DIABETES AND CANCER
AN AACE/ACE CONSENSUS STATEMENT

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Preface

- The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) convened a task force to develop a consensus on the association of obesity, diabetes, and diabetes management with cancer.
- The consensus is based on a conference with 30 global experts in New York City; followed by an exhaustive analysis of the evidence to understand factors associated with cancer development in obesity and diabetes and to evaluate the potential cancer risk of antihyperglycemic medications.
- The purpose of the consensus is to provide practical recommendations and implications for practice to physicians, clinicians, general healthcare, patients and scientists; and to highlight future research needs.
Presentation Outline

• Epidemiology
• Molecular Mechanisms
• Pathophysiology
• Diabetes Management and Cancer Risk
• Regulatory Position
• Implications for Practice
• Future Research and Conclusion
Epidemiology
Obesity Linked to Specific Cancers

Each year, 100,500 new cases of cancer are caused by obesity:

- Breast 33,000
- Endometrial, 20,700
- Kidney, 13,900
- Colorectal, 13,200
- Pancreas, 11,900.
- Esophagus, 5,800.
- Gallbladder, 2,000
Cancer Deaths Associated with Obesity

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men 301,820</th>
<th>Women 275,370</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>29%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td>24%</td>
</tr>
</tbody>
</table>

# BMI & Cancer Risk (men)

<table>
<thead>
<tr>
<th>Cancer site and type</th>
<th>Number of studies</th>
<th>RR (95% CI)</th>
<th>p</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal adenocarcinoma</td>
<td>5</td>
<td>1.52 (1.33-1.74)</td>
<td>&lt;0.0001</td>
<td>24%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4</td>
<td>1.33 (1.04-1.70)</td>
<td>0.02</td>
<td>77%</td>
</tr>
<tr>
<td>Colon</td>
<td>22</td>
<td>1.24 (1.20-1.28)</td>
<td>&lt;0.0001</td>
<td>21%</td>
</tr>
<tr>
<td>Renal</td>
<td>11</td>
<td>1.24 (1.15-1.34)</td>
<td>&lt;0.0001</td>
<td>37%</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
<td>1.24 (0.95-1.62)</td>
<td>0.12</td>
<td>83%</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>6</td>
<td>1.17 (1.05-1.30)</td>
<td>0.004</td>
<td>44%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>7</td>
<td>1.11 (1.05-1.18)</td>
<td>&lt;0.0001</td>
<td>7%</td>
</tr>
<tr>
<td>Rectum</td>
<td>18</td>
<td>1.09 (1.06-1.12)</td>
<td>&lt;0.0001</td>
<td>3%</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>1.05 (1.00-1.10)</td>
<td>0.11</td>
<td>73%</td>
</tr>
<tr>
<td>Gastric</td>
<td>8</td>
<td>0.97 (0.88-1.06)</td>
<td>0.49</td>
<td>35%</td>
</tr>
<tr>
<td>Lung</td>
<td>11</td>
<td>0.76 (0.70-0.83)</td>
<td>&lt;0.0001</td>
<td>63%</td>
</tr>
<tr>
<td>Oesophageal squamous</td>
<td>3</td>
<td>0.71 (0.60-0.85)</td>
<td>&lt;0.0001</td>
<td>49%</td>
</tr>
</tbody>
</table>

Risk ratio (per 5 kg/m² increase)

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# BMI & Cancer Risk (women)

<table>
<thead>
<tr>
<th>Cancer site and type</th>
<th>Number of studies</th>
<th>RR (95% CI)</th>
<th>p</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>19</td>
<td>1.59 (1.50-1.68)</td>
<td>&lt;0.0001</td>
<td>77%</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>2</td>
<td>1.59 (1.02-2.47)</td>
<td>0.04</td>
<td>67%</td>
</tr>
<tr>
<td>Oesophageal adenocarcinoma</td>
<td>3</td>
<td>1.51 (1.31-1.74)</td>
<td>&lt;0.0001</td>
<td>0%</td>
</tr>
<tr>
<td>Renal</td>
<td>12</td>
<td>1.34 (1.25-1.43)</td>
<td>&lt;0.0001</td>
<td>45%</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>7</td>
<td>1.17 (1.04-1.32)</td>
<td>0.01</td>
<td>80%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3</td>
<td>1.14 (1.06-1.23)</td>
<td>0.001</td>
<td>5%</td>
</tr>
<tr>
<td>Postmenopausal breast</td>
<td>31</td>
<td>1.12 (1.08-1.16)</td>
<td>&lt;0.0001</td>
<td>64%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11</td>
<td>1.12 (1.02-1.22)</td>
<td>0.01</td>
<td>43%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6</td>
<td>1.11 (1.07-1.15)</td>
<td>&lt;0.0001</td>
<td>0%</td>
</tr>
<tr>
<td>Colon</td>
<td>19</td>
<td>1.09 (1.05-1.13)</td>
<td>&lt;0.0001</td>
<td>39%</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>5</td>
<td>0.98 (0.92-1.01)</td>
<td>0.05</td>
<td>6%</td>
</tr>
<tr>
<td>Premenopausal breast</td>
<td>20</td>
<td>0.92 (0.88-0.97)</td>
<td>0.001</td>
<td>39%</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
<td>0.80 (0.66-0.97)</td>
<td>0.03</td>
<td>84%</td>
</tr>
<tr>
<td>Oesophageal squamous</td>
<td>2</td>
<td>0.57 (0.47-0.69)</td>
<td>&lt;0.0001</td>
<td>60%</td>
</tr>
</tbody>
</table>

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BMI & risk of second primary cancer

## BMI (post-diagnosis) & breast cancer

### Breast cancer-specific survival

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Study</th>
<th>BMI Category</th>
<th>Event Rate</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Conroy</td>
<td>11.5%</td>
<td>1.45</td>
<td>[0.91, 2.31]</td>
</tr>
<tr>
<td>2008</td>
<td>Dal Masco</td>
<td>16.3%</td>
<td>1.40</td>
<td>[0.97, 2.02]</td>
</tr>
<tr>
<td>2002</td>
<td>Goodwin</td>
<td>1.3%</td>
<td>1.51</td>
<td>[0.32, 7.13]</td>
</tr>
<tr>
<td>2005</td>
<td>Whiteman</td>
<td>18.1%</td>
<td>1.32</td>
<td>[0.94, 1.85]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>47.2%</td>
<td>1.38</td>
<td>[1.11, 1.71]</td>
</tr>
</tbody>
</table>

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Fasting Insulin and Breast Cancer Risk

- Case-control design
- 99 premenopausal T1-3, N0-1, Mo BC
- 99 age-matched premenopausal controls with non-proliferative breast biopsies

<table>
<thead>
<tr>
<th>Insulin Quintile</th>
<th>Level (pmol/L)</th>
<th>Odds Ratio (95% CI) for Breast Cancer (age, weight adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>≤ 35</td>
<td>1.0</td>
</tr>
<tr>
<td>II</td>
<td>&gt;35 - ≤41</td>
<td>1.19 (0.49 – 2.89)</td>
</tr>
<tr>
<td>III</td>
<td>&gt;41 - ≤47</td>
<td>1.33 (0.53 – 3.35)</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;47 - ≤58</td>
<td>1.19 (0.48 – 2.93)</td>
</tr>
<tr>
<td>V</td>
<td>&gt;58 - ≤180</td>
<td>3.72 (1.32 – 10.5)</td>
</tr>
</tbody>
</table>

P (insulin) = 0.02 (2-tail)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>RR (95% CI)</th>
<th>Cancer RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (El-Serag <em>et al.</em> 2006)</td>
<td>2.50 (1.8–3.5)</td>
<td>2.51 (1.9–3.2)</td>
</tr>
<tr>
<td>Pancreas (Huxley <em>et al.</em> 2005)</td>
<td>1.94 (1.53–2.46)</td>
<td>1.73 (1.59–1.88)</td>
</tr>
<tr>
<td>Kidney&lt;sup&gt;a&lt;/sup&gt; (Lindblad <em>et al.</em> 1999, Washio <em>et al.</em> 2007)</td>
<td>1.50 (1.30–1.70)</td>
<td>2.22 (1.04–4.70)</td>
</tr>
<tr>
<td>Endometrium (Friberg <em>et al.</em> 2007)</td>
<td>2.22 (1.80–2.74)</td>
<td>1.62 (1.21–2.16)</td>
</tr>
<tr>
<td>Colon–rectum (Larsson <em>et al.</em> 2005)</td>
<td>1.36 (1.23–1.50)</td>
<td>1.29 (1.16–1.43)</td>
</tr>
<tr>
<td>Bladder (Larsson <em>et al.</em> 2006)</td>
<td>1.37 (1.04–1.80)</td>
<td>1.43 (1.18–1.74)</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma (Mitri <em>et al.</em> 2008)</td>
<td>1.41 (1.07–1.88)</td>
<td>1.12 (0.95–1.31)</td>
</tr>
<tr>
<td>Breast (Larsson <em>et al.</em> 2007)</td>
<td>1.18 (1.05–1.32)</td>
<td>1.20 (1.11–1.30)</td>
</tr>
<tr>
<td>Prostate (Kasper &amp; Giovannucci 2006)</td>
<td>0.89 (0.72–1.11)</td>
<td>0.81 (0.71–0.92)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data on kidney cancer were not obtained from meta-analysis; CI, confidence interval; RR, relative risk.
Diabetes and Cancer Mortality

- Post-operative cancer patients with T2DM have ~85% higher overall mortality compared to patients without T2DM
- Adjusted for confounders the increased mortality is ~50%

---

**Table of Studies**

<table>
<thead>
<tr>
<th>Author/year</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominguez-Ventura et al, 2006</td>
<td>0.71 (0.09, 5.49)</td>
<td>1.68</td>
</tr>
<tr>
<td>Poorn et al, 2002</td>
<td>1.07 (0.24, 4.82)</td>
<td>2.91</td>
</tr>
<tr>
<td>Jullumstro et al, 2009</td>
<td>1.18 (0.46, 3.04)</td>
<td>5.95</td>
</tr>
<tr>
<td>Davia et al, 2005</td>
<td>1.19 (1.04, 1.36)</td>
<td>18.05</td>
</tr>
<tr>
<td>Nagasue et al, 1993</td>
<td>1.35 (0.59, 3.09)</td>
<td>7.12</td>
</tr>
<tr>
<td>Romana and Mark, 1992 (p)</td>
<td>1.40 (0.70, 2.90)</td>
<td>8.49</td>
</tr>
<tr>
<td>Romana and Mark, 1992 (fr)</td>
<td>1.50 (1.10, 2.20)</td>
<td>14.50</td>
</tr>
<tr>
<td>Duque et al, 1997</td>
<td>1.83 (0.68, 4.91)</td>
<td>5.61</td>
</tr>
<tr>
<td>Wilt et al, 1999</td>
<td>1.87 (1.11, 3.15)</td>
<td>11.37</td>
</tr>
<tr>
<td>Aburasra et al, 2005</td>
<td>2.89 (1.08, 7.89)</td>
<td>5.49</td>
</tr>
<tr>
<td>Little et al, 2002</td>
<td>3.63 (1.28, 10.27)</td>
<td>5.21</td>
</tr>
<tr>
<td>Tsugawa et al, 2002</td>
<td>4.13 (0.81, 21.07)</td>
<td>2.54</td>
</tr>
<tr>
<td>Andrén-Sandberg and Ihse, 1983</td>
<td>4.36 (1.23, 15.43)</td>
<td>3.87</td>
</tr>
<tr>
<td>Bakkevold and Kambestad, 1993</td>
<td>5.00 (1.56, 16.70)</td>
<td>4.29</td>
</tr>
<tr>
<td>Koperna et al, 1997</td>
<td>12.00 (1.47, 7.30)</td>
<td>1.62</td>
</tr>
<tr>
<td>Karl et al, 2000</td>
<td>19.94 (1.66, 236.40)</td>
<td>1.20</td>
</tr>
<tr>
<td>Overall (I-squared = 50.5%, P = 0.011)</td>
<td>1.85 (1.40, 2.45)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*NOTE: Weights are from random effects analysis*
Molecular Mechanisms
Cellular Requirements for Tumor Biosynthesis

- Tumor cells depend on multiple energy sources not just glucose
- Genetic mutations and altered metabolism also support tumor growth

Multistage Carcinogenesis

Biological links between obesity, T2DM, and cancer

Study Subject | Estimated Lag Time
--- | ---
Mice | 20 to 50 *weeks*
Humans | 20 to 50 *years*

Pathophysiology
How Can the Metabolic Syndrome, Obesity, and Type 2 Diabetes Affect Cancer Development and Metastases?

Nutrients
IGF-I
Leptin
Adiponectin
Cytokines
Chemokines
Estrogen

Obesity
Diabetes
Cancer

Hyperinsulinemia
Hyperglycemia
Hyperlipidemia

LeRoith D. Presented at: AACE Annual Meeting; May. 2013
Obesity, Insulin, and IGF-1

- Increased BMI has been directly related to increased insulin and free insulin-like growth factor-1 (IGF-1) levels.

Pathways Linking Obesity with Breast Cancer

- **Obesity**
  - ↑ Estrogen Synthesis
  - Insulin Resistance
  - Altered Adipokine and Cytokine Production
    - Adipocytes
    - Macrophages
  - ↓ Insulin, ↑ IGF-1
  - ↓ Adiponectin, ↑ Leptin
  - ↑ IL-6, IL-1β, ↑ TNFα

- ↑ Estradiol
  - ↓ Plasma SHBG
  - ↑ Estradiol Bioavailability
  - VEGF Induction
  - Angiogenesis
  - Cell Proliferation
  - Cell Survival

Breast Cancer Cell

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Potential Mechanisms Linking Diabetes and Cancer

Excess weight/adiposity

- FFA↑, TNFα↑, Resistin↑, Adiponectin↓

- Insulin resistance

Blood and tissue:
- IGFBP1↓, IGFBP2↓
- IGF1 bioavailability↑

Liver
- SHBG synthesis↓
- Insulin↑

Target cells
- Apoptosis↓, Cell proliferation↑

Adipocytes
- Aromatase
- 17β-HSD
- E2, T
- Bioavailable E2, T
- 17β-HSD

Macrophage infiltration of adipose tissue → IL-6, IL1-beta

Nature Reviews | Cancer

Hyperinsulinemia and Cancer (Direct Effects)

- Cell Proliferation
- ER Activation
  (Resistance to antiestrogens)
- Sensitization to Growth Factors
  (Prenylation)
- Synergism with GFs
  (EGF)
- Anti-apoptosis

IR/IGF-1R/Hybrid Receptors

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Fantus IG. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012
Insulin, Insulin-like Growth Factors, and Receptors

IGF-I

IGF-2

Insulin

α α

β β

IGF-I Receptor

Insulin Receptor-A

High expression in fetal and neoplastic tissues

Insulin Receptor-B

Cell Survival, Growth, Proliferation

Metabolic Effects

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Hyperinsulinemia and Cancer (Indirect Effects)

Indirect Effects

↑IGF-1
↓IGFBP-1/2

↑Aromatase
↓SHBG
↑Estrogen

↓AMP-kinase

↑Protein translation mTOR/p70S6K

↑Glucose
↑Free fatty acids
↑Amino acids

↑Inflammatory Adipokines; TNF, IL-6
↓Protective Adipokines; Adiponectin

Figure 2B

Fantus IG. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012
Diabetes Management & Cancer Risk
Risk-benefit of diabetes versus therapy

- Complications of diabetes
- Adverse events associated with therapy
- Risk reduction with intensive diabetes control (Type 2)

Benefits of Intensive (insulin/sulfonylurea) vs conventional therapy in newly diagnosed type 2 diabetes

Benefits of Intensive (metformin) vs conventional therapy in overweight patients with newly diagnosed type 2 diabetes

- MI (prior MI)
- PVD
- Stroke (prior MI)
- MI (no prior MI)
- Stroke (no prior MI)
- Cancer
- Pancreatitis
- Renal replacement therapy
- Blindness
- Thiazolidinedione bone fracture
- Thiazolidinedione CHF
- Severe hypoglycaemia with intensive therapy
- Rosiglitazone MI
- Metformin lactic acidosis
- Incretins pancreatitis
- Diabetes-related death
- MI
- Microvascular disease
- Death
- Diabetes-related death

Events per 1000 patient-years

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Bergenstal, Bailey, kendall, Am J Med 2010, 123, 379-84
Insulin Therapy and Cancer

Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study
L. G. Hemkens · U. Grouven · R. Bender · C. Günster · S. Gutschmidt · G. W. Selke · P. F. Sawicki

Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group
H. M. Colhoun · SDRN Epidemiology Group

The influence of glucose-lowering therapies on cancer risk in type 2 diabetes
C. J. Currie · C. D. Poole · E. A. M. Gale

Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin
Samantha L. Bowker, MSC.1,2, Sumit R. Majumdar, MD, MPH.3, Paul Veugelers, PhD.1, Jeffrey A. Johnson, MPH.1,2

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Malignant Neoplasm in Diabetic Patients with Different Insulin Doses (Glargine vs. Human Insulin)

- N=127,031 T1 and T2 insulin-treated patients. 95,804 human insulin, 23,855 glargine, followed up to 4.4 years (mean 1.6 years), cancer-free in preceding 3 years.

<table>
<thead>
<tr>
<th>Incidence per 1,000 patient-years (95% CI)</th>
<th>&lt;20 U/d</th>
<th>20-40 U/d</th>
<th>&gt;40 U/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td>18.6 (16.5-20.7)</td>
<td>20.3 (17.9-22.9)</td>
<td>52.6 (42.9-63.8)</td>
</tr>
<tr>
<td>Human Insulin</td>
<td>17.3 (16.1-18.6)</td>
<td>23.6 (22.3-25.0)</td>
<td>31.0 (29.6-32.3)</td>
</tr>
</tbody>
</table>

Note high rates of new cancer in the study

ORIGIN Trial Results

Any Cancer

Adjusted HR 1.00 (0.88, 1.13)
Log Rank P = 0.97

Presented at: 72nd Scientific Sessions of the American Diabetes Association, 2012
# The ORIGIN Trial: Lack of Association of Insulin Glargine with Malignancy

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Insulin</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer death</td>
<td>3.0%</td>
<td>3.0%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.4%</td>
<td>0.4%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.3%</td>
<td>1.1%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1.2%</td>
<td>1.1%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2.1%</td>
<td>2.2%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0.2%</td>
<td>0.3%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Other cancer</td>
<td>3.7%</td>
<td>3.9%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total cancers</td>
<td>8.9%</td>
<td>9.0%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

N.S., not significant

Meta-analysis: Insulin Glargine and Cancer Risk

- Findings from an European Medicines Agency (EMA)-commissioned database study indicate significantly decreased risk of all cancer and prostate cancer (glargine vs. non-glargine use).

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Cancer Incidence Summary Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer</td>
<td>0.90 (0.82 – 0.99)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.84 (0.74 – 0.95)</td>
</tr>
<tr>
<td>Breast</td>
<td>1.11 (1.00 – 1.22)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.30 (1.00 – 1.28)</td>
</tr>
</tbody>
</table>
Meta-analysis: Insulin Glargine and Cancer Risk

- Data from the Inovalon MORE 2 registry and the Kaiser Permanente Northern California (KPNC) database showed no significant increased risk of all cancer incidence (glargine vs. NPH use)

<table>
<thead>
<tr>
<th>Database</th>
<th>All Cancer Incidence Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inovalon MORE 2</td>
<td>1.12 (0.95 – 1.32)</td>
</tr>
<tr>
<td>Registry</td>
<td></td>
</tr>
<tr>
<td>KPNC</td>
<td>0.90 (0.90 – 1.00)</td>
</tr>
</tbody>
</table>
Incretin-based Therapies and Cancer

- Studies Demonstrating Effects of GLP-1 agonists on Rodent C Cells:
  - Treatment with GLP-1 agonists caused an increase in number of C cells; prolonged treatment was associated with development of medullary thyroid cancer (MTC)
  - Treatment with liraglutide stimulated increases in serum calcitonin in rodents
  - Rats treated with weekly exenatide for 2 years had increased incidence of thyroid C-cell neoplasms (adenomas and carcinomas) in males and females at all doses tested.

- **Human relevance of findings are unknown**
Percentage of Male Mice or Rats Who Developed C cell Adenomas or Carcinomas with Liraglutide Treatment

104 weeks treatment

- Males mouse (adenoma)
- Male mouse (carcinoma)
- Males rate (adenoma)
- Male Rat (carcinoma)

0.03 mg/kg
0.2 mg/kg
1 mg/kg
3 mg/kg

GLP-1 Agonists and Thyroid Carcinoma

- Thyroid C-cell carcinomas in rats with glucagon like peptide-1 (GLP-1) receptor agonist exposure are not believed to be a cause of concern in humans:
  - Rodents have ~45x more C-cells than humans
  - Only rodent C-cell lines express functional GLP-1 receptors

GLP-1 Agonists and Calcitonin

- Plasma calcitonin levels did not increase in patients with T2DM treated with liraglutide or comparator for two years in the Phase III LEAD-2 & -3 trials (Figures A, B, and C)

- Plasma calcitonin also did not increase in LEAD-6 (liraglutide vs. exenatide BID)

Hegedüs L et al. J Clin Endocrinol Metab. 2011;96:853-60
Thyroid Neoplasms in RCTs

- No great disparity in the incidence of thyroid neoplasms has been observed between GLP-1 receptor agonists and placebo or active comparator.

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>Treatment Group</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>Liraglutide</td>
<td>1.3 cases per 1000 patient-years</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1.0 cases per 1000 patient-years</td>
</tr>
<tr>
<td>Exenatide BID</td>
<td>Exenatide BID</td>
<td>0.3 cases per 100 patient-years</td>
</tr>
<tr>
<td></td>
<td>Comparator</td>
<td>0 cases per 100 patient-years</td>
</tr>
</tbody>
</table>

BID, twice daily; GLP, glucagon-like peptide; RCT, randomized controlled trial
GLP-1 agonists increase β-cell mass in rodents
Sitagliptin & Pancreatic Cancer

- Animal studies are conflicting:
  - Sitagliptin was associated with increased pancreatic ductal proliferation (8/8 rats), ductal metaplasia (3/8) and pancreatitis (1/8)
    - In *human islet amyloid polypeptide transgenic rat model* of type 2 diabetes
    - Potential risk factors for pancreatic cancer
  - Sitagliptin exposure (± metformin) for one year in mice was associated with no increase in pancreatitis, ductal metaplasia, or neoplasia compared to the no treatment group.

Aston-Mourney K et al. *Am J Physiol Endocrinol Metab*. 2013;305:E475-84
GLP-1 Receptor Agonists
Pancreatic ductal metaplasia and tumors?

- Butler – Nauck debate at EASD 2011:
  - “For now, this analysis of the FDA database does not establish that pancreatitis, pancreatic and thyroid cancer are caused by GLP-1 based therapy. It simply raises the level of concern that they may be and that the appropriate prospective studies are required to rule them out.”
  - “...at least a decade between the occurrence of the initiating mutation...”
  - “At least five more years are required for the acquisition of metastatic ability...”

Elashoff M et al. Gastroenterology. 2011;141:150-60
Yachida S et al. Nature. 2010;467:1114-7
Incretin-Based Therapies and Cancer - Pancreas

Exenatide Clinical Studies:
- Pancreatic Cancer
  - Exenatide Incidence: 0.5/1,000 pt-yrs
  - Insulin incidence: 1.6/1,000 pt-yrs
  - Placebo incidence: 0/1,000 pt-yrs.
- Adverse Events Reported:
  - Pancreatic cancer: 6.7/100,000 pt-yrs
- German Adverse Events Database 2011
  - Pancreatic cancer 11 cases in 4 years
    - 15,000 to 25,000 patients treated yearly
    - Average duration of treatment 12 months
Could GLP-1 Be a “Good Guy”?  

- GLP-1 is a potent inducer of cAMP and inhibitor of breast cancer cell proliferation
- Treatment of CT26 colon cancer cells and of CT26 tumor-bearing mice with exenatide → increased tumor apoptosis, reduced growth and survival in CT26 colon cancer
- Human neuroblastoma SH-SY5Y: GLP-1 and exenatide stimulate cell proliferation and increase cell viability, enhance neuroprotection

Li Y et al. J Neurochem. 2010;113:1621
Regulatory Communications (Incretin Mimetics)

- European Medicines Agency (EMA):
  - “Presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines.”
  - “With regard to pancreatic cancer, data from clinical trials do not indicate an increased risk...”

- FDA:
  - “Patients should continue to take their medicine as directed until they talk to their health care professional...”
  - “…health care professionals should continue to follow the prescribing recommendations in the drug labels.”
Meta-Analysis of Metformin and Cancer

All Cancer
• 5 observational studies
  – 4 cohort, 1 case control
• N=29,792, average follow-up ~6 years

Colorectal and breast cancer
• 4 observational studies
  – 2 cohort, 2 case control
• N=18,668, average follow-up ~4 years
Metformin and Cancer

Breast Cancer Incidence

Cancer Mortality

Landman GW et al. *Diabetes Care*. 2010;33:322-6
CT.gov “Metformin and Cancer” Search (September 18, 2013)

- 81 open studies returned
- 53 relevant to cancer
  - Breast: 16
  - Colorectal: 8
  - Prostate: 6
  - Gynecologic: 5
  - Pancreatic: 4
  - Leukemia: 4
  - Other Cancers: 10 (lung, skin, head/neck, heme, etc.)
- Most studies investigating improved patient response to chemotherapy, improved survival, or chemoprevention.
Do Thiazolidinediones (TZDs) Cause Cancer?

Pioglitazone:

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposed n/N</th>
<th>Comparison n/N</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al.¹⁰</td>
<td>90/30 173</td>
<td>791/162 926</td>
<td>1.2 (0.9–1.5)</td>
</tr>
<tr>
<td>Neumann et al.¹⁹</td>
<td>175/155 535</td>
<td>1 841/1 335 525</td>
<td>1.22 (1.05–1.43)</td>
</tr>
<tr>
<td>Tseng²⁰</td>
<td>10/2 545</td>
<td>155/52 383</td>
<td>1.30 (0.66–2.58)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.22 (1.07–1.39)</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0\%$

Rosiglitazone:

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention n/N</th>
<th>Control n/N</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn et al.¹⁶</td>
<td>2/1456</td>
<td>8/2895</td>
<td>0.50 (0.11–2.34)</td>
</tr>
<tr>
<td>Home et al.¹⁷</td>
<td>6/2220</td>
<td>5/2227</td>
<td>1.20 (0.37–3.94)</td>
</tr>
<tr>
<td>Overall</td>
<td>8/3676</td>
<td>13/5122</td>
<td>0.87 (0.34–2.23)</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0\%$
Thiazolidinediones and Cancer

- PROactive: A prospective randomized, controlled multicenter study of the effect of pioglitazone on CV events in patients with T2DM
  - Pioglitazone (n=2605); Placebo (n=2633)
  - Incidence of malignancy was similar in both groups
    - 97 (3.7%) pioglitazone, 99 (3.8%) placebo
  - However:
    - Fewer breast cancer cases with pioglitazone
      - 3 (0.1%) pioglitazone, 11 (0.4%) placebo
    - More bladder cancer cases with pioglitazone
      - 14 (0.5%) pioglitazone, 5 (0.2%) placebo
FDA Safety Communication
(Pioglitazone and Bladder Cancer)

- Five-year interim data from the Kaiser Permanente Northern California health plan indicated no significant increase in the risk of bladder cancer with pioglitazone (HR 1.2, 95% CI 0.9 to 1.5)
  - Nominally significant increased risk for use >2 years (HR 1.4, 95% CI 1.03 to 2.0)
- Practitioners should “not use pioglitazone in patients with active bladder cancer,” and should use “with caution in patients with a prior history of bladder cancer.”
Rosiglitazone Meta-analysis

- Included 80 clinical trials
- Rosiglitazone (N=16,332) vs. Comparator (N=12,522)
- Rosiglitazone combined with placebo or other treatments did not significantly modify cancer risk (OR 0.91, 95% CI 0.71-1.16)
- The incidence of malignancies was significantly lower in rosiglitazone-treated patients than in control groups at 0.23 vs. 0.44 cases/100 patient-years (P<0.05)

Monami M et al. Diabetes Care. 2008;31:1455-60

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# RECORD Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Background Sulfonylurea</th>
<th>Background Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>n</td>
<td>1,122</td>
<td>1,103</td>
</tr>
<tr>
<td>Study exposure, (person-years)</td>
<td>6,126</td>
<td>6,110</td>
</tr>
<tr>
<td>Malignancies, n (%)</td>
<td>69 (6.1)</td>
<td>56 (5.1)</td>
</tr>
<tr>
<td>Rate (per 100 person-years)*</td>
<td>1.15</td>
<td>0.94</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.22 (0.86-1.74)</td>
<td>1.33 (0.94-1.88)</td>
</tr>
</tbody>
</table>

*Adjusted for study exposure; CI, confidence interval; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes
TZDs and Prostate Cancer

A

Thiazolidinediones

Ever-Users

P = 0.005

Never-Users

Survival Time (Years)

Probability

0.0

0.2

0.4

0.6

0.8

1.0

0

2

4

6

8

10

12

C

Thiazolidinediones

+/− Metformin

Ever-Users

P = 0.009

Never-Users

Survival Time (Years)

Probability

0.0

0.2

0.4

0.6

0.8

1.0

0

2

4

6

8

10

12

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TZDs and HER2+ Breast Cancer

Association of TZDs with Decreased Cancer Incidence

- **Lung:**

- **Liver:**

- **Colon/rectum:**

- **Cancers in general:**

- **No clear evidence of an association between use of pioglitazone and risk of the incident cancers examined.**
Sodium-Glucose Cotransporter 2 Inhibitors

• Dapagliflozin, which is currently approved in Europe only, was implicated with an increased incidence of breast and bladder cancer.
  – The increased incidence was not statistically significant
• Canagliflozin which was recently approved in the United States has not been associated with a cancer-related safety signal of concern.
SGLT2 Inhibitors - Potential Signal Identified from Dapagliflozin Clinical Data

- Interim clinical data – May 2011 cutoff
  - Overall incidence of malignancies or unspecific tumors was balanced
  - However, imbalance in some tumor types was noted

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Dapagliflozin (N=4559)</th>
<th>All Control (N=2239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Malignant or Unspecified Tumor</td>
<td>65 (1.4%)</td>
<td>29 (1.3%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>7 (0.15%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Bladder Cancers in Dapagliflozin Studies Were Likely Pre-existent

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>5501</td>
<td>3184</td>
</tr>
<tr>
<td>Exposure</td>
<td>5874 pt-γ</td>
<td>3216 pt-γ</td>
</tr>
<tr>
<td>Subjects with Events</td>
<td>9 of 5501 (0.16%)</td>
<td>1 of 3184 (0.03%)</td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>0.15 (0.07, 0.29)</td>
<td>0.03 (0.00, 0.17)</td>
</tr>
</tbody>
</table>

Incidence Rate Ratio: 5.176 (95% CI: 0.678, 233.92)

*Database Cut of 15 July 2011

Dapagliflozin:
control exposure ratio ~ 1.8

Reilly TP. Presented at: AACE Consensus Conference on Diabetes and Cancer; Sept. 2012

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# Diabetes Medications and Cancer Risk

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Cancer Risk Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>No evidence of cancer risk from RCTs</td>
</tr>
<tr>
<td>Incretins</td>
<td></td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>No evidence of MTC or pancreatic cancer in humans</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>No evidence of MTC or pancreatic cancer in humans</td>
</tr>
</tbody>
</table>
| Metformin        | No discernible cancer risk  
Possible protective benefits on cancer outcomes |
| Thiazolidinediones |                     |
| Rosiglitazone    | No evidence of cancer risk |
| Pioglitazone     | Possible risk of bladder cancer at chronic high doses  
(>24 months and >28,000-mg cumulative dose) |
| SGLT2 Inhibitors | No evidence of cancer risk |

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1; MTC, medullary thyroid carcinoma; SGLT2, sodium-glucose cotransporter 2
Does Bariatric Surgery Affect Mortality? (Utah Obesity Surgery Study)

- Retrospective cohort design:
  - 9949 gastric bypass patients
  - 9628 severely obese (BMI $\geq 35$ kg/m$^2$) driver’s license applicants (control)

<table>
<thead>
<tr>
<th></th>
<th>Surgery Group (n/10,000 person-yrs)</th>
<th>Control Group (n/10,000 person-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of death</td>
<td>37.2</td>
<td>61.1</td>
</tr>
<tr>
<td>CV disease</td>
<td>8.5</td>
<td>19.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.3</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td><strong>5.4</strong></td>
<td><strong>15</strong></td>
</tr>
<tr>
<td>Other disease</td>
<td>11.4</td>
<td>17</td>
</tr>
</tbody>
</table>

SOS Study: Obesity-related Cancers Decrease with Surgically-induced Weight Loss

Figure 3: The unadjusted cumulative fatal plus non-fatal cancer incidence from the start of the intervention by sex in surgically treated obese individuals and in obese control individuals.

Implications for Practice
Implications for Practice
(Cancer Screening)

• Cancer screening and counseling on lifestyle changes, should be a part of regular preventive care in people with obesity and/or diabetes.

• Conversely, people who develop cancer at an early age should be screened for metabolic abnormalities.

• Cancer screening tests of proven benefit for malignancies (breast cancer, colon cancer, skin cancer, etc.) in at-risk individuals should begin relatively early.
Implications for Practice
(Diabetes Treatments)

- The current totality of evidence on diabetes treatments and cancer risk should not change clinical practice.
- The practitioner must decide if remote yet plausible cancer risks weight more heavily than suboptimal glycemic control and a higher likelihood of diabetes complications in patients.
- Healthcare professionals should have greater confidence in prescribing all FDA-approved antihyperglycemic medications according to current clinical practice recommendations.
Future Research and Conclusion
Future Research Needs

• Questions about the relative contributions of obesity and diabetes to cancer development remain.
  – What role, if any, does various levels of hyperglycemia play?
  – Do patients with diabetes and controlled glucose have a decreased risk of cancer compared to those with uncontrolled glucose?

• Future studies of medications should be designed to detect cancer-related outcomes in addition to efficacy and safety outcomes.

• Randomized controlled trials of sufficient size and duration are needed to minimize bias, confounding, and chance.
Conclusion

• Epidemiology demonstrates a significant increase of cancer in obesity, insulin-resistant states, and ultimately diabetes; early cancer screening is critical in patients with these conditions.

• There is currently insufficient evidence to warrant withholding of the use of certain glucose-lowering medications on the basis of cancer concerns.

• Further collaborative research between clinicians, as well as basic, clinical, and epidemiologic researchers, is necessary to complete the evidence on these complex issues.