Increased Risk of Cancer in Obesity and Type 2 Diabetes

Derek LeRoith
Mt Sinai
Disclosures

• Consultant:
  • Merck
  • Bristol Myers Squibb
  • Astrazeneca
  • Sanofi-Aventis

Grant Support:
  • Merck
  • Sanofi
  • Novartis
Order:
  1. Epidemiology
  2. Animal model
  3. Mechanisms
Breast Cancer and Endogenous Insulin Levels

Hazard Ratios

- Q1 <27.0: 1.0
- Q2 27.0-35.3: 1.46 (1.11-1.93)
- Q3 35.3-51.9: 1.78 (1.17-2.72)
- Q4 >51.9: 3.62 (1.41-9.29)

P=0.007
Does Bariatric Surgery Affect Mortality?

University of Utah, 2007

- Retrospective cohort study
  - 9949 gastric bypass patients
  - 9628 severely obese driver’s license applicants (BMI ≥35 kg/m2)

### Does Bariatric Surgery Affect Mortality?

<table>
<thead>
<tr>
<th></th>
<th>Surgery Group (#/10,000 person-yr)</th>
<th>Control Group (#/10,000 person-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All causes of death</strong></td>
<td>37.2</td>
<td>61.1</td>
</tr>
<tr>
<td><strong>CV disease</strong></td>
<td>8.5</td>
<td>19.3</td>
</tr>
<tr>
<td><strong>Diabetes</strong></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><strong>Other disease</strong></td>
<td>11.4</td>
<td>17</td>
</tr>
<tr>
<td><strong>Non-disease causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accident</strong></td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Poisoning</strong></td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Suicide</strong></td>
<td>2.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

A Statistical Study in Cancer Death-Rates

Cancer and Diabetes,

Both diseases have very much the same age distribution. (2) They stand almost alone as being on the increase, while other causes of death show declining rates. (3) The aetiology of both diseases is obscure. (4) Both being diseases of old age ...

... If there were a common factor in the causation of the dual increase a correlation between these diseases might be discovered.

If there was a common factor in the causation of the dual increase.......
How Can Obesity and Diabetes Affect Breast Cancer Development?

- Nutrients
- IGF-I
- Leptin
- Adiponectin
- Cytokines
- Chemokines

- Hyperinsulinemia
- Hyperglycemia
- Hyperlipidemia

Obesity

Diabetes

Cancer
A Mouse Model of Type 2 Diabetes
Etiology of Type 2 Diabetes
Impaired Insulin Secretion and Insulin Resistance

Genes and environment

Impaired insulin secretion + Insulin resistance

Impaired glucose tolerance

Type 2 diabetes
Animal Model of Insulin Resistance

IGF-I/insulin receptor hybrids in muscle → Muscle Insulin Resistance → Increased lipolysis in visceral fat → Increased fatty acids → Fatty acid oxidation

Insulin resistance in adipocytes → Increased lipolysis in visceral fat

Insulin resistance in liver → Increased gluconeogenesis in liver

Increased fatty acids → Fatty acid oxidation

β cell compensation

β cell decompensation → Loss of 1st phase insulin secretion

Impaired glucose tolerance → Increased glucose output → Type 2 Diabetes

Non-Obese

Metabolic Characteristics of MKR Mice

- **Serum Insulin Levels (ng/ml)**
  - Age (weeks): 2 3 4 5 6 7 8
  - Control vs. MKR

- **Blood Glucose Levels (mg/dL)**
  - Age (weeks): 2 3 4 5 6 7 8
  - Control vs. MKR

- **Blood Glucose Levels after Glucose Injection**
  - Minutes after Glucose injection: 0 20 40 60 80 100 120
  - Control vs. MKR

- **Blood Glucose Levels after Glucose Injection**
  - Minutes after glucose injection: 0 20 40 60 80 100 120
  - Control vs. MKR
# Metabolic Abnormalities in MKR Mice

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Obesity</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Insulin resistance

Blood and tissue:
- ↓ IGFBP-1
- ↑IGF-1/2 serum and/or tissue bioavailability

Mammary epithelium:
- ↑↑↑ IR
- ↑ IGF-IR
- ↑ IR/IGF-IR
- ↓ Apoptosis
- ↑ Proliferation
- ↑ Tumor development

↑ Insulin

↑ IGF

Mammary epithelium: IR/IGF-IR hybrids
IR and IGF-IR Receptors

IGF-I, IGF-II

α α

IGF-IR / insulin receptor-A

β β

Cell Survival, growth, proliferation

IGF-I receptor

IGF-IR / insulin receptor-B

β β

Metabolic effects

Insulin receptor-A

β β

IGF-II receptor

β β

IGF-II degradation

IGF-II
Insulin Receptor Isoforms

Mouse Models of Breast Cancer

**Transgenic Model**

Polyoma Middle T Ag (PyVmT) and MKR

Polyoma Middle T Ag/MKR

Polyoma Middle T Ag (PyVmT)

**Cell transformation, Proliferation, Migration, Invasion**

Invasive Malignant Growth

Mitogenic and other biological effects
Transgenic Model: Early Stages of Mammary Tumorigenesis

Polyoma Middle T Ag (PyVmT)
Orthograft Model

PyVmT+ Met-1 cells

WT

PyVmT+ Met-1 cells

MKR

Hyperinsulinemic MKR Mouse

Met-1 tumor growth

Plasma insulin

Novosyadlyy R et al. Cancer Res 2010; 70(2): 741-751
Molecular Mechanisms Underlying Tumor-Promoting Activity in T2DM

Insulin resistance

↑ Insulin

IR / IGF-IR

IRS

PI3K

AKT

↓ Apoptosis

↑ Proliferation

↑ Migration

↑ Invasion

↑ Tumor progression
Insulin resistance

↑ Insulin

IR / IGF-IR

IRS

PI3K

AKT

↓ Apoptosis
↑ Proliferation
↑ Migration
↑ Invasion

↑ Tumor progression

Strategies to Reduce Tumor-Promoting Activity in T2DM
Reduction of Mammary Tumors Using a Tyrosine Kinase Inhibitor, Despite the Marked Hyperinsulinemia

Met-1 tumor growth

- • - WT - vehicle
- ▲ - MKR - vehicle
- ○ - WT - BMS-536924
- △ - MKR - BMS-536924

BMS-536924
100 mg/kg/d

Tumor volume, cm³

Time post-inoculation

Plasma insulin

- • - WT - vehicle
- ▲ - MKR - vehicle
- • - WT - BMS-536924
- ▲ - MKR - BMS-536924

ng/mL

0 10 20 30 40
Strategies to Reduce Tumor-Promoting Activity in T2DM

Insulin resistance

↑ Insulin

IR / IGF-IR

IRS

PI3K

AKT

↓ Apoptosis
↑ Proliferation
↑ Migration
↑ Invasion

↑ Tumor progression
Reduction of Mammary Tumors Associated with a Reduction in the Hyperinsulinemia

PyVmT Oncogene Expressing Cells

Metastases

- Metastases were measured both by in vivo imaging of c-myc (Mvt1)-induced tumors; cells were transfected with luciferase expression vector.
Xenograft Model

Orthotopic Inoculation of Mvt-1 Cells

Monitoring of primary tumor formation and development of pulmonary metastases

Heterotopic Inoculation of Mvt-1 Cells

Monitoring of pulmonary metastases in mice devoid of primary tumors
Figure 2

A

B

C

D

Figure 2

Flux (photons/second/cell)

Tumor volume mm³

Tumor weight (g)

Control

MKR

Weeks post-inoculation

2 weeks post-inoculation

3 weeks post-inoculation

5 weeks post-inoculation

6 weeks post-inoculation

7 weeks post-inoculation

Control

MKR

Control

MKR

Control

MKR

Control

MKR
Metastases

![Graph showing number of pulmonary metastases/mouse between Control and MKR groups.](#)

Control  MKR

**Rosalyn Ferguson unpublished.**
To determine whether the increased metastases in MKR hyperinsulinemic mice was due to larger tumors, we removed tumors when still small (at different stages; earlier in MKR than WT controls. After recovery from survival surgery, mice were followed for another few weeks and then lung metastases quantified.

**Results:** The increased metastases in MKR mice occurred whether from small or larger tumors.

Finally, the reduction in hyperinsulinemia reduced metastases.

**Conclusions:** Hyperinsulinemia maybe the direct cause for increased metastases.