Obesity, Energy Balance and Cancer: Lessons from Translational Studies

Stephen D. Hursting, PhD, MPH

Professor and Chair
Department of Nutritional Sciences
University of Texas at Austin

and

Professor, Department of Molecular Carcinogenesis
University of Texas MD Anderson Cancer Center

Disclosure Information

• I have no financial relationships to disclose

• I will discuss a preclinical study using Afinitor® (everolimus, Rad001) and preclinical and off-label clinical studies of Lovaza® (omega-3-acid ethyl esters)
Today’s Presentation

- The hallmarks of cancer and the scope of the cancer problem
- Links between diet, obesity, metabolism and cancer in humans and animals
- Where are we today? Diet recommendations (focus on phytochemicals, obesity prevention)
- Hot topics in nutrition, obesity and cancer: a focus on mechanisms
- Discussion

Cancer: A Complex Foe

*The essential aberrations of cancer*

- Dysregulated growth signals and cellular energetics
- Inflammation
- Evading growth suppression, apoptosis and immune surveillance
- Genomic instability
- Sustained angiogenesis
- Tissue invasion and metastasis
- Limitless replicative potential

Factors Contributing to Cancer Risk in the United States

Diet/Obesity: ~35%
Tobacco: ~30%
Occupational and Pollution: ~5%
Infection: ~10%
Other: ~20%
  • Familial
  • Sunlight / radiation
  • Alcohol
  • Long-term exposure to some drugs

Doll and Peto, 1981
<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage of cancer caused</th>
<th>Number of deaths in United States</th>
<th>Magnitude of possible reduction (%)</th>
<th>Period of time (years)</th>
<th>Evidence example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>33</td>
<td>188,744</td>
<td>75</td>
<td>10–20</td>
<td>Comparison of lung cancer mortality by state (Fig. 1)</td>
</tr>
<tr>
<td>Overweight and obesity</td>
<td>20</td>
<td>114,390</td>
<td>50</td>
<td>2–20</td>
<td>Bariatric surgery and sustained changes in weight and markers (60)</td>
</tr>
<tr>
<td>Diet</td>
<td>5</td>
<td>28,600</td>
<td>50</td>
<td>5–20</td>
<td>Folate and colorectal cancer (65)</td>
</tr>
<tr>
<td>Lack of exercise</td>
<td>5</td>
<td>28,600</td>
<td>85</td>
<td>5–20</td>
<td>Adolescent physical activity (18)</td>
</tr>
<tr>
<td>Occupation</td>
<td>5</td>
<td>28,600</td>
<td>50</td>
<td>20–40</td>
<td>Asbestos workplace regulation (10)</td>
</tr>
<tr>
<td>Viruses</td>
<td>5</td>
<td>28,600</td>
<td>100</td>
<td>20–40</td>
<td>Liver cancer reduction by vaccine (22)</td>
</tr>
<tr>
<td>Family History</td>
<td>5</td>
<td>28,600</td>
<td>50</td>
<td>2–10</td>
<td>Bilateral oophorectomy for BRCA1/2 (24); again trial for Lynch syndrome (17)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>17,200</td>
<td>50</td>
<td>5–20</td>
<td>Regulation (66)</td>
</tr>
<tr>
<td>UV and ionizing radiation</td>
<td>2</td>
<td>11,400</td>
<td>50</td>
<td>5–40</td>
<td>Reduced medical exposures (65)</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>1</td>
<td>5,720</td>
<td>50</td>
<td>2–10</td>
<td>Hormone therapy-related drop in breast cancer (86)</td>
</tr>
<tr>
<td>Reproductive factors</td>
<td>3</td>
<td>17,200</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Pollution</td>
<td>2</td>
<td>11,400</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Total potential reduction = 54.5%

*Adapted from Walsh et al (97). 1U.S. death estimates from the American Cancer Society (86). **Defined as sum (percentage caused by modifiable exposure x magnitude of reduction).
Fatalistic Beliefs about Cancer

- “Almost everything causes cancer…”
  - almost 50% agree or strongly agree
- “There’s not much a person can do to prevent cancer…”
  - approximately 25%
- “It’s hard to know [which recommendations] to follow…”
  - almost 75%

1940’s Advertisement from the United Kingdom
Diets should contain a variety of plant-based foods

WCRF/AICR 2007
Bioactive Food Components Influence Cancer Processes

DNA Repair

Carcinogen Metabolism

Hormonal Regulation

Cell Cycle

Differentiation

Apoptosis

The Shape of Things to Come. The Economist 12/11/03

(http://www.economist.com/displaystory.cfm?story_id=2282754)
The US Obesity Epidemic

Ogden, et al., JAMA 2014:

- 69% of US Adults Overweight or Obese (BMI >25.0 kg/m²)
- 36% US Adults Obese (BMI >30.0 kg/m²)
- 6.5% US Adults Extremely Obese (BMI >40.0 kg/m²)

Metabolic Syndrome

Describes a state of metabolic dysregulation characterized by:

- Insulin resistance, hyperglycemia*
- Dyslipidemia (↑triglycerides*, ↓HDL-C*)
- ↑Waist circumference*
- Hypertension*
- Proinflammatory state (↑cytokines, ↑chemokines)
- Vascular perturbations (↑PAI-1, ↑VEGF)
- Altered adipokines (↑leptin, ↓adiponectin)
- Elevated bioavailable IGF-1 (NHANES)

- Associated with many types of cancer
  25% (144K) cancer deaths/year in US caused by overweight/obesity
Mortality from Cancer According to BMI for U.S. Women in the ACS Cancer Prevention Study II

LOOMING QUESTION:
How to Decrease Cancer Risk in the ~710 Million Adults Worldwide Currently Obese?

Need a mechanistic approach to identify targets and strategies to break obesity-cancer links

Cancer: A Complex Foe

*Obesity, calorie restriction impact each cancer hallmark*

- Dysregulated growth signals and cellular energetics
- Evading growth suppression, apoptosis and immune surveillance
- Sustained angiogenesis
- Inflammation
- Genomic instability
- Tissue invasion and metastasis
- Limitless replicative potential

Calorie Restriction (~20%) Extends Lifespan in Multiple Species

- Yeast (S. cerevisiae)
- Worm (C. elegans)
- Fly (D. melanogaster)
- Bowl and Doily Spider
- Labrador Retriever
- Hereford Cow

% Increase in Longevity (versus *ad libitum*-fed controls)

Modelling Energy Balance and Human Cancer in Mice by Altering Key Genes and Pathways

Hursting, et al., *Mutation Res*, 2005
### Growth Factor Levels and MMTV-Wnt-1 Mammary Tumor Growth in Lean, Overweight and Obese Mice

<table>
<thead>
<tr>
<th>CR (30%) (29% body fat)</th>
<th>IGF-1 (ng/ml)</th>
<th>Insulin (pg/ml)</th>
<th>Leptin (ng/ml)</th>
<th>Adiponectin (ng/ml)</th>
<th>L/A</th>
<th>Tumor Vol (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=12 mice/group</td>
<td>390</td>
<td>380</td>
<td>1.9</td>
<td>9.5</td>
<td>0.2</td>
<td>120</td>
</tr>
<tr>
<td>Overweight (35% body fat)</td>
<td>526</td>
<td>398</td>
<td>5.3</td>
<td>9.2</td>
<td>0.6</td>
<td>510</td>
</tr>
<tr>
<td>DIO (47% body fat)</td>
<td>718</td>
<td>596</td>
<td>16</td>
<td>9.1</td>
<td>1.8</td>
<td>1485</td>
</tr>
</tbody>
</table>

Dr. Nomeli Nunez


### Transplanted Wnt-1 Tumor Growth in AZIP/F-1 (Fatless) Mice Versus Wild-Type Mice

- **AZIP/F1**
- **Wild-type**

*Hursting et al., Cancer Res, 2007*
Genetic Reduction of Systemic IGF-1

~75% of IGF-1 in serum is produced by liver

Ecuadorians with Laron Syndrome have very low IGF-1 and inflammatory cytokines, increased longevity, and virtually no cancer or diabetes. NY Times 2/16/11.

Transplanted Wnt-1 Mammary Tumor Growth in Wild-Type Control and Liver IGF-1 Deficient (LID) Mice

Dr. Nikki Ford

Ford, et al. Endocrine-Related Cancer, in press
IGF-1 Infusion or mTOR Activation Impacts Transplanted MMTV-Wnt-1 Mammary Tumor Growth in Calorie Restricted Mice

Nogueira et al. *Endocrine-Related Cancer, 2012*

Dietary Energy Balance Modulation of Akt/mTOR Signaling (normal and tumor tissue)

Skin
Liver
Prostate
Colon
Pancreas
Mammary

Hursting, et al., *Cancer Res, 2007*
Moore, et al., *Cancer Prev Res, 2008*
Olivo-Marston, et al., *Mol Carcinogenesis 2009*
deAngel, et al., *Mol Carcinogenesis, 2013*
**RAD001 (Afinitor®) Inhibits mTOR and Wnt-1 Mammary Tumor Growth in Lean, Control and Obese Mice**

![Graph showing tumor weight comparison between Placebo, RAD001 (10mg/kg), and Obese + RAD001 (15mg/kg) groups for Lean, Control, and Obese mice.](image)


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**Cancer: A Complex Foe**

*Obesity, CR impact the essential aberrations of cancer*

- Dysregulated growth signals and cellular energetics
- Evading growth suppression, apoptosis, and immune surveillance
- Sustained angiogenesis
- Limitless replicative potential
- Genomic instability
- Inflammation
- Tissue invasion and metastasis

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Inflammation and Cancer

- Malignancies often arise from areas of chronic infection and inflammation
- Chronic inflammatory conditions linked to tumorigenesis include:
  - Gastritis (H. Pylori) – Gastric Cancer
  - Cystitis – Bladder Cancer
  - Bronchitis – Lung Cancer
  - Esophagitis – Esophageal Cancer
  - Dermatitis – Skin Cancer
  - Ulcerative colitis – Colon Cancer
  - Inflammatory bowel disease – Colon Cancer
  - Hepatitis (including NASH) – Liver Cancer
  - Pancreatitis – Pancreatic Cancer (up to 55-fold increased risk)

Obesity Causes Inflammation in Organs and Visceral Fat

Crown-like Structures (CLS) (Macrophage/Adipocyte/Epithelial Tumor Cell Interactions)


Dietary Energy Balance Affects Pancreatic Tumor-Free Survival in Kras Ink4a+/- Mice

DIO increases, CR decreases:
- Pancreatic steatosis
- Pancreatic CLS
- Serum IGF-1 levels
- Leptin:Adpn
- Serum cytokine levels
- IGF-1R/Akt/mTOR signaling
- NF-kB signaling

Lashinger, et al., Cancer Prev Res 2013

Energy Balance, Metabolism and Cancer: Transdisciplinary Research Approaches
Translational Example 1: CR Pilot Trial in Obese Postmenopausal Women

28 High Risk Women: BMI >30 kg/m² No HRT

6-month NHLBI Step 1 Diet Regimen

Repeat RPFNA

Response Biomarkers

FNA Tissue Markers

Proliferation (Ki-67)

Mammographic Breast Density

Serum insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3

RPFNA; qRT-PCR; insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3

Breast Cancer Res Treat 2013

Favorable modulation of benign breast tissue and serum risk biomarkers is associated with >10 % weight loss in postmenopausal women

Carol J. Fabian · Bruce F. Kimler · Joseph E. Donnelly · Debra K. Sullivan · Jennifer R. Kiem · Brian K. Petreño · Teresa A. Phillips · Trina Metheny · Sonya Avermann · Hung-wen Yeh · Carola M. Zalies · Gordon R. Mills · Stephen D. Hursting
The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women

Michelle Harvie*, Claire Wright1, Mary Pegington1, Debbie McMullan1, Ellen Mitchell1, Bronwen Martin1, Roy G. Cutler3, Gareth Evans1, Sigrid Whiteside1, Stuart Maudsley1, Simona Conlon1, Rui Wang1, Olga D. Carlson1, Josephine M. Egan1, Mark P. Mattson2 and Anthony Howell1

Changes in Benign Breast Tissue (FNA) Biomarkers After 6-Month Diet and Exercise Intervention in Obese Women

Table 7 Summary of favorable adipocytokine, mRNA, and proteomics changes in benign breast tissue, showing number of paired specimens exhibiting either a decrease or an increase in value

<table>
<thead>
<tr>
<th>Biomarker (assay method)</th>
<th>Total cohort</th>
<th>Weight loss &lt;10%</th>
<th>Weight loss &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P value</td>
</tr>
<tr>
<td>Adiponectin:Leptin Ratio (Luminesx)</td>
<td>3</td>
<td>21</td>
<td>0.003</td>
</tr>
<tr>
<td>pS2 (RT-qPCR)</td>
<td>12</td>
<td>5</td>
<td>0.005</td>
</tr>
<tr>
<td>CyclinB1 (RPPA; Epitomics 1495-1™)</td>
<td>16</td>
<td>2</td>
<td>0.001</td>
</tr>
<tr>
<td>Rh pS407-S411 (RPPA; CST 9308™)</td>
<td>14</td>
<td>4</td>
<td>0.005</td>
</tr>
<tr>
<td>S6 pT235-S236 (RPPA; CST 2211™)</td>
<td>14</td>
<td>4</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Bold denotes statistically significant results

* Antibody source and catalog number: CST Cell Signaling Technology

† Wilcoxon signed rank test (2-tailed) assessment of change in values over time (Pre-study to Post-Study)

Example 2. Integrated Phase II Trial and Animal Studies of Lovaza® (omega-3-acid ethyl esters)

Serum/Benign Breast Tissue Biomarkers
1. Response: Ki-67, cytomorphology
2. Mechanism: qRTPCR: ER-genes; miR’s
Proteomics: mTOR, MAPK signaling; Cytokines

Change in Biomarkers

Cancer Endpoint

Lovaza Improves Glucose Tolerance and Decreases Serum Insulin and IGF-1 in Obese Mice

Ford, Fabian and Hursting, unpublished
Lovaza Modulates Mammary Inflammation-Related Genes in Obese Mice

<table>
<thead>
<tr>
<th>Inflammation-Related Genes</th>
<th>Lovaza® (208 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fold change (relative to control)</td>
</tr>
<tr>
<td>Interleukin 10 (IL10)</td>
<td>3.9</td>
</tr>
<tr>
<td>Chemokine (C-X-C motif) ligand 5 (CXCL5)</td>
<td>-2.9</td>
</tr>
<tr>
<td>Chemokine (C-C motif) receptor 3 (CCR3)</td>
<td>-3.2</td>
</tr>
<tr>
<td>Interleukin 3 (IL3)</td>
<td>-4.0</td>
</tr>
<tr>
<td>Interferon alpha 2 (Ifna2)</td>
<td>-5.1</td>
</tr>
<tr>
<td>Interleukin 2 (IL2)</td>
<td>-2.8</td>
</tr>
<tr>
<td>Chemokine (C-C motif) ligand 2 (CCL2)</td>
<td>-2.0</td>
</tr>
<tr>
<td>Interferon beta 1 (Ifnb1)</td>
<td>-5.2</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>-2.4</td>
</tr>
<tr>
<td>Epiregulin (Ereg)</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

Lovaza Ameliorates M-Wnt Mammary Tumor Growth in Obese Mice

Ford, Fabian and Hursting, unpublished
Mechanisms Underlying the Obesity-Cancer Link: 2013?

Epigenetic Regulation

Metabolomics

Obesity and Cancer: Emerging Mechanistic Targets

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