Diet, Weight, and Exercise in Breast Cancer Survivors

Current Topics in Breast Cancer Symposium
March 22, 2019

Jennifer Sheng, M.D.
Fellow in Medical Oncology
Johns Hopkins University

Objectives

1. Review obesity statistics and the relationship between obesity, cancer risk, and survival

2. Explain efforts to reduce burden of obesity in cancer survivors
   - A randomized study evaluating the effect of a remote-based weight loss program on biomarkers (POWER-remote)
   - Survivorship Promotion in Reducing IGF-1 (SPIRIT) Study
   - Physical Activities by Technology Help (PATH)

3. Discuss other ongoing and planned studies to augment approaches
   - The Breast cancer Weigh Loss (BWEL) Study
   - Intervention in women undergoing doxorubicin-based CT
   - Physical activity dose response study
   - Sleep intervention followed by POWER-remote (COIN)
   - Adaptive weight loss study with pharmacotherapy
Obesity

• Over 36.5% of U.S. adults fall into the obese category (Body Mass Index \( \geq 30 \)).
• More than two-thirds of American adults are overweight or obese (BMI \( > 25 \)).
• Factors contributing to obesity may be: genetic, hormonal, environmental, emotional, and cultural.
• 65% of the world’s population live in countries where obesity related illnesses (heart disease, stroke, type 2 diabetes, and certain types of cancer) kill more people than conditions related to malnutrition.

Obesity (Cont.)

• The estimated annual medical cost of obesity in the U.S. was $147 billion in 2008.
• The medical costs for people who are obese were $1,429 higher than those of normal weight.

• Obesity is preventable and treatable.

The Physical Activity Guidelines for Americans

• Adults should do at least:
  – 150 minutes to 300 minutes a week of moderate-intensity, or
  – 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity, or
  – an equivalent combination of moderate- and vigorous-intensity aerobic activity.
• They should also do muscle-strengthening activities on 2 or more days a week.
• Older adults should do multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities.
Prevalence of Obesity Among U.S. Adults >20 or Older, by Sex, Race, Hispanic Origin

Source: CDC 2015-2016 report

Adult Obesity Rate by State, 2017

Select years with the slider to see historical data. Hover over states for more information. Click a state to lock the selection. Click again to unlock.

Percent of obese adults (Body Mass Index of 30+)

Source: http://stateofobesity.org

2017 State Statistics

<table>
<thead>
<tr>
<th></th>
<th>Maryland</th>
<th>Pennsylvania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult obesity rate</td>
<td>31.3%</td>
<td>31.6%</td>
</tr>
<tr>
<td>Rank among states</td>
<td>26/51</td>
<td>24/51</td>
</tr>
</tbody>
</table>

Source: https://stateofobesity.org/states/pa/
### Estimated 2019 Statistics

<table>
<thead>
<tr>
<th></th>
<th>Maryland</th>
<th>Pennsylvania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate new BC cases</td>
<td>5,290</td>
<td>12,070</td>
</tr>
<tr>
<td>Estimated deaths</td>
<td>830</td>
<td>1,900</td>
</tr>
</tbody>
</table>

Source: American Cancer Society 2019

### Weight and Cancer Risk

- Being overweight or obese may increase cancer risk, growth, and progression
- Mechanisms include:
  - Increased levels of insulin and insulin growth factor-1 (IGF-1)
  - Chronic, low-level inflammation
  - Higher concentrations of estrogen produced by fat tissue
  - Fat cells may affect processes that regulate cancer cell growth
- Maintaining a healthy weight is associated with a lower risk of cancer and of cancer recurrence in cancer survivors


### Obesity-Associated Cancers

- Several common cancers are related to obesity
  - Increased incidence
  - Worse disease-free survival
  - Inferior overall survival
- Specific cancers include:
  - Breast
  - Colorectal
  - Uterine
  - Kidney
  - Head and neck
  - Esophageal
  - Pancreatic
  - Prostate
  - Gallbladder
  - Thyroid

Source: Kerr 2017 Lancet Oncology
Breast Cancer and Obesity as a Case Study

- Women with breast cancer who are overweight/obese experience inferior survival outcomes despite optimal local and adjuvant therapy, in particular women with hormone receptor positive disease
- Most women gain weight following diagnosis
- Weight gain increases the risk of recurrence and death by 40-50% and 53-60%, respectively, especially in premenopausal women


Source: Sparano Cancer 2012

Source: Sparano Cancer 2012
Obesity increases risk of comorbidity

- Obesity at and following breast cancer diagnosis is associated with poor quality of life and increased risk of adverse treatment effects including:
  - Postoperative appearance dissatisfaction
  - Loss of sexual interest
  - Neuropathy
  - Lymphedema
  - Chronic fatigue

Source: Greenlee et al. JNCI 2017, Bao BCRT 2016, Imayama et al. BCRT 2014
Women’s Intervention Nutrition Study (WINS)

Women with early stage breast cancer receiving conventional cancer management randomized to a dietary intervention had a 24% lower risk of relapse compared to those in a control group (HR = 0.76; 95% CI = 0.60 to 0.98, p = 0.034)

Body weight was not the primary endpoint, but there was a modest but statistically significant (p = 0.005) weight difference of about 6 pounds between the groups.

Source: Chlebowski JNCI 2006

The Women’s Healthy Eating and Living (WHEL) Randomized Trial

Women with early stage breast cancer receiving conventional cancer management randomized to a dietary intervention

Less than a 1-kg difference in average weight between WHEL Study groups at any time point

Source: Pierce JAMA 2007
Weight and Biomarker Modulation

- In post-menopausal women, weight loss can favorably modulate sex hormones (estradiol), adipokines (leptin, adiponectin), IGF-1, and inflammatory markers (CRP, IL-6)
- Patient reported outcomes (PROs), especially physical function, are improved with weight loss
- Increased waist/hip ratio is associated with hypermethylation of certain breast-related genes (E-cadherin, p16, RAR-β)
  - Physical activity can reduce methylation of certain breast-associated genes (L3MBTL1)
- Genetics may influence weight gain and loss

The signaling of obesity. (A) Changes in the size of adipose depots affect systemic homeostasis; (B) These signaling molecules activate cell surface receptors and drive signaling
Objectives

1. Review obesity statistics and the relationship between obesity, cancer risk, and survival

2. Explain efforts to reduce burden of obesity in cancer survivors
   - A randomized study evaluating the effect of a remote-based weight loss program on biomarkers (POWER-remote)
   - Survivorship Promotion in Reducing IGF-1 (SPIRIT) Study
   - Physical Activities by Technology Help (PATH)

3. Discuss other ongoing and planned studies to augment approaches
   - The Breast cancer WEIGHT Loss (BWEL) Study
   - Intervention in women undergoing doxorubicin-based CT
   - Physical activity dose response study
   - Sleep intervention followed by POWER-remote (COIN)
   - Adaptive weight loss study with pharmacotherapy

---

**Bringing POWER to Breast Cancer Survivors (PI: Stearns)**

**A Randomized Study Evaluating the Effect of a Remote-based Weight Loss Program on Biomarkers in Women with Early Stage Breast Cancer**

**POWER: Practice-based Opportunities for Weight Reduction**

---

**Objective:** Compare % women with early stage breast cancer who lose ≥5% of their baseline body weight after 6 and 12 months between self-directed weight loss and POWER-remote

Eligible:
- Women
- Age ≥18
- BMI ≥25 kg/m²
- Completed planned local therapy and CT

**Baseline**

**Serum Biomarkers**

**Anthropomorphic Measures**

**PROs**

**6 mo**

**12 mo**
POWER-Remote Intervention

Coach calls:
- weekly for months 1-3
- monthly for months 4-12

Dietary recommendations:
- reduced calorie, high vegetable/fruit diet based on the DASH diet

Innergy® Platform (Healthways.com)

Patient Characteristics

![Graph showing patient characteristics](image)

Proportion of patients with at least 5% and 10% weight loss between study arms

- 5% Loss at 6m: POWER-remote 10.9, Self-directed 13, P = 0.002
- 5% Loss at 12m: POWER-remote 20, Self-directed 26, P = 0.001
- 10% Loss at 6m: POWER-remote 0, Self-directed 4.3, P < 0.001
- 10% Loss at 12m: POWER-remote 0, Self-directed 0, P < 0.001

Source: Santa-Maria SABCS 2015
Weight change by group

Baseline 6-month 12-month

Source: Santa-Maria SABCS 2015

5% weight change from baseline to 6 months

Gained 5% or More
Gained 1−4%
No Weight Change
Lost 1−4%
Lost 5−9%
Lost 10−14%
Lost 15% or More

Self-Directed (N=42)
POWER-remote (N=45)

12% Lost 5% or More
88% Gained Weight or Lost < 5%
49% Gained Weight or Lost < 5%
51% Lost 5% or More

Any weight change from baseline to 6 months

Self-Directed (N=42)
POWER-remote (N=45)

40% Lost Weight
80% Lost Weight
55% Gained Some or Lost No Weight
20% Gained Some or Lost No Weight
Changes in Biomarkers at 6 mo According to Treatment Arm

Subgroup Analysis of Patients With at Least 5% Weight Loss

POWER-Remote: Conclusions

- A remotely delivered weight loss intervention is feasible in BC survivors irrespective of endocrine or CT use, resulting in weight loss by 6 mo and sustained at 12 mo.
- Weight loss, and the POWER-remote intervention, resulted in a decrease in leptin, however, no major changes in other cytokines and adipokines.
- PRO analysis ongoing.
- Results will be used to design a new study with a strong physical activity component.
Survivorship Promotion in Reducing IGF-1 (SPIRIT) Study
(PI: Jessica Yeh)

- Any solid tumor
- BMI ≥25
- Randomization (N = 180)
  - Self-directed
  - Coach-directed
  - Metformin

Hypothesis
- Participants in the coach-directed intervention and metformin arms will have greater decreases in IGF-1 and IGF-1GFBP3 compared to the self-directed arm.

Physical Activities by Technology Help (PATH)
(PI: Ahmed Hassoon)

- Objectives:
  - To test which technology intervention will result in increasing physical activities in cancer survivors
  - To test preference between voice interaction over test messages

- Study arms:
  - Control: step target without remote support (self-driven)
  - Automated algorithmic text message intervention (mobile phone)
  - Interactive Digital Voice Assist using Amazon Echo smart speaker

- Design: pilot of 14 patients in each arm; 1 week of run-in followed by 4 weeks of study
  - Primary outcome: Total number of steps (Fitbit Charge HR)

Objectives

1. Review obesity statistics and the relationship between obesity and cancer risk and survival

2. Explain efforts to reduce burden of obesity in cancer survivors
   - A randomized study evaluating the effect of a remote-based weight loss program on biomarkers (POWER)
   - Survivorship Promotion in Reducing IGF-1 (SPIRIT) Study
   - Physical Activities by Technology Help (PATH)

3. Discuss other ongoing and planned studies to augment approaches
   - The Breast cancer Weight Loss (BWEL) Study
   - Intervention in women undergoing doxorubicin-based CT
   - Physical activity dose response study
   - Sleep intervention followed by POWER-remote (COIN)
   - Adaptive weight loss study with pharmacotherapy
Randomized Phase III Trial Evaluating the Role of Weight Loss In Adjuvant Treatment of Overweight and Obese Women with Early Breast Cancer: The Breast cancer WEight Loss (BWEL) Study (Alliance 011401, PI: Jennifer Ligibel)

Objectives

- **Primary**: Assess the impact of a weight loss intervention upon Invasive Disease Free Survival (STEEP)
- **Secondary**
  - Assess the relationship between weight loss and IDFS and OS
  - Assess the impact of the weight loss intervention upon:
    - Overall mortality
    - Distant disease free survival
    - Weight change
    - Hospitalizations for cardiovascular disease or diabetes
    - IDFS in subsets of participants defined by:
      - HR status of the tumor, Menopausal status

- **Correlative end points**

Predictive Role of Baseline Physical Fitness and the Impact of Exercise During Breast Cancer Therapy (PI: Stuart Russell, Seth Martin)

- **Hypotheses**
  - Regular aerobic exercise (10,000 steps a day) being motivated by the Under Armour Health Box will lead to an improvement in peak VO2 in women newly diagnosed with bc undergoing chemotherapy
  - Baseline peak VO2 predicts risk for chemotherapy-induced cardiomyopathy and an improvement in peak VO2 is preventative
**Study plan**

- Enroll 40 patients receiving doxorubicin-based regimen
- Baseline testing including strain echo, exercise gas exchange, body composition
- Encourage to walk 10,000 steps a day total with at least 1 thirty minute walk a day
- Repeat measurement at the end of chemotherapy

Under Armour Health Box fitness tracking system
- Scale
- Band - measures sleep, resting heart rate, steps, and workout intensity when worn with UA Heart Rate
- Heart rate tracker

---

**Cancer, Obesity/Overweight and Insomnia Study (COIN)**

*(PI: Janelle Coughlin)*

- Pilot clinical trial that combines a brief evidence-based cognitive-behavioral intervention for insomnia (CBT-I) with a translational behavioral weight loss intervention (BWL) in women with early-stage breast cancer and insomnia
- Participants (N=30) will be randomized to a 4-week CBT-I vs. education control prior to starting a 6-month BWL intervention
- We will measure outcomes at baseline, 4 weeks (after completing CBT-I or EDU and prior to BWL), 3 and 6 ms (after BWL)
- **Aim 1**: Compare the effects of CBT-I+BWL and EDU+BWL on % weight loss at 3 and 6 ms
- **Aim 2**: Evaluate the extent to which short-term sleep continuity improvements (4 wks and 3 ms) are associated with improvements in daily physical activity, and dietary quality/quantity, and determine their association with 3 and 6 ms weight changes

---

**COIN Schema**
Adaptive Weight Loss Study (PI: Vered Stearns)

• Phase II study in which all participants will receive a coached behavioral weight loss intervention (BWL) for the 6-month study period. At 2 months, women who lose ≥5% of baseline weight, designated fast responders, will continue with BWL alone (FAST-BWL) while those who lose <5%, designated slow responders, will continue BWL and initiate anti-obesity pharmacotherapy (SLOW-BWL).

• Participants (N=55) will be enrolled.

• Aim 1: To assess the proportion of SLOW-BWL patients who attain ≥5% loss with the addition of Contrave to BWL at 6 months from study entry.

• Aim 2: To compare cardiometabolic biomarkers, microbiome composition and patient reported outcomes (PROs) at 2 and 6 months to baseline levels among SLOW-BWL who achieved ≥5% loss.

• To compare characteristics at baseline of (a) SLOW-BWL who achieved ≥5% loss v. the SLOW-BWL who did not achieve 5% loss and (2) all who achieve ≥5% loss at 6 months v. those who are unable to achieve 5% loss.

Weight loss trajectory

Phase III trials with Contrave

<table>
<thead>
<tr>
<th>Phase III Study</th>
<th>Arms</th>
<th>Study population BMI 30 or ≥27 with comorbidities</th>
<th>% Weight loss at 56 weeks</th>
<th>% Weight loss at 56 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB-301 COR-70</td>
<td>Placbo (581)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>Placbo: 16%</td>
</tr>
<tr>
<td>NB16 (578)</td>
<td>Placbo (363)</td>
<td>Age 19-65</td>
<td>Male 10%, Female 90%</td>
<td>NB16: 39%</td>
</tr>
<tr>
<td>NB32 (583)</td>
<td>Placbo (102)</td>
<td>Age 19-65</td>
<td>Male 10%, Female 90%</td>
<td>Placbo: 42%</td>
</tr>
<tr>
<td>NB-302 COR-88</td>
<td>Placbo (320)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>NB32: 46%</td>
</tr>
<tr>
<td>NB16 (578)</td>
<td>Placbo (102)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>NB32: 46%</td>
</tr>
<tr>
<td>NB32 (583)</td>
<td>Placbo (102)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>NB32: 46%</td>
</tr>
<tr>
<td>NB-303 COR-99</td>
<td>Placbo (495)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>Placbo: 17%</td>
</tr>
<tr>
<td>NB16 (370)</td>
<td>Placbo (102)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>NB32: 6%</td>
</tr>
<tr>
<td>NB32 (583)</td>
<td>Placbo (102)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>NB32: 6%</td>
</tr>
<tr>
<td>NB-304 COR-120D</td>
<td>Placbo (570)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>Placbo: 17%</td>
</tr>
<tr>
<td>NB16 (370)</td>
<td>Placbo (102)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>NB32: 6%</td>
</tr>
<tr>
<td>NB32 (583)</td>
<td>Placbo (102)</td>
<td>Age 18-65</td>
<td>Male 15%, Female 85%</td>
<td>NB32: 6%</td>
</tr>
</tbody>
</table>
Adaptive weight loss study schema

Conclusions

- Obesity is associated with increased risk of developing several types of cancer
- Obesity is also associated with inferior outcomes in individuals diagnosed with cancer compared with counterparts whose weight is in the normal range
- Health care teams must review weight loss recommendations with their patients
- Remotely delivered weight loss interventions are feasible in cancer survivors

Future Directions

- New studies with an enhanced physical activity component, dose response, new technologies
- Develop predictive models for weight loss programs
  - Validation of biomarker modulation, and exploration of emerging markers
- By identifying patients who do not have modulation of biomarkers, generating hypotheses of other interventions they may benefit from
Recommendations for Patients

**Obesity**

• It is recommended that primary care clinicians
  – should counsel survivors to achieve and maintain a healthy
    weight (LOE = III);
  – should counsel survivors, if overweight or obese, to limit
    consumption of high-calorie foods and beverages and increase
    physical activity to promote and maintain weight loss (LOE = IA,
    III).

**Physical Activity**

• It is recommended that primary care clinicians should
  counsel survivors to engage in regular physical activity
  consistent with the ACS guideline
  – should avoid inactivity and return to normal daily activities as
    soon as possible after diagnosis (LOE = III);
  – should aim for at least 150 minutes of moderate or 75 minutes of
    vigorous aerobic exercise per week (LOE = I, IA);
  – should include strength training exercises at least 2 days per
    week. Strength training should be emphasized for women who
    are treated with adjuvant chemotherapy or hormone therapy
    (LOE = IA).

**Nutrition**

• It is recommended that primary care clinicians should
  counsel survivors to achieve a dietary pattern that is high
  in vegetables, fruits, whole grains, and legumes; low in
  saturated fats (LOE = IA, III); and limited in alcohol
  consumption (LOE = 0).
Acknowledgments

Medical Oncology:
Vered Stearns
Antonio Wolff
Cesar Santa-Maria
Deb Armstrong
Roisin Connolly
John Fetting
Daniela Jelovac
Karen Smith
Raquel Nunes
Study coordination:
Ashley Carpenter
Stacie Jeter
Biostatistics:
Amanda Blackford
Chung-Yu Huang
Chenguang Wang

Collaborators at Hopkins:
Lawrence Appel
Janelle Coughlin
Arlene Dison
Gerald Gerome
Colleen Schreyer
Mary Armanios
Dipali Sharma
Claire Snyder

GBMC:
Madhu Chaudhry
Gary Cohen
Robert Donegan

Under Armour Collaboration:
Ben Park
Elissa Bantug
Beth Thompson

Thank you

NCI/NIH T32 CA009071-37

American Institute for Cancer Research®

Wellspan Health Network-Johns Hopkins Cancer Research Fund