Obesity and Risk of Breast Cancer

Ayca Gucalp, MD
Assistant Attending
Memorial Sloan Kettering Cancer Center
Instructor of Medicine
Weill Cornell Medical College
September 5th, 2014
Case

- 64 year old postmenopausal female
- Diagnosed with stage I ER/PR+, HER2- IDC
- Treated with lumpectomy/SLNBx, RT and an aromatase inhibitor
- At 8-month follow up the patient reports hot flashes, vaginal dryness, and weight gain
- Pre-diagnosis: height 163 cm, weight 80 kg, BMI 30
- Current: height 163 cm, weight 83.9 kg, BMI 32
Obesity* Trends Among US Adults

BMI = \[\text{weight in kilograms/}(\text{height in meters})^2\]

(*BMI \geq 30, or about 30 lbs. overweight for 5’4” person)

1990

2000

2010

Projected Obesity As Percentage of State Population by 2030

F as in Fat: How Obesity Threatens America’s Future 2013; Trust for America’s Health, Robert Wood Johnson Foundation; September 2013.
Increased BMI is Associated with Postmenopausal Breast Cancer

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barlow 2006</td>
<td>1408</td>
<td>237278</td>
<td>1864</td>
<td>332255</td>
<td>9.3%</td>
<td>1.06 [0.99, 1.13]</td>
</tr>
<tr>
<td>Kerlikowske 2008</td>
<td>1505</td>
<td>93717</td>
<td>1697</td>
<td>119504</td>
<td>9.3%</td>
<td>1.13 [1.06, 1.21]</td>
</tr>
<tr>
<td>Lee 2006</td>
<td>542</td>
<td>17154</td>
<td>843</td>
<td>27107</td>
<td>7.0%</td>
<td>1.02 [0.91, 1.13]</td>
</tr>
<tr>
<td>Sellers 2002</td>
<td>702</td>
<td>12916</td>
<td>567</td>
<td>13205</td>
<td>7.0%</td>
<td>1.27 [1.14, 1.41]</td>
</tr>
<tr>
<td>Setiaawan 2009</td>
<td>1053</td>
<td>26172</td>
<td>1488</td>
<td>40272</td>
<td>8.7%</td>
<td>1.09 [1.01, 1.18]</td>
</tr>
<tr>
<td>Sonnenschein 1999</td>
<td>47</td>
<td>966</td>
<td>55</td>
<td>1955</td>
<td>1.2%</td>
<td>1.73 [1.18, 2.53]</td>
</tr>
<tr>
<td>Suzuki 2006</td>
<td>436</td>
<td>16805</td>
<td>692</td>
<td>29359</td>
<td>6.4%</td>
<td>1.10 [0.98, 1.24]</td>
</tr>
<tr>
<td>Tehard 2006</td>
<td>244</td>
<td>9039</td>
<td>735</td>
<td>30744</td>
<td>5.3%</td>
<td>1.13 [0.98, 1.30]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>414047</td>
<td>594401</td>
<td></td>
<td></td>
<td></td>
<td>1.12 [1.06, 1.18]</td>
</tr>
<tr>
<td>Total events</td>
<td>5937</td>
<td>7941</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.00; Chi² = 15.98, df = 7 (P = 0.03); I² = 56%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.94 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.2.2 Obese

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barlow 2006</td>
<td>977</td>
<td>160573</td>
<td>1864</td>
<td>332255</td>
<td>8.8%</td>
<td>1.08 [1.00, 1.17]</td>
</tr>
<tr>
<td>Kerlikowske 2008</td>
<td>1244</td>
<td>73894</td>
<td>1697</td>
<td>119504</td>
<td>9.0%</td>
<td>1.19 [1.10, 1.27]</td>
</tr>
<tr>
<td>Lee 2006</td>
<td>348</td>
<td>11110</td>
<td>843</td>
<td>27107</td>
<td>6.2%</td>
<td>1.01 [0.89, 1.14]</td>
</tr>
<tr>
<td>Sellers 2002</td>
<td>381</td>
<td>6428</td>
<td>567</td>
<td>13205</td>
<td>6.0%</td>
<td>1.36 [1.22, 1.57]</td>
</tr>
<tr>
<td>Setiaawan 2009</td>
<td>729</td>
<td>17983</td>
<td>1488</td>
<td>40272</td>
<td>8.2%</td>
<td>1.10 [1.01, 1.20]</td>
</tr>
<tr>
<td>Sonnenschein 1999</td>
<td>48</td>
<td>1020</td>
<td>55</td>
<td>1955</td>
<td>1.2%</td>
<td>1.67 [1.14, 2.45]</td>
</tr>
<tr>
<td>Suzuki 2006</td>
<td>156</td>
<td>5659</td>
<td>692</td>
<td>29359</td>
<td>4.2%</td>
<td>1.17 [0.99, 1.39]</td>
</tr>
<tr>
<td>Tehard 2006</td>
<td>58</td>
<td>2074</td>
<td>735</td>
<td>30744</td>
<td>2.3%</td>
<td>1.17 [0.90, 1.52]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>278741</td>
<td>594401</td>
<td></td>
<td></td>
<td></td>
<td>1.16 [1.08, 1.25]</td>
</tr>
<tr>
<td>Total events</td>
<td>3941</td>
<td>7941</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.01; Chi² = 20.20, df = 7 (P = 0.005); I² = 65%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.92 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>692788</td>
<td>1188802</td>
<td>100.0%</td>
<td></td>
<td>1.14 [1.09, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>9878</td>
<td>15882</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.00; Chi² = 37.70, df = 15 (P = 0.0010); I² = 60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.67 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Increased BMI is a Poor Prognostic Factor in Patients with Breast Cancer

Table 1 Sensitivity analyses of pooled hazard ratios of the effect of obesity on survival in breast cancer patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of estimates</th>
<th>Pooled HR (95% CI)</th>
<th>I^2%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival measure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>36</td>
<td>1.33 (1.21–1.47)</td>
<td>73</td>
<td>0.91</td>
</tr>
<tr>
<td>Breast cancer specific</td>
<td>19</td>
<td>1.33 (1.19–1.50)</td>
<td>58</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Obesity measure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>55</td>
<td>1.33 (1.23–1.44)</td>
<td>70</td>
<td>0.95</td>
</tr>
<tr>
<td>WHR</td>
<td>6</td>
<td>1.31 (1.14–1.50)</td>
<td>0</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational cohort</td>
<td>48</td>
<td>1.36 (1.23–1.49)</td>
<td>73</td>
<td>0.53</td>
</tr>
<tr>
<td>Treatment cohort</td>
<td>7</td>
<td>1.22 (1.14–1.31)</td>
<td>0</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>16</td>
<td>1.47 (1.19–1.83)</td>
<td>68</td>
<td>0.25*</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>12</td>
<td>1.22 (0.95–1.57)</td>
<td>70</td>
<td>0.25*</td>
</tr>
<tr>
<td>Both</td>
<td>36</td>
<td>1.33 (1.23–1.43)</td>
<td>61</td>
<td>0.25*</td>
</tr>
</tbody>
</table>

* P-value for pre-versus post-menopausal women (not including studies which did not stratify by menopausal status)

Year of diagnosis

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>No. of estimates</th>
<th>Pooled HR (95% CI)</th>
<th>I^2%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1995</td>
<td>30</td>
<td>1.31 (1.16–1.46)</td>
<td>76</td>
<td>0.17</td>
</tr>
<tr>
<td>Post-1995</td>
<td>11</td>
<td>1.49 (1.31–1.68)</td>
<td>0</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Protani et al. BCRT 2010.
Pathways Linking Obesity with Breast Cancer

- Estrogen Synthesis
  - ↑ Estradiol
  - ↑ Aromatase
  - ↑ Circulating Free Estradiol

- Insulin Resistance
  - ↑ Insulin IGF-1
  - ▼ Circulating Plasma SHBG
  - ▼ VEGF

- Altered Adipokine Production
  - ▼ Adiponectin
  - ↑ Leptin

- Adipocyte
  - PI3K

- Inflammation
  - ↑ TNF-α, IL-6, IL-1β, COX-2, PGE2
  - ↑ Aromatase
  - ↑ Circulating Free Estradiol

- Angiogenesis / Cell Proliferation / Cell Survival

Breast Cancer Cell

Gucalp et al. Disease of the Breast. 2014.
Obesity, Estrogen, and Increased Risk of Postmenopausal Breast Cancer

• After menopause, peripheral aromatization of androgen precursors in adipose tissue is largely responsible for estrogen synthesis.
• Obesity causes inflammation in both visceral and subcutaneous fat.
• A number of inflammatory mediators (specifically PGE₂, TNFα, IL-1β, and IL-6), are all known to induce aromatase.
• A direct link between obesity, breast white adipose tissue inflammation, and aromatase expression was previously unknown.
Obesity Causes An Inflammatory State

Adapted from Olefsky & Glass. Annu. Rev. Physiol 2010.
Preclinical Study To Investigate the Obesity → Inflammation → Aromatase Axis

Female C57BL/6J Mice (n=40)

4 weeks of age Ovariectomy (n=20)

10 weeks of low fat (10kcal%) or high fat (60kcal%) diet

Low Fat
n=10

Low Fat Ovariectomy
n=10

High Fat
n=10

High Fat Ovariectomy
n=10

Diet Induced Obesity Causes Inflammation in the Mammary Gland and Visceral Fat

Obesity is Associated with Increased Levels of Pro-inflammatory Mediators and Aromatase

CLS-B are Common in the Breasts of Overweight and Obese Women

Increasing BMI is Associated with Increased Breast Inflammation

Levels of Pro-inflammatory Mediators and Aromatase are Increased in Inflamed Breast Tissue

CLS-B are Associated with BMI and Postmenopausal Status

Iyengar et al. ASCO Annual Meeting 2014.
Adipocyte Size Correlates with BMI, Menopausal Status, and CLS-B

Iyengar et al. ASCO Annual Meeting 2014.
CLS Status is Concordant Between Adipose Depots

<table>
<thead>
<tr>
<th>Bilateral breast WAT</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant</td>
<td>49/63 (78%)</td>
</tr>
<tr>
<td>CLS-B Positive</td>
<td>32/63 (51%)</td>
</tr>
<tr>
<td>CLS-B Negative</td>
<td>17/63 (27%)</td>
</tr>
<tr>
<td>Discordant</td>
<td>14/63 (22%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abdominal and breast WAT</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant</td>
<td>10/13 (77%)</td>
</tr>
<tr>
<td>CLS-B Positive</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>CLS-B Negative</td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td>Discordant</td>
<td>3/13 (23%)</td>
</tr>
</tbody>
</table>
Paracrine Interactions Establish an Obesity → Inflammation → Aromatase Axis
 Obesity Weight Loss (OWL) Study

Screening Visit 1
- H&P
- Nutrition assessment
- Consent
- EKG, HIV test
- Pedometer instruction

Screening Visit 2
- FASTING blood collection
- Inpatient admission scheduled

n=10

Day 0
- Inpatient Admission
- Fasting blood, urine, stool
- Abdominal fat pad biopsy
- Skin punch biopsy
- Begin 50% calorie reduction

Days 2-3
- 50% calorie-reduced diet
- Option for discharge

Day 4
- Start Very Low Cal Diet (VLCD)

Outpatient Option
- 7-10 weeks
  - Weight diary
  - q1 week telephone eval
  - q2 week visits: Bloods, EKG

Inpatient Option
- 6-7 weeks
  - Daily weight and vitals
  - q2 weeks: Bloods, EKG

VLCD

10% Weight loss

Post-intervention Day 1
- Inpatient admission
- Fasting blood, urine, stool
- Abdominal fat pad biopsy
- Skin punch biopsy

Post-intervention Day 2
- Resume regular diet
- Discharge
- MSKCC Nutrition referral

THE ROCKEFELLER UNIVERSITY HOSPITAL
CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

Memorial Sloan Kettering Cancer Center
Celecoxib Pilot Study

Schema
N = 10

Inpatient

Day
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

- Pre-intervention visit: History/physical, EKG, baseline blood tests
- Post-intervention visit: Urine, blood, stool collection
- Blood, urine, stool collection
- Celecoxib 200 mg BID
- Abdominal fat pad biopsy
Docosahexaenoic Acid Intervention Study

Endpoints

Primary Endpoint:
Change in normal breast tissue TNF-α

Secondary Endpoints:
Changes in breast tissue: COX-2, IL-1β;
Crown-like Structures of the breast (CLS-B),
CLS-B index; age as a predictor of CLS-B and inflammatory biomarkers

Patients w/history of Stage 0-III breast cancer or proliferative benign breast disease
Body Mass Index ≥ 25

Breast Core Bx

DHA 1000 mg twice daily N=38 (30 evaluable)

Placebo twice daily N=38 (30 evaluable)

Total N = 60

12 weeks + 2 weeks

Being conducted at MDACC, MSK, Dana Farber, Columbia, Cornell, Baylor

Gucalp et al. ASCO Annual Meeting. 2014.
Obesity and Cancer Outcomes

Case

- 64 year old postmenopausal female
- Diagnosed with stage I ER/PR+, HER2- IDC on therapy with adjuvant AI
- BMI > 30
Conclusions & Future Directions

- Obesity is associated with risk and worse prognosis in a growing number of malignancies
- Obesity is associated with systemic inflammation manifest as CLS and circulating proinflammatory mediators
- White adipose tissue inflammation in the breast is associated with menopausal status, BMI, and adipocyte size
- The obesity $\rightarrow$ inflammation $\rightarrow$ aromatase axis is active in the breasts of many women
Conclusions & Future Directions

- Do CLS represent a histologic biomarker of risk and/or prognosis?
- Need for non-invasive detection of adipose inflammation
# Acknowledgements

## MSKCC
- Clifford Hudis, MD
- Neil Iyengar, MD
- Patrick Morris, MD
- Monica Morrow, MD
- Dilip Giri, MD
- Jay Boyle, MD
- Luc Morris, MD
- Ronald Ghossein, MD
- David Pfister, MD
- Matthew Fury, MD
- Breast Medicine Service

## Weill Cornell Medical College
- Andrew Dannenberg, MD
- Kotha Subbaramaiah, PhD
- Kathy Zhou, PhD
- Louise Howe, PhD
- Domenick Falcone, PhD
- Abigail Haka, PhD
- Baoheng Du, MD
- Priya Bhardwaj, BA
- Michael Harbus, BS

## Rockefeller University
- Peter Holt, MD
- Jose Aleman, MD, PhD
- Jeanne Walker, RN

## Funding
- Breast Cancer Research Foundation
- Metastasis Research Center, MSKCC
- NIH/NCI Division Cancer Prevention
- Sass Foundation (Carol Litwin Memorial Fellowship in Breast Cancer Research)
- Prostate Cancer Foundation