Diet Modification as a Novel Therapeutic for Cancer Treatment: When Less is More

Objectives:
1. Understand the current metabolic landscape of the United States.
2. Identify the implications of weight change on cancer outcome.
3. Explain how modifications in diet and exercise, in conjunction with radiation, may enhance the effectiveness of cancer treatment.
Diet Modification as a Novel Therapeutic for Cancer Treatment: 
*When Less is More*

Nicole Simone, MD  
Margaret Q. Landenberger, Associate Professor Radiation Oncology  
Co-Leader, Breast Cancer Research Program  
Director of Radiation, Jefferson Breast Center  
Sidney Kimmel Medical College at Thomas Jefferson University  
nicole.simone@jefferson.edu

**Disclosures**

None

**Objectives**

1. Understand the metabolic landscape of America  
2. Understand the implications of weight change on cancer outcomes  
3. Explain how modifications in diet and exercise, in conjunction with radiation, may enhance the effectiveness of cancer treatment

**Commonalities of all cancer phases**

- Diagnosis  
- Treatment  
- Survivorship

**Common links**
Common links in breast cancer phases

Tenet of living well: TAKING CARE OF YOURSELF AND YOUR BODY

Healthy Diet
Decrease Stress
Exercise

Why it’s important to live well: It’s biology

Premenopausal

Postmenopausal

Estrogen
Inflammation
Aromatase
Altered insulin signaling
Adipokine signaling

Problem 1: Cancer Survival Improvement Has Stalled
DESPITE MOLECULAR ADVANCES

Problem 2: Patient population has significantly changed
PARADIGM NEEDS TO SHIFT TO FOCUS ON THE CHANGING PATIENT POPULATION

Obesity Trends

68% of Americans are overweight

Weight gain linked to WORSE CANCER OUTCOMES

- Most patients gain an average of 10 lbs in first year after treatment

Cancer therapies contribute to weight gain
- Breast: anti-estrogen therapies
- Prostate: hormonal therapy
Obesity is an epidemic in America
- 68% of all Americans are overweight
- Close to 34% are obese – increasing with time
Obesity Trends* Among U.S. Adults
BRFSS, 1995
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%          10%–14% 15%–19% ≥ 20%

Obesity Trends* Among U.S. Adults
BRFSS, 1996
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%          10%–14% 15%–19% ≥ 20%

Obesity Trends* Among U.S. Adults
BRFSS, 1997
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data          <10%           10%–14% 15%–19% ≥ 20%

Obesity Trends* Among U.S. Adults
BRFSS, 1998
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data          <10%           10%–14% 15%–19% ≥ 20%

Obesity Trends* Among U.S. Adults
BRFSS, 1999
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data          <10%           10%–14% 15%–19% ≥ 20%

Obesity Trends* Among U.S. Adults
BRFSS, 2000
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data          <10%           10%–14% 15%–19% ≥ 20%
Obesity Trends* Among U.S. Adults
BRFSS, 2007
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

<table>
<thead>
<tr>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%–14%</th>
<th>15%–19%</th>
<th>20%–24%</th>
<th>25%–29%</th>
<th>≥30%</th>
</tr>
</thead>
</table>

Obesity Trends* Among U.S. Adults
BRFSS, 2008
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

<table>
<thead>
<tr>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%–14%</th>
<th>15%–19%</th>
<th>20%–24%</th>
<th>25%–29%</th>
<th>≥30%</th>
</tr>
</thead>
</table>

Obesity Trends* Among U.S. Adults
BRFSS, 2009
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

<table>
<thead>
<tr>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%–14%</th>
<th>15%–19%</th>
<th>20%–24%</th>
<th>25%–29%</th>
<th>≥30%</th>
</tr>
</thead>
</table>

Obesity Trends* Among U.S. Adults
BRFSS, 2010
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

<table>
<thead>
<tr>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%–14%</th>
<th>15%–19%</th>
<th>20%–24%</th>
<th>25%–29%</th>
<th>≥30%</th>
</tr>
</thead>
</table>

Metabolic Landscape

- Obesity is an epidemic in America
  - In 2011, 85,000 cases of cancer were attributable to obesity
  - In 2030 – projected to exponentially rise to 500,000

Metabolic Landscape: Clinical Implications

- Worse clinical outcomes: linked to obesity
  - If overweight at presentation → increased risk of recurrence, metastases and cancer-related death
  - Weight gain after diagnosis = poor outcomes
    - >50% of breast cancer survivors gain weight after initial treatment
    - Average weight gain over 10 lb (postmenopausal 20lb)
Metabolic Landscape: Biology

- Premenopausal
  - Estrogen
  - Inflammation
  - Aromatase
  - Altered insulin signaling
  - Adipokine signaling

- Postmenopausal

503 Women with Breast Cancer
As BMI Increases – more hormones made that can feed cancer

<table>
<thead>
<tr>
<th>BMI</th>
<th>&lt;22</th>
<th>22-25</th>
<th>25-27.5</th>
<th>27.5-30</th>
<th>&gt;30</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone (pg/mL)</td>
<td>19.7</td>
<td>22.3</td>
<td>27.2</td>
<td>26.7</td>
<td>26.5</td>
<td>0.045</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>4.7</td>
<td>8.3</td>
<td>8.5</td>
<td>10.6</td>
<td>10.7</td>
<td>0.042</td>
</tr>
<tr>
<td>DHEAS (ng/dL)</td>
<td>50.5</td>
<td>53.2</td>
<td>56.2</td>
<td>59.2</td>
<td>59.5</td>
<td>0.21</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>73.9</td>
<td>66.2</td>
<td>52.1</td>
<td>43.4</td>
<td>38.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Testosterone (pg/mL)</td>
<td>94.5</td>
<td>188.1</td>
<td>127.4</td>
<td>126.0</td>
<td>176.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Free estradiol (pg/mL)</td>
<td>0.10</td>
<td>0.18</td>
<td>0.20</td>
<td>0.28</td>
<td>0.28</td>
<td>0.0001</td>
</tr>
<tr>
<td>Free testosterone (pg/mL)</td>
<td>2.1</td>
<td>2.9</td>
<td>4.0</td>
<td>7.6</td>
<td>7.6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


Metabolic Landscape: Molecular Effectors

Metabolic Landscape: Treatments

- Tamoxifen
  - Increased metabolic syndrome
    - Population study: TAM associated with higher risk of diabetes (1.24; P = .002)
    - Reversed when TAM was discontinued

- Chemotherapy/Steroids
  - Premature menopause
  - Steroids
  - Lack of exercise: due to the fatigue, nausea, and pain from treatment

- Metformin studies: Direct relationship between metabolic syndromes and cancer outcomes

Metabolic Landscape: Clinical Implications

- Nurses Health Study: 5000 women
  - Weight gain = increased breast cancer recurrence and mortality

Weight Gain - ↓Survival

<table>
<thead>
<tr>
<th>Category of BMI Change</th>
<th>BMI loss</th>
<th>Maintain</th>
<th>Gain 0-2.0</th>
<th>Gain ≥2.0</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>514</td>
<td>677</td>
<td>712</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>Breast cancer death</td>
<td>38</td>
<td>48</td>
<td>77</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

Kroenke CH, J Clin Onc 2005;23: 1570

Metabolic Landscape: Clinical Implications – WINS study

Mature Analysis From the Women’s Intervention Nutrition Study (WINS) Evaluating Dietary Reduction and Breast Cancer Outcomes

- Eligibility Criteria
  - Women 48-79 years
  - Early breast cancer
  - Primary surgery ± RTx
  - Systemic therapy (ER+:
    - tamoxifen/chemotherapy;
    - ER–: chemotherapy)
  - Dietary fat intake > 20% of calories

- Dietary intervention: reduced fat intake (n = 975)
- Control (n = 1462)

Primary endpoint: Recurrence free survival
Randomization 60:40 within a year from primary surgery


Category of BMI Change

<table>
<thead>
<tr>
<th>Category of BMI Change</th>
<th>BMI loss</th>
<th>Maintain</th>
<th>Gain 0-2.0</th>
<th>Gain ≥2.0</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI loss</td>
<td>514</td>
<td>677</td>
<td>712</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>38</td>
<td>48</td>
<td>77</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

Kroenke CH, J Clin Onc 2005;23: 1570

Metabolic Landscape: Clinical Implications – WINS study

Follow-up 5.8 years, median

ER+/PR+  HR 0.79; 95% CI, 0.62-1.00  
ER-/PR-  HR 0.46; 95% CI, 0.26-0.80

Physical Activity and Survival after Breast Cancer Diagnosis

- 2987 female registered nurses in the Nurses’ Health Study  
  Stage I, II, or III breast cancer between 1984-1998
- Tracked physical activity and breast cancer mortality  
  (metabolic equivalent task [MET] hours/week)  
  3 MET hrs = 1 hour average paced walking 2-2.9 mph

From: Physical Activity and Survival after Breast Cancer Diagnosis
  JAMA. 2005;293(20):2479-2486. doi:10.1001/jama.293.20.2479

Metabolic Equivalent Conversion

| METS for 1 hour of that activity |  
|---------------------------------|---|
| Normal pace walking (2-2.9 mph)  | 3  
| Brisk pace walking (3-3.9 mph)  | 4  
| Very brisk pace walking (4+ mph) | 4.5 |
| Jogging (slower than 10 min/mile) | 7 |
| Running (faster than 10 min/mile) | 12 |
| Bicycling  | 7 |
| Tennis, squash, racquetball  | 7 |
| Lap swimming  | 7 |
| Calisthenics, stair machine, other aerobic  | 6 |
| Yoga, stretching, lower intensity exercise  | 4 |
| Other vigorous activities (lawn mowing)  | 6 |

Physical Activity Results: Patients with High BMI benefit most

| Physical Activity Results: Patients with High BMI benefit most |  
|---------------------------------------------------------------|---|
| Table 8. Multivariable Adjusted Relative Risk of Breast Cancer Mortality According to Activity Category Prior to Breast Cancer Diagnosis and BMI  |  
| Physical Activity Prior to Diagnosis, METS (NHANES 2001) |  
| Total | 1-3 | 3-6 | 6-9 | 9-12 | 12-15 | ≥15 | P for Trend  |  
| No. of participants | 1091893 | 94847 | 42420 | 12101 | 2377 | 2414 |  |  
| Multivariate adjusted HR (95% CI):  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |  |  
| No. of participants | 1211368 | 11592 | 42493 | 12100 | 2375 | 2414 |  |  
| Multivariate adjusted HR (95% CI):  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |  |  

Are the ill-effects of obesity modifiable?
- Limited data to support
- Case-control human studies  
  - Decreased incidence of cancer in obese patients who underwent bariatric surgery compared with matched controls
- NCI has estimated that if each adult decreased their BMI by 1 kg/m², the incidence of cancer would decrease by 100,000 cases per year.
**Vision:**

To change the landscape of cancer care by empowering patients to use dietary interventions to improve outcomes

---

**Caloric Restriction - Introduction**

- Caloric restriction (CR):
  - associated with decreased cancer risk
  - 20-40% reduction in diet
- Preclinical models
  - Slow or even prevent tumor growth
  - Dietary intervention causes tumor regression and increased OS compared with western diet

**Use of diet to improve outcomes:**

**WITH RADIATION**

Primary tumor gets much smaller when caloric restriction is added to radiation

**Tumor Regression:**

2 Methods of Diet Modification

- ADF
- 70%

**Mouse Weights:**

2 Methods of Diet Modification

- ADF
- 70%
Use of diet to improve outcomes:

WITH CHEMOTHERAPY

Primary tumor gets much smaller when caloric restriction is added to chemotherapy

Use of diet to improve outcomes:

HELPS METASTASES

Caloric Restriction + Radiation Decreases Metastatic Burden in Several Models of Metastases

Use of diet to improve outcomes:

MOLECULAR CHANGES

Reduces Proliferation

Increases Apoptosis

Downregulates IGF-1R pathway

Prostate Cancer:
Caloric Restriction Decreases Tumor Size

Caloric Restriction Increases Survival and Decreases Weight by 10%

Approach: Transitioning the breakthrough results to immediate clinical impact that empowers patients

Our lab has already shown that caloric restriction augments:

Dietary intervention can be used for all stages of disease — EMPOWERING OUR PATIENTS

Chemotherapy (Docetaxel, Cisplatin)

Radiation

Novel inhibitors (IGF-1R inhibitor)
First in human clinical trial

CaReFOR Trial: Caloric Restriction for Oncology Research

1° Endpoint - Compliancy:

*Compliancy defined as a successful reduction of 25% of total calories based on diet journals in at least 80% of the logged events.

2° Endpoint - Weight Loss:

CaReFOR Trial:

First Trial is Positive and a Success!

Race/Ethnicity (%)

<table>
<thead>
<tr>
<th>Race/Ethnicity (%)</th>
<th>Caucasian</th>
<th>AAF</th>
<th>Hispanic*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Patients</td>
<td>52</td>
<td>44</td>
<td>4*</td>
</tr>
<tr>
<td>Mean Age (yrs)</td>
<td>56.00 (6.76)</td>
<td>57.46 (6.41)</td>
<td>54.42 (7.04)</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>1.64 (1.24)</td>
<td>1.89 (1.41)</td>
<td>1.36 (0.98)</td>
</tr>
</tbody>
</table>

FACT-B Scores Gross Change

BMI trend All Patients

Body Fat Percentage

PROMIS FATIGUE SCORE T-score Change

Gross Change All FU

CaReFOR Trial:

Precision Medicine Guiding Precision Nutrition

Tumor

Patient

Molecular Profiling identifies Tumor and Patient Characteristics

Diet customized to target molecular and metabolic profile of patient.
Our Future Studies:
Precision Medicine Guiding Precision Nutrition

EXAMPLE Myc overexpressing tumor:
Diet enriched in pectin (oranges, carrots), choline (egg yolk, yogurt, almonds) and turmeric (add spice to food, mustard)

Mindfulness-based Stress Reduction (MBSR)

- MBSR is a well-researched, standardized eight-week program that utilizes mindfulness meditation techniques and gentle Hatha Yoga to teach participants the skills to better cope with life stressors.
- Learn to be present, in the moment, non-judgmentally. Learn how to breathe, learn how to relax.
- Use mindfulness to facilitate connection to that which has personal meaning.

Tenet of living well:
TAKING CARE OF YOURSELF AND YOUR BODY

Healthy Diet
Decrease Stress
Exercise

Mindfulness-based Stress Reduction (MBSR)

Differences between Post-training and Pre-training resting scans
Monti et al, Stress & Health (2013)

Mindfulness group (p<0.001) Control group (p<0.005)

Thank you!

Patients!
Collaborators
- Radiation Oncology: Rani Anne, Linda Ferguson
- Breast Surgery: Adam Berger, Theodore Tsangaris, Melissa Lazar
- Integrative Medicine: Dan Monti, Andy Newberg
- Pathology: Juan Palazzo

Lab Members
- Tu Dan
- Ajay Palagani
- Tiziana DeAngelis
- Robert Gitman
- Kamila Nowak

7 years
Questions??