.8
- Lung: RR = 1.15
The Danish study — overall

- All cancers: $RR = 1.2$
- Digestive system: $RR \approx 1.2$, varying between sites
- Liver: $RR_{\text{Men}} = 4$, $RR_{\text{Women}} = 1.8$
- Pancreas: $RR = 2.8$
- Lung: $RR = 1.15$
- Endometrium: $RR = 1.6$
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: $RR = 1.7$
The Danish study — overall

- All cancers: \( RR = 1.2 \)
- Digestive system: \( RR \approx 1.2, \) varying between sites
- Liver: \( RR_{\text{Men}} = 4, \) \( RR_{\text{Women}} = 1.8 \)
- Pancreas: \( RR = 2.8 \)
- Lung: \( RR = 1.15 \)
- Endometrium: \( RR = 1.6 \)
- Kidney: \( RR = 1.7 \)
- Bladder: \( RR_{\text{Men}} = 1.2, \) \( RR_{\text{Women}} = 1.0 \)
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- Bladder: $RR_{Men} = 1.2$, $RR_{Women} = 1.0$
- Prostate: $RR = 0.95$
The Danish study — overall

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- Bladder: $RR_{Men} = 1.2$, $RR_{Women} = 1.0$
- Prostate: $RR = 0.95$
- Brain, lymphomas: $RR = 1.2$
How the Danish study really was

- Well
  - DM
    - Ca (W)
    - Dead (O)
    - Ca (DM)
    - Dead (O)
    - Dead (O)
    - Dead (Ca)
How the Danish study really was

- **Well**
  - **Ca (W)** → **Dead (Ca)**
  - **Dead (O)**

- **DM**
  - **Ca (DM)** → **Dead (Ca)**
  - **Dead (O)**

- **DM+Ins**
  - **Ca (Ins)** → **Dead (Ca)**
  - **Dead (O)**
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

Light color: on insulin

M
F

15/32
Danish study

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- Analyses based only on coarse data:

  - Detection effects: DM and Ins
    - Non-ins user long term RR: 1.1
    - Insulin user long term RR: 1.3
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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, DM+Ins vs No DM

Diabetes duration (years)
All malignant neoplasms

Rate ratio DM+Ins vs DM

Insulin duration (years)
Colorectal cancer

Rate ratio DM, DM+Ins vs No DM

Diabetes duration (years)
Prostate

Breast

Diabetes duration (years)

Rate ratio DM, DM+Ins vs No DM

Prostate Breast

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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
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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
- — from other causes (i.e. before they get cancer)
- NOTE: this also involves the mortality rates!
Cumulative risk of cancer

- Well
  - Ca (W)
  - Dead (O)
  - Dead (Ca)

- DM
  - Ca (DM)
  - Dead (O)
  - Dead (Ca)

- DM+Ins
  - Ca (Ins)
  - Dead (O)
  - Dead (Ca)
Cumulative risk of cancer

Well

DM

DM+Ins

Ca (W) → Dead (Ca)

Ca (W) → Dead (O)

Ca (DM) → Dead (Ca)

Ca (DM) → Dead (O)

Ca (Ins) → Dead (Ca)

Ca (Ins) → Dead (O)
Cumulative risk of cancer

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. \( \Rightarrow \) overall effects on incidence must be evaluated in the long term
Conclusion

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2. ⇒ overall effects on incidence must evaluated in the long term
3. Colorectal, liver, pancreas, corpus uteri, kidney have elevated long-term rates.
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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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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 patients:

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

- Subdivide all newly diagnosed cancer patients (1995–2009) by diabetes status at date of cancer diagnosis:
  - No diabetes
Coarse survival study of Danish cancer ptts:

► Subdivide all newly diagnosed cancer patients (1995–2009) by diabetes status at date of cancer diagnosis:
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  ► Diabetes, not treated with medication
Coarse survival study of Danish cancer patients:

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  - Diabetes, not treated with medication
  - 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 pt:  

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

Mortality RR vs. non−DM  

No med  
OAD  
Insulin  

3633  
262  
1095  
2877  
781  
3221  
209  
747  
366  
209  
781  
577  
1661  

2362  
376  
758  
1891  
373  
1428  
78  
411  
191  
1428  
108  
577  

973  
237  
602  
1034  
187  
719  
56  
206  
108  
593  
206  
425  

No med  
OAD  
Insulin
Interpretation

- Causality is unknown — all studies are necessarily observational
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- 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
References

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