Energy Balance and Cancer:
Carcinogenesis and Cancer Survival

Presentation to
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Fred Hutchinson Cancer Research Center
• Glycemic load, energy balance, and carcinogenesis in animals and humans
• Obesity-related biomarkers and breast cancer survival
The Seattle Transdisciplinary Research on Energetics and Cancer Center

Exposures

Intermediate Biology
Glucose  Inflammation
Insulin  Adipokines
IGF

Models

Cells
Growth
Proliferation
Apoptosis

Animals
Tumorigenesis
Tissue angiogenesis

Humans
Biomarkers of carcinogenesis

Populations
Glycemic Load, Energy Balance and Cancer: A Transdisciplinary Experimental Approach in Animals and Humans

A Collaboration Between Seattle-TREC Projects 2 and 3

Colorado State: Henry Thompson
Fred Hutchinson: Marian Neuhouser, Johanna Lampe
Blood Glucose Concentrations After Ingesting High and Low Glycemic Index Foods

Transdisciplinary Animal and Human Experimental Studies

**Rodent Study:**
Investigates effect of low vs. high glycemic load experimental diets on carcinogenesis and biomarkers in a preclinical model

**Human Study:**
Investigates effect of low vs. high glycemic load experimental diets on cancer-susceptibility biomarkers

**Common set of biomarkers:**
- IGF1
- IGFBP3
- leptin
- adiponectin
- IL-6
- C-reactive protein
- insulin
- glucose
Pre-Clinical Model for Breast Carcinogenesis

- 1-Methyl-1-nitrosourea injected
- Day 21 Tumor Palpation
- Day 50 Study Terminated

$n = 60$ female Sprague Dawley rats

High or Low GL Diet

Graph:
- X-axis: Days Post Carcinogen
- Y-axis: Body Weight (g)
- Two lines: High GL and Low GL

TREC
# Human Feeding Study Diets

## Average Daily Nutrient Content

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Low-GL</th>
<th>High-GL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>Isocaloric, weight maintaining</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>20% kcal</td>
<td>20% kcal</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50% kcal</td>
<td>50% kcal</td>
</tr>
<tr>
<td>Fat</td>
<td>30% kcal</td>
<td>30% kcal</td>
</tr>
<tr>
<td>Glycemic Load</td>
<td>117</td>
<td>244</td>
</tr>
</tbody>
</table>

Source: Noar et al (submitted)
Glycemic Load (GL) Effects of Diet on Cancer Incidence

- High GL
- Low GL

Incidence of Palpable Mammary AC (%)

Days Post Carcinogen

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

20 25 30 35 40 45 50 55 60
Glycemic Load (GL) Effects of Diet on Cancer Multiplicity

Average No. Palpable Mammary AC/Rat

Days Post Carcinogen

High GL

Low GL
Glycemic Load (GL) Effects of Diet on Apoptotic Markers in Tumors

- High glycemic load decreased apoptosis
Effects of High- vs. Low-Glycemic Load Diet on Cancer-Related Biomarkers in Rats

• Increased plasma:
  – Glucose
  – Insulin
  – Insulin-like growth factor 1
  – Interleukin-6
  – Leptin

• Decreased plasma:
  – Adiponectin
Seattle Project 3: Glycemic Load & Obesity Effects on Cancer Biomarkers

• Investigating effects of low- and high-glycemic load diets on cancer-related biomarkers in humans

• Examining extent to which overweight/obesity modifies response to diets

• Design = human feeding study in 88 individuals aged 18-45 years
Summary

- Low-glycemic load diets reduced carcinogenic response in the mammary gland
- Low-glycemic load diets favored reduced cell proliferation and a pro-apoptotic environment in carcinogenesis
- Circulating markers: hypothesized directions
- Cellular mechanisms being pursued
- Human trial (Project 3) in progress
Obesity-related Biomarkers and Breast Cancer Survival

Seattle, USC, NCI
Cross-TREC Developmental Project

Catherine Duggan, Anne McTiernan, Leslie Bernstein,
Rachel Ballard-Barbash
and colleagues
Overweight, Obesity and Breast Cancer Prognosis

• Overweight and obese breast cancer patients have poorer survival and increased recurrence compared with lighter patients

• Of 34 published studies, statistically significant association in 26, non-significant effect in 4, no effect in 4

Source: Cheblowski, Aiello, McTiernan, JCO 2002; 20(4):1128-1143
Study Aim

• Assess associations of obesity biomarkers with breast cancer survival:
  – Adiponectin
  – Insulin
  – Glucose
  – Fructosamine
  – HOMA (marker of insulin resistance)
Health, Eating, Activity, and Lifestyle (HEAL) Cohort of Breast Cancer Survivors

- Population based (SEER registries)
- Multi-center (WA, LA, New Mexico)
- Multiethnic
- Stage 1–IIIA diagnosed 1995 - 1998
- n= 550 with blood ~ 3 years post-diagnosis
- Excluded: Type 2 DM, recurrence/new primary before blood draw
- Followed mean 6 years
Participant Characteristics (n=550)

- Mean age: 57, range 31-89 years
- Mean BMI: 27.3, range 16.2 - 53.3 kg/m²
- SEER Stage
  - Local: n=392
  - Regional: n=158
- Race/ethnicity
  - African-American: n=137
  - White: n=336
  - Hispanic: n=64
  - Other: n=13
Risk of Breast Cancer Death by Adiponectin
(HEAL, 550 Stage I-IIIa, followed mean 6 years)
# Insulin Resistance and Breast Cancer Deaths

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>1.02</td>
<td>0.99-1.04</td>
<td>0.08</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.07</td>
<td>1.01-1.17</td>
<td>0.03</td>
</tr>
<tr>
<td>Fructosamine</td>
<td>0.99</td>
<td>0.99-1.01</td>
<td>0.79</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.00</td>
<td>0.99-1.02</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Summary

• Increased breast cancer deaths with:
  • Lower levels of adiponectin
  • Increased HOMA (↑ insulin resistance)

• Analyses in progress for disease-free survival

• Results suggest biomarkers for association of obesity with reduced breast cancer prognosis
Acknowledgements: Glycemic load, energy balance, and carcinogenesis

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