Exercise Interventions and Bone Health in Breast Cancer Survivors

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No Disclosures

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Purpose

- Identify exercise recommendations for bone health in the postmenopausal woman
- Review the published exercise intervention studies in breast cancer survivors (BCS)
- Present NCI funded exercise trial
- Discuss exercise as a potential multi-targeted therapy
Significance

- 2.9 million Breast Cancer Survivors (BCS) in USA
- BCS are at risk for accelerated bone loss due to chemotherapy, premature induced menopause and anti-estrogen therapies
- Estimated 5%-20% loss first two years after chemotherapy; average ≥ 2% loss annually with Aromatase Inhibitor adjuvant therapy
- Many BCS are medication averse
Exercise and Bone Health in Postmenopausal Women

- Goal for Adults: maintain bone mass
- Weight bearing, weight loading, high intensity resistance exercise can preserve bone mass in postmenopausal women
- Evidence stronger for preservation LS vs hip
- Exercises combining ground and reaction forces superior

Exercise Interventions: Bone Outcomes
Breast Cancer Survivors

- 7 controlled trials
- 1 trial targeted women with bone loss
- 2 trials included a pharmacologic component
- Mean age range 46 yrs-62 yrs
- Sample size: 3/7 trials > 100 subjects
- Setting: home, fitness center, mixed
- Supervised, unsupervised, mixed
- Duration: 5/7 trials were 12 months

## Exercise Interventions: Bone Outcomes With or Without a Bisphosphonate

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Exercise</th>
<th>Setting</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swenson 2009 RCT</td>
<td>N=72 enrolled; 62 evaluable; Mean age 47 yrs 69%-75% pre-menopausal</td>
<td>12 mos (started during chemo) Zolendric acid q 3 mos vs. walking + placebo</td>
<td>Home Goal 10,000 steps/day</td>
<td>Decrease LS, and FN in walking group; increase LS in ZO group (p &lt;.01) and no change FN</td>
</tr>
<tr>
<td>Waltman 2010 RCT</td>
<td>N=249 enrolled; 223 evaluable; post-menopause; 71% osteopenia; 29% osteoporosis</td>
<td>24 mos; weekly risedronate+ST vs. risedronate alone. ST=2x/wk Calcium and Vitamin D supplementation</td>
<td>Home (first 9 mos- with free weights) fitness center (weight machines- mos:15-24)</td>
<td>Both groups increased hip and LS BMD (p=&lt;0.0001); greater increases ST+ drug but not significant. Improved muscle strength and balance in ST.</td>
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</tbody>
</table>

## Bone Outcomes
### Exercise vs. Usual Care Trials (N=3)

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<tr>
<td>Schwartz 2007 RCT</td>
<td>N=72 enrolled; 66 eval; before adj chemo; 55% pre-menopausal</td>
<td>6 month: Aerobic vs. Resistance vs usual care (UC)</td>
<td>Home 4 days/wk; A=15-30 min mod intensity R=Thera Bands 2 sets 8-10 rep 4 days/week</td>
<td>Aerobic group less LS BMD loss vs. UC (p=.02). 23% developed osteopenia</td>
</tr>
<tr>
<td>Irwin 2009 RCT</td>
<td>N=48 (subset of combined N=75)</td>
<td>12 mos aerobic (walking) vs. UC</td>
<td>Home+ gym Goal: 30 min 5 days/wk</td>
<td>BMD no change aerobic vs. loss in UC group (p=.04)</td>
</tr>
<tr>
<td>Saarto et al 2012 RCT</td>
<td>N=498 Pre and postmenopausal BCS</td>
<td>12 mos Aerobic +impact vs. UC</td>
<td>Gym (1x/wk) + home (3x/wk)</td>
<td>Pre menopausal: both lost LS but greater loss FN in UC group Postmenopausal: no difference</td>
</tr>
</tbody>
</table>

## Bone Outcomes

### RCT Aerobic-Resistance vs Stretching Control

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<tr>
<td>Winters-Stone et al. 2011</td>
<td>N=106 postmenopausal BCS</td>
<td>12 mos RCT Resistance + impact (R+I) vs stretching (ST)</td>
<td>Fitness center (2x/wk)+ home (1x/wk)</td>
<td>LS BMD preserved in R+I compared to LS loss in ST (p=&lt;0.01), no change FN, hip.</td>
</tr>
<tr>
<td>Winters-Stone et al. 2013</td>
<td>N=71 Premature menopause BCS Avg age =46 yrs N=48 evaluable</td>
<td>12 mos RCT Resistance + impact (R+I) vs stretching (ST)</td>
<td>Fitness center (2x/wk)+ home (1x/wk)</td>
<td>No significant change in hip, LS, FN. Some benefit for women &gt; 1 yr postmenopause (N=35) vs &lt; 1 yr (N=13)</td>
</tr>
</tbody>
</table>

Health Promotion for Early Postmenopausal Cancer Survivors

- Randomized Controlled Trial
  R01 NIH 2007-2013

- 12 month aerobic resistance exercise intervention compared to a home based health promotion group
Co-Investigators

Karl Insogna, MD, Professor Medicine & Endocrinology, Yale School of Medicine
Barbara Smith, PhD, RN, Professor, Michigan State University
Lyndsay Harris, MD, Co-director Breast Cancer Service, Case Western Reserve
Al Sinusas, MD, Professor of Medicine, Cardiology, Yale School of Medicine
Sangchoon Jeon, PhD, Biostatistician, Yale School of Nursing

Consultants:

Janet Kerstetter, PhD, University of Connecticut, Visiting Professor, Yale School of Medicine
Robert Axtell, PhD, Director Exercise Program, Southern CT State University
Physiologic Framework and Outcomes

Treatment Effects

Aerobic Resistive Exercise Intervention

Bone Mass (LS, hip; serum biomarkers)

Body Composition (%fm, lbm, weight, BMI)

Metabolic Factors (FBS, insulin, lipids, HbA-1C)

Functional Status (strength, cardio fitness, functional ability)
Design-RCT

- **Intervention Group**: aerobic resistance exercise 3 x/week at a fitness center (supervised 6 mos; unsupervised 6 mos). Aerobic activity on most other days. Resistance (weighted belt, lower body exercises).

- **Health Promotion Group**: moderate intensity physical activity most days of the week

- **Both groups**: nutrition teaching, Vitamin D (400 IU) and Calcium replacement (1200 mg based on dietary intake)
Data Collection
Baseline, 6 ands 12 months

**Bone Mass**: BMD LS and Hip (baseline & 12 mos); serum bone biomarkers (osteocalcin, CTX)

**Body Composition**: Weight, BMI, Waist circumference, Whole Body DEXA

**Metabolic Risk Factors**: Fasting serum (lipids, cholesterol, insulin, glucose, HbA1-C)

**Functional Ability**: Exercise stress test (baseline & 6 mos), strength (sit and stand), SF-36

**Level of Physical Activity** (IPAQ q mos)

**Serum Vitamin D levels**
Target sample: 150
N=154 enrolled

N= 132 for Bone Outcomes
Mean age: 51.9 yrs
Mean WC: 86.5 cm
Mean BMI: 29.5
<table>
<thead>
<tr>
<th></th>
<th>Spine BMD</th>
<th>Hip BMD</th>
<th>Troch BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Therapy Type</td>
<td>Baseline</td>
<td>12 months</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Delta±StdErr&lt;sup&gt;a&lt;/sup&gt;</td>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aromatese Inhibitor</td>
<td>0.991 (0.118)</td>
<td>-0.018±0.006</td>
<td>.0035</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1.010 (0.125)</td>
<td>-0.007±0.005</td>
<td>.2077</td>
</tr>
<tr>
<td>No Hormone Therapy</td>
<td>1.025 (0.159)</td>
<td>-0.001±0.005</td>
<td>.8816</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>.1139</td>
<td></td>
</tr>
</tbody>
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Table C-1: Bone Mineral Density Change by Hormone Therapy Types

Note. (<a>) represents the estimated delta (i.e. changed amount of BMD from baseline) and standard error after controlling for age, BMD, BMI, and vitamin D at baseline.
Yale FIT  Spine BMD

![Graph showing the relationship between Spine BMD at baseline and Spine BMD at 12 months for Exercise and Health Promotion groups. The graph includes data points and linear regression lines. The Exercise group has a slope of 0.989±0.004, while the Health Promotion group has a slope of 0.993±0.004. The p-value is indicated as NS, suggesting no significant difference.]
Yale FIT Hip BMD

P=NS
Yale FIT Femoral Neck BMD
# Yale FIT

## Serum Vitamin D Levels
Baseline, 6 and 12 months

<table>
<thead>
<tr>
<th>Vitamin D Level</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 20 ng/mL</td>
<td>22 (14.3%)</td>
<td>12 (10.6%)</td>
<td>9 (6.9%)</td>
</tr>
<tr>
<td>20-29 ng/mL</td>
<td>55 (35.7%)</td>
<td>45 (39.8%)</td>
<td>35 (26.9%)</td>
</tr>
<tr>
<td>30 ng/mL +</td>
<td>77 (50%)</td>
<td>56 (49.6%)</td>
<td>86 (66.2%)</td>
</tr>
</tbody>
</table>
Yale FIT

Vitamin D and Bone Mineral Density

- Least Square Mean (LSM) was estimated after controlling for baseline BMD
- * indicates significant difference in BMD reduction by Vitamin D level
Yale FIT
Summary and Future Analyses

- BMD spine, hip, greater trochanter significantly decreased in women on AI therapy, after controlling for age, BMD, BMI and Vitamin D at baseline but not significantly different compared to Tamoxifen or no endocrine therapy.
- Changes in BMD are not significantly different by intervention group by type of endocrine therapy.
- Exercise dose and degree of osteogenic stimulus to preserve bone in BCS may need to be greater than in healthy postmenopausal women.
- Inflammatory cytokines will be explored at 6 and 12 months with bone outcomes.
Exercise Prescription  Therapeutic Target (s)
What is the Target?
Acknowledgements

- NCI R01CA122658
- Yale FIT Team
- All the women who participate