DIABETES and CANCER

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RELATIVE RISK (RR) OF CANCER IN TYPE 2 DIABETIC PATIENTS

<table>
<thead>
<tr>
<th>Cancer</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Liver (El-Serag et al. 2006)</td>
<td>2.50 (1.8-3.5)</td>
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<tr>
<td>Pancreas (Hubley et al. 2005)</td>
<td>1.94 (1.53-2.46)</td>
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<tr>
<td>Kidney (Lindblad et al. 1999)</td>
<td>2.22 (1.04-4.70)</td>
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<tr>
<td>Endometrium (Friberg et al. 2007)</td>
<td>2.22 (1.80-2.74)</td>
</tr>
<tr>
<td>Colon-rectum (Larsson et al. 2005)</td>
<td>1.36 (1.23-1.50)</td>
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<tr>
<td>Bladder (Larsson et al. 2006)</td>
<td>1.43 (1.18-1.74)</td>
</tr>
<tr>
<td>NonHodgkin’s lymphoma (Faivre 2006)</td>
<td>1.41 (1.07-1.88)</td>
</tr>
<tr>
<td>Breast (Larsson et al. 2007)</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>
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</tbody>
</table>

MAJOR FACTORS IN DIABETES THAT MAY INFLUENCE CANCER RISK

• Hyperinsulinemia and Insulin Resistance
• Insulin Receptor Overexpression
• Fetal Insulin Receptor
OTHER FACTORS IN DIABETES THAT MAY INFLUENCE CANCER RISK

- Obesity
- Hyperglycemia
- Elevated Fatty Acids
- Oxidative Stress
- Chronic Inflammation

**Insulin Resistance**

- Genetic Influences → Insulin Resistance → Acquired Factors
  - \(\beta\)-Cells Activated → Hyperinsulinemia
  - Compensation with Normal Glucose Tolerance
  - Impaired Glucose Tolerance
  - Lipo and Gluco Toxicity
  - \(\beta\)-Cell Failure → Type 2 Diabetes

**INSULIN RESISTANCE**

- Acquired
Acquired Insulin Resistance

The Economist, Dec.

INSULIN RESISTANCE

- Intrinsic/ Genetic

INSULIN RESISTANCE

Insulin resistance clusters in families and racial groups and has a heritable component
REAVEN HYPOTHESIS

• In 30% of non-obese, non-diabetics, intrinsic insulin resistance is present in muscle, fat and liver. This resistance causes hyperinsulinemia
• Insulin and insulin resistance leads to Type 2 diabetes, Metabolic Syndrome, and Cancer

Long-Term Follow-up of Insulin Sensitive and Resistant Non Obese Non-Diabetics

![Graph showing number of chronic events vs. diabetes status](image)

Reaven et al. JCEM, 2001

Why Should The Hyperinsulinemic Insulin Resistant State Lead To Cancer?

• High levels of insulin stimulates normal cell growth
• Cancers may not be insulin resistant
• Cancers overexpress the insulin receptor
• Cancers express the fetal insulin receptor (IR-A)
Insulin, Insulin Receptors and Breast Cancer

- Insulin is mitogenic in cultured breast cells
- Insulin increases breast cancer growth
- Insulin receptors are overexpressed in breast cancers and are the fetal type
Evidence for a Role of Insulin and the Insulin Receptor in Breast Cancer

- Cell culture
- Animal Studies
- Human Clinical

INSULIN INDUCES HUMAN BREAST CELL GROWTH

CONTROL

INSULIN

Insulin Stimulates Proliferation in Breast Cancer Cell Lines

Belfiore et al. 1997
EFFECT OF GLUCOSE AND INSULIN ON THE GROWTH OF BREAST CANCERS IN RATS

EFFECT OF DIABETES ON THE GROWTH OF BREAST CANCERS IN RATS

Insulin levels And Human Breast Cancer Risk
Human Clinical Data

- High insulin is associated with breast cancer risk in most studies
- Insulin levels predict outcome in patients
- Breast cancers overexpress insulin receptors
- Breast cancers have the more mitogenic fetal form of the insulin receptor (IR-A)

Elevated Insulin Levels and Breast Cancer Risk

<table>
<thead>
<tr>
<th>Case-control study</th>
<th>Relative Risk (quintiles)</th>
<th>Odds Ratio (quintiles)</th>
<th>Odds Ratio (tertiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>2.9 (1.7-5.1)</td>
<td>2.6 (1.2-6.5)</td>
<td>2.7 (1.2-5.9)</td>
</tr>
<tr>
<td>Canada</td>
<td>2.8 (1.2-6.6)</td>
<td>2.8 (1.2-6.6)</td>
<td>2.7 (1.2-5.9)</td>
</tr>
<tr>
<td>China</td>
<td>2.7 (1.2-5.9)</td>
<td>2.7 (1.2-5.9)</td>
<td>2.7 (1.2-5.9)</td>
</tr>
<tr>
<td>Japan</td>
<td>4.6 (1.8-10.5)</td>
<td>4.6 (1.8-10.5)</td>
<td>4.6 (1.8-10.5)</td>
</tr>
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Low Insulin levels Predict Improved Survival in Human Breast Cancers

(Goodwin et al 2002)

Survival

Low High
Increased Insulin Receptor Expression is a Feature of Human Breast Cancers

Fetal IR and Adult IR

1. Fetal IR (IR-A), missing exon 11, plays a critical role in fetal growth, and is activated by both insulin and IGF-II

2. Adult IR (IR-B), has exon 11, and regulates glucose metabolism by insulin

Two Isoforms of the Insulin Receptor
IR-A is Overexpressed in Human Breast Cancers

IR Signaling in Breast Cancer Specimens

Mammary Gland Hyperplasia in Fetal IR Transgenic mice
How Can We Ameliorate Insulin Resistance To Possibly Prevent Cancer Occurrence and/or Progression?

• Reduce obesity
• Exercise
• Medications?
Obesity and Cancer Mortality - Women

Body Mass Index (kg/m²)

- 18.5-24.9
- 25-29.9
- 30-34.5
- 35-39.9

Relative Risk of Death

- Colorectal
- Liver
- Breast
- Uterus
- Ovary

Physical Activity and Breast Cancer Survival
(Holmes et al JAMA 2005)

- 2987 nurses with breast cancer followed for up to 14 years
- Physical activity reduced the risk of death

Metformin and Cancer
METFORMIN INHIBITS THE GROWTH OF BREAST CANCER CELL LINES

Alimova et al

EFFECT OF METFORMIN ON PROSTATE CANCER GROWTH

Ben Sahra et al

Pathologic Complete Responses (Pcr) to Metformin In Breast Cancer

Proposed Mechanism Of Metformin Action In Breast Cancer - Goodwin

Insulin Treatment and Risk of Cancer

- In 2009 4 studies were published in Diabetologia. Several suggested that insulin, especially insulin glargine was associated with cancer.
- These studies involved statistical manipulation of epidemiologic data.
- There were fundamental internal disagreements and multiple inconsistencies.

FDA Early Communication About Safety of Insulin Glargine
July 1, 2009

“Four observational studies evaluated large patient databases and all reported some level of association between the use of insulin glargine, and other insulin products, and various types of cancer. The duration of patient follow-up in all 4 studies was shorter than what is generally considered necessary to evaluate for cancer risk from drug exposure. Further, inconsistencies in findings within and across individual studies raise concerns as to whether an association between the use of insulin glargine and cancer truly exists.”
ADA Statement on Insulin Glargine and Cancer

June 26, 2009

“Four different population-based studies were reported and published in Diabetologia and the data within these studies and between these studies are conflicting and confusing. Until more information is available, the American Diabetes Association advises patients using insulin not to stop taking it”

CONCLUSIONS

• Insulin resistance is a risk factor for cancer
• Insulin stimulates cancer growth
• Cancers overexpress IR-A
• Diet, exercise, and metformin may help prevent cancers
• No convincing evidence that insulin therapy causes or promotes cancer