Restricting energy metabolism or increasing physical activity – which is more important for cancer prevention?

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2013 AICR Conference on Food, Nutrition, Physical Activity and Cancer
November 8, 2013
AICR’s 2013 Annual Research Conference on Food, Nutrition, Physical Activity and Cancer
November 7-8, 2913
Hyatt Regency Bethesda
Name of Speaker: Jennifer Ligibel

No Relevant Financial Relationship
Obesity is associated with increased cancer risk and mortality

Calle et al. NEJM 2003; 348: 1625-38
Obesity is a result of energy “imbalance”: too much energy in and not enough out.
Questions?

• What is the evidence linking energy intake and physical activity to cancer?

• Do we know that decreasing caloric intake and/or increasing physical activity prevents cancer/reduces mortality?

• Do we have enough evidence to conclude that one type of energy balance intervention—decreasing energy intake or increasing physical activity--holds the most promise for cancer prevention?
Observational evidence shows link between inactivity and cancer risk

Meta-analysis of physical activity and colon cancer risk

Figure 2  Meta-analysis of physical activity and colon cancer: cohort studies.
Inactivity after diagnosis also linked to risk of mortality

Post-diagnosis physical activity and breast cancer prognosis

Ballard-Barbash et al. JNCI 2012;104:815-840
Nurses’ Health Study: Physical activity after breast cancer diagnosis

50% FEWER CANCER RECURRENCES IN WOMEN WHO EXERCISED > 3 HOURS/WEEK

*p=0.05

Holmes et al. JAMA 2005; 293: 2479-2486
Preliminary data suggests changes in activity after diagnosis also linked to outcomes

- **HEAL study cohort:**
  - 933 women with stage I-III breast cancer
  - Enrolled 6 months post-dx

- **Collected physical activity data:**
  - Year before breast cancer diagnosis
  - 2 years post-diagnosis

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Irwin et al. JCO 2008; 26:3958-64
Energy intake also linked to cancer risk

20% increase in calorie consumption and cancer risk in WHI

Intake of energy dense foods also linked to mortality in individuals with early cancer

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<tr>
<th>Study</th>
<th>Macronutrients and Dietary Patterns</th>
<th>Hazard Ratio (Log Scale)</th>
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A few studies have looked at diet and physical activity simultaneously.

Women’s Healthy Eating and Living Study: Diet and exercise after dx
So does this help us answer our question about which intervention is more likely to reduce cancer risk?

- Observational evidence shows relationships between cancer and both physical activity and energy intake.

- Most studies examine one factor at a time.

- Limited data suggested synergy and/or an independent affect of diet and energy intake on cancer risk/mortality.

...so not really.
How can we determine which type of interventions holds most promise?

• Optimal data:
  – Randomized trials testing the impact of different energy balance factors on cancer risk and outcomes (*not available*)

• Available data:
  – RCT’s testing impact of changes in one factor on cancer risk/outcomes
  – Animal models comparing different energy balance interventions
  – Studies looking at the impact of energy balance interventions upon biomarkers linked to cancer risk/outcomes
Most direct evidence that restricting energy intake impacts cancer comes from Women’s Interventional Nutrition Study

- Randomized 2400 women with early-stage breast cancer to low-fat diet intervention or control group
- Intervention involved one-on-one meetings with dietician, cooking classes
- WINS diet: reduce fat to 15% of total calories

WINS-Results

Chlebowski, JNCI 2006: 98: 1767-76
The Women’s Healthy Eating and Living Study (WHEL)

- Included 3088 women with early-stage breast cancer
- Randomized to phone-based diet intervention or control
- WHEL Diet:
  - High fruits and vegetables
  - Low fat
  - High fiber

Pierce et al., JAMA 2007; 298: 289-98.
Impact of Dietary Intervention on DFS

Disease-Free Survival

HR, 0.99; 95% CI, 0.83-1.17; P = .87
Adjusted HR, 0.96; 95% CI, 0.80-1.14; P = .63

Pierce et al., JAMA 2007; 298: 289-98.
What do WINS and WHEL tell us about energy balance and cancer?

- WINS provides the only available evidence that an energy balance intervention could affect cancer mortality.

- Results of WINS and WHEL seem to provide evidence that weight loss, presumably achieved through restriction of energy intake, could impact cancer risk/outcomes.

- Caveats:
  - Neither study was designed as a weight loss/energy restriction trial.
  - We do not know if the women who did better in WINS were the ones who lost weight.
  - We do not know anything about changes in exercise behaviors in WINS.
CHALLENGE: Colon Health and Life-Long Exercise Change trial

High risk Stage II or stage III colon cancer - completed adjuvant chemotherapy within 2-6 months

REGISTRATION

Baseline Testing

STRATIFICATION

Disease stage high risk III; centre; BMI ≤ 27.5 vs. > 27.5;
ECOG PS 0 vs. 1

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

Animal models of energy balance and cancer

• Provide opportunity to evaluate impact of energy balance factors in a controlled environment

• Good platform for correlative analyses to learn more about potential mechanisms through which energy balance could impact cancer risk/outcomes

• Challenges:
  • Physical activity models more difficult to implement than dietary restriction
  • Unclear that animal models adequately represent human condition where complex interactions exist between different energy balance factors
Some data suggest that achieving negative energy balance through physical activity could be at least as beneficial as caloric restriction.

135 Sprague-Dawley rats injected with 1-methyl-1-nitrosurea and randomized after 7 days:

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<tr>
<th>Tumor</th>
<th>Incidence</th>
<th>Multiplicity</th>
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<tr>
<td>Sedentary Controls</td>
<td>98%</td>
<td>3.6</td>
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<tr>
<td>Energy restriction*</td>
<td>89%</td>
<td>3.1</td>
</tr>
<tr>
<td>Physical Activity*</td>
<td>84%</td>
<td>2.6</td>
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*92% net energy balance as compared to control group

Animal models also allow us to study mechanisms through which interventions impact cancer

- In model organisms, short term starvation (fasting) puts normal cells into a protective mode

- Significant changes in glucose and IGF-1 lower cell proliferation

- Pilot project of 10 individuals who fasted around chemotherapy demonstrates protection from toxicity

Raffaghello et al. Cell Cycle 2101; 9:4474-76
How does fasting affect cancer cells?

- Concern that protective effects of fasting vs. chemotherapy could extend to cancer cells
- Led to series of trials testing effects of fasting on chemotherapy in pre-clinical models
- Found that oncogenes prevent cancer cells from entering protective mode (Differential Stress Resistance)

Mouse model of chemotherapy and fasting

Lee et al. Sci Transl Med 2012;4:124
Differential Stress Resistance

Lee et al. Sci Transl Med 2012;4:124
Does any of this help answer our question?

- Randomized trials suggest weight loss, likely achieved through energy restriction could impact cancer

- No data comparing energy restriction and exercise

- Animal data suggest both strategies could affect cancer risk

- Remaining option: impact of energy restriction and increased physical activity upon intermediate markers
Intermediate Biomarkers

↑ Dietary-Weight Loss and Physical Activity

↑ Immune  ↓ Inflammation  ↓ Sex Hormones  ↓ Body Fat  ↓ Insulin  ↓ IGFs  ↓ Adipokines

↓ Breast Cancer Recurrence and Mortality

IGFs ↓ IGF - 1  ↓ IGFBP - 3

↑ Adiponectin  ↓ Leptin

One study compares impact of energy balance interventions upon biomarkers of cancer risk

Nutrition and Exercise Study for Women (NEW Trial)

- Designed to evaluate the impact of dietary weight loss and exercise upon hormones 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
NEW Study demonstrates most significant impact from weight loss

Weight Change:

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

However, exercise appears to have an independent effect in some populations

*Exercise and Insulin Study in Breast Cancer Survivors*

- Enrolled 101 overweight, sedentary breast cancer survivors (average BMI 30.0 kg/m²)
- Randomized to 16-week mixed strength and aerobic training intervention vs. usual care
- Endpoints:
  - Primary: change in insulin
  - Secondary: change in anthropometric measures, glucose, strength

Ligibel et al. JCO 2008; 26: 907-912
Exercise Outcomes

Strength:

Aerobic Activity: Increase of 100 minutes/week (11 vs 110)
Exercise and % change in metabolic hormones over 16 weeks

*P=0.07, **p=0.02

So which is more important: energy restriction or increased activity?

- Observational evidence shows links between both energy intake and physical activity and cancer.

- Randomized data comparing the impact of individual factors on cancer outcomes not available.

- The WINS and WHEL data suggest that weight loss/energy restriction may impact cancer mortality, but studies not designed to evaluate this.

- Animal models demonstrate some activity of both increased physical activity and energy restriction in cancer prevention.

- Biomarker data suggest that weight loss has a significant impact on markers linked to cancer risk and mortality, but effect of individual factors may differ by population.
So?????

• Not possible to determine which factor most promising based on current data

• Evidence from WINS and NEW study suggest weight loss may be key factor in cancer prevention

• Need more data to evaluate if it matters how weight loss achieved and if this varies by population