Results of a Structured Diet, Exercise, & Behavior Modification Intervention in Post-Menopausal Breast Cancer Survivors: Quality of Life

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April 2012
Impact of Weight on Breast Cancer Risk

- **Before diagnosis**: Overweight and obese postmenopausal women have a 1.3 to 1.5 increased risk of developing breast cancer.
- **At diagnosis**: Obese women have a 1.5 to 2.5 increased risk of recurrence or death.
- **After diagnosis**: Women who gain weight (13 lbs+) have 1.5 increased risk of recurrence or death.
Weight, Recurrence, & Survival in Early-Stage Breast Cancer

BMI (kg/m$^2$)

Estimated Relative Risk of Adverse Event

- Distant Recurrence, $p=0.0005$
- Death, $p=0.0007$

Goodwin et al, *JCO* 2002
Deaths From Breast Cancer and Other Causes Increased in Overweight Women

53,816 with Early-Stage Breast Cancer in Denmark 1977 to 2006.

Ewertz M et al. JCO 2011;29:25-31

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75% of Breast Cancers are Estrogen Receptor Positive

Estrogen (and progesterone) stimulate growth by "turning on" hormone receptors in the breast cancer cells. Without these hormones, the cancer cells are not stimulated to grow.

Androstenedione $\leftrightarrow$ Testosterone

Aromatase (subcutaneous fat liver, muscle, normal breast, breast cancer)

Estrone $\leftrightarrow$ Estradiol

Aromatase inhibitor (e.g. anastrozole)

Tamoxifen

ER$^-$ cells $\leftrightarrow$ ER$^+$ cells

Breast tumor
ATAC -- Arimidex, Tamoxifen Alone or in Combination

Companion Studies
- Bone metabolism (BMD) [n = 306 + 46 control patients]
- Endometrial survey [n = 285]
- Pharmacokinetics [n = 357]
- Quality of life [n = 1105]
ATAC: Recurrences Greater with Increasing BMI

Sestak I et al. JCO 2010;28:3411-3415

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Obesity Associate With Poorer Long Term Outcomes

• AIs may not have an advantage over tamoxifen in overweight and obese women
• Obesity effect may be most pronounced in women with ER+ tumors and may not show significance for 10 yrs.
• Obese women have larger tumors and more co-morbidities.
• Taking these factors into account they have higher distant recurrence rates, worse disease free, disease specific and overall survival.
Step 1: Weight Management for Rural Breast Cancer Survivors
Pilot showed significant 6-month changes across multiple outcomes

<table>
<thead>
<tr>
<th>Weight and waist</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>-27.5 lbs</td>
</tr>
<tr>
<td>% Weight loss</td>
<td>13.9%</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>-9.4 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diet and Physical Activity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PA kcal/week</td>
<td>+1235</td>
</tr>
<tr>
<td>Diet kcal/day</td>
<td>-349</td>
</tr>
<tr>
<td>FV servings/day</td>
<td>+3.7</td>
</tr>
<tr>
<td>% kcal from fat</td>
<td>-12.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>-16.7%</td>
</tr>
<tr>
<td>Leptin</td>
<td>-37.1%</td>
</tr>
</tbody>
</table>

Befort et al., Breast Cancer Res Treat, 2012; 132: 631-639
Quality of life changes among rural breast cancer survivors enrolled in 6 month weight loss program

Mean weight loss = 13.9%, 90% session attendance
Enrolling now into 5 year study

208 rural breast cancer survivors

6 month group weight loss phase

6 to 18 months weight loss maintenance group phone intervention

18 to 24 months transition to self-reliance

6 month group weight loss phase

6 to 18 months weight loss maintenance mailed newsletter comparison

18 to 24 months transition to self-reliance

R01 CA155014
PI: Befort
Step 2: Develop and Test a Structured Diet, Exercise, & Behavior Modification Program for Breast Cancer Survivors
Study Objectives

• **Primary Objective:**
  – To determine if overweight, post-menopausal breast cancer survivors will participate and adhere to a diet/exercise/behavioral modification program and lose 5% of their weight.

• **Secondary Objective:**
  – To determine if post-menopausal BrCa survivors who participate in a structured diet/exercise/behavioral modification demonstrate modulation on markers of breast cancer risk and quality of life.
Trial Design

- Pilot Study
- Single institution:
  - Breast Cancer Survivorship Center
- Post-Menopausal BrCa Survivors
- > 3-months from treatment (surgery, chemotherapy, XRT)
  - Can be on anti-hormonal therapy (> 6 months)
- Physician release to participate in the Energy Balance Study
- Recruitment time: 1 year
Breast Cancer Risk Biomarkers and Energy Balance in Post-Menopausal Breast Cancer Survivors

BrCa Survivors BMI >25-45M²

Pre-Test Assessment
• Body Composition
• Blood Work
• Quality of Life Surveys

6-Month Energy Balance Intervention
Structured Diet & Exercise Program targeted to BrCa Survivors

Post-Test Assessment
• Body Composition
• Blood Work
• Quality of Life Surveys
Baseline and Follow-up Measures

– Body composition
  • Height
  • Weight
  • Waist and hip circumferences
  • Total Body Composition: DEXA scan

– Quality of Life
  • BCPT Symptom Check List (breast cancer symptom checklist)
  • SF36 (health related quality of life)
  • PHQ-9 (measure of depression)
  • Brief Fatigue Inventory

– Serum- fasting blood draw
  • Hormones: bioavailable estradiol, estrone, estrone sulfate, SHBG, testosterone, prolactin, FSH, interleukin-6, IGF1, and IGFBP3,
  • Cholesterol, glucose
  • Bank lymphocytes for gene expression
Baseline and Follow-up Measures

• Chart Review/Physician Verification/Medical Tests
  – Medical history
  – Blood pressure, pulse, temperature

• Diet
  – 3 day food log (including 1 work day:2 weekend days)
  – Daily dietary intake log: # of shakes, pre-packaged meals, fruits/vegetables

• Physical Exercise
  • Fitness assess: resting and active
  • Daily Activity Log- minutes & type/intensity of activity
  • Pedometers- Step Count
Intervention

• Calorie Controlled (1200-1600 cal/day)
  – 2 pre-packed meals/day
  – 3 Low Calorie/High Protein shakes/day

• Exercise
  – Aerobic
  – Resistance Training
  – Assessment & Instruction: ACSM Cancer Certified Trainer

• Curriculum
  – Modified DPP + Content specific to Breast Cancer
  – Topics Highlighting BrCa Late Effects

• Accountability/Group format
  – Weekly weigh-in and meeting (90 minutes)
  – 75% participation required
Total Group Participant Characteristics & Weight Loss, n=52

- Median age = 51
- Median time since diagnosis: 4.25 yrs
- Current anti-hormone therapy = 65%
- Menopausal status at diagnosis: 62% pre-menopausal

<table>
<thead>
<tr>
<th></th>
<th>At Diagnosis</th>
<th>Pre-Intervention</th>
<th>Post-Intervention</th>
<th>Change from Pre- to Post-Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (lbs)</td>
<td>187.9</td>
<td>202</td>
<td>178.3</td>
<td>↓ 23.6 lbs (~12% of the starting weight)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.2</td>
<td>32.6</td>
<td>28.2</td>
<td>↓ 13.5%</td>
</tr>
</tbody>
</table>

## Completers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=45</td>
<td></td>
</tr>
<tr>
<td>Age (years +/-SD)</td>
<td>52.9 (7.8)</td>
</tr>
<tr>
<td>Time since diagnosis (years +/-SD)</td>
<td>5.7 (4.9)</td>
</tr>
<tr>
<td>Weight at Diagnosis (kg)</td>
<td>84.1 (15.4)</td>
</tr>
<tr>
<td>BMI at Diagnosis (kg/m²)</td>
<td>31.1 (5.6)</td>
</tr>
<tr>
<td>Stage (range 1-3)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Surgical Management</strong></td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>20</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>25</td>
</tr>
<tr>
<td>Radiation</td>
<td>25</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>29</td>
</tr>
<tr>
<td>Hormone Receptor Status (ER+)</td>
<td>29</td>
</tr>
<tr>
<td><strong>Anti-hormonal Therapy (ever)</strong></td>
<td>29</td>
</tr>
<tr>
<td>Current use: aromatase inhibitor</td>
<td>17</td>
</tr>
</tbody>
</table>
Baseline and 6-month measures among study completers

<table>
<thead>
<tr>
<th>N=45</th>
<th>Baseline Median (SD)</th>
<th>6-month Median (SD)</th>
<th>Absolute Change Median (SD)</th>
<th>Percent Change Median (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt (kg)</td>
<td>91.2 (13.0)</td>
<td>81.0 (12.5)</td>
<td>-10.7 (6.1)*</td>
<td>-12.3 (6.1)*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.2 (4.9)</td>
<td>28.2 (4.6)</td>
<td>-3.8 (2.2)*</td>
<td>-12.4 (6.0)*</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>119.8 (11.0)</td>
<td>109.5 (20.3)</td>
<td>-9.9 (17.5)*</td>
<td>-8.3 (14.1)*</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>98.1 (11.6)</td>
<td>89.0 (12.4)</td>
<td>-9.9 (8.8)*</td>
<td>-9.75 (8.8)*</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>49.5 (4.0)</td>
<td>45.0 (6.7)</td>
<td>-5.6 (4.5)*</td>
<td>-9.8 (9.4)*</td>
</tr>
</tbody>
</table>

*P=<0.001
Change in Weight
Pre to Post Intervention (kgs)
# Changes in Serum Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline Mean (SD) N=45</th>
<th>6-month Mean (SD) N=45</th>
<th>Absolute Change Mean (SD)</th>
<th>Percent Change Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (uIU/ml)</td>
<td>11.4 (4)</td>
<td>5.4 (4.3)</td>
<td>-3.6 (6.6)*</td>
<td>-37.6 (51.9)*</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>101.67 (19.9)</td>
<td>94.0 (15.2)</td>
<td>-2.0 (21.0)</td>
<td>-1.0 (10.4)</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>39.4 (19.4)</td>
<td>15.65 (13.61)</td>
<td>-18.1 (13.7)*</td>
<td>-54.2 (34.5)*</td>
</tr>
<tr>
<td>Adiponectin (ug/ml)</td>
<td>8.08 (6.1)</td>
<td>8.251 (6.523.9)</td>
<td>.889 (1.947)*</td>
<td>7.5 (21.2)*</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>42.8 (28.1)</td>
<td>42.75 (32.74)</td>
<td>7.7 (15.9)*</td>
<td>23.4 (39.4)*</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>63.8 (34.7)</td>
<td>69.00 (33.28)</td>
<td>2.7 (19.8)*</td>
<td>6.5 (141.0)*</td>
</tr>
<tr>
<td>Estradiol (pc/mL)</td>
<td>22.7 (48.8)</td>
<td>8.18 (5.37)</td>
<td>-1.5 (14.1)</td>
<td>-16.9 (68.8)</td>
</tr>
<tr>
<td>Free estradiol (pc/mL)</td>
<td>1.8 (1.0)</td>
<td>.56 (.4)</td>
<td>-1.2 (1.0)*</td>
<td>-60.2 (25.7)*</td>
</tr>
</tbody>
</table>

*p<0.05
Significant Changes in Fatigue & Depression

Lower scores on the BFI & PHQ9 were correlated with greater change in % weight loss, p-values =0.037 & 0.004, respectively.
Collaborators

• Clinical research collaborators
  – Christi Befort, PhD
  – Carol Fabian, MD
  – Debra Sullivan, PhD
  – Qamar Khan, MD
  – Bruce Kimler, PhD
  – Henry Yeh, PhD

• Project staff
  – Sonya Cox, RD, MPH
  – Katherine Harvey, RD, MS

• Support
  – Back in the Swing
  – NIH BIRCWH K-12