Diabetes and cancer - what is the link?

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Emerging links

Diabetes and cancer are both:
- Common
- Increasing
- Occurring more often than expected
Focusing on:

- Epidemiology of links between diabetes and cancer
- Possible mechanisms
- Diabetes treatment and cancer risk
- Red flags for cancer in diabetes
Epidemiology

- Now large studies
- Mostly observational cohort studies
- Early studies suggested reduced risk 1
  - based on UK death certificates
- Hard to correct for confounders such as age and obesity
- Causality

1 Fuller et al Diabetologia 1983
Increased BMI is a risk factor for cancer

Recent Studies

- Large studies (>60,000 participants)
- Multiple corrections (age, BMI, smoking etc)
- Different methods for determining diabetes
- Self reported
- Use of diabetes drugs
- Glucose measurements
- 8-10 year follow up
Diabetes as a risk factor for cancer

- High Risk (~2x)
  - Endometrial
  - Liver
  - Pancreas
- Intermediate (1.2-1.5x)
  - Breast
  - Colon
  - Bladder
Diabetes as a risk factor for cancer

Inconclusive
– Non-Hodgkin Lymphoma
– Kidney

Reduced Risk
– Prostate
Increased risk at higher glucose levels

Table 2. Age-Adjusted Mortality Rate per 100,000 Men for Death Due to All Causes, All Cancers, and Various Cancers by Fasting Serum Glucose Level in Korean Men, 1993-2002*

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Fasting Serum Glucose Level, mg/dL†</th>
<th>P Value for Trend</th>
<th>Diabetes (n = 41,868)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;90 (n = 429,370)</td>
<td></td>
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<tr>
<td></td>
<td>90-109 (n = 304,362)</td>
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<tr>
<td></td>
<td>110-125 (n = 58,020)</td>
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<tr>
<td></td>
<td>126-139 (n = 11,459)</td>
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</tr>
<tr>
<td></td>
<td>≥140 (n = 26,559)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death rate§</td>
<td>677.3</td>
<td></td>
<td>1207.7</td>
</tr>
<tr>
<td>HR (95% CI)∥</td>
<td>1.00 (1.02-1.06)</td>
<td>.01</td>
<td>1.83 (1.79-1.88)</td>
</tr>
<tr>
<td>All cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death rate§</td>
<td>266.0</td>
<td></td>
<td>333.0</td>
</tr>
<tr>
<td>HR (95% CI)∥</td>
<td>1.00 (1.01-1.07)</td>
<td>.003</td>
<td>1.27 (1.22-1.33)</td>
</tr>
</tbody>
</table>

*Note: *All causes* includes all deaths due to any cause, while *all cancer* includes deaths from cancer only.

†Fasting serum glucose levels are measured in mg/dL.

∥HR (95% CI) denotes hazard ratio and its 95% confidence interval.

Jee et al. JAMA 2005.
... and the effect is independent of BMI

Risk of cancer and HbA1c

Yang et al Diabetes 2010
Why?

- **Direct Causation**
  - Hyperglycaemia
- **Indirect Causation**
  - Hyperinsulinaemia
  - Inflammation
  - Genetics
- **Common Risk Factors**
  - Obesity
- **Reduced risk of prostate cancer**
Hyperglycaemia and cancer

- Glucose is a cellular fuel
- Cancer cells are dividing rapidly and therefore have high metabolic demands
- .....ergo higher glucose levels fuel this demand
Warburg Hypothesis

Warburg in 1931 noted that cancer cells showed:
- Increased glycolysis
- Decreased oxidative metabolism
Net effect is that cancer cells are primed to use glucose to fuel their metabolism
- "addicted to glucose"
- Adaptation to cope with reduced oxygen
Metabolism Overview

[Diagram showing the interconnections between carbohydrate, fat, lactate, acetyl CoA, citric acid cycle, and oxidative phosphorylation.]
Warburg Hypothesis - mechanisms

- Mutations in genes required for mitochondrial function
- Mutations in genes of the TCA cycle
- Gain of function to provide substrates for the dividing cell
A sample mechanism

Fumarate → Succinate Dehydrogenase

Succinate → a-Ketoglutarate

HIF-1α → HIF-1α – OH → Proline hydroxylase

X

↑Glycolysis

Angiogenesis

Proline hydroxylase → VHL → Degredation
SDHx mutations

Can result in:
- Phaeochromocytoma
- Extra adrenal sympathetic paraganglioma
  - Both secrete catecholamines
- Head and Neck Parasympathetic paraganglioma
  - Only 5% produce catecholamines
- Variability in sites and malignant potential
- Proof of principle that metabolic derangements can lead to cancer
..back to diabetes

- Cancer cells more dependant of glycolysis
- “Addicted to glucose”
- Elevated glucose levels could therefore promote the growth of cancer cells
- Fits epidemiological data
- Cell models
C

MCF-7

% Dead cells

Control  Doxorubicin (1 μM)  Control  Paclitaxel (50 μM)  Control  5-Fluorouracil (10 μM)

D

T47D

% Dead cells

Control  Doxorubicin (1 μM)  Control  Paclitaxel (125 μM)  Control  5-Fluorouracil (40 μM)

Endoc related cancer 2010 May; 17(2): 539-551
..but glucose unlikely to be the whole story

- Not all studies show link to glycaemic control
- Patients undergoing follow up after colonic adenoma
- Mean HbA1c did not differ between those who did and did not develop second tumour
- Intensive glucose control not been shown to reduce risk
- Increased risk in insulin resistant states
- Differing risks with different treatments

Yang et al Cancer Epidemiol Biomark 2010, Yang et al Diabetes 2010, Johnson and Bowker Diabetologia 2011
Insulin as a risk factor for cancer

- Diabetes and obesity are characterised by insulin resistance
- This results in hyperinsulinaemia
- Insulin
  - Is a mitogen
  - Cross reacts with IGF-1 signalling
**Insulin Signalling**

![Insulin Signalling Diagram](Image)

- **insulin** binds to the **insulin receptor**.
- **PI3K** signalling pathway:
  - PI3K activates PDK1
  - PDK1 activates PKC
  - PKC activates GLUT-4
- **MAPK** signalling pathway:
  - MEK activates ERK
  - ERK regulates cell growth and survival
- Additional pathways:
  - mTOR
  - Foxa2 and FoxO
  - BAD
  - gluconeogenesis
  - hepatic triglyceride production
  - apoptosis
  - cell cycle arrest

**Cell Growth and Survival**

**Cell Proliferation**
Insulin and growth

- Insulin promotes growth
- Insulin receptors are over expressed in some cancers
- Forced over expression of IR can transform cells
- Insulin administration enhances tumour development in rat model of colon cancer
Insulin and IGF-1

- Insulin increases expression of hepatic GH receptors, enhancing IGF-1 production
- Insulin suppresses certain IGF Binding Proteins, increasing free IGF-1 levels
- At high concentrations insulin can cross react with IGF-1 receptors
- Insulin receptor / IGF-1 receptor hybrids occur and share common signalling pathways
IGF-1 and Cancer

- Epidemiological data shows a strong correlation between IGF-1 levels and cancer risk
  - Increased risk of breast, colon and prostate cancer with higher IGF-1 levels
- Patients with acromegaly have elevated IGF-1 levels and increased risk of colon cancer
IGF-1 and cancer

- IGF-1 and Insulin receptors signal through similar pathways:
  - Insulin *predominately* regulates metabolism
  - IGF-1 *predominately* regulates growth and pro-survival pathways

Chart 5. Effect of CR-MSA (△) and BSM (○) on the growth of T-47D cells grown on plastic substratum. The procedures used for this study are described in "Materials and Methods." Bars, S.D. *, p < 0.01.

Myal et al Cancer Res 1984
Insulin and IGF-1 and cancer

Net effect likely to be cancer promoting rather than cancer causing.

Is insulin / IGF-1 signalling the culprit?
mTOR and cancer

- Mouse model with skeletal muscle IGF-1 receptor knockout (MKR) has high insulin levels but only mildly elevated glucose
- Overexpressed either middle T or ErbB2 oncogenes to induce mammary tumours
- Examined tumour progression with and without the mTOR inhibitor rapamycin
Insulin Signalling

- Insulin binds to the insulin receptor.
- IRs (Insulin Receptor Subunit) are activated.
- IRS (Insulin Receptor Substrate) phospho-relieves and activates PDK1.
- PDK1 phosphorylates and activates Akt (Protein Kinase B).
- Akt regulates cell growth and survival, cell proliferation, apoptosis, cell cycle arrest, gluconeogenesis, and hepatic triglyceride production.

- MAPK signalling and PI3K signalling pathways are indicated.

Cell growth and survival:
- Akt inhibits p21Ras.
- Akt activates Raf and MEK.
- MEK activates ERK.
- ERK regulates cell growth and survival.

Cell proliferation:
- Akt activates p70S6k.
- p70S6k regulates cell proliferation.

Apoptosis:
- Akt inhibits BAD.
- BAD regulates apoptosis.

Gluconeogenesis:
- Akt inhibits FoxO.
- FoxO regulates gluconeogenesis.

Hepatic triglyceride production:
- Akt inhibits FoxO.
- FoxO regulates hepatic triglyceride production.
mTOR inhibitors

- Rapamycin worsened hyperglycaemia in the MKR mice
- MKR mice had larger tumours than WT, but rapamycin abrogated this

Fierz et al Endo Relat Cancer 2010
Insulin and other hormones

– Insulin lowers SHBG levels, enhancing oestrogen signalling
– Insulin increases adrenal androgen production in women
– Elevated oestrogen and androgen signalling is a risk for breast and endometrial cancer
Inflammation and Oxidative Stress

– Obesity and Type 2 diabetes are pro-inflammatory conditions
– Several inflammatory cytokines have pro-proliferative effects
– Possible effects on host-cancer cell interactions may promote tumourgenesis
– Insulin Resistance is associated with increased ROS production which may lead to DNA damage
Common Risk Factors

- Diabetes and cancer share common risk factors:
  - Age
  - Obesity
  - Diet
  - Reduced exercise
  - Smoking
  - Alcohol
Cancer and Diabetes Medication

Does the treatment of diabetes modify the risk of cancer?

- Metformin
- Insulin
  - Insulin Glargine
Case control studies

- Numerous studies have compared cancer risk between diabetes treatments
- Multiple pitfalls:
  - Treatment allocation is not random
  - Treatments used sequentially
  - Very hard to adequately control
  - Cancer has multiple risk factors, so comparing studies difficult
  - Risk may vary at different cancer sites
Metformin and Cancer

- Population studies suggest a protective effect relative to other diabetes therapies
  - Evans et al BMJ 2005
    - 923 patients with diabetes and diagnosis of cancer
    - OR for cancer if on Metformin 0.86 (0.73-1.02)
    - OR for cancer if ever on Metformin 0.79 (0.67-0.93)
  - Risk reduction correlated with duration of treatment and cumulative dose
**Metformin and Cancer**

- Libby et al Diabetes Care 2009
  - Large Scottish Study of patients with diabetes on metformin, and controls matched by year of diagnosis of diabetes
  - OR for cancer if on metformin 0.46 (0.4-0.53)
  - Remained significant even after adjustment for BMI, HbA1c and smoking
- Bodmer et al Diabetes Care 2010
  - >22,000 patients from UK GP Research Database
  - Breast Cancer
  - Long term metformin OR 0.63 (0.39-1)
  - Long term metformin vs no metformin OR 0.42 (0.21-0.87)
Metformin and Cancer

- Franciosi et al PLoS One 2013
  - Systematic review of all studies up to 2012 (randomised (12) and observational (41))
  - Total of over 1 million patients
  - OR for all malignancies 0.65 (0.53 to 0.8) in observational studies
  - No difference in randomised studies
Metformin and Cancer

- ...but
  - Metformin tends to be used early in T2DM
    - Younger patients
    - Better Glucose control
  - Control studies may not adequately correct for this
  - Recent meta-analysis of all RCTs of metformin that report cancer or cancer deaths showed no difference
  - Relatively short follow up periods

Stevens et al Diabetologia 2012
Metformin in patients with Cancer

- Single study looking at women with diabetes and breast cancer suggests better outcomes in those on metformin
- Increased mortality after incident cancer in those with diabetes, but reduced in those on metformin monotherapy
- Caution with observational studies
- Trials under way of metformin as adjuvant treatment in Breast Cancer – eg NCT10210911

Currie et al Diabetes Care 2012
# Diabetes Drugs and Cancer

<table>
<thead>
<tr>
<th>Metformin</th>
<th>SU</th>
<th>TZD</th>
<th>Insulin</th>
<th>GLP-1 / DPP-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Risk</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
Metformin and Cancer

– Lowers Glucose
– Lowers Insulin
– Inhibits AMPK
AMP Kinase

Metformin

LKB1

AMP Kinase

Oxidative Metabolism

Gluconeogenesis
Protein Synthesis
Lipid Synthesis

TSC2

mTOR
Insulin Glargine

- Long acting insulin analogue
- Widely used in both Type 1 and Type 2 Diabetes
- Reduced risk of hypoglycaemia compared to human insulin
Glargine and Cancer

- Sept 2009
- 4 papers suggesting possible link between Insulin Glargine and Cancer
Glargine and Cancer

- Hemkens et al
  - German Insurance Registry
    - Insulin treated diabetic patients
    - 1.6 year follow up
    - Statistical modelling to compare risk at different doses
    - Increased risk for Glargine cf human insulin (1.31 at 50U/day)
  - After submission, editors requested further studies....
Glargine and Cancer

Swedish study:
  – Overall no increased risk with Glargine
  – Increased risk of breast cancer in women receiving glargine alone (1.97 (1.3-3))
  – No significant increase if received glargine in combination with other insulins

Scottish study:
  – Increased risk of breast cancer in one subgroup

UK Study:
  – No overall change in risk
Glargine and Cancer

– Observational Studies
– Limited corrections
– Glargine alone more likely to be used in older patients and overweight patients
### Glargine and Cancer

<table>
<thead>
<tr>
<th>Analog</th>
<th>Insulin receptor affinity (%)</th>
<th>Insulin receptor off-rate (%)</th>
<th>Metabolic potency (lipogenesis) (%)</th>
<th>IGF-I receptor affinity (%)</th>
<th>Mitogenic potency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulin</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>B10Asp</td>
<td>205 ± 20</td>
<td>14 ± 1*</td>
<td>207 ± 14</td>
<td>587 ± 50</td>
<td>975 ± 173</td>
</tr>
<tr>
<td>Aspart</td>
<td>92 ± 6</td>
<td>81 ± 8*</td>
<td>101 ± 2</td>
<td>81 ± 9</td>
<td>58 ± 22</td>
</tr>
<tr>
<td>Lispro</td>
<td>84 ± 6†</td>
<td>100 ± 11†</td>
<td>82 ± 3</td>
<td>156 ± 16</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Glargine</td>
<td>86 ± 3</td>
<td>152 ± 13</td>
<td>60 ± 3</td>
<td>641 ± 51</td>
<td>783 ± 132</td>
</tr>
<tr>
<td>A21Gly</td>
<td>78 ± 10</td>
<td>162 ± 11</td>
<td>88 ± 3</td>
<td>42 ± 11</td>
<td>34 ± 12</td>
</tr>
<tr>
<td>B31B32diArg</td>
<td>120 ± 4</td>
<td>75 ± 8</td>
<td>75 ± 5</td>
<td>2,049 ± 202</td>
<td>2,180 ± 390†</td>
</tr>
<tr>
<td>Detemir</td>
<td>46 ± 5†/18 ± 2§</td>
<td>204 ± 9</td>
<td>ca 27</td>
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</tr>
</tbody>
</table>
ADA Position Statement

- “Cancer risk should not be a major factor in choosing between available diabetes therapies for the average patient”
- “patients with very high risk for cancer ... or recurrence of specific cancer types .... require more careful consideration”
Latest Data

- ORIGIN trial - 6 years of Glargine or usual care in newly diagnosed diabetes / IGT
- No increase in cancer risk
- Further cohort studies and meta-analysis - no increased risk

? Drug scare

Diabetes in patients with cancer

- Worse outcome in cancer patients with cancer
- Meta-analysis showed 1.4 x risk of death in all patients with cancer and diabetes compared to normoglycaemic controls
- Systematic reviews show HR for cancer specific mortality of 1.38 in breast and 1.3 in colorectal cancer
- Also increased risk of death after cancer surgery

Conclusions

- Strong Epidemiological links between diabetes and cancer
- Diabetes as risk factor for development of cancer
- Multiple plausible mechanisms
- *Possible* treatment effects
- Ongoing impact of diabetes in those with cancer