A tale of two diseases: diabetes and cancer

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Disclosures

Speaker`s bureau: Sanofi

Advisory board: Eli Lilly
Aim

To discuss possible associations between diabetes (DM) and cancer (Ca) and resulting implications for clinical practice in primary care
Objectives

To evaluate:

- plausibility of link between DM and Ca (pathophysiology, risk factors, clustering)
- epidemiological data (Ca incidence in DM patients)
- diabetes treatment and Ca risk
Presentation outline

▪ Definitions revisited
  ▪ Comorbidity
  ▪ Multimorbidity

▪ Plausibility of link between DM and Ca
  ▪ Theories
  ▪ Epidemiological evidence

▪ Implications for clinical practice in primary care
  ▪ Exposure and prevention
  ▪ Modifiable risk factors environmental or iatrogenic?
  ▪ Necessity of a person-centred approach
Definitions

Comorbidity

• Biological – etiological link between index disease and co-morbid condition (classical “risk factor” theory, “index disease”)

Multimorbidity

• Co-existence – clustering of diseases and/or conditions without plausible biological explanation
Plausibility of link between DM and Ca

**Comorbid association?**
- due to direct metabolic effects of DM (index disease DM)
- due to effects of pancreatic Ca on glucose regulation (index disease Ca: “reverse causality”)

**Multimorbid association?**
- indirectly mediated
- due to conditions related to;
  - health care
  - “shared” risk factors
Theories: comorbidity

Neoplasia - carcinogenesis

• Cell proliferation and tissue growth mediated by:
  • untreated hyperglycaemia (“glucose addiction” of Ca cells)
  • the insulin / IGF-1 axis
    • Reduced insulin sensitivity with compensatory hyperinsulinemia
      • elevated levels of IGF-1
      • IGF-1 receptor activation
      • increase in the IGF-1 availability to the IGF-1 receptor
Theories: multimorbidity

- Lower levels of preventive care in obese-diabetic individuals
- “Shared” risk factors common to DM and Ca
  - Modifiable (obesity, physical inactivity, diet, smoking, alcohol)
  - Unmodifiable (age, gender)
- Epigenetics....
- Diabetes treatments
  - Insulin secretagogues
  - Insulin and a certain insulin analogue
  - TZDs ?
  - Incretin based therapies
Multimorbidity and preventive care

- **Obesity and likelihood of preventive care**
  - Obese women (class III) less likely for:
    - Mammography (OR 0.79)*
    - Pap-Smear (OR 0.62)**

- **Diabetes and likelihood of preventive care**
  - Diabetic women less likely for:
    - Mammography (OR 0.83)***
    - Colorectal Screening (OR 0.79)***

- **Diabetic women 24-27% more likely to be diagnosed in the late stage of breast cancer****

Multimorbidity and Ca treatment

Diabetic patients with cancer;

- might be more likely to be treated for their cancer less aggressively
- are more likely to have Ca recurrence and severe complications increasing Ca mortality
DM treatment and multimorbidity

Possible Ca risk?
- Secretagogues*
- Exogenous insulins**
- Thiazolidinediones
  - Bladder?***, *****
  - Thyroid?****
  - Pancreas?****
- Incretins (DPP-4 Inhibitors, GLP-1 Agonists)
  - Pancreas
  - Thyroid

Ca protective
- Metformin*****

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*****Habib SL, Rojna M. Diabetes and Risk of Cancer.ISRN Oncology 2013, Article ID 583786;16 pages.

Epidemiological evidence

- Obesity and cancer mortality
- Diabetes and cancer morbidity
Relative Risk and 95% CI

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancers (&gt; 40)</td>
<td>1.5</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (&gt; 35)</td>
<td>1.7*</td>
</tr>
<tr>
<td>All other cancers (&gt; 30)</td>
<td>1.8</td>
</tr>
<tr>
<td>Kidney (&gt; 35)</td>
<td>1.9*</td>
</tr>
<tr>
<td>Multiple myeloma (&gt; 35)</td>
<td>1.7</td>
</tr>
<tr>
<td>Gall bladder (&gt; 30)</td>
<td>1.8</td>
</tr>
<tr>
<td>Colon &amp; Rectum (&gt; 35)</td>
<td>1.8</td>
</tr>
<tr>
<td>Esophageal (&gt; 30)</td>
<td>1.9*</td>
</tr>
<tr>
<td>Stomach (&gt; 35)</td>
<td></td>
</tr>
<tr>
<td>Pancreas (&gt; 35)</td>
<td></td>
</tr>
<tr>
<td>Liver (&gt; 35)</td>
<td>4.5</td>
</tr>
</tbody>
</table>

* RR for men who never smoked

E. E. Calle et al. NEJM 2003; 348: 1625-38
Cancer mortality and BMI, women

Relative Risk and 95% CI

* RR for women who never smoked

E. E. Calle et al. NEJM 2003; 348: 1625-38
### Table 1: Cancer risks in diabetes.

<table>
<thead>
<tr>
<th>Study method (reference)</th>
<th>First author (year of publication)</th>
<th>Country</th>
<th>Sample</th>
<th>Followup duration</th>
<th>Risk of cancer among DM participants (95% CI or P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective cohort [23]</td>
<td>Jee, 2005</td>
<td>Korea</td>
<td>1,298,385</td>
<td>10 years</td>
<td>Men HR = 1.24 (1.20–1.28) Women HR = 1.33 (1.25–1.41)</td>
</tr>
<tr>
<td>Prospective cohort [40]</td>
<td>Yeh, 2012</td>
<td>USA</td>
<td>18,280 (599 diabetic subjects)</td>
<td>17 years (exclusion of cancer cases in first 2 years)</td>
<td>HR = 1.22 (0.98–1.53)</td>
</tr>
<tr>
<td>Retrospective cohort [41]</td>
<td>Lee, 2012</td>
<td>Taiwan</td>
<td>985,815 (104,343 diabetic subjects)</td>
<td>11 years</td>
<td>RR = 1.56 (1.43–1.71)</td>
</tr>
<tr>
<td>Retrospective cohort [42]</td>
<td>Lo, 2012</td>
<td>Taiwan</td>
<td>895,434 in DM cohort and 895,434 in controls</td>
<td>13 years</td>
<td>HR = 1.19 (1.17–1.20)</td>
</tr>
<tr>
<td>Prospective cohort [43]</td>
<td>Hense, 2011</td>
<td>Germany</td>
<td>26,742 diabetic subjects</td>
<td>5 years</td>
<td>SIR = 1.14 (1.10–1.21)</td>
</tr>
<tr>
<td>Retrospective cohort [44]</td>
<td>Geraldine, 2012</td>
<td>Belgium</td>
<td>17,746 (13,737 diabetic subjects)</td>
<td>Mean observation time: 5 years</td>
<td>HR = 1.84 (1.51–2.24)</td>
</tr>
<tr>
<td>Retrospective cohort [45]</td>
<td>Zhang, 2012</td>
<td>China</td>
<td>7950 diabetic subjects</td>
<td>Mean observation time: 8 years</td>
<td>Men SIR = 1.331 (1.143–1.518) Women SIR = 1.737 (1.478–1.997)</td>
</tr>
<tr>
<td>Meta-analysis [38]</td>
<td>Noto, 2011</td>
<td>12 cohorts</td>
<td>257,222 diabetes subjects</td>
<td>—</td>
<td>Men RR = 1.14 (1.06–1.23) Women RR = 1.18 (1.08–1.28)</td>
</tr>
<tr>
<td>Meta-analysis [39]</td>
<td>Noto, 2010</td>
<td>4 cohort and 1 case-control study, all Japanese</td>
<td>250,479 subjects</td>
<td>—</td>
<td>OR = 1.70 (1.38–2.10)</td>
</tr>
</tbody>
</table>

Habib SL, Rojna M. Diabetes and Risk of Cancer. ISRN Oncology, 2013, Article ID 583786, 16 pages.
DM and Ca association

Positive association:
- NHL*
- Bladder*
- Breast*
- Colorectum*
- Endometrium*
- Liver*,**
- Pancreas*,**

Negative association:
- Prostate*

Methodology


Table 1: Description of 27 meta-analyses of type 2 diabetes and cancer incidence or mortality included in umbrella review

<table>
<thead>
<tr>
<th>Study</th>
<th>Association between diabetes and*</th>
<th>No of cases/population</th>
<th>Summary relative risk (95% CI)</th>
<th>Fixed P value</th>
<th>Random P value</th>
<th>95% prediction interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu, 2013</td>
<td>Bladder cancer</td>
<td>50 876/12 500 009</td>
<td>1.26 (1.22 to 1.30)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.51 to 3.02</td>
</tr>
<tr>
<td>Lansor, 2007</td>
<td>Breast cancer</td>
<td>30 858/14 227 786</td>
<td>1.19 (1.16 to 1.23)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.11 to 1.43</td>
</tr>
<tr>
<td>Lansor, 2007</td>
<td>Breast cancer mortality</td>
<td>444 211 000</td>
<td>1.21 (1.10 to 1.34)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.40 to 1.14</td>
</tr>
<tr>
<td>Jing, 2012</td>
<td>ICD</td>
<td>38 021/9 413 865</td>
<td>1.08 (1.07 to 2.11)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.11 to 3.49</td>
</tr>
<tr>
<td>Jing, 2012</td>
<td>ECD</td>
<td>26 331/9 955 190</td>
<td>1.03 (1.04 to 1.10)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.51 to 3.00</td>
</tr>
<tr>
<td>Jiang, 2011</td>
<td>Colorectal cancer</td>
<td>61 600/8 244 732</td>
<td>1.25 (1.22 to 1.30)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.11 to 1.54</td>
</tr>
<tr>
<td>Jiang, 2011</td>
<td>Colorectal cancer mortality</td>
<td>49 844/10 303 334</td>
<td>1.34 (1.27 to 1.40)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.12 to 1.59</td>
</tr>
<tr>
<td>Fritarg, 2012</td>
<td>Endometrial cancer</td>
<td>874 242 081</td>
<td>1.70 (1.67 to 1.71)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.23 to 3.16</td>
</tr>
<tr>
<td>Friborg, 2007</td>
<td>Endometrial cancer mortality</td>
<td>103 671 964</td>
<td>1.14 (0.99 to 1.14)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.90 to 1.93</td>
</tr>
<tr>
<td>Huang, 2011</td>
<td>Oesophageal cancer</td>
<td>220 121 496 112</td>
<td>1.30 (1.18 to 1.42)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.86 to 2.16</td>
</tr>
<tr>
<td>Ren, 2011</td>
<td>Gall bladder cancer</td>
<td>182 121 503 906</td>
<td>1.44 (1.28 to 1.62)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.99 to 2.32</td>
</tr>
<tr>
<td>Se, 2011</td>
<td>Gastric cancer</td>
<td>15 975/9 907 117</td>
<td>1.08 (1.05 to 1.11)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.67 to 1.56</td>
</tr>
<tr>
<td>Tian, 2012</td>
<td>Gastric cancer mortality</td>
<td>26 439 586 74</td>
<td>1.24 (1.15 to 1.33)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.67 to 2.49</td>
</tr>
<tr>
<td>Wang, 2012</td>
<td>HCC</td>
<td>30 765/7 110 641</td>
<td>1.73 (1.68 to 1.78)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.66 to 5.02</td>
</tr>
<tr>
<td>Wang, 2012</td>
<td>HCC mortality</td>
<td>29 214 150 795</td>
<td>2.22 (1.93 to 2.53)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.78 to 7.54</td>
</tr>
<tr>
<td>Bao, 2013</td>
<td>Kidney cancer</td>
<td>12 585/6 292 381</td>
<td>1.38 (1.24 to 1.53)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.56 to 3.40</td>
</tr>
<tr>
<td>Bao, 2013</td>
<td>Kidney cancer mortality</td>
<td>25 642 347 284</td>
<td>1.10 (1.01 to 1.20)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.67 to 1.97</td>
</tr>
<tr>
<td>Cao, 2013</td>
<td>Lung cancer</td>
<td>207 454/15 900 000</td>
<td>0.80 (0.73 to 0.89)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.70 to 1.25</td>
</tr>
<tr>
<td>Castillo, 2012</td>
<td>Larynx cancer</td>
<td>41 586/4 173 005</td>
<td>1.28 (1.22 to 1.34)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.56 to 2.84</td>
</tr>
<tr>
<td>Castillo, 2012</td>
<td>Multiple myeloma</td>
<td>31 513 473 856</td>
<td>1.10 (1.03 to 1.17)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.56 to 2.08</td>
</tr>
<tr>
<td>Castillo, 2012</td>
<td>Non-Hodgkin's lymphoma</td>
<td>12 355/6 200 392</td>
<td>1.10 (1.05 to 1.15)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.70 to 1.80</td>
</tr>
<tr>
<td>Cao, 2013</td>
<td>Ovarian cancer</td>
<td>78 512/12 127 812</td>
<td>1.12 (1.03 to 1.22)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.79 to 1.73</td>
</tr>
<tr>
<td>Cao, 2013</td>
<td>Prostatic cancer</td>
<td>52 440/10 005 932</td>
<td>2.22 (2.15 to 2.29)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.97 to 4.34</td>
</tr>
<tr>
<td>Bartsal, 2013</td>
<td>Prostatic cancer</td>
<td>59 709/19 927 925</td>
<td>0.89 (0.89 to 0.91)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.79 to 0.91</td>
</tr>
<tr>
<td>Schmidt, 2013</td>
<td>Thyroid cancer</td>
<td>129 940/9 860 860</td>
<td>1.16 (1.07 to 1.26)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.76 to 1.68</td>
</tr>
<tr>
<td>Nabi, 2011</td>
<td>Total cancer</td>
<td>35 019/1 419 520</td>
<td>1.11 (1.03 to 1.19)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.90 to 1.35</td>
</tr>
<tr>
<td>Nabi, 2011</td>
<td>Total cancer mortality</td>
<td>11 966/2 320 678</td>
<td>1.21 (1.17 to 1.35)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.80 to 1.70</td>
</tr>
</tbody>
</table>

*HCC=hepatocellular carcinoma; ICC=intracranial carcinomas; ECD=extracranial cholangiocarcinoma.
*Incidence unless otherwise specified.
*P value of fixed effects.
*P value of summary fixed effects estimate.
Methodology

Fig 2 Summary random effects estimates with 95% confidence and prediction intervals from 27 meta-analyses of type 2 diabetes and incidence of cancer or mortality (evidence for bias assessed with extrapolation of Egger regression line to study of infinite sample size and with excess significance test). HCC=hepatocellular carcinoma; ICC=intrahepatic cholangiocarcinoma; ECC=extrahepatic cholangiocarcinoma.
Methodology

What is already known on this topic

Multiple studies and meta-analyses have claimed that type 2 diabetes is associated with an increased risk of developing cancer at several sites including liver, pancreas, endometrium, colorectum, breast, and bladder, and with a decreased risk of prostate cancer.

If causal, these associations would be of great importance for public health given the substantial global burden of these diseases.

Some claimed associations might be caused by biases in the literature, in particular selective reporting biases favouring the publication of significant associations, and causing either false positive or inflated estimates of association.

What this study adds

Only a minority of associations between type 2 diabetes and risk of developing cancer or death from cancer for 20 cancer sites have robust supporting evidence without hints of bias.

Evidence could be substantiated only for the associations between type 2 diabetes and risk of developing breast, intrahepatic cholangiocarcinoma, colorectal, and endometrial cancer.

Cancer incidence in type 2 diabetes patients - first results from a feasibility study of the D2C cohort

Cancer incidence in type 2 diabetes patients - first results from a feasibility study of the D2C cohort.
Implications for clinical practice in primary care

“The selection of the most appropriate pharmacologic agent(s) for each patient, involves clinical decision-making process that includes an ongoing risk/benefit analysis.”*

“It is also relevant to stress that cardiovascular risk remains a major threat for diabetic patients, thereby optimal glucose control, which reduces the risk of diabetes- associated complications, should be a central goal of proper diabetes management.”**

**Habib SL, Rojna M. Diabetes and Risk of Cancer. ISRN Oncology, 2013, Article ID 583786, 16 pages.,
Implications for clinical practice in primary care

“..In the absence of clear correlation, practitioners and patients should continue to feel comfortable utilizing medications to control diabetes, because the correlation between uncontrolled diabetes and cancer is stronger than the correlation between diabetic medications and cancer. In patients with other risk factors for malignancy (such as a strong family history or personal history of cancer), providers may wish to be more thoughtful in their selection of agents to manage diabetes by utilizing the data provided in the studies mentioned.”

Summary of recommendations from the literature

**Exposure-prevention**
- Elevated Ca risk in DMII
  - Morbidity
  - Mortality
- Healthy lifestyle
  - Advise all pts
- Screening for Ca
  - Start with pre-diabetes!

**Modifiable risk factors**
- Causal (co-morbidity)
  - Hyperglycemia (duration and dose-response)
- Shared (multimorbidity:mediates)
  - High body fat
  - Hyperinsulinemia
  - Epigenetics?
- DM treatment:
  - Metformin protective*
  - “limited or inconclusive evidence for association of specific drugs with Ca incidence in diabetic individuals”**

**Person-centredness**
- “Cancer risk should not be a major factor in choosing diabetes therapies for the average patient. Selected patients with high risk for Ca should be evaluated individually for DM therapy options”**

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*Habib SL, Rojna M. Diabetes and Risk of Cancer. ISRN Oncology, 2013, Article ID 583786, 16 pages.,

Managing Ca risk in people with DM in PC
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29-30 April 2016 Barcelona (Spain)
www.2016pcdeconference.org