Evidence Gaps that Current Trials Will Address, Gaps that Remain, and How These Gaps Can be Filled

Jennifer Ligibel, MD
Dana-Farber Cancer Institute
National Cancer Policy Forum
February 13, 2017
A brief recap of what we know about weight, physical activity and health outcomes for cancer survivors
Obesity and inactivity are associated with poor prognosis in many cancers

Table 1. Individual and pooled risk estimates from prospective cohort studies that related postdiagnosis physical activity to cancer-specific mortality, by cancer site.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of events/cases</th>
<th>Effect estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bradshaw, 2014 (10)</td>
<td>195/1,033</td>
<td>0.27</td>
<td>0.17-0.42</td>
</tr>
<tr>
<td>Helick, 2008 (26)</td>
<td>109/4,482</td>
<td>0.49</td>
<td>0.27-0.89</td>
</tr>
<tr>
<td>Borch, 2015 (9)</td>
<td>155/1,337</td>
<td>0.50</td>
<td>0.15-1.62</td>
</tr>
<tr>
<td>Holme, 2005 (27)</td>
<td>269/2,987</td>
<td>0.60</td>
<td>0.40-0.89</td>
</tr>
<tr>
<td>Irwin, 2011 (18)</td>
<td>86/2,980</td>
<td>0.61</td>
<td>0.39-0.99</td>
</tr>
<tr>
<td>Irwin, 2008 (28)</td>
<td>116/933</td>
<td>0.65</td>
<td>0.25-1.87</td>
</tr>
<tr>
<td>Williams, 2014 (8)</td>
<td>46/666</td>
<td>0.76</td>
<td>0.62-0.92</td>
</tr>
<tr>
<td>de Gools, 2014 (12)</td>
<td>39/435</td>
<td>0.77</td>
<td>0.26-2.12</td>
</tr>
<tr>
<td>Stensfeld, 2009 (29)</td>
<td>102/1,970</td>
<td>0.87</td>
<td>0.40-1.59</td>
</tr>
<tr>
<td>Borugian, 2004 (7)</td>
<td>112/593</td>
<td>1.00</td>
<td>0.63-1.60</td>
</tr>
</tbody>
</table>

| Pooled Estimate (I² = 61%) | 1,239/17,666     | 0.62           | 0.40-0.80 |

<table>
<thead>
<tr>
<th>Colorectal</th>
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<tbody>
<tr>
<td>Kupfer, 2002 (13)</td>
<td>50/606</td>
<td>0.29</td>
<td>0.11-0.77</td>
</tr>
<tr>
<td>Meyerhardt, 2006 (30)</td>
<td>80/573</td>
<td>0.39</td>
<td>0.19-0.82</td>
</tr>
<tr>
<td>Meyerhardt, 2009 (31)</td>
<td>86/661</td>
<td>0.47</td>
<td>0.24-0.92</td>
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<tr>
<td>Aren, 2015 (14)</td>
<td>126/3,737</td>
<td>0.53</td>
<td>0.27-1.03</td>
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<td>Campbell, 2013 (15)</td>
<td>379/2,256</td>
<td>0.87</td>
<td>0.69-1.24</td>
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<tr>
<td>Baade, 2011 (9)</td>
<td>347/8,823</td>
<td>0.88</td>
<td>0.67-1.15</td>
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</table>

| Pooled Estimate (I² = 56.6%) | 1,076/9,666   | 0.62           | 0.40-0.86 |

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<tr>
<td>Kerfelden, 2011 (47)</td>
<td>112/2,705</td>
<td>0.42</td>
<td>0.20-0.88</td>
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<tr>
<td>Friedenreich, 2016 (18)</td>
<td>170/830</td>
<td>0.56</td>
<td>0.35-0.90</td>
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<td>Bonn, 2015 (9)</td>
<td>194/4,623</td>
<td>0.73</td>
<td>0.51-1.05</td>
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| Pooled Estimate (I² = 0.8%) | 476/8,108    | 0.62           | 0.47-0.82 |

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<td>Lee, 2014 (20)</td>
<td>337/5,023</td>
<td>0.62</td>
<td>0.44-0.87</td>
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<td>Inoue-Choi, 2013 (20)</td>
<td>184/2,017</td>
<td>0.72</td>
<td>0.47-1.10</td>
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<thead>
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<th>Overall</th>
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<tr>
<td>Pooled Estimate (I² = 47.9%)</td>
<td>3,307/38,560</td>
<td>0.65</td>
<td>0.54-0.73</td>
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</table>

Mechanistic data support biologic plausibility of link between obesity/physical activity and cancer.

Interventional studies show benefits of weight loss/increased PA in cancer survivors.

Impact of exercise interventions on fatigue

- All studies: N=1662, -0.23 (-0.33 to -0.13)
- Studies during treatment: N=929, -0.18 (-0.32 to -0.05)
- Studies after treatment: N=491, -0.37 (-0.55 to -0.18)
- Breast cancer studies: N=977, -0.36 (-0.49 to -0.23)

Impact of exercise interventions on quality of life

Cochrane Review 2008; Buffart L et al. Cancer Treatment Reviews 2017
Obesity and inactivity are common in cancer survivors

Table 2. Percentage of Cancer Survivors Meeting the Recommendations for Physical Activity, Fruit and Vegetable Consumption, and Smoking by Cancer Group

<table>
<thead>
<tr>
<th>Cancer Group</th>
<th>Physical Activity (%)</th>
<th>5-A-Day (%)</th>
<th>Smoking (%)</th>
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<tr>
<td>Breast</td>
<td>37.1</td>
<td>18.2</td>
<td>88.1</td>
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<td>Prostate</td>
<td>43.2</td>
<td>15.6</td>
<td>91.6</td>
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<tr>
<td>Colorectal</td>
<td>35.0</td>
<td>15.9</td>
<td>91.3</td>
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<tr>
<td>Bladder</td>
<td>36.0</td>
<td>16.3</td>
<td>82.6</td>
</tr>
<tr>
<td>Uterine</td>
<td>29.6</td>
<td>19.1</td>
<td>91.1</td>
</tr>
<tr>
<td>Skin melanoma</td>
<td>47.3</td>
<td>14.8</td>
<td>89.0</td>
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</table>

Abbreviation: 5-A-Day consumed five servings of fruits and vegetables each day.

Unanswered questions

- Does weight loss/increased PA after cancer diagnosis reduce risk of recurrence and mortality?

- If so, what dose and duration are needed to impact cancer outcomes?

- What is most important? Weight? Physical activity? Diet?

- Do all patients benefit equally from lifestyle interventions? Is this cancer-specific or based on host characteristics?

- How can lifestyle interventions be disseminated across diverse populations of cancer survivors?
How do on-going trials fill these evidence gaps?
Lifestyle intervention trials with recurrence/mortality outcomes

**CHALLENGE: Colon Health and Life-Long Exercise Trial**

**REGISTRATION**
- Eligibility: Higher risk stage II or Stage III colon ca
- Completed adjuvant chemo w/in 2-6 mos

**RANDOMIZATION**

**ARM 1**
- Physical Activity Program + General Good Health Education Material (Intervention Arm)

**ARM 2**
- General Health Education Materials (Control Arm)

**Assessment of disease-free survival every 6 months for first 3 years and annually from years 4-10**

GAP4 Study-Metastatic Prostate Cancer

Figure 2. Study Design

**ARM A: Exercise Group**
- 12 month supervised exercise programme
  - Cycle 0: x3 days/week
  - Cycles 1-8: x2 days/week
  - Cycles 9-11: x1 day/week
- 12 month self-managed exercise programme
- Behavioural support
- Psychosocial support
- Exercise assessments (Cycles 0, 6, 9, 12, 18, 24)
- Constant Load Tests (Cycles 1-5, 7-11, 13-17 & 19-23)
- Frequent exercise monitoring (Cycles 0-12)
- Metabolic biomarker assessments (Cycles 0, 6, 12, 24)
- QoL assessments (Cycles 3, 6, 9, 12, 15, 18, 21, 24, 36)

**ARM B: Control Group**
- Psychosocial support
- Exercise assessments (Cycles 0, 6, 12, 18, 24)
- Metabolic biomarker assessments (Cycles 0, 6, 12, 24)
- QoL assessments (Cycles 3, 6, 9, 12, 15, 18, 21, 24, 36)

Slide courtesy of Kerry Courneya
Study Schematic for GOG 0225 – LIVES study

Stage II-IV Ovarian Cancer (N=1070)
>6 weeks to ≤ 6.5 months Post-primary therapy
Stratify on stage, consolidation therapy

RANDOMIZE

Control Health Education

Progression-free Survival
Quality of Life Bowel Health

Diet and Activity Intervention

PI: Thomson and Alperts
Lifestyle Intervention for Ovarian Cancer Enhanced Survival

• Centralized telephone coaching
  • English and Spanish

• Multi-modal intervention
  • Telephone, print, SMS, email, blog

• Participant centered intervention
  • Grounded in Social Cognitive Theory utilizing Motivational Interviewing

• Promotion of high vegetable, fiber and fruit diet with low fat and +4000 steps daily

• Control: attention control health education group
GOG-0225 Accrual (Current accrual: 962)
### Patient Characteristics, first 529 patients

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<th>Characteristic</th>
<th>N (%)</th>
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<td><strong>Age</strong></td>
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<tr>
<td>≤50</td>
<td>100 (18.8%)</td>
</tr>
<tr>
<td>51-60</td>
<td>171 (32.2%)</td>
</tr>
<tr>
<td>61-70</td>
<td>181 (34.1%)</td>
</tr>
<tr>
<td>71+</td>
<td>70 (14.9%)</td>
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<tr>
<td><strong>Race/ethnicity</strong></td>
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<tr>
<td>Non-Hispanic White</td>
<td>459 (86.8%)</td>
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<tr>
<td>Non-Hispanic Black</td>
<td>22 (4.2%)</td>
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<tr>
<td>Hispanic</td>
<td>30 (5.6%)</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
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<tr>
<td>&lt;25 kg/m²</td>
<td>197 (37.2%)</td>
</tr>
<tr>
<td>25-29.9 kg/m²</td>
<td>177 (33.5%)</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>149 (28.2%)</td>
</tr>
<tr>
<td><strong>Disease Stage</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>82 (15.4%)</td>
</tr>
<tr>
<td>III</td>
<td>376 (70.8%)</td>
</tr>
<tr>
<td>IV</td>
<td>72 (13.8%)</td>
</tr>
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</table>
The Breast Cancer Weight Loss Trial A011401

PI’s: Ligibel and Goodwin
**BWEL Study Schema**

3136 participants

**Key Eligibility:**
- Stage II-III breast cancer
- HER-2 -
- BMI ≥ 27 kg/m2

**Objectives**

**Primary:** Assess the impact of the weight loss intervention on iDFS

**Secondary:**
- Assess impact of intervention upon:
  - OS, DDFS
  - Comorbidities
  - Weight, diet and exercise
- Correlative science and PRO

2-year telephone-based weight loss intervention + Health education

Health Education Alone
Weight Loss Intervention Overview

• Centralized, 2 year telephone-based weight loss program

• Each patient paired with a weight loss coach, based at DFCI
  • Patients receive 42 phone calls over 2 years
  • Receive a workbook to accompany calls, tools to help increase exercise and reduce calories (Fitbit, wireless scale, food scale, protein shakes)

• Intervention goals:
  • 10% weight loss
  • 500-1000 kcal/day deficit
    » Portion control -- meal replacements, structured menus
    » Basic diet stresses fruits, vegetables, whole grains, lower in fat
  • Increased physical activity
    – 150-200 minutes moderate-intensity activity in first 6 months
    – Goal of 45-60 minutes of activity/day in maintenance phase
BWEL Study Update

- Protocol activated August 29, 2016

- Currently open in 897 sites in US

- Two step registration/randomization process for first 514 patients to allow for detailed diet and exercise data
  - 292 patients registered
  - 234 patients randomized

- Next steps
  - Activation in Canadian centers planned for early spring 2017
  - Additional of Spanish version of intervention planned summer 2017
Other ongoing trials testing lifestyle change on breast cancer outcomes

Diana-5: Calorie restricted Mediterranean diet + Increased PA vs control

- Potentially eligible patients (n = 1,667)
  - (BC diagnosed within the previous 5 years, age 35-70, no previous cancer, no clinical contraindication to dietary change or exercise, no social impediment)

- Baseline eligibility examinations
  - (Testosterone, insulin, waist circumference, glucose, triglycerides, HDL cholesterol)

- Biological bank
  - (plasma, serum, red blood cells, buffy coat)

- ER-negative or metabolic syndrome or high testosterone or insulin level

- NO (n = 453)
  - Observation only (orange) group

- YES (n = 1214)

  - RANDOMIZATION
    - (stratified by study site, age, ER, nodal status)

  - Control (green) group
    - (n = 607-4 withdrawn = 603)

  - Intervention (blue) group
    - (n = 607-2 withdrawn = 605)

Villarini et al. Tumori. 2012;98 (1)
<table>
<thead>
<tr>
<th></th>
<th>BWEL</th>
<th>CHALLENGE</th>
<th>DIANA 5</th>
<th>GAP4</th>
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<tr>
<td>N</td>
<td>3136</td>
<td>962</td>
<td>1241</td>
<td>866</td>
<td>1040</td>
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<tr>
<td>Disease</td>
<td>Breast</td>
<td>Colon</td>
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<td>Ovarian</td>
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<tr>
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<td>3-yr Ex</td>
<td>4+ yr Med diet + Ex</td>
<td>2-yr Ex</td>
<td>2-yr Diet + Ex</td>
<td>2-yr Weight loss</td>
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<td>DFS</td>
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<td>Blood</td>
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</tbody>
</table>

Summary of RCT’s with disease recurrence/mortality end points
Will these trials fill the evidence gaps?

• Studies will test impact of lifestyle change after cancer diagnosis on recurrence and mortality in common malignancies

• Each trial examines impact of a specific intervention on recurrence/mortality in a single malignancy
  • Some trials are large enough to evaluate the impact of interventions on subsets of patients defined by tumor or host characteristics

• Can these trials help answer other unresolved questions?

• Can we generalize the information learned from these studies to other malignancies?
Correlative science

• Each of the on-going large-scale trials include biospecimen collection
  • Serial collection of fasting blood for biomarker analysis
  • Baseline collection of tumor and benign tissue
  • DNA

• Assessment of predictors of intervention benefit
  • Potentially define population to whom intervention should be prescribed

• Development of potential intermediate biomarkers
  • Provide a way to determine whether an intervention is “working”
  • Streamline future research
  • Enhance interpretation of prior studies
Lifestyle interventions affect metabolic and inflammatory pathways

*Nutrition and Exercise Study for Women (NEW Trial)*

- Designed to evaluate the impact of dietary weight loss and exercise upon biomarkers linked to breast cancer risk
- Enrolled 439 sedentary, overweight or obese, postmenopausal women
- Participants randomized to 1 of 4 groups:
  - Dietary weight loss
  - Exercise
  - Dietary weight loss + exercise
  - Control
- Endpoints:
  - Primary: change in sex steroids
  - Secondary: change in insulin, metabolic and inflammatory hormones
Weight loss led to significant reductions in metabolic and inflammatory biomarkers.

Weight Change:

- Diet: -10.8%
- Diet + Exercise: -11.9%
- Exercise: -3.3%
- Control: -0.6%

CHOICE Study: Impact of low fat vs. low carb diet on biomarkers in breast cancer survivors

370 participants

Key Eligibility:
- Breast Cancer diagnosis
- BMI 25-35 kg/m²
- Completed with chemotherapy/RT
- Not being treated for diabetes

Group assigned according to patients’ choice
- 6 Month Low Fat, High Carb Diet
- 6 Month Low Carb, High Fat Diet
- Control

Primary Question: How does fat loss achieved by different dietary approaches impact biomarkers of breast cancer risk?
- Glucose Homeostasis
- Inflammation
- Cellular oxidation
- Sex steroid metabolism

Sedlacek et al. BMC Cancer 2011; 11
Cumulative Loss of Body Weight, Body Fat, and Lean Body Mass According to Study Group

A. Cumulative Weight Loss

B. Cumulative Fat Weight Loss

C. Cumulative Lean Muscle Mass Loss

Change in fasting glucose by diet group

Thompson et al. Breast Cancer Res. 2012; 14 (1)
Change in glucose by arm and weight change (high vs. low)
**Do on-going trials provide a path to widespread dissemination in cancer survivors?**

<table>
<thead>
<tr>
<th></th>
<th>BWEL</th>
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<td><strong>Recruitment sites</strong></td>
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Potential avenues for implementation of exercise interventions in cancer survivors

80% OF U.S. HOUSEHOLDS WITHIN 5 MILES OF A YMCA

SERVING MORE THAN 22 MILLION MEMBERS EACH YEAR IN MORE THAN 10,000 COMMUNITIES.
After Referral to Outpatient Rehabilitation

Visit 1  
PT Evaluation And Clearance

Visit 2  
Lymphedema Education Session

Visit 3  
Teach Warm-up, cool down, teach 2-3 exercises

Visit 4  
Have pt repeat Visit 3 activities, answer questions, teach 2-3 exercises

Visit 5  
Have pt repeat visit 4 activities, answer questions, teach 2-3 exercises

Visit 6  
Discharge Day
Pt. demonstrates complete protocol.

Discharge may only occur when the pt demonstrates understanding of:
1. Good form with exercises
2. Progression
3. Deconditioning
4. Overall arm work
5. Monitoring symptoms
6. When to call for a follow-up appt

Additional visits will be scheduled for pts not ready for discharge at visit 6.

Resistance delivered to home or purchased by patient.
New technologies may allow for development of distance-based exercise interventions

- Wearable activity monitors allow for transmission of objective activity and biometric data to trainers/investigators

- Mobile platforms allow for delivery of content in real-time and also allow for individualized coaching from afar

- More work is needed

- On-going work will explore balance of technology and traditional coaching methods
Can we generalize information from on-going trials to other diseases/populations?

- Observational data connects obesity and inactivity to increased risk of cancer recurrence and related mortality in many diseases.

- On-going trials focus on a small sub-set of these cancers.

- Trials also need to focus on a single intervention in a narrow subset of patients to keep sample size feasible.

- As oncology treatments become more “personalized”, focusing on development of individual treatment plans for subsets of patients within a particular disease, path to broader generalization of trial results remains unclear.
Which evidence gaps will be addressed by current trials?

- Evidence from on-going trials will provide information about the impact of weight loss and increased physical activity on cancer recurrence and mortality.

- Trials address specific interventions in individual diseases.

- Correlative work may provide tools to extend the knowledge gained from these studies:
  - Predictive markers: define populations most likely to benefit
  - Intermediate biomarkers: facilitate work to compare different interventions and doses

- Still significant unanswered questions:
  - Best ways to disseminate interventions to diverse groups of cancer survivors, especially exercise interventions
  - Unclear how much generalization can occur across diseases
Study team

- **PI:** Jennifer Ligibel
- **Co-Chairs**
  - Correlative Science Co-Chair: Pam Goodwin (Co-PI)
  - Health Behaviors Co-Chair: Dawn Hershman (SWOG)
  - Community Oncology Co-Chair: Judy Hopkins
  - Health Disparities Co-Chair: Electra Paskett
  - Breast Committee Chairs: Eric Winer & Cliff Hudis
- **Statistics:** Bill Barry, Linda McCourt, Amylou Dueck
- **Advocates:** Patty Spears and Liz Frank
- **Funding:** CTEP, DCP, DCCPS, ACS, Komen

- **Intervention Oversight Committee:**
  - Chair: Tom Wadden
  - Behavioral Science: Catherine Alfano
  - Exercise Physiology: Melinda Irwin
  - Nutrition: Marian Neuhouser
  - Call Center: Linda Delahanty
  - Remote Intervention Delivery: Cyndi Thomson

- **Steering Committee Members**
  - Vered Stearn (ECOG)
  - Julia White (NRG)
  - Rachel Ballard (NIH)
  - Worta McCaskill-Stevens (NCI)
  - Linda Nebeling (NCI)
  - Vanessa Bernstein