Non-Pharmacologic Approaches
to Ovarian Cancer Prevention and Control

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Rationale for Studying Non-Pharmacological Approaches to Ovarian Cancer

• While disease stage and grade, age at diagnosis and residual disease following surgery are the most important predictors of survival time, none of these factors are amenable to intervention to improve survival.

• Little is know about the role of non-pharmacological factors, such as weight and exercise, on ovarian cancer risk and survival.
Rationale for Studying Non-Pharmacological Approaches to Ovarian Cancer

• Surgery and treatment are associated with several negative side effects.

• Common side effects of cancer and its treatment include
  • Fatigue and reduced quality of life
  • Changes in body weight, bone density and lean mass
  • Lymphedema
  • Peripheral neuropathy
  • Risk of recurrence and/or new cancer diagnoses

• Certain non-pharmacological approaches, e.g., exercise and weight management, may prevent or control many of these side effects.
Obesity Trends Among U.S. Adults
(BMI ≥30)

1990: 15% are obese

2000: 20% are obese

2010: >30% are obese

2030: >60% are obese

cdc.gov
Obesity and Cancer Mortality

BMI and Ovarian Cancer RISK

- ~50 epidemiological studies of BMI and ovarian cancer risk have been conducted.
- Obesity associated with greater risk of ovarian cancer.
- A 1 unit increase in BMI is associated with 3% increase in ovarian cancer incidence.
- BMI and Ovarian Cancer risk may be limited to never-users of hormone therapy.

BMI and Ovarian Cancer Mortality

• ~14 epidemiological studies of BMI and ovarian cancer mortality have been conducted.

• Poorer survival among obese compared with non-obese women.
  – HR = 1.17 (1.03-1.32)

• High BMI at age 20 associated with higher mortality
  – HR = 1.82 (1.02-3.27)

• Weight change from age 20 to diagnosis associated with higher mortality
  – HR = 1.68 (1.11-2.55)

Protani M. Cancer Prev Res 2012;
Zhou Y. Gynecol Oncol 2011
Weight and Ovarian Cancer

- Women who are obese prior to, or at diagnosis, may have more biologically aggressive tumors.

- Adiposity is associated with up-regulation of a number of cellular proliferation pathways, leading to increased tumor growth and metastasis.

- Obesity may:
  - Delay diagnosis
  - Hinder optimal surgical and cytotoxic treatment
  - Cause postoperative complications
  - Be associated with other chronic diseases, such as CVD and diabetes, which may impair their tolerance to chemotherapy, affecting survival

- As obesity rates increase, the impact of BMI in the clinical management of ovarian cancer becomes increasingly significant.
Physical Activity and Ovarian Cancer Risk

- A meta-analysis of 12 studies reported a pooled estimate of a ~ 20% reduction in ovarian cancer risk when comparing the highest to lowest categories of recreational physical activity.

- Proposed mechanisms for the protective effects include:
  - Prevention of weight gain
  - Effects on ovulation
  - Sex hormone levels
  - Metabolic pathways
  - Inflammatory markers
  - Immune markers

Olsen, CM. CEBP 2007
Physical Activity and Ovarian Cancer Mortality

HR = 0.69 (0.47-1.00)
Body mass index, physical activity, and mortality in women diagnosed with ovarian cancer: Results from the Women’s Health Initiative

Baseline Characteristics

- Mean age 63.0 ± 6.9 years old
- Mean 3.9 ± 3.4 years from diagnosis to death
- Mean BMI 27.5 ± 5.9 kg/m²
- 89% Non-Hispanic White
- 68% were diagnosed with Distant SEER stage disease
## Associations between ovarian cancer outcomes and physical activity

<table>
<thead>
<tr>
<th></th>
<th>Pre-Diagnosis Physical Activity (MET hr/wk)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PA = 0</td>
<td>PA &gt; 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N=439)</td>
<td>(N=161)</td>
</tr>
<tr>
<td><strong>Total Deaths</strong></td>
<td></td>
<td>n=260</td>
<td>n=86</td>
</tr>
<tr>
<td>Age-Adjusted HR (95% CI)</td>
<td></td>
<td>1.00</td>
<td>0.83 (0.65-1.06)</td>
</tr>
<tr>
<td>Multivariate Adjusted HR* (95% CI)</td>
<td></td>
<td>1.00</td>
<td><strong>0.76 (0.58-0.98)</strong>$^1$</td>
</tr>
<tr>
<td><strong>Ovarian Cancer Deaths</strong></td>
<td></td>
<td>n=228</td>
<td>n=73</td>
</tr>
<tr>
<td>Age-Adjusted HR (95% CI)</td>
<td></td>
<td>1.00</td>
<td>0.80 (0.61-1.04)</td>
</tr>
<tr>
<td>Multivariate Adjusted HR* (95% CI)</td>
<td></td>
<td>1.00</td>
<td><strong>0.74 (0.56-0.98)</strong>$^1$</td>
</tr>
</tbody>
</table>

**Abbreviations:** PA, Physical Activity; HR, Hazard Ratio

*Multivariate Model adjusted for age, stage, histology, time from study enrollment to ovarian cancer diagnosis, BMI, hormone therapy use, smoking, history of diabetes and status in calcium and vitamin D trial, diet modification trial, hormone therapy trial and observational study.

$^1p<0.05$
## Associations between ovarian cancer outcomes and pre-diagnosis BMI

<table>
<thead>
<tr>
<th></th>
<th>Pre-Diagnosis BMI, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI &lt; 18.5 (N=13)</td>
</tr>
<tr>
<td><strong>Total Deaths</strong></td>
<td></td>
</tr>
<tr>
<td>Age-Adjusted HR (95% CI)</td>
<td>1.44 (0.71-2.95)</td>
</tr>
<tr>
<td>Multivariate Adjusted HR* (95% CI)</td>
<td>1.14 (0.55-2.40)</td>
</tr>
<tr>
<td><strong>Ovarian Cancer Deaths</strong></td>
<td></td>
</tr>
<tr>
<td>Age-Adjusted HR (95% CI)</td>
<td>1.22 (0.54-2.77)</td>
</tr>
<tr>
<td>Multivariate Adjusted HR* (95% CI)</td>
<td>0.90 (0.39-2.11)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, Hazard Ratio  
*Multivariate Model adjusted for age, stage, histology, time from study enrollment to ovarian cancer diagnosis, BMI, hormone therapy use, smoking, history of diabetes and status in calcium and vitamin D trial, diet modification trial, hormone therapy trial and observational study.

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**Note:** The highlighted values in the table indicate the adjusted hazard ratio for the outcome of interest with BMI ≥ 30, which is discussed in the text about the association between BMI and ovarian cancer outcomes.
Potential pathways directly linking obesity with cancer

van Kruijsdijk R C et al. CEBP 2009;18:2569-2578
Obesity Increases Tumor Aggressiveness in Genetically Engineered Mouse Model of Ovarian Cancer
Observational Studies of Physical Activity in Women Diagnosed with Ovarian Cancer

• Quality of life is often the most compromised in ovarian cancer patients.

• Stevinson C, Gynecol Oncol 2007
  – N = 359
  – 31% meeting PA guidelines
  – PA associated with better QOL
Primary Aims:

• To examine, in 144 ovarian cancer survivors, the effect of 6-months of exercise vs. attention control on:
  • Quality of Life and Fatigue
  • Biological markers
    – Insulin, IGFs, CRP, leptin, osteopontin, MIF, prolactin, CA-125
  • Body composition
    – Weight, % body fat, bone mass, lean mass
  • Lower leg lymphedema
  • Peripheral Neuropathy
  • Salivary Cortisol levels
Data Collection

Recruit Women with Ovarian Cancer from Tumor Registry
↓
Check Eligibility (telephone)
(≤75 yrs, Stage I-IV, not exercising, completed chemotherapy)
↓
Baseline Visit
↓
Baseline Clinic Visit
↓
Randomize (N = 144)
↓
Health Education + Exercise (n = 75)
↓
6-Month Clinic Visit
↓
Health Education/Attention Control (n = 69)
Study Groups

• Aerobic Exercise Group (75 women)
  • Exercise Goal:
    – 2.5 hr/wk of moderate-intensity aerobic exercise (e.g., brisk walking)
    – Work personally with certified personal trainer via weekly phone calls

• Attention-Control Health Education Group (69 women)
  • Weekly phone calls scheduled at a convenient time
  • Discuss ovarian health education topics using booklet provided
  • Personalized exercise program developed after 6-month clinic visit
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Table 1. Baseline Characteristics, mean ± SD or % (N = 144)

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<th>Characteristic</th>
<th>(N = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57.3 (8.6)</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>98%</td>
</tr>
<tr>
<td>African American</td>
<td>1%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1%</td>
</tr>
<tr>
<td>Education (%)</td>
<td>97%</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>1.7 (1.0)</td>
</tr>
<tr>
<td>Disease Stage (%)</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>24%</td>
</tr>
<tr>
<td>Stage II</td>
<td>21%</td>
</tr>
<tr>
<td>Stage III</td>
<td>40%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15%</td>
</tr>
<tr>
<td>Chemotherapy (%)</td>
<td>93%</td>
</tr>
<tr>
<td>BMI</td>
<td>29.0 (7.0)</td>
</tr>
<tr>
<td>Physical Activity (min/wk)</td>
<td>28.3 (41.6)</td>
</tr>
</tbody>
</table>
## Adherence to Exercise Intervention

<table>
<thead>
<tr>
<th>Adherence to Exercise</th>
<th>Exercise</th>
<th>Adherence to Calls</th>
<th>Attention Control</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD), min/week</td>
<td>166.0 (66.1)</td>
<td>Mean attendance to calls</td>
<td>21.7 (5.5)</td>
<td>20.4 (5.6)</td>
</tr>
<tr>
<td>% of goal (2.5 hr/wk)</td>
<td>111%</td>
<td>% of goal (26 calls)</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>% of subjects Adhering to:</td>
<td></td>
<td>% of subjects adhering to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 150 Min/week (100%)</td>
<td>65%</td>
<td>≥ 25 calls (100%)</td>
<td>47%</td>
<td>19%</td>
</tr>
<tr>
<td>≥ 120 Min/week (80%)</td>
<td>84%</td>
<td>≥ 20 calls (80%)</td>
<td>80%</td>
<td>74%</td>
</tr>
<tr>
<td>≥ 90 Min/week (60%)</td>
<td>92%</td>
<td>≥ 15 calls (60%)</td>
<td>89%</td>
<td>87%</td>
</tr>
<tr>
<td>≥ 60 Min/week (40%)</td>
<td>92%</td>
<td>≥ 10 calls (40%)</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td>≥ 30 Min/week (20%)</td>
<td>99%</td>
<td>≥ 5 calls (20%)</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>&lt; 30 Min/week (0%)</td>
<td>100%</td>
<td>≥ 0 calls (0%)</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
WALC Exercise Characteristics

- High exercise adherence
  - Ave 166 min/wk
  - 2/3rds of exercisers have exceeded the exercise goal
Outcomes of Interest

Fatigue

- Functional Assessment of Cancer Therapy-Fatigue (FACT-F)
  - Higher FACT-F score indicates less fatigue burden

HRQOL

- Disease specific: FACT-Ovarian (FACT-O)
- General health: Short Form-36 (SF-36)
  - In both, a higher score denotes better HRQOL
Lower Limb Lymphedema (LLL)

Prevalence of LLL

- 23% via certified lymphedema specialist evaluation
- 26% via questionnaire
- 21% via perometer
Future Directions

• Future studies to examine benefit of exercise on ovarian cancer recurrence and mortality

• Disseminate findings related to exercise
  – Bring interventions into the community
  – Yale Survivorship Clinic
  – Encourage programs like LIVESTRONG at the YMCA™
NRG/GOG 0225
Can Diet and Physical Activity Modulate Ovarian Cancer Progression-Free survival?

The Lifestyle Intervention for Ovarian cancer Enhanced Survival (LIVES)

Thomson, Alberts, Walker, Basen-Engquist, Mannel
March 16, 2015
**Study Design Schematic**

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

- **Control Health Education**
- **Diet and Activity Intervention**
- **Progression-free Survival**
  - Quality of Life Bowel Health

**Yale Cancer Center**

A Comprehensive Cancer Center Designated by the National Cancer Institute

**Smilow Cancer Hospital at Yale-New Haven**
Aims: Biomarker R01

To determine if randomization to the lifestyle intervention as compared to comparison group results in:

• Reduced fasting insulin / insulin resistance
• Improved lipid profile
  – Cholesterol, HDL-C, LDL-C and TGL
• IL-6
• Omentin (ITLN1)
• Central adiposity (clinical CT scans quantification)

NIH R01 CA186700-01A1 (Thomson, PI, Basen-Engquist Co-PI, Irwin, Co-I)
GOG-0225 Enrollment by Quarter (Total N= 540)

Expected accrual 17/mo
Accrual rate 25/mo since July 2014
Goal: 1070

Qtr 4 2012 | Qtr 1 2013 | Qtr 2 2013 | Qtr 3 2013 | Qtr 4 2013 | Qtr 1 2014 | Qtr 2 2014 | Qtr 3 2014 | Qtr 4 2014
Baseline Characteristics

- Age – 58.9 ± 9.6 years
- BMI – 27.6 ± 5.7 kg/m²
- Waist circumference – 91.3 ± 10.1 cm
  - 62% have a waist circumference >88cm
- Months since treatment – 2.9
- Stage: >75% stage III
Ovarian Cancer Summary

• Obesity and physical activity are associated with ovarian cancer risk and mortality (observational studies).

• Women diagnosed with ovarian cancer are interested in participating in exercise programs.

• Exercise may improve quality of life outcomes in ovarian cancer patients.

• Whether exercise, diet or weight improves biological markers or ovarian cancer mortality is not yet known (from randomized trials).
How do we help patients improve lifestyle behaviors after a cancer diagnosis?

ASCO Priorities to Address Obesity-Cancer:

1. Increase providers’ and patients’ knowledge about obesity and cancer

2. Develop tools and resources to help oncology providers address obesity with their patients

3. Obesity and cancer research

4. Improve access to obesity treatment services for cancer patients/survivors