Type 2 Diabetes and Cancer: Is there a link?

Sonali Thosani, MD
Assistant Professor
Department of Endocrine Neoplasia & Hormonal Disorders
MD Anderson Cancer Center
No relevant financial disclosures
Objectives

• Diabetes and risk of site specific cancers
• Mechanism of how diabetes confers increased risk
• Drugs used to treat diabetes and associated cancer risk
• Cancer outcomes in diabetic patients
• Diabetes Cancer
Patient Case

• 56 year old scientist referred to your clinic for diabetes management

• Diagnosed with pancreatic cancer 1 month ago.

• Patient notes that he had diabetes controlled by diet till recently

• He is not very concerned about diabetes management and would really like to focus on pancreatic cancer treatment
Patient Case

- Past medical history is significant for obesity, hypertension
- Family history is significant for diabetes

Questions:
Did my diabetes contribute to cancer development?
How does my diabetes affect cancer outcome?
DIABESITY

Obesity

Insulin Resistance

High Insulin Levels

High Blood Sugar

Image borrowed from Acupuncture and Nature Medicine Clinic
A Morbid Association

Pancreatic Cancer

Breast Cancer

Colon Cancer

Hepatobiliary Cancer

Diabetes

Uterine Cancer

Renal Cell Cancer

Non-Hodgkins Lymphoma

Lung Cancer

Bladder cancer

Handelsman, et al. AACE consensus
Gastrointestinal Cancers

- Cancers of the GI tract have highest risk in diabetic population
  - Hepatobiliary carcinoma
    - High frequency of non-alcoholic fatty liver disease, and hepatitis
  - Colorectal carcinoma
    - Slower bowel transit time increases exposure to toxins

Pancreatic Cancer

- Diabetes can be a risk factor and occur secondary to pancreatic cancer
- Exocrine pancreatic cells exposed to high concentrations of insulin due to shared blood supply
Breast and Uterine Cancer

- Cell proliferation of normal human breast tissue and breast cancer cell lines enhanced by insulin
- Hyperinsulinemia → decreases SHBG → increased bioactive estrogen

There is only one cancer that occurs less frequently in diabetics...

Prostate cancer
Shared risk factors?

- Age
- Sex
- Race/Ethnicity
- Diet
- BMI
- Lifestyle
- Genetics

Mechanisms of carcinogenesis

• Chronic hyperinsulinemia

• Chronic hyperglycemia

• Chronic inflammation
Insulin receptor expression

- IGF-1R and IR is overexpressed in cancer cells due to mutations of tumor suppressor genes
- Elevated IR levels are seen in larger, higher grade breast cancer
- Clinical significance of these expressions have yielded conflicting results
Chronic hyperinsulinemia

- Cancer cells overexpress the fetal isoform A of insulin receptor
- Upregulation of hypoxia inducible factor-1 alpha (HIF-1α) → leptin overexpression → upregulates VEGF
- Higher concentration of hybrid receptors in cancer tissues
- Decreased production of IGFBPs → increased bioavailable IGF-1
Chronic hyperglycemia

• Cancer cells thrive in glucose rich environment but also rely on amino acids for energy
• Hyperglycemia upregulates miRNA → neoangiogenesis and endothelial dysfunction
• Advanced glycation end-products increase inflammation and oxidative stress
• Independent role of hyperglycemia is less clear
Chronic hyperglycemia

Glucose tolerance and risk of cancer mortality

<table>
<thead>
<tr>
<th>Mortality Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Pre-Diabetes</td>
</tr>
<tr>
<td>Newly Diagnosed Diabetes</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
</tbody>
</table>

Chronic Inflammation

- Poorly controlled diabetes is a pro-inflammatory state
- Obesity
  - Adipose tissue increases production of IL-6, FFA, Leptin and TNF-alpha \( \rightarrow \) malignant transformation of cells
- Inflammation favors cancer progression
Patient case

• He had a visit with his oncologist recently who is concerned about his weight loss
• His current BMI is 35 (after weight loss)
• His oncologist has advised him to eat whatever he wants so patient has been eating ice cream every night
• Glucose levels are in 200-300s
• Doesn’t want to get on insulin→cancer
# Diabetes Drugs and Cancer Risk

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Clinical Evidence of potential Cancer Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (Metformin)</td>
<td>↓ pancreatic, breast, colon, HCC, lung cancer</td>
</tr>
<tr>
<td></td>
<td>↓ cancer-related mortality in prostate and cervical cancer</td>
</tr>
<tr>
<td>Sulfonylureas (Glipizide, Glyburide)</td>
<td>↓ overall cancer incidence</td>
</tr>
<tr>
<td>Thiazolidinediones (Rosiglitazone, Pioglitazone)</td>
<td>↓ breast cancer (pio) colorectal cancer (rosi)</td>
</tr>
<tr>
<td></td>
<td>↑ bladder cancer (conflicting data)</td>
</tr>
<tr>
<td>GLP-Receptor Agonist (exenatide, liraglutide)</td>
<td>No evidence of thyroid C-cell hyperplasia in humans</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>↔ Pancreatic cancer</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>↔ Overall cancer rates (dapagliflozin)</td>
</tr>
<tr>
<td></td>
<td>↔ Bladder, breast, renal, malignant adrenal tumors (canagliflozin)</td>
</tr>
<tr>
<td>Insulin analogs</td>
<td>↔ Cancer incidence (glargine)</td>
</tr>
</tbody>
</table>

Adapted from Gallagher, et al. JCO. December 2016.
Metformin

- Stimulates hepatic AMP kinase phosphorylation $\rightarrow$ decreases gluconeogenesis $\rightarrow$ decreases circulating insulin levels
- Downregulates mTOR/AKT pathway
- Decreases inflammatory signals in cancer cells
- >200 phase II/III trials studying metformin effects on cancer-related outcomes

Gallagher, et al. JCO. December 2016
Cancer mortality in Type 2 DM patients

Thiazolidinediones

• Studies of the effect of TZDs on cancer have been inconsistent
  – Pioglitazone associated with increased bladder cancer risk with exposure >24 months or doses >28,000 mg (RR 2-2.5)
  – TZDs decrease risk of colorectal, lung and breast cancer
  – PROactive study: 14 bladder cancers (0.5%) in pioglitazone vs 6 (0.2%) in placebo – 6 yr follow up (23 vs. 22)

Colmers et al. CMAJ. September 2012
Colmers et al. Diabetes Metab. Dec 2012
Incretin-based therapies

• Liraglutide found to increase risk of MTC and serum calcitonin in rats and mice
• Sitagliptin found to increase pancreatic ductal hyperplasia in transgenic rodent model
• 2011: FDA AE reported increased rates of pancreatic cancer with incretin-based drugs
• Limitations: reporting bias, lack of information regarding pancreatic cancer risk factors, MTC not seen in humans

Elashoff et al. Gastroenterology 2011
Incretin based therapies

16,000 patients followed for median 2 years: rates of pancreatitis similar in saxagliptin vs. placebo group

18000 patients: DPP-4 vs sulfonylureas → HR 0.6 (95% CI 0.4-0.9)
30,000 patients: DPP-4 vs. TZDs → HR 1.0 (95% CI 0.7-1.4)
Insulin Analogs

- Mitogenic effects of human insulin have been noted in vitro, in vivo and in human studies
- Registry study showed increased risk of cancers with use of insulin glargine
  - Further analysis showed dose dependent (>40 units daily)
- ORIGIN trial: cancer incidence 7.6% in glargine vs. standard of care
- Large scale patient databases showed no increased risk of cancer with insulin glargine
What is known about cancer outcomes in patients with diabetes?
• Observational study ~800,000 people in 97 prospective studies
• 123,000 deaths
• Hazard ratios for cause-specific death in patients on baseline diabetes status and fasting glucose level
• ~40,000 patients had diabetes at baseline
• Limitations: Diet, physical activity, aspirin use, types of anti-diabetic medications used
Cancer Death: Diabetes

Emerging Risk Factors Collaboration. NEJM. March 2011
• No known history of diabetes
• Excluded patients with known cardiovascular disease
• HR 1.39 (95% CI 1.22-1.59) for fasting glucose > 7 mmol/L (126 mg/dL)

Emerging Risk Factors Collaboration. NEJM. March 2011
Breast Cancer Outcomes with Diabetes

Patients with diabetes had 50% greater all-cause mortality
Diabetes ↔ Cancer treatment

• Certain chemotherapies and targeted therapies contribute to hyperglycemia
  – PI3 kinase/AKT inhibitors
  – mTOR inhibitors
• Glucocorticoids contribute to hyperglycemia
• Immune checkpoint inhibitor mediated insulin dependent diabetes
Future Directions

• How does duration of diabetes affect cancer risk?
• Do patients with well controlled diabetes have decreased risk of cancer compared to those with poorly controlled diabetes?
• How do new therapies for diabetes affect cancer risk?
Summary

• Diabetes increases the risk of multiple malignancies
• The link between diabetes and cancer may be due to many shared risk factors
• No definite evidence that diabetes medications contribute to cancer development
• Age and risk-factor appropriate cancer screening should be done in diabetic patients
Thank You & Questions?

TX-AACE Board of Directors
Steve Sherman
Victor Lavis